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Prone position for acute respiratory failure in adults (Review)

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[Intervention Review]

Prone position for acute respiratory failure in adults

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ABSTRACT

Background

Acute hypoxaemia de novo or on a background of chronic hypoxaemia is a common reason for admission to intensive care and for provision of mechanical ventilation. Various refinements of mechanical ventilation or adjuncts are employed to improve patient outcomes. Mortality from acute respiratory distress syndrome, one of the main contributors to the need for mechanical ventilation for hypoxaemia, remains approximately 30-40%. Ventilation in the prone position may improve lung mechanics and gas exchange and could improve outcomes.

Objectives

The objectives of this review are to ascertain whether prone ventilation offers a mortality advantage when compared with traditional supine or semi recumbent ventilation in adult patients with severe acute respiratory failure requiring conventional invasive artificial ventilation.

Search methods

We searched CENTRAL, MEDLINE, EMBASE, CINAHL and LILACS up to May 2020 for eligible randomized controlled trials using an updated version of the search strategy from the earlier version of the review. We added a search in the Cochrane COVID 19 Register.
We also searched for studies by hand-searching reference lists and citations of relevant articles, by contacting colleagues, by hand-searching published proceedings of relevant journals. We searched trial registers for ongoing studies in November 2020. We applied no language or publication status constraints.

Selection criteria

We included randomized controlled trials (RCTs) that examined the effects of prone position versus supine/semi recumbent position during conventional mechanical ventilation in adult participants with acute hypoxaemia.

Data collection and analysis

We used standard methodological procedures expected by Cochrane. We analysed data using Review Manager software and pooled included studies to determine the risk ratio (RR) for mortality and the risk ratio or mean difference (MD) for secondary outcomes; we also performed subgroup analyses and sensitivity analyses.

Main results

We identified nine relevant open-label (unblinded) RCTs (12 publications), which enrolled a total of 2165 participants. All recruited participants suffered from disorders of lung function causing moderate to severe hypoxaemia and requiring mechanical ventilation, so they were fairly comparable within what is the great diversity of specific disease diagnoses in intensive care. Blinding of participants, carers, clinical trialists and other decision-makers to treatment allocation was not possible (face-up vs face-down). This predisposes to bias with regards to use of co-interventions and also initiation of with-holding or withdrawing life-support, a common practice in intensive care.

Primary analyses of short- and longer-term mortality pooled from six trials demonstrated an RR of 0.84 to 0.86 in favour of the prone position (PP), but findings were not statistically significant: In the short term, mortality for those ventilated prone was 33.4% (363/1086) and supine 38.3% (395/1031). This resulted in an RR of 0.84 (95% confidence interval (CI) 0.69 to 1.02). For longer-term mortality, results showed 41.7% (462/1107) for prone and 47.1% (490/1041) for supine positions, with an RR of 0.86 (95% CI 0.72 to 1.03). The quality of the evidence for both outcomes was rated as low as a result of important potential bias and serious inconsistency.

Subgroup analyses for mortality identified three groups consistently favouring PP: those recruited within 48 hours of meeting entry criteria (five trials; 1024 participants; RR of 0.75 (95% CI 0.59 to 94)); those treated in the PP for 16 or more hours per day (five trials; 1005 participants; RR of 0.77 (95% CI 0.61 to 0.99)); and participants with more severe hypoxaemia at trial entry (six trials; 1108 participants; RR of 0.77 (95% CI 0.65 to 0.92)). The quality of the evidence for these outcomes was rated as moderate as a result of potentially important risk of bias.

Prone positioning appeared to influence adverse effects: pressure ulcers (four trials; 823 participants) with an RR of 1.25 (95% CI 1.06 to 1.48) and tracheal tube obstruction with an RR of 1.78 (95% CI 1.22 to 2.60) were increased with prone ventilation. Reports of arrhythmias were reduced with PP, with an RR of 0.64 (95% CI 0.47 to 0.87).

Authors' conclusions

We found no convincing evidence of benefit nor harm from universal application of PP in adults with hypoxaemia, mechanically ventilated in intensive care units (ICUs). This is despite the benefits observed in one of the open-label trials restricted to participants with greater disease severity. Three subgroups (early implementation of PP, prolonged adoption of PP and severe hypoxaemia at study entry) suggested that prone positioning may confer a benefit for mortality, but these results should be interpreted with caution. Additional adequately powered studies would be required to definitively confirm or refute these observations of subgroup benefit. This is problematic, given the results of the most recent open-label trial showing a benefit and recommendations derived from several published subgroup analyses. If replication and confirmation of such trial results, which would be desirable, are not realistic, formal meta-analysis of individual patient data and post-trial observational studies (as occur after phase III clinical drug trials) could be utilised to confirm apparent benefit in at-risk populations. Complications such as tracheal tube obstruction and pressure ulcers are increased with the use of prone ventilation. Long-term mortality data (12 months and beyond), as well as functional, neuro-psychological and quality of life data, are required if future studies are to better inform the role of PP in the management of hypoxaemic respiratory failure in the ICU.

PLAIN LANGUAGE SUMMARY

Prone (face-down) position for mechanical ventilation of adults with acute respiratory failure

Review question

This review sought to investigate whether face-down ventilation could improve important outcomes by, for instance, reducing the death rate (mortality) among individuals requiring mechanical ventilation in intensive care. We also wanted to identify disadvantages and complications associated with prone positioning, as well as long-term benefits.

Background

People who are admitted to an intensive care unit and need assistance with breathing provided by a ventilator (mechanical ventilation) because of lung damage caused by illness have a high risk of dying. Lungs that are affected by conditions such as pneumonia will consist of normal and abnormal or diseased areas. Recovery of diseased areas takes time, and a person may need support with ventilation while this occurs. Ventilation support is potentially lifesaving, as it maintains proper oxygen levels in the blood while removing carbon dioxide waste. However, the ventilator itself can cause inflammation and thus additional lung complications. The harder a ventilator has to work to achieve normal oxygenation and removal of carbon dioxide, the more likely it is that healthy, normal areas of the lung may be damaged, and the person's condition made worse. Ventilation with the person lying face-down (prone) instead of face-up (supine) might improve how well the ventilator works, thereby reducing these undesirable side effects.

Search date

The evidence is current to 01 May 2020.

Study characteristics

We identified and included in this review randomized controlled trials of adults that compared conventional mechanical ventilation in the face-down versus the face-up position.

Key results

Reports from nine trials of 2165 participants (12 publications) show that prone ventilation did not appear to be of benefit for all participants requiring ventilation. The evidence suggested some situations in which it may improve survival. One group of participants with the most severe lung damage appeared to have reduced mortality, as did participants who received treatment early and for prolonged periods.

Complications were described. The most common of these were pressure sores (or ulcers) and tracheal tube blockage or obstruction. Low blood pressure and abnormal heart rhythms were also seen. The application of prone position to all participants in intensive care who have low oxygen levels was not supported by the evidence identified, but some particular groups of participants, for example, those with especially low oxygen levels, may benefit from prone positioning. Further clinical trials would assist in clarifying potential benefits for such patient groups but further trials may not take place because of the very large treatment benefit observed in the most recent clinical trial of participants with very low oxygen levels. In the absence of new trials, meta-analysis of individual patient data may facilitate further assessment as well as further observational studies in at risk populations.

Quality of the evidence

The quality of the evidence for primary outcomes of this systematic review was low as a result of serious inconsistency and important potential bias.

Summary of findings 1. Mortality: prone position compared with supine for acute respiratory failure in adults requiring mechanical ventilation in intensive care

Mortality: prone position compared with supine for acute respiratory failure in adults requiring mechanical ventilation in intensive care

Patient or population: adults with acute respiratory failure
Settings:
Intervention: mortality: prone position compared with supine

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Mortality: prone position compared with supine				
Short-term mortality (STM) Alive or dead Follow-up: 10 to 30 days	**Study population**		**RR 0.84** (0.69 to 1.02)	2117 (8 studies)	⊕⊕⊝⊝ **Low** [a,b]	
	383 per 1000	**322 per 1000** (264 to 391)				
	Moderate					
	450 per 1000	**378 per 1000** (310 to 459)				
Longer-term mortality (LTM) Alive or dead Follow-up: 31 to 180 days[c]	**Study population**		**RR 0.86** (0.72 to 1.03)	2141 (8 studies)	⊕⊕⊝⊝ **Low** [a,b]	
	470 per 1000	**404 per 1000** (339 to 484)				
	Moderate					
	525 per 1000	**452 per 1000** (378 to 541)				
Subgroup analysis of longer-term mortality: severe hypoxaemia Alive or dead Follow-up: 31 to 180 days[c]	**Study population**		**RR 0.77** (0.65 to 0.92)	977 (7 studies)	⊕⊕⊕⊝ **Moderate** [a]	
	547 per 1000	**421 per 1000** (356 to 503)				

	Moderate				
	653 per 1000	**503 per 1000** (424 to 601)			
Subgroup analysis of longer-term mortality: lower tidal volume ventilation Alive or dead Follow-up: 31 to 180 days[c]	**Study population**		**RR 0.73** (0.55 to 0.96)	911 (5 studies)	⊕⊕⊕⊖ **Moderate** [a]
	451 per 1000	**329 per 1000** (248 to 433)			
	Moderate				
	523 per 1000	**382 per 1000** (288 to 502)			
Subgroup analysis of longer-term mortality: ARDS only Alive or dead Follow-up: 31 to 180 days[c]	**Study population**		**RR 0.85** (0.71 to 1.01)	1758 (8 studies)	⊕⊕⊕⊖ **Moderate** [a]
	483 per 1000	**411 per 1000** (343 to 488)			
	Moderate				
	522 per 1000	**444 per 1000** (371 to 527)			
Subgroup analysis of longer-term mortality: ≥ 16 hours/d prone Alive or dead Follow-up: 31 to 180 days[c]	**Study population**		**RR 0.77** (0.61 to 0.99)	1005 (5 studies)	⊕⊕⊕⊖ **Moderate** [a]
	470 per 1000	**362 per 1000** (286 to 465)			
	Moderate				
	526 per 1000	**405 per 1000** (321 to 521)			
Subgroup analysis of longer-term mortality: enrolment ≤ 48 hours after entry criteria/ventilation Alive or dead Follow-up: 31 to 180 days[c]	**Study population**		**RR 0.75** (0.59 to 0.94)	1024 (5 studies)	⊕⊕⊕⊖ **Moderate** [a]
	469 per 1000	**352 per 1000** (277 to 441)			
	Moderate				
	523 per 1000	**392 per 1000**			

			(309 to 492)		

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI)
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low quality: We are very uncertain about the estimate

[a]Blinding of participants and carers was not possible. Researchers also may not have been adequately blinded. All analyses were downgraded because of this important potential bias, leading the quality of all subgroup analyses to be rated as moderate
[b]For the primary outcomes, inconsistency across studies reflected different patient populations, different management strategies generally and differences in adaptations to resulting effects of the intervention. This led to further downgrading of the quality of evidence for the primary outcomes to low
[c]Longer-term mortality = 31 to 180 days OR hospital mortality

BACKGROUND

Description of the condition

Acute respiratory failure can arise from numerous diseases or disease processes, and is a common reason for admission to hospital. Patients with profound gas exchange abnormalities unresponsive to ward-based strategies (such as oxygen therapy or continuous positive airways pressure (CPAP) for hypoxaemic respiratory failure, or non-invasive ventilation (NIV) for hypercapnic ventilatory failure) may be referred to intensive care units (ICUs) for further management. Patients whose problems are predominantly related to oxygenation include those with pneumonia, pulmonary oedema, pulmonary aspiration pneumonitis and pulmonary thromboembolism. Acute lung injury and acute respiratory distress syndrome (Bellani 2016; Bernard 2005; MacCallum 2005; Matthay 2019; Phua 2009; Rubenfeld 2007) are reported in an important subset of patients treated for hypoxaemia within the ICU. Acute respiratory distress syndrome (ARDS) as the phrase suggests is only a syndrome and not a specific or single disease process, It may arise as a result of a wide variety of disparate pulmonary and extrapulmonary disease processes (Rezoagli 2017; Walkey 2012), as can its less physiologically severe counterpart previously called acute lung injury (ALI). Redefinition of ARDS, which has occurred since most studies were designed or published, ALI has been renamed as "mild ARDS" (ARDS definition workforce 2012). For the new criteria of mild, moderate and severe ARDS, mortality is quoted as 27%, 32% and 45% (ARDS definition workforce 2012). The commonly described histological finding of diffuse alveolar damage is found in only 50% of cases (de Hemptinne 2009), and doubt has been cast on the usefulness of the ARDS paradigm (Marini 2008; Soni 2010). Nevertheless, the concept is considered clinically useful by most intensivists (Bernard 2005). Recently different ARDS phenotypes are recognised as important (Reilly 2019; Matthay 2019; Wilson 2020). This has been especially so for ARDS associated with COVID-19 pneumonia (Marini 2020; Robba 2020). ARDS, originally an abbreviation for Adult Respiratory Distress Syndrome remains a signature medical condition process that intensive care personnel strive to research and improve patient outcomes but is only a subset of conditions that cause acute respiratory failure in adult intensive care.

Mechanical ventilation is also used in younger patients (neonates, infants, children through to adolescents) for paediatric ARDS (PARDS). It is important to stress that the adult-based definitions of ARDS may not be applicable to paediatrics for a variety of reasons (Cheifetz 2017). These include anatomic and physiologic differences which render infants and children more vulnerable to severe respiratory insult, greater metabolic demand and less cardiorespiratory reserve than adolescents and adults. Special considerations are often necessary to optimise management approaches across the heterogeneous paediatric spectrum ranging from neonates to adolescents. Thomas and colleagues also note children have considerable variability in the predisposing conditions and etiology; their response to therapy was different and often better; and pre-existing conditions and underlying etiology appeared to influence outcome to a greater extent than the severity of the lung injury itself. They (Thomas 2013) highlight a medical axiom that children should not be considered as "*little adults*." Kneyber *et al* also note that with regards to ventilator induced lung injury (VILI) that given the physiological and biological differences in the respiratory systems of infants, children, and adults, it is difficult to directly extrapolate clinical practice from adults to children (Kneyber 2014). For the above discussed reasons children are not considered together with adults in this systematic review. Children and neonates have also been the subject of separate Cochrane Systematic Reviews (Gillies 2012; Rivas-Fernandez 2016)

Patients with ventilatory failure and hypercapnia include those with chronic obstructive pulmonary disease (COPD) and those receiving central nervous system depressant drugs; patients with neuromuscular problems may also require mechanical ventilation. Thus a wide variety of patients may require mechanical ventilation within the adult ICU. Variability is great with regards to severity of illness and severity of structural lung damage. The reversibility of disease-driving processes is also inconsistent.

Description of the intervention

Patients with profound hypoxaemia present a significant challenge for carers in dealing with both hypoxaemia and underlying process(es). Although hypoxaemia often is not perceived as the ultimate cause of death in these patients, it does have deleterious effects (Strachan 2001). Avoidance of profound hypoxaemia is one of the goals of supportive therapy in ICU, and a variety of manoeuvres are employed to ameliorate hypoxaemia. Including: positive end-expiratory pressure (PEEP), inverse ratio ventilation (IRV), alveolar recruitment manoeuvres, restrictive fluid administration strategies, inhaled pulmonary vasodilators such as nitric oxide and prostacyclin, corticosteroids and neuromuscular blockers and mechanical ventilation in the prone position (Adhikari 2004; Adhikari 2007; ARDSnet 2006b; ARDSnet 2006a; Cranshaw 2002;Fielding-Singh 2018; Klein 2004; Mentzelopoulos 2005; Papazian 2010). All of these therapies have been shown to improve oxygenation, but few have demonstrated a mortality benefit in randomized controlled trials (Diaz 2010; Papazian 2010; Petrucci 2013). Athough a systematic review of high-frequency oscillation (HFO) suggested their possible utility in the management of ARDS (Fan 2010; Sud 2013), two RCTs reported in 2013 have not confirmed benefit (Ferguson 2013; Young 2013). Notably one of the trials was discontinued early as a result of increased mortality in the treatment group (Ferguson 2013). Extracorporeal membrane oxygenation (ECMO) has been shown to be of benefit (Noah 2011; Noble 2010; Aoyama 2019) but is available only in relatively few specialized centres. Traditional mechanical ventilation, which normally is utilized in supine and semi recumbent patients, while ensuring short-term survival, may also contribute to lung injury and other deleterious effects (Soni 2008). Ventilator-induced lung injury has been demonstrated in both experimental animal models and in human participants to perpetuate or even accentuate the original injury to the lung and can cause dysfunction of distant organs (Verbrugge 2007) in the form of barotrauma, volutrauma and biotrauma.

Under normal circumstances, patients ventilated in ICUs are cared for in the semi-recumbent position, often described as the supine position. This supine or semi-recumbent position allows better access for carers to provide interventions such as mouth care and airway and vascular access procedures. It is also more appropriate for critical manoeuvres such as cardiopulmonary resuscitation, should this be required. This position is more comfortable for patients and allows them better interaction with their environment when compared with the prone, face-down position.

This systematic review explores the intervention of placing patients in the prone position (face-down) while they are mechanically ventilated for severe hypoxaemic respiratory failure via a tracheal tube.

How the intervention might work

Chatte 1997 and others have showed that ventilation provided with the patient in the prone position could have beneficial effects on oxygenation (Gattinoni 2001; Mure 2001). Recent studies in humans and in experimental animal models, have confirmed that ventilation in the prone position is associated with improved oxygenation in most individuals. More than 70% of patients with lung injury show clinical improvement in oxygenation with prone mechanical ventilation. In a retrospective multi-variate analysis, prone positioning was independently correlated with positive outcomes in patients with ARDS (Venet 2003). The mechanisms by which prone position improves gas exchange include alveolar recruitment, redistribution of ventilation towards dorsal areas that remain well perfused, homogenization of tidal volume distribution and possible improved postural drainage of secretions (Gattinoni 2006; Guerin 2006). Postural drainage has also been suggested to reduce ventilator-associated pneumonia, although theoretically this could spread organisms and inflammatory mediators within lung tissue, leading to increased damage (Graf 2008; Marini 2010). Homogenization of tidal volume distribution may reduce tissue stress/strain and consequently may diminish the well-described injurious effects of mechanical ventilation, thus providing additional benefit over and above that associated with improved oxygenation (Gattinoni 2012; Gattinoni 2013; Mentzelopoulos 2005; Slutsky 2013). Other effects include improvements in haemodynamics (Guerin 2014).

Thus, three phenomena might improve survival among patients (Charron 2011).

- Reduced extent and duration of severe hypoxaemia.
- Reduced propensity to ventilator-induced lung injury.
- Reduced occurrence of nosocomial or ventilator-associated pneumonia.

Adverse effects associated with the prone position for ventilation most notably include (Faculty of Intensive Care 2019):

- unplanned extubation and risk of an episode of potentially catastrophic hypoxaemia;
- inadvertent bronchial intubation, which will also worsen hypoxaemia and increase risk of barotrauma (e.g. pneumothorax);
- development of pressure sores / ulcers (most cited injury);
- facial / periorbital edema;
- ocular complications including severe corneal abrasions and possible ischaemic neuropathy with permanent sight loss;
- cardiovascular instability;
- intravenous line displacement;
- kidney dialysis / filtration line flow problems interfering with renal support;
- intracranial hypertension, which can compromise cerebral circulation;
- brachial plexus injuries; and
- staff injuries, especially if insufficient trained staff are available to perform required turns in sedated intubated patients

Improved oxygenation with the prone position could allow additional time for lung reparative processes, and, by reducing secondary lung infection or injury, has the potential to accelerate recovery and lessen mortality among adults with acute respiratory failure. Adverse effects and complications related to the prone position might reduce the overall impact of these potential benefits.

Why it is important to do this review

Patients admitted to the ICU with severe hypoxaemia are at high risk for mortality (ARDS definition workforce 2012; Walkey 2012). For example, Phua and colleagues reported overall mortality in the important subset of ICU patients with ARDS of 44% in observational studies and 36% in randomized controlled trials. This rate of mortality does not seem to have been significantly reduced since 1994, when the American-European Consensus Conference redefined ARDS (Phua 2009). Any intervention that reduces mortality, especially one that can be easily implemented at little additional cost, requires adequate exploration. This interim amendment of the original review (Bloomfield 2015) seeks to update evidence from any new randomized clinical trials and evaluate all evidence in the context of current theory and practice. This amendment may be superseded by a complete review update in the future.

OBJECTIVES

The objectives of this review are (1) to ascertain whether prone ventilation offers a mortality advantage when compared with traditional supine or semi recumbent ventilation in participants with severe acute respiratory failure requiring conventional invasive artificial ventilation, and (2) to supplement previous systematic reviews on prone ventilation for hypoxaemic respiratory failure in an adult population.

METHODS

Criteria for considering studies for this review

Types of studies

We included all randomized controlled trials (RCTs) comparing conventional modes of mechanical ventilation in the supine or semi recumbent position versus mechanical ventilation in the prone position in adults with acute respiratory failure. We did not include observational studies due to the perceived higher risk of bias.

We included unpublished studies and abstracts when identified.

We imposed no language restrictions.

Types of participants

We included studies on adults with critical illness in an ICU setting requiring conventional mechanical ventilation for acute severe respiratory failure.

We excluded studies primarily investigating participants with chronic respiratory impairment such as COPD. This review focused on acute severe respiratory failure.

We excluded studies on neonates or paediatric participants (i.e. younger than 16 years), which are covered separately in updated Cochrane reviews (Gillies 2012; Rivas-Fernandez 2016) and because of other differences in physiology, aetiology, definitions, comorbidities, cointerventions and rescue treatments for paediatric patients with acute respiratory failure (Cheifetz 2017; Kneyber 2014; Thomas 2013).

Types of interventions

We examined interventions comparing conventional methods of ventilation in the supine or semi recumbent position (which could encompass lateral positioning as part of routine pressure care) versus the prone position.

We excluded studies that used primary positions other than supine or semi recumbent. We excluded rotational therapies provided in the prone position. We excluded studies comparing conventional prone ventilation versus other experimental modes of ventilation such as high-frequency jet ventilation (HFJV) or high-frequency oscillation (HFO).

Types of outcome measures

We sought information on the following main outcomes.

Primary outcomes

- Short-term mortality (10 to 30 days, or ICU mortality).
- Longer-term mortality (> 30 days, or hospital mortality).

Secondary outcomes

We also sought information on the following.

- Rate of ventilator-associated pneumonia, as defined in the original studies.
- Number of days on a ventilator.
- Length of ICU stay.
- Length of hospital stay.
- Improvement in oxygenation.
- Adverse events.
- Quality of life.
- Economic outcomes.

Search methods for identification of studies

Electronic searches

We searched for eligible randomized controlled trials as described in the Cochrane Handbook of Systematic reviews of Interventions Chapter 4 (Lefebvre 2019).

We applied no language or publication status constraints.

We searched the following databases:

- CENTRAL, Cochrane Central Register of Controlled Trials (2020, Issue 4)
- MEDLINE ALL (Ovid SP; 2014 to 01 2020 May)
- EMBASE (Ovid SP; 2014 to 01 May 2020)
- CINAHL, Cumulative Index to Nursing and Allied Health Literature (Ebsco; 2014 to 01 May 2020)
- LILACS, Latin American Caribbean Health Sciences Literature (2014 to 01 May 2020)
- Cochrane COVID 19 Register

We updated the search strategy of Bloomfield 2015 with extra search terms and added filters for randomized controlled trials. The searches were run from 1 January 2014 to 1 May 2020 using the search strategy provided in Appendix 1.

For the earlier version of this review (Bloomfield 2015), we searched: CENTRAL (2014, Issue 1), MEDLINE (Ovid SP; 1950 to 31 January 2014), EMBASE (Ovid SP; 1980 to 31 January 2014), CINAHL (1982 to 31 January 2014) and LILACS (1992 to 31 January 2014).

Searching other resources

We also searched for studies by:

- hand-searching reference lists and citations of previous trials and review articles to May 2020;
- hand-searching books related to critical care and mechanical ventilation;
- communicating with colleagues, particularly published trialists; and
- performing a subject-specific search of the following journals to look for published proceedings abstracts of clinical trials.
  - *American Journal of Respiratory and Critical Care Medicine,* volumes 175 to 189, 2007 to January 2014.
  - *Critical Care*, volumes 11 to 18, 2007 to January 2014.
  - *Critical Care Medicine,* volumes 35 to 42, 2007 to January 2014.
  - *Intensive Care Medicine,* volumes 33 to 40, 2007 to January 2014.

We searched for relevant ongoing trials at the following websites (searched 20 November 2020):

- ClinicalTrials.gov (https://www.clinicaltrials.gov/)
- ISRCTN Registry (http://www.isrctn.com/)
- World Health Organization - International Clinical Trials Registry Platform (ICTRP) (www.who.int/clinical-trials-registry-platform)
- Cochrane Covid-19 study register (https://covid-19.cochrane.org/)

We checked the included studies for retractions in the Retraction Watch Database and in PubMed.

Data collection and analysis

Selection of studies

Two review authors (RB and DWN) independently screened and classified all citations as potential primary studies, review articles or others for inclusion. Two review authors (RB and DWN) examined all potential primary studies and decided whether they should be included in the review. We resolved all disagreements by discussion.

Data extraction and management

Two review authors (RB and DWN) independently extracted in duplicate from each study data on methods and outcomes

(Appendix 2). A third review author (AS) checked data subsequently entered onto a Microsoft Excel spreadsheet.

Assessment of risk of bias in included studies

We judged study quality using the Cochrane Risk of bias tool on the basis of criteria and mechanisms described in Table 8.5.d by Higgins et al (Higgins 2011a), which were based on:

- adequacy of randomization;
- allocation concealment;
- blinding of participants and investigators;
- blinding of outcome assessment;
- completeness of outcome data;
- selective reporting; and
- other relevant potential bias.

We addressed the impact of methodological quality on results and performed a sensitivity analysis that excluded studies at high risk of bias. We rated the quality of evidence by using the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system (Guyatt 2008; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c), as described below.

Measures of treatment effect

For dichotomous outcomes, we calculated risk ratios (RRs). We used odds ratios (ORs) when outcomes were rare. We used standardized mean differences (SMDs) or mean differences (MDs) as appropriate for continuous outcomes.

Unit of analysis issues

We identified no specific issues.

Dealing with missing data

We did not specify in the original protocol how missing data issues would be managed (Bloomfield 2009).

Assessment of heterogeneity

We measured heterogeneity by using the Higgins test, whereby an I^2 statistic greater than 25% is considered to show significant heterogeneity. This test describes the percentage of total variation across studies that is due to heterogeneity rather than to chance (Higgins 2003). We used a fixed-effect model when the Higgins test showed good homogeneity (low heterogeneity) between studies; otherwise, we used a random-effects model. Higgins has defined an I^2 statistic of 25%, 50% or 75% as low, moderate or high (Higgins 2003). When present, we planned to explore heterogeneity by considering these options listed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

- Avoiding formal meta-analysis when fewer than two studies provided quantitative data for primary outcomes.
- Ignoring heterogeneity.
- Using random-effects meta-analysis to ascertain mean effect and confidence intervals of the mean effect size. (Deeks 2019)
- Exploring heterogeneity by using pre-specified subgroup analyses or meta-regression when we identified sufficient (> 10) studies.
- Excluding studies as part of a sensitivity analysis (Deeks 2011).

Assessment of reporting biases

We used a funnel plot to assess the risk of small study effects or reporting bias (Higgins 2011a).

Data synthesis

We reviewed data from included studies qualitatively, and then, when possible, we combined data quantitatively by population, intervention and outcome, using Cochrane's statistical software, RevMan 5.40. We based quantitative analyses of outcomes on "intention-to-treat" results (i.e. results based on the intention-to-treat principle). We followed the recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* regarding data synthesis. In cases of very substantial (high) heterogeneity (Higgins 2003), we would not pool the results to perform statistical analysis. We used a fixed-effect model when homogeneity between studies was good, and a random-effects model when it was not.

Subgroup analysis and investigation of heterogeneity

We planned to undertake the following subgroup analyses (SGA).

- Duration of daily ventilation in the prone position (< 16 hours/d vs ≥ 16 hours/d). As any benefit from prone ventilation may be a dose (time)-related phenomenon, daily duration of time in that position would appear potentially important.
- Duration of supine ventilation before randomization. As ventilatory-induced lung injury is relatively rapid in onset, any randomized trials and outcomes reporting very limited exposure to supine ventilation before randomization should be identified.
- Outcome according to severity (oxygenation index; PaO_2/FIO_2 ratio or quotient; severity of illness score, e.g. Simplified Acute Physiology Score II (SAPS II)). As patients with more severe lung injury benefit from prone ventilation, this may be an important subgroup to explore. SAPS II and similar scores may indirectly reflect the severity of inciting injury and may be relevant.
- Tidal volume (size of the mechanical breath given to the participant) in relation to body weight has been shown to affect survival and outcomes between high tidal volume (> 10 mL/kg of ideal body weight), moderate tidal volume (8 to 10 mL/kg of ideal body weight) and low tidal volume (≤ 8 mL/kg of ideal or predicted body weight) and will be explored if the data permit. (Actual body weight exceeds ideal or predicted body weight by a mean factor of as much as 1.25 (Bloomfield 2006) and therefore underestimates the standard metric of tidal volume, which is based on ideal body weight.) We considered "ideal" and "predicted body weight" as interchangeable and based on height and sex of participants.
- We analysed studies of acute lung injury (ALI) together with acute respiratory distress syndrome (ARDS) separately from those examining other causes of acute severe hypoxaemic respiratory failure.
- We further sub-classified acute lung injury and ARDS into pulmonary and extrapulmonary causes and as conditions that may behave differently with different ventilatory strategies (Walkey 2012; Ware 2000). We planned to explore differences in outcomes in these subcategories if collected data allowed.

We explored evidence of substantial heterogeneity in primary outcomes as indicated by the Higgins test by performing subgroup analyses, and, if we identified more than 10 primary studies,

by performing meta-regression (Deeks 2011). We did not employ statistical techniques or adjustments for multiple comparisons when conducting these prespecified analyses.

Sensitivity analysis

We undertook a sensitivity analysis of primary outcomes with regards to the quality of data. We excluded from the sensitivity analysis studies with two or more "red flags" due to the high risk of bias.

Summary of findings and assessment of the certainty of the evidence

We used the principles of the GRADE system (Guyatt 2008; Guyatt 2011a; Guyatt 2011b; Guyatt 2011c) to assess the quality of the body of evidence associated with specific outcomes. In the case of RCTs, the GRADE system allows downgrading of the overall rating of evidence from "high quality" by one or two grades on the basis of study limitations (risk of bias), indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

We applied the GRADE system to these primary outcome measures.

- Short-term mortality.
- Longer-term mortality.

We also applied this system to four subgroup analyses related to longer-term mortality.

- Participants with severe hypoxaemia.
- Mechanical ventilation with lower tidal volumes.
- Outcomes for participants with ALI or ARDS.
- Maintenance of the prone position for 16 or more hours per day.
- Enrolment within 48 hours of meeting study criteria.

We chose these outcomes for GRADE analysis after the protocol was published, as this tool was not used by The Cochrane Collaboration at that time.

RESULTS

Description of studies

See Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies.

Results of the search

Details of the original search are reported in Bloomfield 2015. The results of the updated search from 1st January 2013 to 1st May 2020 are presented in a study flow diagram (Figure 1).

Figure 1. Flow diagram of results from updated search (January 2014 to 1st May 2020)

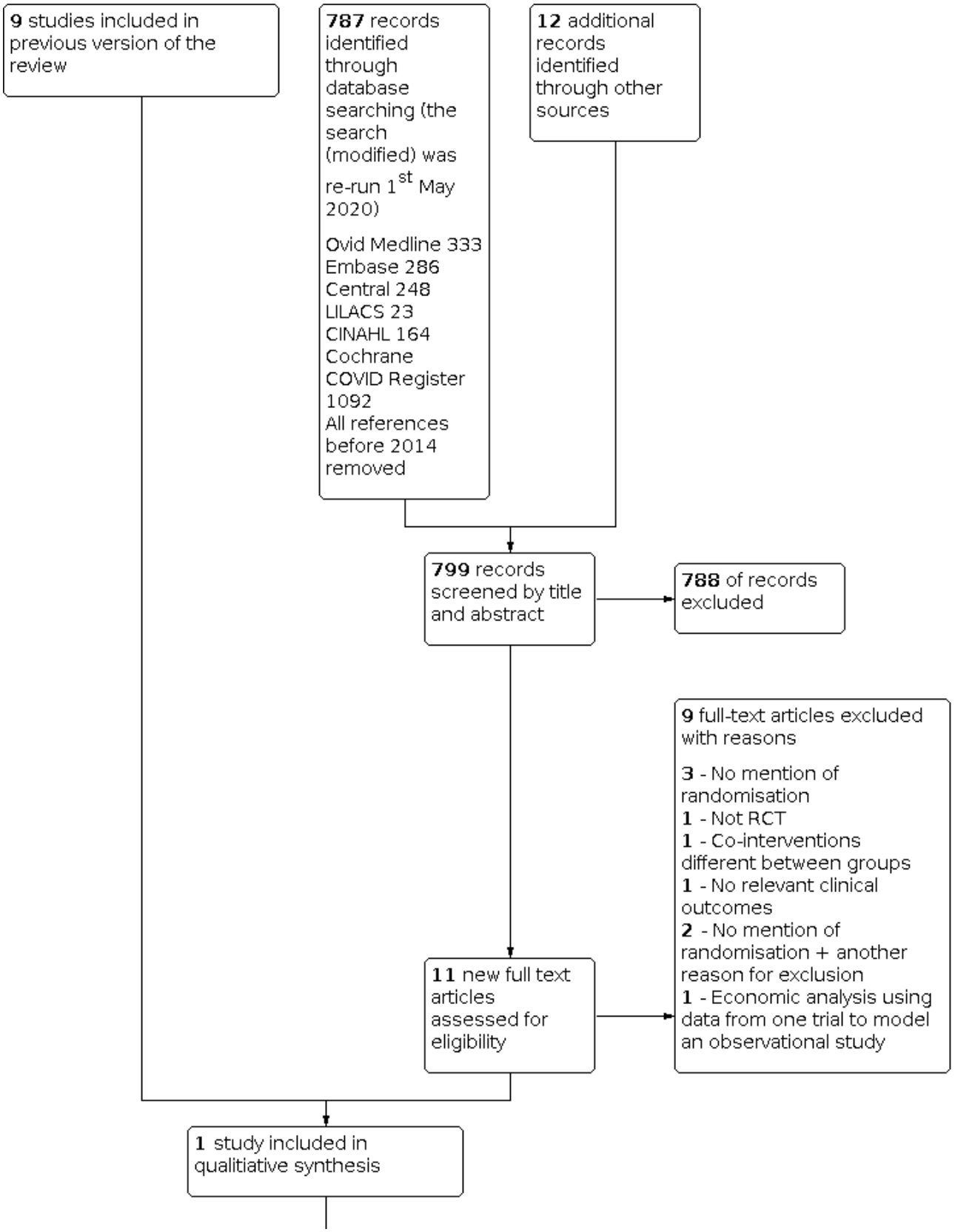
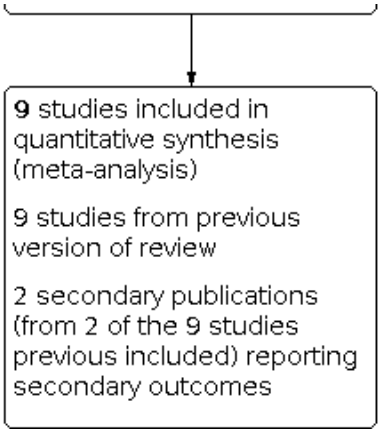


Figure 1. (Continued)



A search of proceedings supplements of the *American Journal of Respiratory and Critical Care Medicine*, *Critical Care*, *Critical Care Medicine* and *Intensive Care Medicine* yielded no additional relevant RCTs.

Included studies

We extracted data from nine primary studies reported in 13 publications. Eight were primary studies published in full form in peer-reviewed journals (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Mancebo 2006; Taccone 2009; Voggenreiter 2005). One study was reported as an abstract, with supplementary information given in presentation slides provided by Jan Friederich (Leal 1997). We found additional data regarding some of the primary studies in seven journal publications (Ayzac 2016; Chiumello 2012; Gattinoni 2010; Girard 2014; Sud 2008b; Sud 2010; Sud 2014). These provided additional information on subgroups of participants with very severe hypoxaemia from four studies (Gattinoni 2001; Guerin 2004; Mancebo 2006; Taccone 2009) and on an ARDS subgroup from one study (Sud 2014). Chiumello *et al* (Chiumello 2012) reported one-year mortality at five of the centres that contributed to the Taccone 2009 study. Sud *et al* provided additional data regarding severity of illness through SAPS II scores (Sud 2008b). Chiumello *et al* reported pulmonary function and quality of life data (Chiumello 2012). Most studies recruited participants with ALI or ARDS, although the largest single study (Guerin 2004) also recruited individuals who would have been excluded from the ALI/ARDS trials. Some information for this subgroup was later made available (Sud 2014).

Two secondary publications were identified in the latest search update and reported new data from the primary trial of Guerin (Guerin 2013) regarding pressure ulcers (Girard 2014) and ventilator associated pneumonia (Ayzac 2016). They are incorporated into this amendment.

Excluded studies

We excluded five studies that were included in other published meta-analyses. Two studies (Demory 2007; Papazian 2005) investigated the short-term effects of high-frequency oscillatory ventilation (HFOV) in prone and supine participants. One was a prevention study (Beuret 2002) in patients with coma, and one (Watanabe 2002) applied an intervention of neuromuscular blockade to the prone group that has been associated with improved outcomes in some but not all trials (Ho 2020; Papazian 2010) and failed to report mortality data. Another study (Curley 2005) included predominantly very young children with a median age of two years and no adults. Two of these studies (Beuret 2002; Watanabe 2002) were conducted in the pre-low tidal volume ventilation era.

The updated search for this amendment identified eight further studies for possible inclusion (Cao 2014; Cheng 2016; Li G 2015; Li J 2015; Peng 2018; Wang 2015; Yan 2015; Zhou 2014) two directly from the literature search and six from the systematic review of Du (Du 2018). All were ultimately excluded from analysis (Characteristics of excluded studies). Five (Cao 2014; Cheng 2016; Li J 2015; Wang 2015; Yan 2015) did not mention randomization. One (Li G 2015) was a retrospective study. The 60 patient 4-limb randomized clinical study of Peng *et al* (Peng 2018) was primarily a short-term physiological investigation with a single episode of prone intervention. It did not report mortality and had major baseline imbalances with regards to age and APACHE scores of participants. Such deficiencies in reporting of trials in the Chinese literature have been previously documented (Zhang 2008). The randomized trial of Zhou *et al* (Zhou 2014) compared supine position alone versus two interventions, prone position combined with recruitment manoeuvres and was also excluded.

One systematic review (Yue 2017) listed Charron 2011 as a randomized clinical trial in their meta-analysis. Re-examination of this study data confirmed results were derived from a clinical database and not a randomized clinical trial.

Studies awaiting classification

There are no additional studies awaiting classification.

Ongoing studies

Three ongoing studies were identified. This included one trial (NCT03891212) comparing prone versus supine positioning in mechanically ventilated patients with severe pneumonia, and two trials (NCT04139733; NCT04607551) comparing prone versus supine positioning in mechanically ventilated patients receiving ECMO (see Characteristics of ongoing studies).

Risk of bias in included studies

We have graphically presented in Figure 2 review authors' assessment of bias within individual studies, and in Figure 3, bias across studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

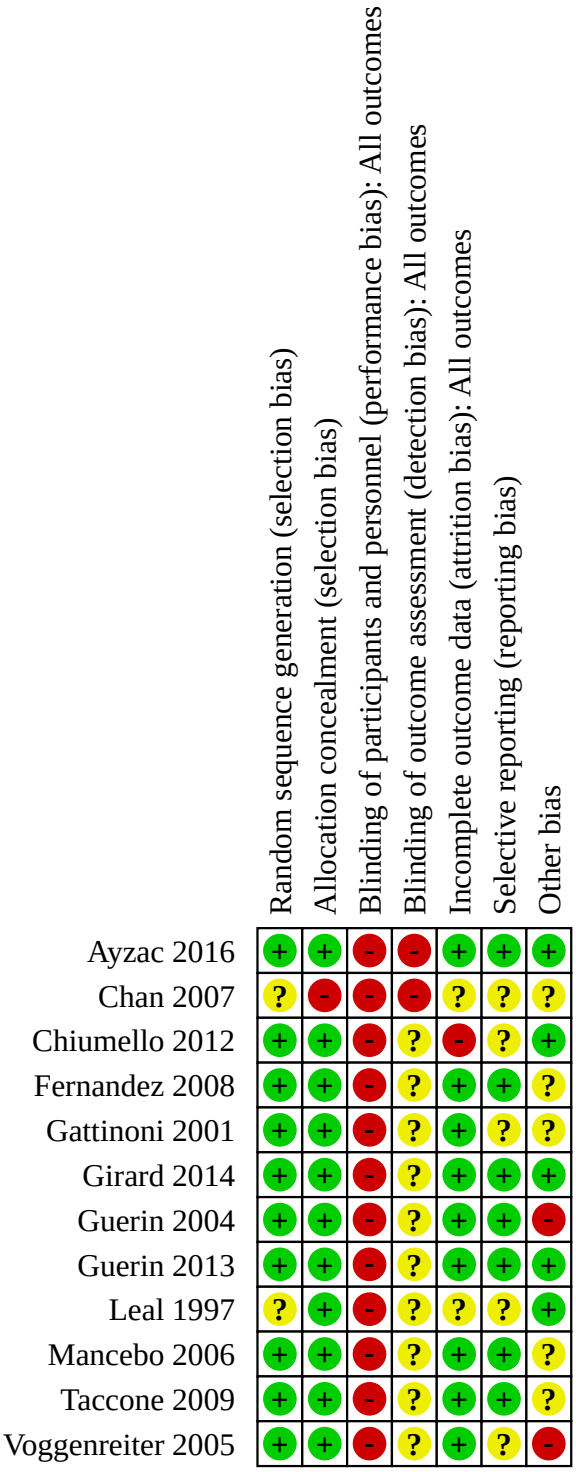
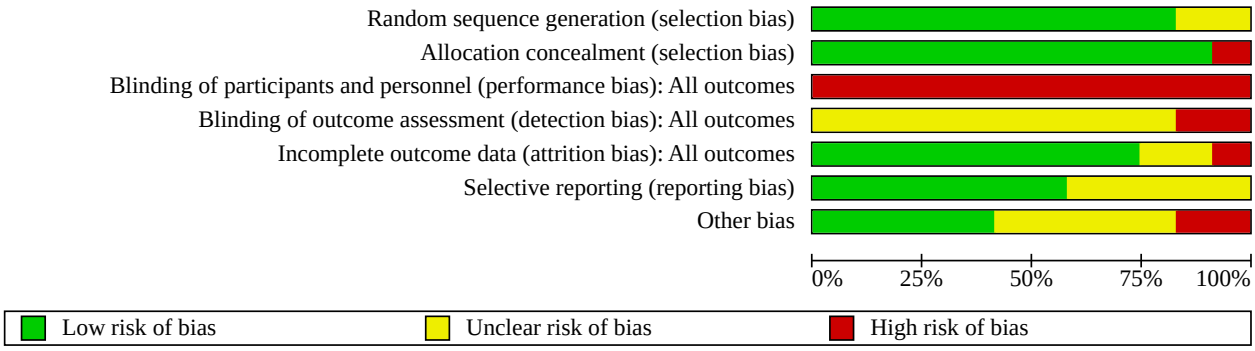


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Allocation sequence generation was of a high standard overall, with most studies employing computer-generated sequences and blinding sequence allocation by using a computer-telephone allocation system of sealed opaque envelopes. Allocation bias seems likely for the study of Chan *et al* (Chan 2007).

Blinding

Complete blinding of participants and clinical staff to allocation would be impossible because participants were placed either with face and feet up or with face and feet down. Some blinding of processes and decision making could be incorporated into trial procedures together with some standardised or protocolised approaches to important co-interventions to improve methodological rigour. Such measures have not been systematically applied across studies.

Lack of blinding could affect application of important related co-interventions (Cummings 2013) such as decisions on futility, non-escalation of treatment, withdrawal of treatment or continuation of active treatment (Forbes 2013; Morgan 2014; Stapleton 2005; Turnbull 2014). We downgraded the quality of evidence assessed by the GRADE system in all analyses in which it was utilized as important clinical decisions would be made with full knowledge of treatment allocation (Jadad 2007). A double downgrade was considered but not applied. It is not clear whether investigators were blind to participant allocation when performing data analyses.

Incomplete outcome data

Most studies reported participants lost to follow-up and used the intention-to-treat principle. Missing data for primary and some major secondary outcomes were small (0 to 5% of participants), and this was unlikely to affect interpretation of findings. However, for some secondary outcomes, the disparity in reporting rates between studies suggests differences in outcome definition, priority for data collection or efforts to minimize these complications.

Selective reporting

Selective reporting within studies was unlikely for the primary outcomes and for subgroup analyses in which death was the outcome of interest. Most studies were conducted at multiple centres, and a pre-study protocol would define criteria for most reported study endpoints. *Post hoc* analyses might be at risk of selective reporting e.g. choice of 88 mmHg (11.7 kPa) PaO_2/FIO_2 quotient as cutoff for *post hoc* mortality subgroup analysis (Gattinoni 2001).

Other potential sources of bias

For most studies, cross-over of participants from one limb of the study to another was modest. However, cross-over or non-adherence to the protocol was considerable for the study of Guerin 2004. Eighty-one (21%) participants crossed over from supine to prone, and 170/413 (41%) in the prone group were never actually put in prone position, or the prone position was discontinued before the study met prone weaning criteria (Guerin 2004; Sud 2008). This effect would assume even greater importance in subgroup analyses of sicker participants that included an even higher proportion of cross-over participants. Although strictly not bias, this will reduce the efficiency (Lipsey 1990) of a trial and will "silently" increase the risk of type II statistical error. Supplementary per-protocol analysis (Hernan 2017; Sheiner 1995) would be useful for assessing the impact of cross-overs and of partial and full protocol violations. In addition, one study described differential use of co-interventions (e.g. blood transfusion, neuromuscular blockers) that would be expected to influence outcomes (Voggenreiter 2005). Participant losses for main analyses were small (0 to 4.2%), and reasons were detailed. Supplementary analyses were not performed as a result of these small participant losses. Several of the trials (Chan 2007; Fernandez 2008; Gattinoni 2001; Mancebo 2006; Voggenreiter 2005) were discontinued early which can also be a source of bias (Bassler 2010).

Effects of interventions

See: **Summary of findings 1** Mortality: prone position compared with supine for acute respiratory failure in adults requiring mechanical ventilation in intensive care

Before the last published trial (Guerin 2013) was included, statistical heterogeneity was low overall as assessed by the I^2 method. Most analyses had an I^2 statistic = 0. With inclusion of this last trial (Guerin 2013), heterogeneity was substantial, and heterogeneity for the primary analyses moved from 0% without the last study to 60% or greater with its inclusion (Analysis 1.1). Among subgroup analyses of mortality that included data from this trial

(Guerin 2013), only one had an I^2 statistic = 0, and the remaining nine analyses demonstrated I^2 values ranging from 39% to 56%. With the last trial of Guerin excluded from the same analyses, all 10 trials had an I^2 statistic = 0 (Analysis 1.3; Analysis 1.4; Analysis 1.6; Analysis 1.9; Analysis 1.11).

For reasons of inconsistency and heterogeneity, the quality of the evidence for primary outcomes based on the GRADE system was down-rated further and was classified as low. The option of not exploring and analysing these results was avoided, and a random-effects model was employed. The number of studies (<10) available for analysis were insufficient to justify meta-regression techniques (Deeks 2019).

Fixed-effect and random-effects models were determined by I^2 statistical value and are presented in the text as appropriate. Presentation of short- and longer-term outcomes in the same forest plot has restricted use of one or the other model for these data pairs, and for some outcomes, minor discrepancies between text and figures may be noted for this reason.

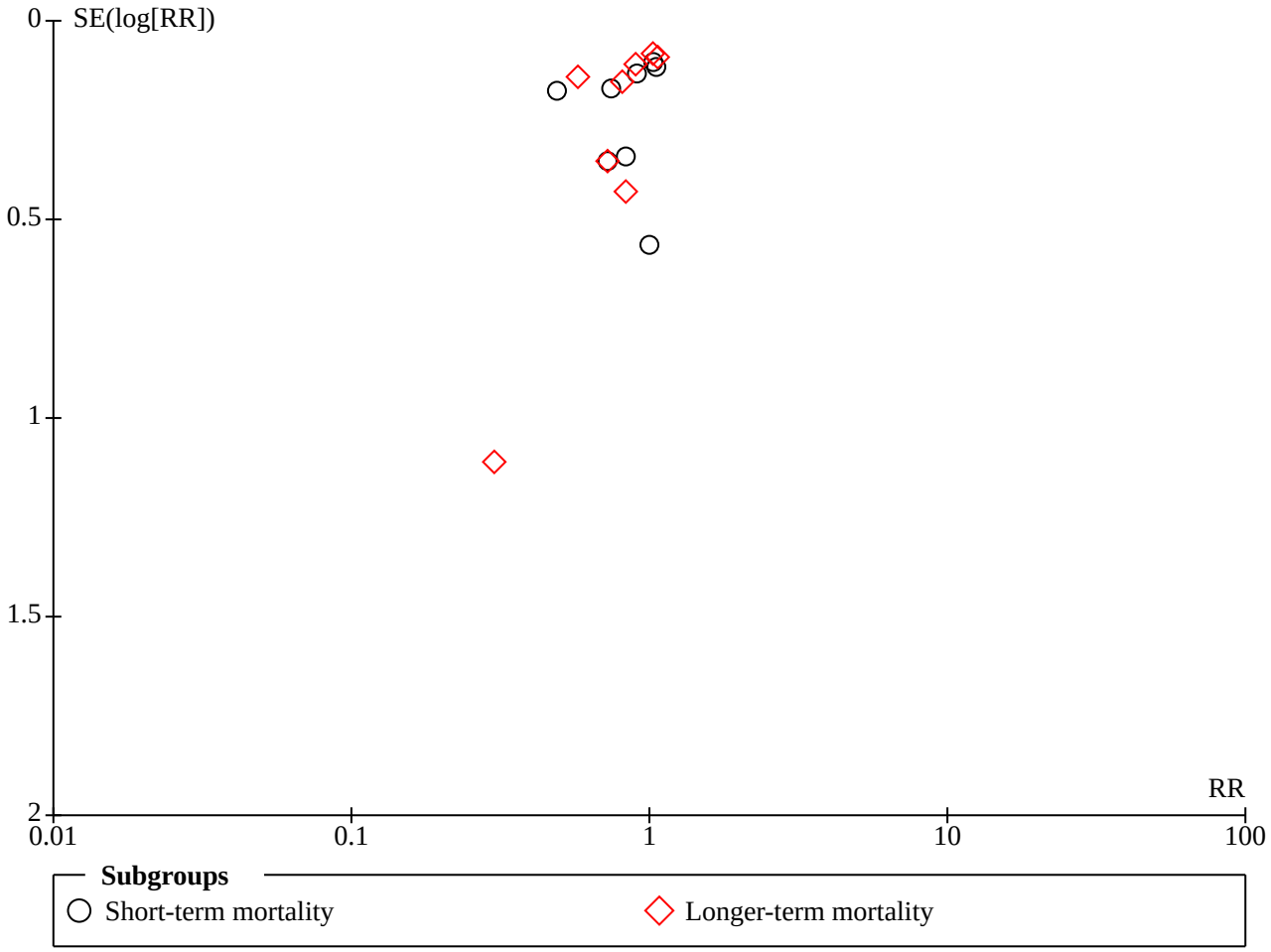
Primary outcomes

Short-term mortality

Eight clinical trials with 2117 participants reported on short-term mortality (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009) and were included in this analysis (Analysis 1.1). Overall mortality of participants was 756/2117 (35.7%). Mortality for those ventilated prone was 33.4% (363/1086), and supine 38.3% (395/1031) resulting in a risk ratio of 0.84 (95% CI 0.69 to 1.02) in favour of the prone position.

Prior to the inclusion of the most recent study (Guerin 2013), which exclusively enrolled participants with more severe hypoxaemia than was seen in earlier studies and had a risk ratio for mortality of 0.49, the risk ratio from other seven studies was close to unity at 0.95. In the Higgins test, the I^2 statistic moved from 0% to 60% with inclusion of the most recent study (Guerin 2013). Visual inspection of the funnel plot was not supportive of major small study effect or reporting bias (Figure 4). Removal of one study, which applied prone ventilation for only one day (Leal 1997), did not alter the risk ratio, which remained at 0.84.

Figure 4. Funnel plot of comparison: 1 Mortality, outcome: 1.1 Mortality.



Longer-term mortality

Eight clinical trials with 2140 participants (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Mancebo 2006; Taccone 2009; Voggenreiter 2005) reported longer-term mortality (952/2140), which overall approximated 44.5% (Analysis 1.1). Mortality for prone (462/1099; 42.0%) and supine (490/1041; 47.1%) ventilated participants resulted in a risk ratio of 0.86 (95% CI 0.72 to 1.03) in favour of the prone position. Before inclusion of the last study (Guerin 2013), which had an individual risk ratio of 0.58, the risk ratio from the other studies was again close to unity at 0.97. In the Higgins test (Higgins 2003), the I^2 statistic moved from undetected (0%) to "moderate" heterogeneity at 61%, with the addition of Guerin 2013. Visual inspection of the funnel plot was not supportive of major small study effect or reporting bias (Figure 4).

Use of the GRADE system to assess the quality of evidence for major risks of bias from lack of blinding (Guyatt 2011a) and from inconsistency of effect (Guyatt 2011c) reduced the overall rating of evidence quality to "low" for both of these primary outcomes.

One-year mortality

Only one study (and therefore not part of the quantitative meta-analysis) reported 12-month mortality (113/187) in a secondary publication approximating 60% mortality overall (Chiumello 2012). This population of 187 participants accounted for approximately 55% of the original study population. The point estimate for the risk ratio in this secondary study was 1.13 (95% CI 0.89 to 1.42) in favour of supine positioning in this single-study *post hoc* analysis. This is a reversal from the findings the parent study (Taccone 2009) which reported a 6 month mortality risk ratio of 0.90 (95% CI 0.73-1.11) in favour of prone positioning.

Results for primary outcomes and for selected subgroup analyses are included in Summary of findings 1.

Secondary outcomes

Rate of ventilator-associated pneumonia

Five studies (Ayzac 2016; Fernandez 2008; Guerin 2004; Mancebo 2006; Voggenreiter 2005) reported rates of ventilator-associated pneumonia (VAP) with 1473 participants for analysis (Analysis 3.1). The overall rate of VAP for participants (226/1007) was 22.7%. The proportion of participants with VAP for prone positioning was 0.21 compared with 0.22 for the supine position. The risk ratio for VAP of 0.97 (95% CI 0.80 to 1.18) close to unity. The additional data from the PROSEVA trial (Ayzac 2016) for this amendment had the effect of shifting the point estimate closer to unity for this complication.

Number of days on a ventilator

Three studies (Fernandez 2008; Guerin 2004; Voggenreiter 2005) reported duration of mechanical ventilation in 871 participants (Analysis 4.1). Mean duration of ventilation was reduced by 0.47 days (95% CI -1.53 to 0.59) for participants in the prone position.

Length of ICU stay

Five studies (Fernandez 2008; Guerin 2004;Guerin 2013 Mancebo 2006; Taccone 2009) with 1775 participants reported ICU length of stay (Analysis 5.1), which was increased for participants in the prone position by a mean of 1.06 (95% CI -1.13 to 3.26) days.

Analysis of log (base 10) transformed data provided similar results, with an increase (geometric mean) of 1.07 days for participants treated in the prone position (95% CI -1.3 to 1.5 days).

Length of hospital stay

Only one study (and therefore not part of the quantitative meta-analysis) of 40 participants reported hospital length of stay. This very small study favoured the supine position by a mean of 5.8 (range -7.9 to 19.5) days.

Improvement in oxygenation

Four studies (Gattinoni 2001; Guerin 2004; Mancebo 2006; Voggenreiter 2005) with 827 participants reported improvement in oxygenation (PaO_2/FIO_2 ratio or quotient) over seven to 10 days (Analysis 6.1). The mean difference in improvement in the PaO_2/FIO_2 quotient was 24.6 mmHg (95% CI 13.9 to 35.2 mmHg) compared with baseline measurements at study entry. This equates to 3.3 kPa (95% CI 1.8 to 4.7 kPa) (P value < 0.00001). Variance for two studies (Guerin 2004; Mancebo 2006) was estimated by using the higher of the "paired" variances for the study population. Inflating the entered standard deviations by approximately 50% to 120.0 for these two studies had no impact on inferences. The second study of Guerin (Guerin 2013) was not included in the analysis because of the formal reduction in PEEP mandated by improving oxygenation.

One study (and therefore not part of the quantitative meta-analysis) provided data for the PaO_2/FIO_2 quotient for a very small subset of participants (26) (Chiumello 2012) included in one of the primary studies (Taccone 2009; 342 participants) at 12-month follow-up. PaO_2 data (Chiumello 2012) on air showed a change in the PaO_2/FIO_2 quotient of 43 mmHg (95% CI 15.8 to 70.2 mmHg) in favour of supine ventilation (P value = 0.002). This equates to a PaO_2/FIO_2 quotient of 5.7 kPa (95% CI 2.1 to 9.4 kPa).

Adverse events

Several adverse events were documented across studies and were reported in two different ways: Most reported events per participant group, but two studies reported some data as events per participant day. These were analysed separately.

New pressure sores or ulcers

Four studies (Chan 2007; Gattinoni 2001; Girard 2014; Voggenreiter 2005) with 823 participants reported pressure ulcer (or sore) events per participant per group (Analysis 7.1), and one additional study of 791 participants and 10,944 event days presented results on pressure sores as events per day. The four studies reported an event rate of 43% for participants ventilated prone and 34.2% for those ventilated supine, with a risk ratio of 1.25 (95% CI 1.06 to 1.48; P value = 0.01). The addition of data from the PROSEVA trial (Girard 2014) with a doubling of participants for analysis moved the point estimate closer to unity and increased the precision of that analysis. The single study (Guerin 2004) reporting events per day (and therefore not part of the quantitative meta-analysis) reported pressure sores on 3.6% of event days in prone groups and 3.0% in supine groups, with an odds ratio of 1.20 (95% CI 0.97 to 1.48; P value = 0.09). Both analyses favoured the supine position to avoid this adverse event.

Tracheal tube displacement

Eight studies (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Leal 1997; Taccone 2009; Voggenreiter 2005) of 2021 participants provided information on tracheal tube displacement or accidental extubation (Analysis 7.1). Participants ventilated prone experienced a 10.5% event rate compared with 9.2% among those ventilated supine. The risk ratio was 1.09 (95% CI 0.85 to 1.39).

Tracheal tube obstruction

Three studies (Guerin 2004; Guerin 2013; Taccone 2009) of 1599 participants reported the complication of tracheal obstruction. These three studies strongly favoured the supine position, although moderate heterogeneity was noted, with I^2 statistic= 31% requiring use of a random-effects model for analysis (Analysis 7.1). The overall incidence of tracheal obstruction for those ventilated prone was 15.9% compared with supine, which was 9.7%. The risk ratio was 1.78 (95% CI 1.22 to 2.60); P value = 0.003).

Pneumothorax

Four studies (Chan 2007; Fernandez 2008; Guerin 2013; Mancebo 2006) of 664 participants reported an event rate for pneumothoraces (Analysis 7.1), and one study (Guerin 2004) of 791 participants (and therefore not part of the quantitative meta-analysis) reported pneumothoraces per participant day. The four studies reported an overall event rate of 6.6% for participants ventilated prone and 5.4% for those ventilated supine, with a risk ratio of 1.16 (95% CI 0.65 to 2.08). The largest single study reported risk for pneumothorax per participant day of 0.38% for prone ventilated participants and 0.54% for supine ventilated participants, with an odds ratio of 0.71 (95% CI 0.40 to 1.24).

Arrhythmias

Three studies (Guerin 2013; Mancebo 2006; Voggenreiter 2005) of 642 participants reported on the prevalence of arrhythmias including bradyarrhythmias and cardiac arrest, noting a rate of 15.3% for those ventilated prone and 24.7% for those ventilated supine (Analysis 7.1). This analysis was dominated by one study (Guerin 2013) which had a risk ratio of 0.64 (95% CI 0.47 to 0.87). One other study (Guerin 2004) of 791 participants and 10,942 event days (and therefore not part of the quantitative meta-analysis) reported bradycardic episodes per participant day as well as cardiac arrests per participant day. For bradycardic episodes per participant day, the rate was 1.41% for prone ventilation and 1.39% for supine ventilation, with an odds ratio of 1.01 (95% CI 0.74 to 1.40). For cardiac arrest, the prevalence for prone ventilation was 1.51% per participant day and for supine 1.70% per participant day, with an odds ratio of 0.89 (95% CI 0.66 to 1.20).

Composite outcome of hypotension, arrhythmias and increased vasopressor use per participant day

This composite outcome was reported by one study (and therefore not part of the quantitative meta-analysis) of 342 participants and 5524 participant days (Taccone 2009). The reported rate of such cardiovascular compromise was 18% for participants ventilated prone and 12.4% for those ventilated supine, with a risk ratio of 1.45 (1.28 to 1.65; P value < 0.00001) favouring the supine position.

Quality of life

Only one study (Chiumello 2012) (and therefore not part of the quantitative meta-analysis) reported on quality of life for a small subset of 26 participants from five centres (187 participants) followed up from the Taccone 2009 study of 342 participants. The main quality of life metrics employed were the Short Form-36 (SF-36) questionnaire, which reported on eight items, and the Saint George's Respiratory Questionnaire (SGRQ), which reported on four items. For all domains in the SF-36 questionnaire, results were similar for both groups. For all four SGRQ items, the prone group performed better, but none of these results were statistically significant.

With regards to pulmonary function assessment with standard pulmonary function tests and quantitative evaluation of CT scans, 15 items were evaluated. Two results were statistically significant, and one was of borderline significance. These were PaO_2 (P value = 0.03) - reported as the PaO_2/FIO_2 quotient in the oxygenation section above; and over-aerated lung tissue on CT scan analysis of 12.5% of total lung weight for participants treated prone versus 5.3% for those treated supine (P value = 0.008). Mean results for well-aerated lung tissue between groups showed 64.0% for participants treated prone versus 70.2% for those treated supine (P value = 0.052).

Economic outcomes

None of the identified primary papers provided data on economic outcomes. One economic analysis (Baston 2019) is available modelled on results from most recent trial of Guerin (Guerin 2013) and an observational study (Bellani 2016). They conclude based on short-term mortality outcomes and after extensive modelling, interventions that increase utilization of prone positioning would be cost-effective from both societal and hospital perspectives under many plausible cost and benefit assumptions. However this modelling is based on the results of a single unblinded trial that has been described as having, "a treatment effect virtually unprecedented in modern medicine." (Soo Hoo 2013). Baston *et al* did not take into account any requirement for increased staffing required to accomplish patient-turning in sparsely staffed ICUs.

Planned subgroup analyses (SGA)

Analyses combining short- and longer-term mortality allow for one model (fixed-effect or random-effects) only per analysis. In two cases (Analysis 1.6; Analysis 1.10), short- and longer-term analyses required different models. Results presented in the text show actual result based on the correct model. All other analyses presented are correct.

Duration of daily ventilation in the prone position (< 16 hours/d vs ≥ 16 hours/d)

Mean daily application of prone ventilation for the nine included studies (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009; Voggenreiter 2005) was 16.3 hours (range 7 to 24 hours/d) given over a mean of 6.2 days (range 1 to 11.9 days). Mean total hours of prone ventilation for participants in each study ranged from 24 hours (Leal 1997) to 238 hours (Fernandez 2008), with a mean of 100 hours across included studies.

Two studies (Gattinoni 2001; Guerin 2004) of 1095 participants reported short-term mortality for participants ventilated less than 16 hours/d in the prone position (Analysis 1.2). Mortality was 37.3% for participants ventilated prone and 36.2% for those ventilated supine, yielding a risk ratio for mortality of 1.04 (95% CI 0.89 to 1.21). Three studies (Gattinoni 2001; Guerin 2004; Voggenreiter 2005) of 1135 participants reported on longer-term mortality for participants ventilated in the prone position for less than 16 hours per day. Mortality was 47.1% for participants ventilated prone and 45.9% for those ventilated supine, yielding a risk ratio for mortality of 1.03 (95% CI 0.92 to 1.17).

Six studies (Chan 2007; Fernandez 2008; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009) of 1022 participants reported on short-term mortality for participants ventilated 16 or more hours per day, with moderate heterogeneity identified (I^2 statistic = 41%) (Analysis 1.3). Short-term mortality was 29.2% for participants ventilated prone and 40.5% for those ventilated supine, yielding a risk ratio of 0.73 (95% CI 0.58 to 0.93; P value = 0.01). Five studies (Chan 2007; Fernandez 2008; Guerin 2013; Mancebo 2006; Taccone 2009) of 1005 participants also reported longer-term mortality of participants ventilated prone for 16 or more hours per day. Longer-term mortality was 36.1% for those ventilated prone and 48.6% for those ventilated supine, with a risk ratio of 0.77 (95% CI 0.61 to 0.99; P value = 0.04).

The statistical test for subgroup differences for longer-term outcomes regarding daily duration of prone ventilation was significant (P value = 0.03; I^2 statistic = 78.0%), which provides stronger evidence for the benefit of longer duration prone position ventilation (Analysis 2.1). The quality of the evidence as rated by GRADE was moderate (Summary of findings 1), with downgrading based on the potential for risk of bias.

Duration of supine ventilation before randomization (< 48 hours vs ≥ 48 hours)

Five studies (Fernandez 2008; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009) of 1000 participants enrolled most participants within 48 hours of initiation of mechanical ventilation, allowing exploration of effects on short-term mortality (Analysis 1.4). Moderate heterogeneity was noted (I^2 statistic = 51%). Short-term mortality among prone participants was 29.0% compared with 40.6% among those in the supine group, with a risk ratio of 0.72 (95% CI 0.56 to 0.93; P value = 0.01). Five studies (Fernandez 2008; Guerin 2013; Mancebo 2006; Taccone 2009; Voggenreiter 2005) of 1024 participants enrolled most of their participants up to 48 hours after initiation of mechanical ventilation with regards to longer-term mortality (Analysis 1.4). Moderate heterogeneity (I^2 statistic = 50%) was noted. Longer-term mortality among prone participants was 34.3% compared with 46.9% in participants assigned to supine ventilation, with a risk ratio of 0.75 (95% CI 0.59 to 0.94; P value = 0.01).

Three studies (Chan 2007; Gattinoni 2001; Guerin 2004) of 1117 participants enrolled most participants more than 48 hours after initiation of mechanical ventilation (Analysis 1.5). Short-term mortality for prone participants was 37.7% compared with 36.2% in the supine group, with a risk ratio of 1.04 (95% CI 0.89 to 1.21). For longer-term mortality three studies (Chan 2007; Gattinoni 2001; Guerin 2004) of 1116 participants enrolled participants after 48 hours or did not state enrolment time. For those ventilated prone, reported mortality was 48.6% compared with 47.2% for those ventilated supine. The overall risk ratio was 1.04 (95% CI 0.92 to 1.17).

The statistical test for subgroup differences for longer-term outcomes regarding timing of enrolment for prone ventilation was significant (P value = 0.01; I^2 statistic = 84.4%), providing stronger evidence for the benefit of longer duration of prone positioning (Analysis 2.2). The quality of evidence as rated by GRADE was moderate (Summary of findings 1), with downgrading based on the potential for risk of bias.

Outcome according to severity (PaO_2/FIO_2 ratio; severity of illness score, e.g. Simplified Acute Physiology Score II (SAPS II); oxygenation index)

With regards to short-term outcomes, six studies (Gattinoni 2001; Guerin 2004; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009) of 744 participants explored the effects of prone position in a subset of participants with severe hypoxaemia - PaO_2/FIO_2 quotient < 150 mmHg (< 20.0 kPa) (Leal 1997); < 105 mmHg Guerin 2013); or < 100 mmHg (< 13.3 kPa) - and in four others based on reanalysis of original data (Gattinoni 2010; Sud 2010). For short-term mortality among participants with severe hypoxaemia (Analysis 1.6), adoption of prone ventilation was associated with 40.6% mortality in comparison with mortality of 50.1% for those ventilated supine, yielding a risk ratio of 0.80 (95% CI 0.68 to 0.93; P value = 0.003) when a fixed-effect model was used with I^2 statistic = 0. (The figure in the analysis presents results of the random-effects model, as longer-term outcomes required application of a random-effects model.) Twenty-eight-day mortality data (as opposed to short-term mortality) resulting from the combination of original studies and a review (Gattinoni 2010) yielded near identical results, with a risk ratio of 0.80. For longer-term mortality, seven studies (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Mancebo 2006; Taccone 2009) of 977 participants with severe hypoxaemia recorded mortality of 41.5% for participants ventilated prone and 54.7% for those ventilated supine, with a risk ratio of 0.77 (95% CI 0.65 to 0.92; P value = 0.003) when a random-effects model was used (Analysis 1.6). Moderate heterogeneity was detected (I^2 statistic = 39%). These results for short-term and longer-term mortality remained significant without inclusion of the most recent trial (Guerin 2013), which itself recorded highly significant results for short- and longer-term mortality (P value < 0.001 for both time periods in favour of prone positioning). The quality of the evidence as rated by GRADE was moderate (Summary of findings 1), with downgrading based on the potential for risk of bias.

For participants with less severe hypoxaemia, no apparent benefit was observed (Analysis 1.7). Short-term mortality from four trials (Gattinoni 2001; Guerin 2004; Mancebo 2006; Taccone 2009) of 1095 participants with milder hypoxaemia (PaO_2/FIO_2 ≥ 100 mmHg to 300 mmHg) failed to establish benefit of prone positioning, with a risk ratio of 1.03 (95% CI 0.87 to 1.21; I^2 statistic = 0). Although data from one other study (Guerin 2013) were available, this study included only participants with PaO_2/FIO_2 ≥ 105 mmHg to 150 mmHg and did not reflect the full spectrum of milder disease, as was evident in the other studies. Therefore, this study was excluded from the analysis. Data were also available from six studies (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Mancebo 2006; Taccone 2009) of 1108 participants undertaken to explore longer-term effects of the prone position applied in milder hypoxaemia (PaO_2/FIO_2 > 100 mmHg to 300 mmHg). The risk ratio for this group

of participants was 1.06 (95% CI 0.93 to 1.21) and heterogeneity was negligible (I^2 statistic = 1%). For long-term outcomes with regards to severity of hypoxaemia, the statistical test for subgroup differences (Analysis 2.3) was significant (P value = 0.005; I^2 statistic = 85.7%).

Two studies (Gattinoni 2001; Mancebo 2006) provided sufficient data to allow exploration of the effects of physiological severity of illness on outcome, with data for one study derived from a journal comment (Sud 2008b). Heterogeneity between studies was considerable. For participants (327) with an SAPS II score of 49 or less, short-term mortality was 25.8% among those ventilated prone in comparison with 28.5% in those ventilated supine, yielding a risk ratio of 0.85 (95% CI 0.45 to 1.60; I^2 statistic = 69%) (Analysis 1.8). For participants (113) with greater severity of illness (SAPS II ≥ 50), short-term mortality among those ventilated prone was 34.7% and 56.8% for those ventilated supine, with a risk ratio of 0.60 (95% CI 0.25 to 1.40; I^2 statistic = 79%). Amalgamated data for two different time intervals (Gattinoni 2001 provided 10-day mortality data and Mancebo 2006 provided ICU mortality data) were not available for analysis of longer-term mortality.

Data regarding oxygenation index, most commonly reported in paediatric studies, were not available for analysis. (Oxygenation index was calculated as mean airway pressure × FIO_2 × 100/PaO_2 in mmHg and was expressed as a unit-less number.)

Tidal volume (6 to 8 mL/kg vs > 8.0 mL/kg of ideal body weight)

Three studies (Chan 2007; Guerin 2013; Taccone 2009) of 830 participants reported on the effects of ventilation with lower tidal volumes (mean of 6 to 8 mL/kg ideal body weight) on short-term mortality (Analysis 1.9). Mortality for the prone subgroup was 25.5% compared with 36.7% among those ventilated supine. The risk ratio was 0.72 (95% CI 0.43 to 1.20; P value = 0.2). Substantial heterogeneity was noted (I^2 statistic = 76%). Five studies (Chan 2007; Fernandez 2008; Guerin 2013; Taccone 2009; Voggenreiter 2005) of 910 participants reported on longer-term mortality among participants ventilated with low tidal volumes (mean 6 to 8 mL/kg ideal body weight). Mortality for those ventilated prone was 32.5% and for those ventilated supine 45.1%, with a risk ratio of 0.73 (95% CI 0.53 to 0.96; P value = 0.02). Heterogeneity was moderate (I^2 statistic = 43%).

Three studies (Gattinoni 2001; Guerin 2004; Mancebo 2006) of 1231 participants utilized high tidal volumes (mean > 8.0 mL/kg ideal body weight) and reported on short-term mortality (Analysis 1.10). Mortality for participants ventilated prone was 38.1% and for participants ventilated supine was 38.5%, with a risk ratio of 0.99 (95% CI 0.86 to 1.14; I^2 statistic = 38%; random-effects model). Those studies (Gattinoni 2001; Guerin 2004; Mancebo 2006) with 1231 participants also reported on longer-term mortality among participants ventilated with high tidal volumes. Mortality for those ventilated prone was 48.8% and for participants ventilated supine 48.5%, with a risk ratio of 1.01 (95% CI 0.9 to 1.13; I^2 statistic = 19%; fixed-effect model).

We categorized studies on the basis of mean tidal volumes (mL/kg) derived from ideal body weight (IBW) as provided by primary studies or imputed from actual body weight data. Two studies provided no measurements (Leal 1997; Voggenreiter 2005). The upper 95% confidence limit for tidal volumes was 7.3, 9.4, 9.8, 11.3, 14.6, 14.7 and 15.8 mL/kg IBW for the seven studies of Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Mancebo 2006 and Taccone 2009. Notably, only one study (Guerin 2013) actually achieved the 6 to 8 mL/kg ideal body weight envelope in terms of the 95% CI approximating what is currently considered best clinical practice (Needham 2012).

A random-effects model used to test for subgroup differences between low and high tidal volume ventilation strategies yielded significant findings (P value = 0.04; I^2 statistic = 76.5%), strengthening evidence for the prone position in combination with lower tidal volumes (Analysis 2.4). The quality of evidence as rated by GRADE was moderate (Summary of findings 1), with downgrading based on the potential for risk of bias.

Analysis of studies of ALI and ARDS separate from other causes of acute severe hypoxaemic respiratory failure

Seven studies (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009) were included in this subgroup analysis of 1326 participants ventilated for ARDS with regards to short-term mortality (Analysis 1.11). Data from Guerin's first study were not included, as inclusion criteria for participants were broader than the other clinical trials (Guerin 2004). Mortality for those ventilated prone in these subgroups of ARDS participants was 34.0% compared with 42.6% for those ventilated supine. The risk ratio was 0.79 (95% CI 0.63 to 1.00; P value = 0.05). Heterogeneity was moderate (I^2 statistic = 57%).

Eight studies (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Mancebo 2006; Taccone 2009; Voggenreiter 2005) were included in this subgroup analysis of 1758 participants ventilated for ARDS with regards to longer-term mortality. Ninety-day mortality for ARDS participants (PaO_2/FIO_2 quotient < 300 mmHg) from the first study of Guerin (Guerin 2004) became available through a recent meta-analysis (Sud 2014). Very minor adjustments were made to original data from another trial (Gattinoni 2001) on the basis of information obtained from this same meta-analysis. Mortality for those ventilated prone in these subgroups of ARDS participants was 41.3% compared with 48.3% for those ventilated supine. The risk ratio was 0.85 (95% CI 0.71 to 1.01; P value = 0.07), and heterogeneity was moderate (I^2 statistic = 56%). The quality of the evidence as rated by GRADE was moderate (Summary of findings 1), with downgrading based on the potential for risk of bias.

Pulmonary and extrapulmonary causes of ALI or ARDS

Data were insufficient to allow any analysis.

Use of meta-regression to explore heterogeneity between subgroups

Identified studies were insufficient to meet criteria for use of meta-regression techniques (Deeks 2011).

Sensitivity analysis based on potential risk of bias or confounding

Removing studies on the basis of potential risk of bias or confounding had little effects on most results. Excluding the studies of Guerin (Guerin 2004) on the basis of the high percentage of cross-over participants; of Voggenreiter (Voggenreiter 2005) because of the hugely disparate blood transfusion requirements between groups and differential use of muscle relaxants; and of Chan (Chan

2007) because all risk of bias assessments were rated as "unclear" or "high" (Figure 2), produced a small shift in risk ratio for short-term mortality from 0.84 to 0.79 (95% CI 0.61 to 1.01), and from 0.87 to 0.82 (95% CI 0.65 to 1.04) for longer-term mortality.

DISCUSSION

Summary of main results

The main findings of this review are presented here.

Primary outcomes

Among all-comers entered into identified randomized but unblinded clinical trials, a statistically insignificant signal of benefit was seen for prone ventilation, with risk ratios of 0.84 and 0.86 for short-term and longer-term mortality. The last published trial (Guerin 2013) approximately halved mortality in its cohort of more severely hypoxaemic participants compared with other included studies, and changed heterogeneity as measured by the I^2 statistic from 0% to 60% or more for both primary outcomes. The risk ratio before publication and inclusion of this study was close to unity. This suggests that unselected participants with moderate to severe hypoxaemia requiring mechanical ventilation and ventilated in the prone position may be too diffuse a target population for this intervention. When the GRADE (Grades of Recommendation, Assessment, Development and Evaluation) system was applied, evidence for benefit in unselected populations was rated low (Summary of findings 1), as the overall rating of quality of evidence was downgraded as a result of risk of bias and inconsistency (Guyatt 2008; Guyatt 2011a; Guyatt 2011c). Longer-term mortality would seem a more important patient-centred outcome when compared with short-term mortality for primary outcomes and for prespecified subgroup analyses of mortality (Hough 2012; Wang 2014; Williams 2008), and formal application of the GRADE approach was limited to primary outcomes and to selected subgroup outcomes for longer-term mortality only.

One trial later reported a subset of 187 participants, for whom additional 12-month mortality data were reported (Chiumello 2012). This subset from five centres based in or near Milan, Italy, comprised more than 50% of the population of the original or primary trial (Taccone 2009). For this subset, there was no evidence of benefit for prone ventilation in unselected participants with regards to 12-month mortality, as the risk ratio was slightly greater than unity (favouring supine positioning), although findings were statistically insignificant. We note this trial (Taccone 2009) was the second most recent published trial and employed low tidal volume ventilation.

With regards to heterogeneity, primary outcomes fell into the moderate heterogeneity category (Higgins 2003), and formal analysis was undertaken with a random-effects model, wherein the I^2 statistic exceeded 25%. In addition, recommended approaches for exploring heterogeneity through pre-specified subgroup analyses and for excluding studies in sensitivity analyses were undertaken. With only eight studies available for each of the two primary outcomes (short-term mortality - Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009; and longer-term mortality - Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Mancebo 2006; Taccone 2009; Voggenreiter 2005), we did not utilize meta-regression techniques, in accordance with best practice (Deeks 2011).

Secondary outcomes

Pneumonia

Ventilator associated pneumonia (VAP) is an important complication, which definitely increases resource utilization and prolongs intensive care unit (ICU) and hospital length of stay with uncertain attributable mortality. Analysis of data from nearly 1500 participants after the addition of data from the PROSEVA trial (Ayzac 2016) showed little signal of benefit from prone positioning with regards to VAP. The incidence of VAP varied across studies, and to what extent this was driven by different patient populations (patient diversity) and criteria used to diagnose pneumonia (methodological diversity) is uncertain. The diagnosis of ventilator-associated pneumonia is problematic, given the various criteria in clinical use (Klompas 2008; O'Brien 2011; Stevens 2014; Sud 2008) over the 15-year time span of these clinical trials.

Duration of mechanical ventilation

Duration of mechanical ventilation was reported in three studies of more than 800 participants (Fernandez 2008; Guerin 2004; Voggenreiter 2005). A small signal suggested benefit from prone positioning. However, the point estimate amounted to less than a half-day and cannot be considered a major patient-centred benefit. Such data are complicated to interpret due to differential patient mortality between groups, which will affect time data such as duration of mechanical ventilation and length of stay.

Length of stay (LOS)

Length of stay (LOS) data are difficult to interpret in that they are often skewed (Weissman 1997), and LOS will be influenced in diverse and opposite ways by the effectiveness of treatment. LOS may be reported as median and interquartile range (IQR), and sometimes as mean and standard deviation. The former data pose difficulties for meta-analysis, although they can be used if it is assumed that the median approximates the mean together with a statistical multiplication factor used to impute the standard deviation (Higgins 2011b). For skewed data, reporting of means and standard deviations may be misleading. It is recommended that both should be reported (Weissman 1997). Furthermore, effective treatment may reduce the LOS of participants already destined to survive but will lengthen the stay of those who would have died but have survived as a result of receiving the intervention. The overall effect will be determined by the balance of these two effects.

In this systematic review, mean and standard deviation were imputed for one study on the basis of non-parametric data (Taccone 2009). Point estimates for ICU LOS were similar with and without this study and favoured supine, with the mean difference in LOS between 1.34 and 1.37 days and not statistically significant. Only one study (Fernandez 2008) of 40 participants reported on hospital LOS; this again favoured supine ventilation, with the point estimate showing a difference of 5.8 days. Reduction in ICU LOS was not apparent with the use of prone ventilation in the four relevant studies (Fernandez 2008; Guerin 2004; Mancebo 2006; Taccone 2009). Data for hospital LOS were too sparse to allow meaningful comment.

Improved oxygenation

Improved oxygenation in participants ventilated prone was apparent at seven to 10 days in the outcome studies included in this systematic review. The mean difference in the PaO_2/FIO_2 quotient of 24.6 mmHg or 3.3 kPa is clinically meaningful and was statistically highly significant (P value < 0.00001). In a very small subset of participants (26) from the original Taccone trial (384 participants) examined at 12 months, residual benefit was not apparent, and a small but statistically significant benefit favoured supine-ventilated participants (Chiumello 2012). Thus oxygenation was substantially improved while participants were critically ill (Analysis 6.1), but robust evidence that this benefit is carried on to or beyond 12 months was not available.

We did not include the second study of Guerin (Guerin 2013) in the analyses, as formally mandated reduction in PEEP would negatively impact oxygenation and would confound such results.

Adverse effects

Studies show that pressure sores and tracheal tube obstruction were increased by mechanical ventilation provided in the prone position. Cardiac arrhythmias were reduced with use of the prone position. This was described in different ways by different studies and required separate analyses for the same complication, sometimes leading to inconsistent results. An important factor for interpretation is how vigorously these events were classified and sought within individual studies (Bent 2006; Ioannidis 2006).

- With regards to pressure ulcers, four studies (Chan 2007; Gattinoni 2001; Girard 2014; Voggenreiter 2005) demonstrated a statistically significant effect of pressure sores per participant among those ventilated prone (P value = 0.02). Another single study, reporting in such a way that it could not be included in the meta-analysis, demonstrated the same trend but with borderline statistical significance (P value = 0.09). All five studies favoured the supine position with regards to development of pressure sores. This finding would be consistent with the area of tissue in contact with the bed during supine and prone ventilation and is biologically plausible.
- Tracheal tube displacement, which might be considered a natural consequence of moving patients from supine to prone position and back, showed differing results across studies, with moderate statistical heterogeneity. For example, the short-term (24-hour) study of Leal 1997 reported 50% tracheal tube displacement, whereas Chan 2007, which utilized at least 72 hours of prone positioning per participant, reported a zero rate of displacement. Overall the risk ratio was 1.09 and was statistically insignificant. However, a clear increase in risk of tracheal tube obstruction was evident. Such obstruction might result from increased inspissated secretions or from kinking of the tracheal tube in the face-down participant. The risk ratio for this complication was 1.78 and was statistically significant (P value = 0.003).
- Pneumothoraces were counted as events per participant in four studies (Chan 2007; Fernandez 2008; Guerin 2013; Mancebo 2006), and as events per participant day in one study (Guerin 2004). Three studies favoured the supine position (Chan 2007; Guerin 2013; Mancebo 2006), and two favoured the prone position (Fernandez 2008; Guerin 2004): Evidence favouring one position or another is weak.
- With regards to arrhythmias or bradycardias results from different studies are not concordant. The most recent study (Guerin 2013) heavily influences overall findings for the incidence of arrhthymias The point estimate was 0.64 (P value = 0.005) in favour of the prone position. A statistically insignificant trend from a single study (Guerin 2004) also favoured the prone position with regards to cardiac arrests. However, Taccone 2009, when using the composite endpoint of "hypotension, arrhythmias or increased vasopressor requirements", strongly favoured the supine position (P value = 0.001) (Glantz 2005).
- Small clinical trials may not reliably quantitate the incidence of uncommon adverse effects: Ocular complications are described among patients undergoing undergoing general anaesthesia, for therapeutic purposes, with prone positioning an associated risk factor, and the incidence of perioperative visual loss ranges between 0.028% and 1.3% (Uribe 2012) in this setting. Permanent blindness can result from ischaemic optic neuropathy or from central artery occlusion, and the zero numerator from this systematic review of 1107 prone participants still indicates a 95% confidence interval of 0 to 0.27% for the incidence of such events (Hanley 1983). Clinicians should remain vigilant for ocular complications, given the potentially important long-term consequences; a recent abstract has highlighted one such case (Ayoubieh 2014). Brachial Plexus injury is also a potential serious long-term injury that may result from prone positioning (Goettler 2002)

It is difficult to gauge the relevance of some of the reported findings in terms of the methodological rigour of their detection (Ioannidis 2006) and their clinical importance. Guidelines have been produced to assist prevention of such complications (Faculty of Intensive Care 2019).

Quality of life (QOL)

With regards to quality of life (QOL), only one study of 26 participants has addressed this issue - Chiumello 2012. No clear benefit was seen in this very small study, which encompassed a subgroup of participants originating in the Taccone 2009 trial. Firm conclusions with such a small number of participants would seem inappropriate. More evidence is required.

Intensive care patients comprise a diverse population of individuals admitted from all different hospital specialities, and the aetiology of acute respiratory distress syndrome (ARDS) is also varied (Walkey 2012). The more inclusive umbrella of hypoxaemic respiratory failure is even more disparate. This participant heterogeneity reduces the power of studies and increases the sample size required to avoid type II statistical error (Lipsey 1990). The power of studies to detect differences in outcome is hindered by participants who have crossed over to the opposite treatment, when results are analysed using intention to treat analyses only. Cross-overs occurred in several studies to a greater or lesser extent (34% of participants in one study, Guerin 2004). This may be important for this systematic review, for which participant numbers available for exploratory analyses are only modest to moderate. Given the importance of optimum treatment of severely hypoxaemic patients in ICUs, it is disappointing that five studies had to be terminated prematurely because of poor participant accrual (Chan 2007; Fernandez 2008; Gattinoni 2001; Mancebo 2006; Voggenreiter 2005).

The almost complete absence of long-term survival data (12 months and beyond), physiological function data, QOL life data and economic data is notable and is a major limitation with regards to overall evaluation of the benefits (or otherwise) of prone positioning as an adjunct to conventional mechanical ventilation. Such data are likely to be more relevant to patients, their families and society, when compared with short-term mortality outcomes alone (Herridge 2011; Hough 2012; Wang 2014).

Subgroup analyses

Given clinical diversity in terms of diagnoses and severity of illness (hypoxaemia), as well as methodological diversity, which has contributed to substantial statistical heterogeneity, pre-specified exploration of subgroups was warranted, and data will be of interest to stakeholders.

Important issues and limitations associated with subgroup analysis include reduced statistical power, increasing type II statistical error; multiple statistical testing, increasing type I error and ecological fallacy in study-level meta-analyses. The multiple subgroup analyses reported below should be viewed in this light (Counsell 1994; Lagakos 2006; Oxman 1992; Reade 2008; Sun 2014) as well as noting the relatively few studies (8 or less) which were available for analysis in each subgroup.

Subgroup analyses are presented for short-term (10 to 30 days) and longer-term mortality (31 to 180 days, or hospital mortality). As mentioned earlier, longer-term mortality would seem more important than short-term mortality from the patient perspective, given reduced longer-term survival and the ongoing burden of disease following acute lung injury and intensive care stay (Herridge 2011; Hough 2012; Iwashyna 2010; Wang 2014; Williams 2008). Five subgroups are included in the Summary of findings 1, and all subgroup analyses were downgraded on the basis of potential for important risk of bias. Downgrading of evidence as a result of imprecision was considered on the basis of Figure 5 and Table 1 of Guyatt and colleagues (Guyatt 2011b), both of which base achievement of optimal information size (OIS) on sample size or number of events. Four of the subgroup analyses of longer-term mortality (Analysis 1.3; Analysis 1.4; Analysis 1.6; Analysis 1.11) clearly met suggested requirements for OIS, with the number of events (deaths) in the subgroup analyses ranging from 411 to 736. For the remaining analysis (Analysis 1.9) exploring the subset of participants ventilated with lower tidal volumes (Summary of findings 1), events were fewer, at 353. Nevertheless, we also judged the OIS to have been met by taking into consideration the control event rate and the actual relative risk reduction in this subgroup. Although all subgroup analyses demonstrated substantial heterogeneity, as indexed by I^2 statistical methods, further downgrading on the basis of inconsistency for these analyses was considered but not implemented, also in keeping with the approach recommended by Guyatt and colleagues (Guyatt 2011c).

A relatively small number of studies are available for these analyses and they must all be interpreted with appropriate caution. For random effects models adjustments or alternatives to the DerSimmonian-Laird approach used in REVMAN such as the Hartung-Knapp-Sidik-Jonkman adjustment are recommended in the current Cochrane Handbook for Systematic Reviews of Interventions (Deeks 2019). These approaches would likely widen confidence intervals in random-effects model analyses (Borenstein 2019; Graham 2020).

Duration of prone ventilation

First, the duration or "dose" of prone ventilation might have an impact on outcomes, and we examined the effects of short periods and longer periods of prone ventilation per day. Short periods of ventilation in the prone position appeared to confer no benefit for participants with a risk ratio very close to unity. Periods of prone ventilation for 16 or more hours per day yielded point estimates of 0.73 and 0.75, which were statistically significant for both short-term (P value = 0.01) and longer-term mortality (P value = 0.04). We rated the quality of evidence as moderate using the GRADE structure (Summary of findings 1). We calculated dose of prone ventilation (with a two-hour change in cutoff) as per our published protocol (Bloomfield 2009). Other methods not employed in this review might also be considered. Total dosage of prone positioning might be equally valid and might produce different results. For example, the most recent trial (Guerin 2013), despite prone positioning participants for 17 hours per day, applied it for only four days (68 hours), and in terms of total hours prone for participants ranks as the fourth shortest across the nine included trials (Characteristics of included studies), after Leal 1997, Gattinoni 2001 and Guerin 2004. Two of the studies excluded from our review but not from others (Characteristics of excluded studies) applied prone ventilation for a single episode of 12 hours (Demory 2007; Papazian 2005), and two other excluded studies applied prone positioning over six days, for a total of 24 hours only (Beuret 2002; Watanabe 2002).

Timing of intervention

We investigated whether early intervention offered an advantage as a strategy with the potential to ameliorate lung injury, as adoption later in the illness might limit benefit. Short-term mortality and longer-term mortality analyses of available data showed a risk ratio close to unity for three studies (Chan 2007; Gattinoni 2001; Guerin 2004), which enrolled more than 1000 participants after 48 hours. Participants enrolled earlier in five other studies (short-term mortality - Fernandez 2008; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009; longer-term mortality - Fernandez 2008; Guerin 2013; Mancebo 2006; Taccone 2009; Voggenreiter 2005) demonstrated a large effect favouring prone ventilation, with risk ratios of 0.72 and 0.75, which were statistically significant (P values = 0.01 and 0.01) for short-term and longer-term mortality for a participant sample of 1000 or more. The quality of the evidence was rated as moderate when the GRADE structure was applied (Summary of findings 1).

Severity of injury

It has been postulated that prone positioning might benefit participants with the most severe lung insult, and data are available from original trials and from further published analyses of the original trials (Gattinoni 2010; Sud 2010). With all trials included that provided data for participants with the most severe hypoxaemia, a large and statistically significant apparent benefit can be seen, with point estimates of 0.80 and 0.74 for short- and longer-term mortality (P values = 0.003 and 0.003). The quality of the evidence was rated as moderate according to the GRADE structure (Summary of findings 1). Removing data for two additional studies (Gattinoni 2001; Guerin 2004) provided by Sud et al, in which the precise timing of mortality assessment was not specified (Sud 2010), did not change the outcome of this subgroup

analysis. Prone ventilation of participants with milder hypoxaemia appeared to confer no benefit, with risk ratios of 1.03 and 1.06 for short- and longer-term mortality. However, the second study of Guerin et al (Guerin 2013) was influential in the overall analysis: Overall short-term mortality in control groups of the other studies that reported participants with severe hypoxaemia was 58.5%, with mortality of 49.6% among participants treated prone. These rates differ substantially from those of Guerin et al (Guerin 2013), who reported percentage rates of 33.9 and 20.7 with absolute risk reductions of 8.9% for all other studies and 13.2% for Guerin et al. Of particular note is the much lower control mortality observed in the study of Guerin *et al* compared with other studies which might be explained by the more rigid application of available evidence-based practices not fully utilized by earlier investigators (ARDS Network 2000). However, this does not fully explain the apparent differences in absolute risk reduction resulting from application of prone positioning.

With regards to overall severity of acute illness (SAPS II scoring system), heterogeneity between studies was considerable. Total numbers of participants studied and actual events (deaths) were low, generating unacceptable imprecision (Guyatt 2011b) which further reduces the relevance and credibility of this analysis. Additionally, two different short-term outcomes were reported and amalgamated (Gattinoni 2001;.Mancebo 2006; Alsaghir 2008; Sud 2008b): Gattinoni 2001 provided 10-day mortality data for analysis (70 deaths), whereas Mancebo 2006 provided ICU mortality data. ICU mortality data from Gattinoni 2001 would have provided another 80 deaths for analysis, and the comment in this paper that “These differences in [10 day] mortality rate did not persist after discharge from the intensive care unit (data not shown)” suggests limited relevance of these published data. Use of a random-effects model to combine data demonstrated lower mortality for participants ventilated in the prone position for both lower and higher severity of illness, but with wide confidence intervals. Both studies were conducted during the high tidal volume ventilation era, making their results even less relevant in the low tidal volume ventilation era. For multiple reasons, as listed above, available data do not support severity of acute illness (SAPS II) as a basis for selection of participants for application of prone ventilation.

Ventilation strategy

As mentioned in the previous section, before publication of the first ARDS Network study (ARDS Network 2000), high tidal volume ventilation was in widespread use, but since low tidal volume ventilation has become the standard of care in clinical trials of adult patients, it is increasingly used in clinical practice (ARDS Network 2000; Needham 2012; Petrucci 2013). Studies conducted before adoption of this standard may be carried out differently and may be less relevant to current practice (Verbrugge 2007). For studies using higher tidal volume ventilation, both short-term and longer-term risk ratios for mortality were close to unity. All four studies (Gattinoni 2001; Guerin 2004; Leal 1997; Mancebo 2006) totaling 1200 participants commenced recruitment of participants before the ARDS Network study was published (ARDS Network 2000). Slightly smaller numbers of participants (830 to 911) from identified trials were available for analysis of low tidal volume strategies. All of these trials except the most recent (Guerin 2013) did not achieve tidal volumes of 6 mL/kg of ideal body weight, and low tidal volumes were considered to be 6 to 8 mL/kg of ideal body weight for pragmatic reasons. These showed a risk ratio in favour of prone ventilation for both short-term (0.72) and longer-term mortality (0.73), which was statistically significant for longer-term mortality only (P value = 0.02). For longer-term mortality, this analysis also utilized the Voggenreiter 2005 study, which, although initiated before publication of the ARDS Network study (ARDS Network 2000), states it employed a low tidal volume lung-protective strategy. The quality of the evidence was rated as moderate according to the GRADE structure (Summary of findings 1). Analysis of more than 1200 participants ventilated with higher tidal volumes demonstrated modest or little benefit, with a risk ratio of 0.97 for longer-term mortality. As use of higher tidal volumes is no longer recommended because of the propensity of this approach to cause ventilator-induced lung injury (Slutsky 2013), some may consider these older trials that pre-date lung-protective ventilation to have very limited relevance to current clinical practice. Notably, only the most recent study (Guerin 2013) truly employed an evidence-based low tidal volume lung-protective ventilation strategy (ARDS Network 2000), which is now considered a standard of care by many (Needham 2012). Guerin (Guerin 2013) reported a mean tidal volume of 6.1 mL/kg ideal body weight (95% CI 4.9 to 7.3). For all other studies, the 95% CI breached the 8 mL/kg ideal body weight upper limit for "lung-protective ventilation" (Characteristics of included studies), and a substantial proportion of participants in studies identified as having received "lung-protective ventilation" will not have achieved this if reported data were normally distributed.

Aetiology of hypoxaemia

Many aetiologies of hypoxaemia have been identified in ICU populations. Some involve specific treatments and may be effectively and rapidly reversible with non-ventilatory treatments such as diuretics or haemofiltration for fluid overload and pulmonary oedema. A major group of conditions collectively labelled as acute respiratory distress syndrome (ARDS) (Walkey 2012; Matthay 2019) are of particular interest to intensivists and warrant separate exploration. Acute lung injury, recently re-termed 'mild ARDS' (ARDS definition workforce 2012), is a less severe form of ARDS, is less threatening to life and is less of an immediate concern for intensive care physicians compared with ARDS (Walkey 2012; ARDS definition workforce 2012).

Only one study of 791 participants included a large proportion of participants with conditions other than ARDS or ALI (Guerin 2004). Outcomes of participants from this clinical trial (Guerin 2004) became available in a recent systematic review (Sud 2014), providing more than 1700 participants for analysis of longer-term outcomes, but these results changed little overall. The subgroup of participants with predominantly ARDS or ALI (mild ARDS) demonstrated risk ratios of 0.79 and 0.82 (P values = 0.05 and 0.07). This compares with analyses of all-comers with hypoxaemia who had risk ratios of 0.84 and 0.86 for short- and longer-term mortality. The quality of the evidence was rated as moderate in accordance with the GRADE structure (Summary of findings 1).

The first study conducted by Guerin *et al* also reported a high rate (32%) of cross-over (Guerin 2004; Sud 2008), and removal of this trial on the basis of inclusion of patients without ARDS serves as a sensitivity analysis for excessive cross-overs - that is, removal from the above analysis also results in exclusion of the only study with a very large cross-over population.

Overall completeness and applicability of evidence

Primary outcomes analyses of all available studies provides only weak evidence of benefit for application of prone ventilation to all-comers with hypoxaemic failure who met trial entry criteria in the included studies. Evidence suggests that targeted application to certain subgroups would be appropriate.

The most recently published study (Guerin 2013) has had a large impact on overall results and interpretation of the impact of prone ventilation on primary analyses and subgroup analyses for that intervention. This study investigated the effectiveness of prone ventilation in what would be a population subset of most of the other cited studies (more severe hypoxaemia as a fundamental trial entry criterion). In the study of Guerin et al (Guerin 2013), mortality was approximately halved, which is extraordinary for any medical intervention. The accompanying editorial for this study noted, "The 28-day mortality with prone ventilation was halved (16.0% vs. 32.8% with supine ventilation, P<0.001), a treatment effect virtually unprecedented in modern medicine" - (Soo Hoo 2013). Consequently, this single study has had a large impact on overall effect size and on assessment of heterogeneity in this systematic review.

Additionally, many studies (Gattinoni 2001; Guerin 2004; Leal 1997; Mancebo 2006) were conducted in an era before lung-protective ventilation became a standard of practice, thus reducing external validity; results of those studies are likely to be very limited in relation to current practice. Restriction to studies that employed a more lung-protective strategy with means of 6 to 8 mL/kg tidal volume did result in a risk ratio point estimate of 0.71 for longer-term mortality, which was statistically significant (P value = 0.05). The study of Voggenreiter *et al* (Voggenreiter 2005) was also conducted (1999-2001) before low tidal volume became a standard of care in clinical trials but the text indicates they used a low tidal volume strategy even before the low-tidal volume era.

The intervention of prone positioning would involve very low cost with adequate staffing (or equipment) to safely turn patients from the supine to the prone position and back again, as required. If the intervention was effective with regards to patient-centred outcomes, this would almost certainly be translated into an intervention that was also cost-effective, provided that complications for patients and long-term injuries to staff from additional lifting of patients did not occur. Cost-effectiveness data and modelling or other economic data based on more than one study are currently not available.

One subgroup analysis that requires specific mention is the analysis of mortality of patients with severe hypoxaemia. For short-term mortality in six studies of 744 participants (Gattinoni 2001; Guerin 2004; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009), the risk ratio was 0.80 (95% CI 0.68 to 0.93; P value = 0.003) in favour of prone positioning with a fixed-effect model. For longer-term mortality, seven studies of 977 participants (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Mancebo 2006; Taccone 2009) also demonstrated a risk ratio in favour of prone positioning of 0.77 (95% CI 0.70 to 0.95; P value = 0.003) using a random-effects model. Although the quality of the evidence was rated as moderate according to the GRADE structure (Summary of findings 1), findings appear consistent in that the most recent trial (Guerin 2013), which focuses on participants with more severe hypoxaemia, on its own has shown a remarkable survival advantage for participants. This subgroup meta-analysis with the study included is highly statistically significant, and the subgroup meta-analysis remains significant when this recent study is removed from the analysis. The subgroup exploration fully supports the conclusions of the most recent randomized controlled trial (Guerin 2013) and adds support to use of prone position ventilation in this specific patient population.

This systematic review found no important signal of benefit among participants recruited after 48 hours upon meeting entry criteria and ventilated prone for less than 16 hours per day, nor among those ventilated with higher tidal volumes or among those with milder hypoxaemia. An earlier systematic review (Sud 2010) also suggested no benefit for patients with moderate hypoxaemia only.

Quality of the evidence

With regards to the primary outcome of mortality, eight studies (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Leal 1997; Mancebo 2006; Taccone 2009) were available for short-term mortality, and eight studies (Chan 2007; Fernandez 2008; Gattinoni 2001; Guerin 2004; Guerin 2013; Mancebo 2006; Taccone 2009; Voggenreiter 2005) were available for longer-term mortality. Each analysis included data from more than 2100 participants, and internal validity of results must be considered good in that regard. Clinical diversity and methodological diversity (for some outcomes at least) may have contributed to statistical heterogeneity as assessed by the Higgins (I^2 statistical) method.

The trials were not fully blinded, and some bias would seem inevitable. With regards to bias, Cummings *et al* state (Cummings 2013), "*In a randomized trial blinding is as important as randomization. Randomization minimises the effects of confounding variables at the time of randomization but has no impact on differences that develop between groups during follow-up. Blinding minimizes post-randomization sources of bias such as co-interventions and biased outcome ascertainment and adjudication*". Jadad and Enkin consider, "*... that the control of bias is the reason d' être for clinical trials and accept control of bias is the most important factor in diminishing inevitable error*." (Jadad 2007).

We rated all studies to be at risk of bias in at least one domain (performance bias): all primary studies had at least one risk, as it would be difficult to blind participants, carers and carer-researchers from their treatment allocation (face-up or face-down). Although actual assessment of alive or dead could not be affected (Guyatt 2011a), end-of-life practices are universal but varied and poorly delineated clinically within and between ICUs. End of life practices were not standardized in the included trials in a fashion to minimise such bias by carers as well as trialists. The decision to continue with active management for individual participants or to actively withdraw life-sustaining treatments, or to move to non-escalation of treatment (Morgan 2014; Turnbull 2014) is perhaps the most fundamental decision / intervention made in ICU. Differential employment of these or other co-interventions for trial participants, could be influenced by personal views. It is our assessment that some level of bias with regards to patient management is highly probable at various levels in all included studies. Centres were not chosen at random, but rather by interest in this topic: An early study (Gattinoni 2001) was terminated "*largely* [because of] *an increasing unwillingness among caregivers to forgo the use of prone positioning*". Another study (Guerin 2013) stated, "*Patients were recruited from 26 ICUs in France and 1 in Spain,*

all of which have used prone positioning in daily practice for more than 5 years". Unblinded trials are associated with exaggerated estimates of effect (Forbes 2013; Karanicolas 2010; Psaty 2010), and, although outcomes such as death are usually considered as relatively immune to bias, we believe this is not the case in intensive care, where mortality is high over a short time frame and death often is not directly related to hypoxaemia (Stapleton 2005; Turnbull 2014) but to active withholding or withdrawal of care. Of note Ferrand found that "*In France, there are no guidelines available on withholding and withdrawal of life-sustaining treatments, and information on the frequency of such decisions is scarce*", (Ferrand 2001). More recent studies also document the similar issues (Ay 2020; Gristina 2018; Mark 2015). It is surprising that important potential bias has been overlooked, disregarded or dismissed by some contributors. For example, in the Scandinavian clinical practice guideline on mechanical ventilation in adults with the acute respiratory distress syndrome with regards to downgrading GRADE ratings they state, "*In keeping with the GRADE methodology, the quality of evidence for an intervention (i.e. our confidence in the effect estimates) was rated down for identified risks of bias (e.g. due to lack of blinding...)... Importantly, however, when the outcome in question was death at any stage, we did not downgrade evidence due to lack of blinded outcome assessment.*"(Claesson 2015). Aoyama and colleagues (Aoyama 2019) adopted a similar approach, "*For performance and detection bias domains, we judged that, because mortality is objective it was unlikely to be influenced by lack of blinding....*". Others (Griffiths 2019) disagree with that view and identify serious risk of bias also stating, "*All trials demonstrated performance bias, because of the impossibility of blinding patients and carers with respect to the intervention. All trials also demonstrated detection bias, where outcome assessors were not blinded to intervention allocation*".

Our GRADE assessment of quality of evidence for the primary outcomes of this systematic review was rated weak on the basis of bias (as discussed above) (Guyatt 2011a) and inconsistency (Guyatt 2011c). The Cochrane risk of bias assessment indicated that one trial had three different risks (Chan 2007) and two primary trials had two different risks (Guerin 2004; Voggenreiter 2005). These trials were subjected to a sensitivity analysis.

A small *post hoc* subgroup of 187 participants from one study (Chiumello 2012) allowed analysis of results at 12 months, which showed no signal of benefit for the prone position and so was inconsistent with the primary outcome measures. The quality of evidence for secondary outcomes and subgroup analyses varied in terms of numbers of participants available for analysis (113 to 1350) and quality of measurement, aspects of which have been mentioned in the secondary outcomes and subgroup analysis sections of the Discussion. Subgroups may not be independent, and this underscores the need to consider most as hypothesis-generating only in this study-level meta-analysis e.g. Subgroups with the worst hypoxaemia will have the highest levels of PEEP, an analysis of one will be inextricably linked to the other and the analyses cannot be considered as independent.

Removal of the Voggenreiter study (Voggenreiter 2005) from our meta-analysis as part of a sensitivity analysis, which did include a higher proportion of participants with acute lung injury (mild ARDS) and yielded a threefold higher rate of transfusion in the supine group as well as increased usage of neuromuscular blockers among participants treated prone, made little difference to this analysis. Also with regards to change in trial findings over time, the discrepancy between study initiation or completion and study publication was not constant. The time lag between study start (a surrogate of final trial protocol) and publication of results varied between five and eight years for published studies in this review. Time lag from study completion to publication varied from one to four years. Publication date may not be of greatest relevance for tagging studies with regards to the start of the lung-protective ventilation era and may lead to incorrect data interpretation. The study of Voggenreiter 2005, although commenced in 1999 and completed in 2001, actually started using lung-protective ventilation before the influential ARDS Network study was published (ARDS Network 2000).

Potential biases in the review process

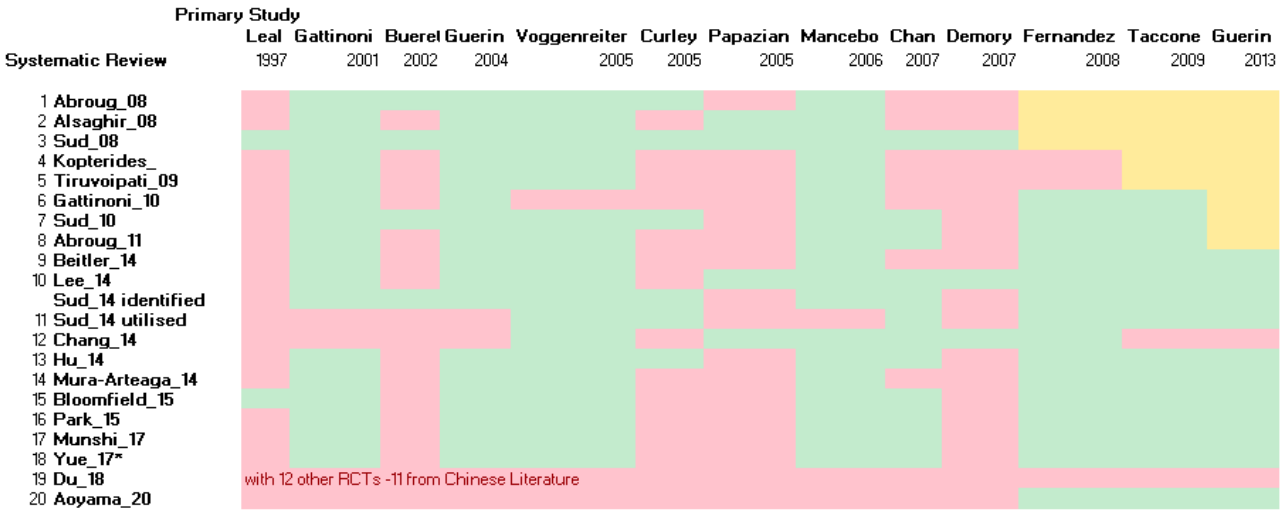
We believe that the likelihood of bias in the review process of evaluated material is low. Processes used to identify relevant studies included in this review have been supplemented by several high-quality systematic reviews, which also have involved nearly all of the key trialists. Therefore, it is likely that all relevant studies up to 1st May 2020 were identified. Adherence to most prespecified study inclusion and exclusion criteria in the protocol stage was maintained in the review stage. The cutoff in one subgroup analysis (long-duration prone positioning) was changed by two hours from 18 hours per day to 16 hours per day *post hoc* in an effort to allocate and analyse the last published study (Guerin 2013) in the most biologically plausible manner consistent with the original protocol. Ecological fallacy or bias cannot be excluded in a study-level systematic review of participant subgroups (Porta 2008; Reade 2008).

Agreements and disagreements with other studies or reviews

At least 21 other systematic reviews of prone ventilation have been published and been considered in this review (Abroug 2008; Abroug 2011; Alsaghir 2008; Aoyama 2019; Ball 1999; Beitler 2014; Chang 2014; Curley 1999; Du 2018; Gattinoni 2010; Hu 2014; Kopterides 2009; Lee 2014; Mora-Arteaga 2015; Munshi 2017; Park 2015; Sud 2008; Sud 2010; Sud 2014 Tiruvoipati 2008; Yue 2017). Eleven have been published as full papers since the last major and influential clinical trial of Guerin *et al* (Guerin 2013). In addition we identified recent abstracts which did not contain additional data (Sim 2014; Sud 2011a; Tabula 2015; Yankech 2017). We also identified one selective overview of systematic reviews which examined seven recent systematic reviews (Dalmedico 2017).

The primary studies the systematic reviews include are tabulated, Figure 5 . None of the 19 other meta-analyses appear to have published protocols pre-specifying their approach to data collection, management and analysis, which, since 2009, is a preferred option according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (Moher 2009), with the possible exception of Sud 2014. Publication of protocols which to some extent protects from the consequences of data dredging, is an important safeguard and is an integral part of Cochrane Systematic Reviews.

Figure 5. Primary RCTs incorporated in various published Systematic Reviews. Green denotes primary study was incorporated; Pink denotes primary study was not utilised; Yellow denotes primary study was not available to reviewers. *Yue_17 also included non-RCT.



Three systematic reviews (Gattinoni 2010; Sud 2010; Sud 2014) are extensively represented by authors of primary studies: In the systematic reviews of Sud *et al* (Sud 2010; Sud 2014), 13 of 17 listed review authors represent 10 of the 13 primary studies with mortality data. In the systematic review of Gattinoni (Gattinoni 2010), five of six review authors represent the four primary studies included in those analyses. In the recent systematic review of Munshi *et al* (Munshi 2017) Mancebo and Pesenti are co-authors so several influential systematic reviews are authored by primary study investigators. Although benefits regarding data clarification and of cooperation are evident, independence and potential conflict of interest issues must also be considered in assessment of these systematic reviews.

The earliest systematic reviews we identified (Ball 1999; Curley 1999) did not contain meta-analyses and pre-dated the seminal outcome trial conducted by Gattinoni and colleagues (Gattinoni 2001).

Some subsequent systematic reviews (Abroug 2008; Alsaghir 2008; Curley 1999; Gattinoni 2010; Kopterides 2009; Sud 2008; Tiruvoipati 2008) did not include the two most recent trials (Guerin 2013; Taccone 2009) and despite some valuable insights are now less relevant in terms of both current clinical practice and volume of appropriate data for analysis. Inclusion criteria have differed between reviews, and those with larger numbers of studies have not included exactly the same studies for analyses, even analyses carried out by the same group (Figure 5). For example, Abroug *et al* included the study of Curley 2005 in one meta-analysis (Abroug 2008) but not in their updated review (Abroug 2011). In this regard, two of the most recent reviews (Beitler 2014; Lee 2014) identified different numbers of studies for analysis: One (Beitler 2014) identified seven primary studies only and split one study into two to achieve eight data sets for their subgroup meta-analysis; the other (Lee 2014) identified 11 studies for inclusion in their analyses. Two of the analyses of Sud *et al* included 10 of 13 primary studies with mortality data (Sud 2010; Sud 2014), but review authors excluded three studies from their original systematic review (Sud 2008). In their most recent review, the review authors state, "*Reviewers were in total agreement about the included studies*"; however, reviewers were authors of 10 of 11 of the included primary investigations (Sud 2014).

Our systematic review specified at the protocol stage which studies would be included and which excluded; resulting in fewer studies for analysis compared with some of the reviews mentioned above (Bloomfield 2009). In particular, our review consisted of adult participants receiving conventional mechanical ventilation as treatment for hypoxaemia. Thus trials that studied children, prevention and non-conventional modes of ventilation were not considered for inclusion, and this largely accounts for the differences in numbers of participants studied in primary, secondary and subgroup analyses. Our review did include the small study of Leal (Leal 1997) which had only been included in one other systematic review (Sud 2008) as it met our pre-specified inclusion criteria. Different studies have also provided different analyses. For example, in this systematic review, mortality was partitioned into short-term mortality, longer-term mortality and *post hoc* to 12-month mortality. Other reviews have aggregated the latest available data for mortality and have not split data into short-term and longer-term categories (Sud 2010). This has resulted in the advantages of increasing numbers of studies and participants available for analysis but obscures where any advantages for participants lie: longer-term mortality may be of greater relevance to participants (and patient-centred) than short-term-mortality if "short-term" still equates to being on a ventilator, or still requiring ICU care with the associated discomfort, invasive procedures and clinical burden that it entails. Nevertheless, the primary outcomes of this systematic review are in agreement with most other systematic reviews on this topic - analysis of all studies fails to demonstrate unequivocal benefit for all participants with acute respiratory failure in terms of short- or longer-term mortality. It also is consistent with all reviews in finding that oxygenation is improved and pressure ulcers/sores are increased (Sud 2010). This systematic review (Sud 2010) used data provided by the original investigators in many of the original trials and included many as co-review authors: their report provided data (from last follow-up) on participants with severe hypoxaemia and moderate (or less severe)

hypoxaemia. These data indicate that participants with moderate hypoxaemia only, did not appear to benefit from prone ventilation, with a risk ratio 1.07 (95% CI 0.93 to 1.22; P value = 0.36) in favour of supine ventilation, which is consistent with the risk ratio of 1.06 obtained in our analysis.

One published systematic review (Abroug 2011) reached some conclusions that differed from the findings of our review. They concluded that no increase occurs in airway complications related to the prone position. However, we found an increase in airway obstruction, as did Sud *et al* (Sud 2010), and clinicians should be aware of this potentially serious problem. In this regard, we found a risk ratio of 1.78 in favour of the supine position (P value = 0.003) when using a random-effects model for analysis. Analysing data from four studies only, Sud *et al* observed a statistically significant mortality benefit in a subgroup of studies enrolling ARDS participants only. They excluded the study of Gattinoni (Gattinoni 2001), although nearly 95% of participants in that study met ARDS criteria. Only with publication of the most recent study (Guerin 2013) could we identify any strong signal of support, and this study included only participants with more severe ARDS. Even with inclusion of this study, statistical significance was not achieved for longer-term mortality in our analysis.

Early systematic reviews (Abroug 2008; Alsaghir 2008; Kopterides 2009; Sud 2008; Tiruvoipati 2008) generally considered the totality of evidence for prone positioning, but more recent aggregate-level systematic reviews (Abroug 2011; Beitler 2014; Hu 2014; Munshi 2017; Park 2015; Sud 2010; Sud 2014) have focused on particular subgroups of patients and therefore are potentially subject to the problem of ecological fallacy as well as other biases eg data-dredging bias (Jadad 2007) and limitations of subgroup analysis which means they should be considered as "*entirely observational in their nature*" (Borenstein 2019; Deeks 2019) and preclude causal inference.

We have evaluated three recent systematic reviews (Beitler 2014; Lee 2014; Sud 2014), which include the most recent clinical trial of Guerin and colleagues (Guerin 2013).

One review (Lee 2014) focusing on ARDS included studies that we specifically excluded (Beuret 2002; Demory 2007; Papazian 2005) for reasons listed in the Characteristics of excluded studies section. Inclusion of these studies reduced statistical heterogeneity but increased clinical diversity in the meta-analysis (Bloomfield 2014). The former effect resulted in a statistically significant result for their primary analysis but we remain sceptical that inclusion of these three primary studies is justified on scientific grounds (Bloomfield 2014). Our published protocol specifically excluded such studies *a priori*. The immense influence of the PROSEVA study (Guerin 2013) was not highlighted. Review authors also rated the risk of bias from lack of blinding of participants and personnel as low, in contrast to our rating of such bias as discussed earlier. Further, they excluded Gattinoni et al (Gattinoni 2001) from their ARDS analysis, although nearly 95% of participants in that study met ARDS criteria (Bloomfield 2014). This meta-analysis has drawn criticism from other workers similar to the criticisms described above (Iftikhar 2015).

The second systematic review (Beitler 2014), which focused on ARDS in the low tidal volume era, did not include the small study of Chan (Chan 2007), listing it as an observational study without a clearly defined control group, nor that of Leal (Leal 1997). This review explored reasons for heterogeneity but did not address the consistent and most important determinant of heterogeneity in this regard - results from the PROSEVA study of Guerin *et al* (Guerin 2013). Review authors split the data from one trial (Taccone 2009) into two groups for their analysis, which we consider methodologically problematic. In this last regard, application of mechanical ventilation to more severely ill participants will almost inevitably lead to reduced mechanical ventilation tidal volumes (which was their justification for splitting one trial into two), as clinicians strive to reduce mean and peak ventilatory pressures, even though the two subgroups form one study sharing a single protocol over one study epoch. Their exploration of heterogeneity is puzzling in that almost unprecedented effect size of the PROSEVA trial (Guerin 2013) is not discussed at all (Soo Hoo 2013; Tekwani 2014; Tonelli 2014).

Sud and colleagues (Sud 2014) have updated their original meta-analysis and have adopted a restrictive approach with regards to study selection for their primary analysis focused on ARDS. This review identified 11 studies, of which only six were used for the primary analysis. Thirteen of the 17 authors of this review contributed to 10 of the original studies, and they selected 11 for inclusion in their study-level meta-analysis. The primary analysis was restricted to a subset of studies describing participants with a diagnosis of ARDS and was further restricted to those receiving low tidal volume ventilation. Review authors included studies specifically excluded in this review (Beuret 2002; Curley 2005; Watanabe 2002) for reasons already described (Characteristics of excluded studies). Only one was used in the primary analysis (Curley 2005), which studied a paediatric population with a median age of two years. Review authors rated the quality of findings of their systematic review as high according to the GRADE structure in comparison with our and others (Griffiths 2019) assessment of low quality for our primary analyses and moderate quality for our main subgroup analyses (Summary of findings 1). A finding of low heterogeneity was emphasized, but no emphasis was placed on the substantial increase since the previous review (Sud 2010), most obviously resulting from inclusion of the most recent trial (Guerin 2013). The classification of heterogeneity is highly subjective, and a variety of ranges are suggested (Deeks 2011; Hatala 2005; Higgins 2003) for low, moderate and high heterogeneity using the I^2 approach. We used a more conservative approach and would have rated most of these analyses as demonstrating moderate heterogeneity. Likewise, the GRADE approach to assessment of the quality of evidence is also subjective. We considered the risk of bias to be high, as others have (Griffiths 2019; Park 2015). The inconsistency and increased heterogeneity of results before and after inclusion of the most recent trial (Guerin 2013) could have led to further downgrading of the quality of evidence for this subgroup analysis of participants with an ARDS diagnosis. In this regard, analyses performed before publication of this trial (Guerin 2013) and those that did not include it (nine of 11 analyses) yielded an I^2 statistic of 0% for short-term mortality. For longer-term mortality, nine of 11 studies also had an I^2 statistic = 0, and 10 of 11 had an I^2 statistic less than 25%. In contrast, with inclusion of the trial for short-term mortality, only one of six analyses revealed an I^2 statistic = 0 or less than 25%, and for longer-term mortality, zero analyses of six had an I^2 statistic = 0% or less than 25% (i.e. 19 of 22 analyses had zero or low heterogeneity without inclusion of data from Guerin 2013, in contrast to one of 12 analyses with inclusion of these data). With regards to statistical significance,

despite increased heterogeneity and increased use of the random-effects model, the pattern was opposite: A probability value of 0.05 or less was observed in two of the 22 analyses that did not include this influential study but in eight of 12 analyses that included it. The substantial impact of this trial is also apparent upon visual inspection of forest plots for mortality.

Our subgroup analysis results agree in part with the main findings of Sud (Sud 2014), in that longer-term mortality appears reduced among participants receiving lower tidal volume ventilation (RR 0.73, 95% CI 0.55 to 0.96) and in severely hypoxaemic participants (RR 0.77, 95% CI 0.65 to 0.92), but results for participants with ARDS are only borderline in the analysis (RR 0.85, 95% CI 0.71 to 1.01). All three are only subgroup analyses of the greater body of evidence and in our view show moderate quality when assessed by the GRADE structure.

For this amendment, additional systematic reviews were identified.

Chang (Chang 2014) and colleagues presented a systematic review which incorporated nine randomized or pseudo-randomized controlled trials and 10 non-randomized ("comparable cohort / case-control") studies. It did not identify the recent clinical trials of Taccone *et al* nor that of Guerin *et al* nor some older ones and so was not considered further.

Hu and co-workers also published a systematic review of prone positioning (Hu 2014) and identified eight primary investigation of adult participants and one paediatric study (Figure 5) for their primary outcome of 28-30 day mortality. An apparent benefit of prone positioning was demonstrated in a subgroup analysis. A proposed benefit of higher positive end-expiratory pressure (PEEP) in subgroup analyses is doubtful in our view because of primary study misclassification and because of the association of higher PEEP levels with other factors explored in other subgroup analyses. The PROSEVA trial supplement indicates mean PEEP levels below 10cm water (low PEEP category) but appears in the Hu analysis as in the 10-13cm (high PEEP category). The substantial impact of the PROSEVA trial, exploration of bias and limitations of subgroup analysis are inadequately explored, in our view.

Mora-Arteaga and colleagues published their systematic review (Mora-Arteaga 2015) with the primary objective of determining whether ventilation in the prone position reduces mortality in patients with ARDS compared with traditional ventilation in the supine position. With regards to bias assessment they stated, "*it was not possible to blind the patients or the treating medical team---though we consider that this had no effect upon the results*". No basis for this judgement is provided. In the Cochrane Risk of Bias tool all seven primary studies were assessed as having low risk of performance bias (blinding of participants and personnel). They explored multiple sub-group analyses with stratification and presented results broadly similar to other groups who have also explored the same data. The limitations of subgroup analyses are not highlighted.

Park *et al* (Park 2015) also published a systematic review with the aim "*to evaluate the effects of prone positioning on mortality rates, particularly*
with respect to the duration and concurrent use of protective lung strategies". The primary outcome measure was the overall mortality at the longest available follow-up. Notably, with regards to bias they stated, "*Because the prone position with ventilator was always shown and patient progress was explained to the family and patients in the intensive care unit, blinding of participants or outcome measure was not possible. Therefore, there were high selection and detection biases in all included studies* **".** (Our emphasis). This seems reasonable and we are in agreement but their view contrasts the assessment of nearly all other systematic reviews on this topic. In particular, their Cochrane risk of bias assessment figure is substantially different to that of Mora-Arteaga *et al* (Mora-Arteaga 2015). As with several other systematic reviews on prone positioning they categorised statistical heterogeneity to be low for I^2=25-49%, moderate for I^2= 50- 74%, and high for I^2≥75% and all their analyses are presented as fixed effect models. Notably, the authors requested raw data for all included primary studies, to allow for analysis of subgroups of patients, "*however most authors did not respond and one author refused our request*". This is unfortunate scientifically, in our opinion, as many primary study authors have previously provided such data for other systematic reviews. Finally although Park *et al* describe limitations of available evidence they do not specifically discuss the limitations of analysis of multiple subgroup effects.

Munshi *et al* aimed to determine the effect on mortality (primary outcome) in adults with ARDS in the prone position versus ventilation exclusively in the supine position (Munshi 2017) to inform European and North-American Societies of Intensive Care formulating mechanical ventilation guidelines (Fan 2017). They considered a study's overall risk of bias to be high if any domain was judged to be at high risk of bias, with the exception of caregiver blinding, which effectively increased their quality of evidence assessments by GRADE which they rated as moderate to high for their subgroup analyses. In contrast using the same GRADE system we rated the quality of evidence as moderate (due to bias) or low (due to bias and inconsistency) Summary of findings 1. A recent guideline (Griffiths 2019) generally accords with our GRADE assessments. Many of the primary subgroup analyses of Munshi *et al* are in broad agreement with our own analyses presented in this Cochrane systematic review. For one subgroup analysis exploring moderate to severe ARDS they excluded the Gattinoni study (Gattinoni 2001) even though nearly 95% of participants in that trial met the the criteria for moderate to severe ARDS. In a secondary publication from that trial (Gattinoni 2010) data for severe ARDS was made available to researchers exploring the impact of disease severity. We do not understand why such data was excluded from analysis. In our own analyses of short and longer term mortality using their selected studies, exclusion and inclusion of Gattinoni's RCT (Gattinoni 2001) would change the conclusions that might be made from this particular subgroup analysis and so their conclusions cannot be considered robust. This systematic review (Munshi 2017) also only managed to identify and reference two other systematic reviews (Beitler 2014; Lee 2014) published after the PROSEVA trial, thus failing to identify contributions made by Hu, Sud, Park and Mora-Arteaga groups (Hu 2014; Sud 2014; Mora-Arteaga 2015; Park 2015) as well as the earlier version of this Cochrane Systematic Review. Additional insights generated by this review to the understanding of prone positioning seem limited (Møller 2017; Ioannidis 2016) given the systematic reviews listed above. We also consider their assessment of carer-researcher bias substantially underestimates its potential impact in an ICU setting.The limitations of subgroup analysis (Guyatt 2008a) and the cautions required making inferences from a multiplicity of subgroup analyses (Borenstein 2019; Deeks 2019) are inadequately highlighted in our view.

Yue and co-workers (Yue 2017) published a cumulative meta-analysis in Chinese of nine primary English language studies categorised as randomized controlled trials (RCTs). Results of this cumulative meta-analysis are invalidated by inclusion of an influential study which clearly is not a RCT (Charron 2011).

Du and colleagues (Du 2018) have provided a systematic review of prone positioning predominantly from the Chinese Language literature encompassing all age groups with pneumonia with the primary outcome of interest, oxygenation. They interrogated PubMed, EMBASE, Cochrane Library, Wanfang, VIP, CNKI databases and identified 12 randomized clinical trials in total. They did not identify or include any of the trials used in this or other systematic reviews but their systematic review provided an additional six studies of adult participants (Cao 2014; Li G 2015; Li J 2015; Wang 2015; Yan 2015; Cheng 2016) for potential inclusion in this amended Cochrane systematic review. Ultimately none were suitable for inclusion (Excluded studies). The other trials identified by Du *et al* were of paediatric populations and therefore not relevant to this review.

Aoyama *et al* conducted a network meta-analysis (Aoyama 2019) with three studies only chosen from randomized trials of prone positioning (Fernandez 2008; Guerin 2013; Taccone 2009). They concluded with regard to prone positioning, that "*Specifically our study supports the use of prone positioning (i.e. significant reduction of mortality and high ranking)*.....". With regards to their approach to potential bias they stated, "t*hat for performance and detection of bias domains, we judged that because mortality is objective, that it was unlikely to be influenced by lack of blinding as long as a strict protocol for both groups was provided*". As intensive care support is routinely and subjectively withheld or withdrawn by care providers as part of end of life care we remain surprised by such statements and consider this judgement of lack of bias over-optimistic. We also note that if we had restricted our Cochrane systematic review to these three studies only, clear and unequivocal evidence of benefit would not be apparent despite inclusion of the PROSEVA study (Guerin 2013) which has been described as having "*a treatment effect virtually unprecedented in modern medicine*" (Soo Hoo 2013). Our *post hoc* analysis (generated by the study of Aoyama *et al*) using these three trials only found the mean effect size confidence interval for longer-term mortality wide 0.73 (95%CI 0.51-1.03) breaching unity, not statistically significant and so not in concordance with the results of this network meta-analysis.

Generally in the more recent systematic reviews discussion of bias is largely limited to "publication bias" and tests thereof in contrast to very little consideration of more serious uncontrolled performance bias with lack of blinding of carers (nurses, attending physicians, other therapists, trialists etc). There were wide differences between studies in Risk of Bias Tool assessments and wide discrepancies regarding judged quality of evidence using the GRADE tool. Subgroup analyses were prominent in recent systematic reviews but their limitations (Oxman 2012; Sun 2014) received relatively little attention. Newer techniques that are now recommended by Cochrane (Deeks 2019) for random effects meta-analyses to provide better effect size estimates (eg HKSJ adjustment IntHout 2014) have not been applied in this interim amendment nor in the systematic reviews listed in this section.

It is worth noting that despite recent contributions incorporating the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology (Mustafa 2013) that findings and recommendations based on largely the same data are substantially discordant (Claesson 2015; Fan 2017; Griffiths 2019; Hashimoto 2017) despite apparently transparent defined processes (Packer 2016).

AUTHORS' CONCLUSIONS

Implications for practice

Results of this systematic review do not provide strong support for use in all patients with hypoxaemic respiratory failure who are intubated and mechanically ventilated in intensive care. Although the risk ratio for short-term mortality and longer-term mortality with inclusion of the last published study provided a signal for benefit, evidence was weak for all participants with acute respiratory failure (Summary of findings 1). Indeed, *post hoc* analysis of a small subset of 187 participants examined at 12 months (Chiumello 2012) actually favoured supine ventilation for these participants but with wide confidence intervals. It must also be borne in mind that all studies of prone position for acute respiratory failure included in this systematic review are open-label and not blinded. Thus the potential for important bias due to deviations from intended interventions and measurement of outcomes must also be considered in any critical appraisal (Cummings 2013; Jadad 2007).

Oxygenation improvement persisted after adoption of the prone position seven to 10 days after enrolment, but many studies have shown that improvement in oxygenation (e.g. with use of nitric oxide) is not a reliable surrogate for improved patient-centred outcomes (Adhikari 2007; Diaz 2010). This again appears to the case for the primary analyses of this systematic review of prone ventilation.

Complications were increased for pressure sores and for airway and some cardiovascular events, and, although these did not translate into excessive mortality, clinicians need to be aware of these issues. A widely varying rate was reported for some of these complications across studies, reflecting perhaps that "low priority data" were provided by these studies (Ioannidis 2006), or that better implementation of preventative measures in some studies led to reduced complication rates.

Exploratory subgroup analyses, which are widely utilized in published studies and in this systematic review, must be treated with caution. Risks of type I and type II statistical errors are increased through reduced statistical power derived from decreased participant numbers and increased numbers of hypotheses tested and by risks of ecological fallacy associated with aggregate-level meta-analyses (Lagakos 2006; Oxman 1992; Reade 2008; Sun 2014). Thus subgroup analyses must be interpreted with all these weaknesses in mind. Analyses of subgroups from this systematic review revealed subgroups in which prone ventilation appeared to have no benefit, with a risk ratio of close to unity; subgroups with point estimates suggestive of benefit but with wide confidence intervals; and subgroups for which the point estimate was both suggestive of benefit and statistically significant.

- In particular, point estimates close to unity for prone ventilation of short daily duration, later application of prone ventilation after onset of hypoxaemia, milder hypoxaemia and ventilation with > 8 mL/kg ideal body weight indicated that prone

positioning in these circumstances would be unlikely to provide benefit.

- In contrast, ventilation prone for 16 or more hours per day, early intervention with prone positioning after entry criteria were met, and presentation of severe hypoxaemia point estimates suggest that prone positioning might be beneficial in these circumstances. Point estimates for risk ratio ranged from 0.72 to 0.80 in favour of prone ventilation. In the absence of alternative evidence, it is recommended that prone position should be actively considered for such patients. With regards to severe hypoxaemia, meta-analysis of studies before publication of the most recent contribution of Guerin *et al* (Guerin 2013) strongly suggests benefit; the study of Guerin *et al* itself demonstrates clinically important and statistically significant benefit; and the combination of that study with other studies reaffirms that benefit. Thus although this is one of several subgroup analyses, evidence strongly favours prone positioning of mechanically ventilated patients exhibiting severe hypoxaemia.

Implications for research

Clinical practices should not and will not be universally adopted unless data are robust (Noble 2004), but with the addition of the most recent study (Guerin 2013) to systematic reviews, residual uncertainty as to whether prone positioning can improve important patient-centred outcomes in patients with severe hypoxaemia has seemingly been reduced by this single moderate-sized trial, as well as by this and other meta-analyses suggestive of survival benefit. There are important caveats. The issue that all of the included clinical trials were open label, must be considered and weighed. Treatment allocation would be known to caregivers so important bias may be present in all these studies particularly when death occurs after a decision to withdraw or with-hold life-sustaining supportive care. Also with regard to the PROSEVA trial (Guerin 2013) which dominates findings in this systematic review, a large number of baseline differences favouring outcomes for prone positioning were present (Festic 2016; Tekwani 2014) and may have exaggerated the substantial reduction mortality risk from application of prone positioning in this study. These factors would need to be considered against substantial apparent benefits before any future judgement as to the need to conduct further clinical trials.

Deficiencies in current knowledge arise from:

- reliance on aggregate-level subgroup analyses to identify more specific populations that *might* better benefit from this intervention in the short term or over the longer term;
- limited data from the lung-protective ventilation era, as only four reported trials (n ~ 830) were initiated after 2001 (Chan 2007; Fernandez 2008; Taccone 2009; Guerin 2013). Although one trial (n = 40) used a lung-protective strategy before this date (Voggenreiter 2005), investigators did not provide recorded data. These five studies account for approximately 40% of participants in this review;
- uncertain effect of bias as all data are from open label studies;
- limited generalizability worldwide, as more than 95% of all participants were enrolled by three European Research Groups;
- very sparse data for participants beyond six months, with the available data showing no signal of benefit for prone ventilation in terms of mortality at 12 months (Chiumello 2012);
- lack of sufficient functional, physiological, neuropsychological or quality of life data (Bernard 2017; Chiumello 2016; Lamas 2014). Only one study of 26 patients (Chiumello 2012) has provided such data;
- overall lack of healthcare economics data (Sud 2011); and
- inconsistent reporting of data amongst studies, making analyses and aggregation of data for meta-analysis more difficult.

Current evidence may be enhanced by the use and publication of formal individual patient data (IPD) meta-analyses (Reade 2010; Riley 2010; Sud 2011a). Gattinoni *et al* (Gattinoni 2010) combined data from four primary studies in a review in what they describe as an "individual patient meta-analysis". However, their paper does not provide any methodological description of the procedures undertaken to combine data from the four included studies (Stewart 2015; Tierney 2019).

With the publication of the most recent trial and the benefits demonstrated (Guerin 2013), equipoise to allow future studies to be undertaken would seem problematic, unless long-term outcomes (12 months or longer) indicate transient benefits only. Nevertheless, it must also be noted that many promising therapies based on randomized trials are not always confirmed in follow-up trials (Goodwin 2012) and ideally replication of the PROSEVA trial would occur (KNAW 2018; The Academy of Medical Sciences 2015). Further insights on particular groups of patients and adequately described ARDS phenotypes (Marini 2020; Matthay 2019) will require formal individual patient data meta-analyses (Stewart 2015) rather than additional study-level meta-analyses, as well as examination of outcomes beyond mortality data alone. Outcome data is very limited in scope. In this regard, it is hoped that investigators in some of the trials conducted to date might be able to provide stakeholders with information regarding long-term outcomes and functional data (Wunsch 2010), as has already been provided for a limited number of patients by one group of investigators (Chiumello 2012; Taccone 2009). Funding bodies and critical care organisations should consider supporting long term outcome mortality analyses from previous trials conducted in the low tidal volume ventilation era and studies that will ascertain long term functional outcomes of survivors. Prospective observational data collection and analysis should have a role too (Frieden 2017) as it does in the pharmaceutical industry in the form of phase IV drug trials (Strom 2006). Future observational and epidemiological studies as well as interventional trials of ARDS even though not directly addressing prone positioning should report in detail on its use (Cheung 2020; Constantin 2019). This serves two purposes. Firstly such data can corroborate and perhaps calibrate the impact of prone position ventilation on mortality (Fletcher 2005) as suggested by selective subgroup analyses in this and other systematic reviews and by the results of the PROSEVA trial (Guerin 2013). Secondly, the internal and external validity of these new studies of ARDS would be strengthened by taking into account an intervention that may reduce mortality by more than 40% in some ARDS populations.

Searches of trial registries indicated that there are few ongoing studies addressing the use of prone versus supine positioning in patients receiving mechanical ventilation for acute respiratory failure (Characteristics of ongoing studies). The majority of ongoing trials investigating this intervention in the context of emergency and critical care are focused on determining the effectiveness of early use of this intervention in non-mechanically ventilated

(i.e., awake, non-intubated) patients. In addition, some ongoing trials address questions regarding the specific prone positioning protocols used in mechanically ventilated patients. These trials include comparisons of early versus later initiation of prone positioning, longer versus shorter duration of prone positioning, and the use of prone positioning in patients receiving ECMO. These may be relevant questions to address in a future update of this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ayzac 2016

Study characteristics	
Methods	Further analysis of PROSEVA randomized controlled trial (Guerin 2013)
Participants	466 Participants of PROSEVA trial. Analysed on an "Intention To Treat " basis ARDS - American–European Consensus Conference criteria • Endotracheal intubation and mechanical ventilation for ARDS < 36 hours • Severe ARDS (defined as PaO_2:FIO_2 ratio < 150 mmHg, with FIO_2 ≥ 0.6, PEEP ≥ 5 cm of water and tidal volume ~ 6 mL/kg ideal body weight • Confirmed after 12 to 24 hours of mechanical ventilation in the participating intensive care unit. Volume-controlled ventilation combined with PEEP table
Interventions	Prone position for ≥ 16 hours/d vs semi recumbent position Tidal volume: 6.1 mL/kg IBW (~ 95% CI 4.9 to 7.3 mL/kg IBW)
Outcomes	Ventilator-associated pneumonia
Notes	Initial VAP diagnosis made by principal investigator for each site and not blinded to patient allocation.

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization - central
Allocation concealment (selection bias)	Low risk	Nothing in text to suggest post-randomization bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Site investigator screened patients for VAP. Patients with labelled as having VAP then further adjudicated by blinded independent assessor.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat listed as method of analysis. Eight participants from original cohort excluded (with explanation)

Ayzac 2016 *(Continued)*

Selective reporting (reporting bias)	Low risk	Multi-centre trial - conduct and outcome measure likely agreed in advance
Other bias	Low risk	Low cross-over rate

Chan 2007

Study characteristics	
Methods	Participants were assigned to supine (n = 11) or prone (n = 11) position ventilation *according to the discretion of the physician in charge*. All participants had a Swan-Ganz catheter, and an arterial line was inserted for haemodynamic monitoring and blood sampling. Oxygen saturations were measured with a pulse oximeter. Sedation was given to all participants via continuous infusion of midazolam and neuromuscular blockade with atracurium besylate. Antibiotics were given to participants according to American Thoracic Society guidelines for CAP and based on the clinical judgement of the in-charge physician. All participants were intubated and underwent volume-controlled mechanical ventilation
Participants	22 patients with community-acquired pneumonia (fever plus cough with purulent sputum production and infiltrates on chest x-ray within 72 hours of admission) during an SARS epidemic. All patients met the criteria for ARDS as defined by the American-European Consensus Conference, with onset within 72 hours before enrolment
Interventions	Prone position ventilation vs supine Participants in the intervention group were ventilated in the prone position and were maintained in this position for ≥ 72 hours. Participants were turned supine once they maintained an SpO_2 > 90% with FIO_2< 60 for more than 24 hours after 72 hours of prone positioning Tidal volume: 7.7 mL/kg IBW (95% CI ~ 5.6 to 9.8 mL/kg IBW)
Outcomes	Primary outcomes: plasma cytokine levels at baseline and at 24 hours and 72 hours after enrolment Secondary outcomes: PaO_2/FIO_2 and complications. 14-day mortality is recorded
Notes	Randomization methods were unclear, with contradictory comments included in the manuscript and in subsequent correspondence. Described as "prospective observational study" in original paper, which also stated, "Patients were assigned to either continuous prone position ventilation (PRONE) or traditional supine ventilation (SUPINE) *a*ccording to the in-charge physician's decision." In subsequent correspondence, study authors stated, "after agreement of the in-charge physician patients were enrolled and then assigned to either PRONE or SUPINE according to a computer run randomization table" (Chan 2008). Trial was discontinued for slow enrolment due to SARS outbreak. Trial commenced in 2002, was completed in 2003 and was published in 2007 Mean of 105.6 hours prone per participant

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The conflicting statements (above) make assessment unclear
Allocation concealment (selection bias)	High risk	Bias stated by study authors

Chan 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Bias stated by study authors
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinded assessment not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Few endpoints and short follow-up, but comments regarding physician decisions and effects of the SARS outbreak make the risk of this sort of bias unclear
Selective reporting (reporting bias)	Unclear risk	No pre-specified protocol reported
Other bias	Unclear risk	Study was ended prematurely, and such studies have been associated with inflated effect size (Bassler 2010)

Chiumello 2012

Study characteristics	
Methods	Follow-up of subgroup of participants from Taccone 2009. Five Italian centres (of the 25 original centres - 23 Italian and 2 Spanish)
Participants	Quality of life and physiological data available for 26 participants (13 prone, 13 supine) from 67 eligible patients 12 months after enrolment. (The original study recruited 344 patients.) Mortality data from 187 patients also available
Interventions	Randomly assigned to receive supine or prone ventilation for acute respiratory distress syndrome (see Taccone 2009)
Outcomes	12-Month mortality; blood gas analysis; pulmonary function tests including CO diffusion; walking test; health-related quality of life using Short Form-36 (SF-36) and St George's Respiratory Questionnaire (SGRQ); quantitative lung CT scan analysis Mortality at 12 month follow-up, 60% overall.
Notes	Small subgroup of participants with large attrition rate; participant samples may not be representative. Low power to detect clinically meaningful differences with regards to outcomes. Trial commenced in 2004, was completed in 2008 and was published in 2012

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Centralized telephone randomization system - as for main study (Taccone 2009)
Allocation concealment (selection bias)	Low risk	Centralized telephone randomization system
Blinding of participants and personnel (performance bias)	High risk	Not blinded and assigned treatment readily identified

Chiumello 2012 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Participants may remember and divulge allocation to "blinded" assessors
Incomplete outcome data (attrition bias) All outcomes	High risk	Very high dropout rate. 13/29 assessed in the prone group. 13/38 assessed in the supine group. Not likely to be random
Selective reporting (reporting bias)	Unclear risk	Post hoc follow-up tests
Other bias	Low risk	No other bias identified

Fernandez 2008

Study characteristics	
Methods	Multi-centre, open, randomized controlled trial over 12 months. Participants were randomly assigned by computer-generated random sequence to supine (n = 19) or early (within 48 hours) and continuous prone (n = 21) ventilation with further stratification of randomization according to severity using the SAPS II score and the type of ARDS
Participants	40 mechanically ventilated patients with early, refractory ARDS despite early protective supine ventilation 25 male, 15 female Inclusion: intubated adult patients within 48 hours of ARDS diagnosis (North American-European Consensus Conference (NAECC) criteria) Exclusion: severe hypotension requiring vasopressors (cardiovascular SOFA score 3 to 4), traumatic brain injury (TBI), unstable pelvic or spinal column fracture, moribund condition or enrolment in another trial
Interventions	After a 1-hour protocolized ventilation period, participants were placed in the assigned position (prone or supine), in which they were maintained for up to 20 hours per day. Prone participants were turned supine once PaO_2/FIO_2 quotient was < 250 mmHg (33.3 kPa) for longer than 12 hours. Mechanical ventilation appeared to be volume controlled and pressure limited Tidal volume: 7.25 mL/kg IBW (~ 95% CI 5.1 to 9.4 mL/kg IBW)
Outcomes	Primary: 60-day survival. NB ICU mortality identical, as no participant died after discharge up to the 60 days studied Secondary: length of mechanical ventilation and ICU stay
Notes	Study was prematurely stopped because of low participant recruitment. Two participants were lost to follow-up (4.8%) (1/group) and 2 supine participants were crossed over to prone. Both cross-over participants died. Criteria for new pneumonia (ventilator-associated pneumonia) not defined Trial commenced in 2003, was completed in 2004 and was published in 2008 Mean hours prone per participant not clear from text. Clarification sought but not obtained
Risk of bias	

Fernandez 2008 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralized control centre produced randomization codes
Allocation concealment (selection bias)	Low risk	The above would minimize selection bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Risk of assessment bias different for different outcomes. Mortality has low risk of bias; other less well-defined outcomes (e.g. pressure sores) have higher risk of outcome assessment bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants lost to follow-up and 2 crossed over to prone ventilation during first week of care
Selective reporting (reporting bias)	Low risk	No mention of pre-study publication protocol, but multi-centre trial would require explicit protocol for each centre
Other bias	Unclear risk	Study was ended prematurely, and such studies have been associated with inflated effect size (Bassler 2010)

Gattinoni 2001

Study characteristics	
Methods	Multi-centre, randomized trial over 34 consecutive months. Randomization to supine (n = 152) or prone (n = 152) position ventilation was done centrally by telephone based on a permuted block algorithm, allowing for stratification according to intensive care unit
Participants	304 mechanically ventilated patients with ALI or ARDS 214 males, 90 females Inclusion: PFR < 200 with PEEP > 5, or PFR < 300 with PEEP > 10, bilateral pulmonary infiltrates, pulmonary-capillary wedge pressure ≤ 18 mmHg or absence of clinical evidence of left atrial hypertension Exclusion: < 16 years old, cardiogenic pulmonary oedema, cerebral oedema or intracranial hypertension, proning contraindications or severe haemodynamic instability
Interventions	Participants randomly assigned to the prone group were maintained in the prone position continuously for ≥ 6 hours per day for 10 days Tidal volume: 10.3 mL/kg IBW (~ 95% CI 4.8 to 15.8 mL/kg IBW)
Outcomes	Primary: 10-day mortality (end of the prone period), mortality at discharge from ICU and 6 months post randomization Secondary: improvement in respiratory failure and organ dysfunction at 10 days
Notes	Twelve participants (7.9%) were crossed over from supine to prone position during the trial. 41 of 152 (27.0%) participants missed ≥ 1 scheduled proning sessions. Subgroup percentages were provided for

Gattinoni 2001 *(Continued)*

more severely ill participants, etc, but not numbers of participants. Possible selection reporting bias for subgroup cutoffs (e.g. PaO_2/FIO_2 quotient of 88 mmHg (11.7 kPa). Compare these results vs the cut-off of 100 mmHg (13.3 kPa) in their recent systematic review (Gattinoni 2010). No apparent loss to follow-up and apparent strict Intention-to-treat analysis with supplementary per-protocol analyses. Trial was discontinued early by investigators and data and monitoring safety board because of slow recruitment ascribed to increasing unwillingness of investigators to forgo the use of prone positioning.

Trial commenced in 1996, was completed in 1999 and was published in 2001

Mean of 32.9 hours prone per participant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization - central telephone service
Allocation concealment (selection bias)	Low risk	Nothing in text to suggest selection bias following randomization
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Risk of assessment bias different for different outcomes. Mortality has low risk of bias; other less well-defined outcomes have higher risk of outcome assessment bias. Pressure sore assessment was well described in this study
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat listed as method of analysis. No mention of participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No mention of pre-study publication protocol, but multi-centre trial would require explicit protocol for each centre. Possible bias in reporting post hoc analyses (e.g. outcomes of participants with PaO_2/FIO_2 quotient of 88 mmHg (11.7 kPa)
Other bias	Unclear risk	Study was ended prematurely; such studies have been associated with inflated effect size (Bassler 2010), although little signal of effect was evident

Girard 2014

Study characteristics

Methods	Further analysis of PROSEVA randomized controlled trial (Guerin 2013)
Participants	ARDS - American–European Consensus Conference criteria • Endotracheal intubation and mechanical ventilation for ARDS < 36 hours • Severe ARDS (defined as PaO_2:FIO_2 ratio < 150 mmHg, with $FIO_2 \geq 0.6$, PEEP ≥ 5 cm of water and tidal volume ~ 6 mL/kg ideal body weight • Confirmed after 12 to 24 hours of mechanical ventilation in the participating intensive care unit. Volume-controlled ventilation combined with PEEP table

Girard 2014 *(Continued)*

Interventions	Prone position for ≥ 16 hours/d vs semi recumbent position Tidal volume: 6.1 mL/kg IBW (~ 95% CI 4.9 to 7.3 mL/kg IBW)
Outcomes	Pressure ulcers (sores) using National Pressure Ulcer Advisory Panel's Updated Pressure Ulcer Staging System (NPAUP)
Notes	Provides additional information on a secondary outcome

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization - central
Allocation concealment (selection bias)	Low risk	Nothing in text to suggest post-randomization bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified. Some participants had treatment withdrawn. Prone 14/237 vs supine 30/229; bias regarding differential use of co-interventions is also possible (providing a treatment or withholding a treatment).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Investigators making assessments were not blinded but assessments were described as being standardized using the NPAUP scoring system..
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat listed as method for primary analysis. Eight participants from original cohort excluded (with explanation) from primary study. A further attrition of 10 patients described, 5 at randomization and five at day 7 (patients died or were discharged).
Selective reporting (reporting bias)	Low risk	Multi-centre trial - conduct and outcome measure likely agreed in advance
Other bias	Low risk	Low cross-over rate

Guerin 2004

Study characteristics

Methods	Prospective, unblinded, multi-centre, randomized controlled trial over 48 consecutive months. Randomization was computer-generated and was done separately for each ICU, with participants to supine (n = 378) or prone (n = 413) position ventilation
Participants	791 participants 593 males, 198 females Inclusion: mechanical ventilation (oral or nasal tracheal intubation or tracheostomy), $PaO_2/FIO_2 \leq 300$, ≥ 18 years of age, expected duration of mechanical ventilation > 48 hours, written informed consent from next of kin Exclusion: prone position for ≥ 6 hours per day in the 4 days preceding enrolment, contraindications to proning (ICP > 30 mmHg, cerebral perfusion < 60 mmHg, massive haemoptysis, bronchopleural fistula, tracheal surgery or sternotomy in the past 15 days, MAP < 65 with or without vasopressors, DVT, pace-

Guerin 2004 *(Continued)*

	maker inserted for fewer than 2 days, unstable fracture), therapeutic limitation indicated in the first 24 hours of ICU admission, high risk of death in the next 48 hours, chronic respiratory failure requiring mechanical ventilation and inclusion in another protocol with mortality as a primary endpoint
Interventions	Participants were randomly assigned to the supine or the prone group, in which they were placed in a prone position for ≥ 8 hours per day Tidal volume: 10.1 mL/kg IBW* (~ 95% CI 5.5 to 14.7 mL/kg IBW). *Imputed from measured body weight data (Bloomfield 2006)
Outcomes	Primary: 28-day mortality Secondary: 90-day mortality, duration of mechanical ventilation, rate of ventilator-associated pneumonia and oxygenation
Notes	VAP was well defined; 11 of 802 participants (1.4%) recruited, lost from final analysis Trial commenced in 1998, was completed in 2002 and was published in 2004 Mean of 36.9 hours prone per participant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Detailed methods provided
Allocation concealment (selection bias)	Low risk	Detailed methods provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Risk of assessment bias different for different outcomes. Mortality has low risk of bias; other less well-defined outcomes have higher risk of outcome assessment bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 of 802 participants (1.4%) recruited, lost from final analysis
Selective reporting (reporting bias)	Low risk	Multi-centre trial - conduct and outcome measure likely agreed in advance
Other bias	High risk	Very high cross-over rates reported: "At day 28, 83 (27.9%) of 297 patients in the supine group died, 36 (44.4%) of the 81 patients who had crossed over from the supine group died, 76 (31.3%) of 243 patients in the prone group died, and 58 (34.1%) of 170 patients who crossed over from the prone group died (P value = .85)". Overall, 32% of participants in the trial were crossed over to the opposite limb of the study. This level of cross-over events makes reported effects difficult to interpret. This level of selective cross-over of participants impairs the statistical power of the study and leads to bias against a positive result (Lipsey 1990; Porta 2008)

Guerin 2013

Study characteristics	
Methods	Multi-centre, randomized, controlled, open-label trial conducted in France and Spain
Participants	ARDS - American–European Consensus Conference criteria • Endotracheal intubation and mechanical ventilation for ARDS < 36 hours • Severe ARDS (defined as PaO_2:FIO_2 ratio < 150 mmHg, with FIO_2 ≥ 0.6, PEEP ≥ 5 cm of water and tidal volume ~ 6 mL/kg ideal body weight • Confirmed after 12 to 24 hours of mechanical ventilation in the participating intensive care unit. Volume-controlled ventilation combined with PEEP table
Interventions	Prone position for ≥ 16 hours/d vs semi recumbent position Tidal volume: 6.1 mL/kg IBW (~ 95% CI 4.9 to 7.3 mL/kg IBW)
Outcomes	Primary endpoint: 28-day all-cause mortality Secondary endpoints: mortality at day 90; rate of successful extubation; time to successful extubation; length of stay in the ICU; complications; use of non-invasive ventilation; tracheotomy rate; number of days free from organ dysfunction; and ventilator settings of arterial blood gases and respiratory system mechanics measurements during the first week after randomization
Notes	30 deaths in the supine group (n = 229) had an end-of-life decision; 14 deaths in the prone group (n = 237) had an end-of-life decision. Assist/control ventilation mode is not commonly utilized in Europe. PEEP table mandated high levels of PEEP. Improved oxygenation allowed reduction of these high levels - so differential PEEP reduction of mandated PEEP may be a potential mechanism of benefit (Soni 2008) that accentuates benefit of prone positioning in this study. 8 of 474 participants recruited (1.7%) were lost from the final analysis Trial commenced in 2008, was completed in 2011 and was published in 2013 Mean of 68 hours prone per participant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization - central
Allocation concealment (selection bias)	Low risk	Nothing in text to suggest post-randomization bias
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified. Some participants had treatment withdrawn. Prone 14/237 vs supine 30/229; bias regarding differential use of co-interventions is also possible (providing a treatment or withholding a treatment).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Risk of assessment bias different for different outcomes. Mortality has low risk of bias; other less well-defined outcomes have higher risk of outcome assessment bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat listed as method of analysis. Eight participants from original cohort excluded (with explanation)

Guerin 2013 *(Continued)*

Selective reporting (reporting bias)	Low risk	Multi-centre trial - conduct and outcome measure likely agreed in advance
Other bias	Low risk	Low cross-over rate

Leal 1997

Study characteristics	
Methods	Single-centre RCT, sequential sealed envelope allocation, no cross-overs
Participants	16* patients with ARDS (8 participants per group). PaO_2/FIO_2 quotient < 150 mmHg and diagnosis to enrolment time < 24 hours (additional information from Sud 2008a) *2 additional participants were included in the actual meeting presentation (made available in Microsoft PowerPoint™ slides by Dr Jan Friederich, Toronto, Canada)
Interventions	24 hours prone ventilation (fixed duration and single application only)
Outcomes	Mortality; complications; early effects on gas exchange Tidal volume not listed
Notes	Abstract and Microsoft PowerPoint presentation of original authors supplied by Dr Jan Friederich through Professor Brian Cuthbertson. Data limited. Outcomes assumed to be short-term data in line with physiological nature of the study. Although single application lasted for 24 hours, the total application time during mechanical ventilation in the ICU was therefore limited Trial commencement and finish dates not available; abstract published in 1997. 50% of participants placed prone had airway complications despite proning only once per study participant Mortality in original abstract occurred in 5 of 7 participants in each group. With the addition of 1 participant to each group, mortality became 5 of 8 for participants randomly assigned to prone vs 6 of 8 randomly assigned to supine. The investigation was short-term (72 hours), and mortality rates are assumed to be short-term Mean of 24 hours total prone per participant

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomization not stated
Allocation concealment (selection bias)	Low risk	Sequential sealed envelope allocation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Risk of assessment bias different for different outcomes. Mortality has low risk of bias; other less well-defined outcomes have higher risk of outcome assessment bias

Leal 1997 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Missing data not described. Small single-centre study; not able to assess risk of attrition bias
Selective reporting (reporting bias)	Unclear risk	No mention of pre-study publication protocol
Other bias	Low risk	No other bias identified

Mancebo 2006

Study characteristics	
Methods	Multi-centre, randomized controlled trial over 45 months. Randomization was computer-generated, assigning participants to the supine (n = 60) or the prone (n = 76) position group. Participants were enrolled within 48 hours of tracheal intubation for severe ARDS
Participants	136 participants 86 males, 50 females Inclusion: intubation, mechanical ventilation, > 18 years of age, ARDS (American-European Consensus Conference definition), diffuse bilateral infiltrates on chest x-ray Exclusion: > 48 hours since inclusion criteria were met, participation in other trials, pregnancy, systolic BP < 80 despite vasopressors, pelvic or spinal fracture, cranial trauma and/or clinical suspicion of raised ICP, considered moribund
Interventions	Participants were randomly assigned to the supine group or to the prone group, which received continuous prone position ventilation for 20 hours per day. Mechanical ventilation with volume assist-control mode Tidal volume: 10.6 mL/kg IBW* (~ 95% CI 6.5 to 14.6 mL/kg IBW) *Correction for use of measured body weight rather than IBW (Bloomfield 2006)
Outcomes	Primary: ICU mortality Secondary: hospital mortality, associated complications and length of stay
Notes	Study was prematurely stopped because of low participant recruitment. 5 participants crossed over to prone ventilation from original assignment. (All died.) High tidal volumes were used. Up to 10 mg/kg actual body weight was allowed in the protocol and maximum plateau pressures up to 40 cm H_2O. Some participants received tidal volumes in excess of 10 mL/kg and in excess of their 2 targets of 35 and 40 cm H_2O. (See supplement.) This decreases relevance to currently accepted targets of tidal volumes of 6 mL/kg ideal body weight and plateau pressures < 30 cm H_2O. 5 cross-overs from the supine group to the prone group were reported. 6 of 142 participants (4.2%) enrolled were lost after randomization Trial commenced in 1998, was completed in 2002 and was published in 2006 Mean of 171.7 hours prone per participant

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Mancebo 2006 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated random sequence
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Risk of assessment bias different for different outcomes. Mortality has low risk of bias; other less well-defined outcomes have higher risk of outcome assessment bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Six participants (4.2%) were not included in the final analysis: 3 because of lost forms, 2 because data were lacking and 1 as the result of transfer to a cardiac surgery centre for possible surgery
Selective reporting (reporting bias)	Low risk	No mention of pre-study publication protocol, but multi-centre trial would require an explicit protocol for each centre
Other bias	Unclear risk	Study was ended prematurely; such studies have been associated with inflated effect size (Bassler 2010)

Taccone 2009

Study characteristics	
Methods	Multi-centre, unblinded, randomized controlled trial. Randomization to the supine (n = 174) or the prone (n = 168) position group was computer-generated, and participants were stratified according to severity of hypoxaemia and participating centre. Prospective subgroup analysis defined the moderate subgroup as PaO_2/FIO_2 quotient of 100 to 200 mmHg, and severe as PaO_2/FIO_2 < 100 mmHg
Participants	342 participants 244 males, 98 females Inclusion: ARDS criteria (PFR ≤ 200 mmHg for PEEP 5 to 10 cm H_2O) Exclusion: < 16 yo, > 72 hours since diagnosis of ARDS, history of solid organ or bone marrow transplantation, contraindication to proning (raised ICP, spine/pelvic fracture)
Interventions	Participants were randomly assigned to supine or prone position ventilation, which required maintaining prone position ≥ 20 hours per day until resolution of ARDS or the end of the 28-day study period Tidal volume: 8.0 mL/kg IBW (~ 95% CI 4.7 to 11.3 mL/kg IBW)
Outcomes	Primary: 28-day all-cause mortality Secondary: 6-month and ICU discharge mortality, organ dysfunction, complication rate related to prone positioning
Notes	It is noted that more participants randomly assigned to prone ventilation received increased sedation or muscle relaxants. This co-intervention can improve survival (Papazian 2010)

Taccone 2009 *(Continued)*

Trial commenced in 2004, was completed in 2008 and was published in 2009. Participants were enrolled a median of 0 days (IQR 0 to 1) after mechanical ventilation. 20 participants (11.5%) randomly assigned to the supine position were crossed over to the prone group as rescue therapy for hypoxaemia. 34 participants (20.2%) assigned to prone did not receive the intervention but were included in the ITT analysis. Ventilator-associated pneumonia was not defined

Mean of 149.4 hours prone per participant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralized telephone randomization system
Allocation concealment (selection bias)	Low risk	Centralized telephone randomization system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Risk of assessment bias different for different outcomes. Mortality has low risk of bias; other less well-defined outcomes have higher risk of outcome assessment bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants in each group were lost to follow-up. All 4 were assumed alive for the follow-up period. 2 additional participants (1 per group) was ineligible; both were removed before protocol initiation
Selective reporting (reporting bias)	Low risk	Protocol published
Other bias	Unclear risk	11.5% of participants randomly assigned to supine position were crossed over to the prone position as part of the pre-defined rescue protocol. 34 participants (20.2%) assigned to prone did not receive intervention but were included in the ITT analysis

Voggenreiter 2005

Study characteristics

Methods	2 (trauma)-centre prospective randomized trial. Randomization assigned participants to supine (n = 19) or prone (n = 21) position group and was conducted centrally by telephone, using a permuted-block algorithm, allowing for stratification according to ICU, participant age, ISS, AIS-chest, AIS-head and interval between injury and randomization
Participants	40 participants 33 males, 7 females Inclusion: multiple trauma patients 18 to 80 years of age; ISS > 16; *modified* ALI/ARDS criteria (PaO_2/FIO_2 quotient for ALI or ARDS; "lung infiltrates"; and absence of evidence of left atrial hypertension) Exclusion: cardiogenic pulmonary oedema, cerebral oedema, ↑ ICP, other contraindications to prone (e.g. haemodynamic instability, unstable fracture)

Voggenreiter 2005 *(Continued)*

Interventions	Participants were randomly assigned to the supine or the prone ventilation group, in which participants were continuously maintained in the prone position ≥ 8 hours and for a maximum of 23 hours per day. Mean of 11 hours (SD 5) of prone applied, and applied on a mean of 7 (SD 4) occasions
Outcomes	Primary: duration of mechanical ventilation Secondary: days with ARDS (PaO_2:FIO_2 < 200), ALI (PaO_2:FIO_2 200 to 300); days with LIS > 2, course of PaO_2:FIO_2, Qs/Qt score, total static lung compliance, PIP, PEEP, LIS, TISS-28, SOFA score, sepsis, prevalence of pneumonia, mortality within the 90-day study period, complications/adverse events and ARDS following ALI
Notes	Participants in the supine limb received 3 times as many packed red cells (mean of 28.2 vs 9.5 packs of red cells per participant) (i.e. 19 more packs of red cells per participant, on average). Possible fluid overload and effects of RCC on infection and leucocytosis could confound pneumonia diagnosis. Neuromuscular blockers were used more in participants ventilated prone (7.8 days/patient vs 5.6 days/patient; P value = 0.06). Neuromuscular blockade is an intervention that could independently improve mortality (Papazian 2010) Trial commenced in 1999, was completed in 2001 and was published in 2005. A variety of modes of ventilation were used: BIPAP (n = 19), CPPV (n = 20) and SIMV (n = 1), but "lung protective strategy" was used. Actual data for tidal volumes are not available. Listed as enrolled < 48 hours from meeting criteria (Sud 2010). Pneumonia (VAP), new pneumonia within 90 days - reasonably well-defined criteria - but results could be affected by differential RCC transfusion, as noted above. No apparent loss to follow-up Mean of 77 hours prone per participant

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralized telephone randomization system
Allocation concealment (selection bias)	Low risk	Centralized telephone randomization system
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded, and assigned treatment readily identified
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Risk of assessment bias different for different outcomes. Mortality has low risk of bias; other less well-defined outcomes have higher risk of outcome assessment bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants lost to follow-up
Selective reporting (reporting bias)	Unclear risk	No published protocol. 2-centre study
Other bias	High risk	Markedly different red cell transfusion rates for 2 groups of participants (high risk). Sample size not predefined (unclear risk). Study was ended prematurely, and such studies have been associated with inflated effect size (Bassler 2010) (unclear risk)

AIS = Abbreviated injury scale; ALI = Acute lung injury; ARDS = Acute respiratory distress syndrome; BIPAP = Bi-phasic positive airways pressure; BP = Blood pressure; CAP = Community-acquired pneumonia; CO = Cardiac output; CPPV = Controlled positive-pressure ventilation; CT = Computed tomography; DVT = Deep venous thrombosis; IBW = Predicted ideal body weight; ICP = Intracranial pressure; ICU = Intensive care unit; ISS = Injury severity score; ITT = Intention-to-treat; IQR = Interquartile range; LIS = Lung injury score; MAP = Mean arterial pressure; n = number; NAECC = North American-European Consensus Criteria; NB = Note well; PEEP = Positive end-expiratory pressure; PFR = Pulmonary arterial-fractional inspired oxygen ratio; PIP = Peak inspiratory pressure; RCC = Red cell concentrate; RCT = Randomized controlled trial; SAPS = Simplified acute physiology score; SARS = Severe acute respiratory syndrome; SD = Standard deviation; SF-36 = Short Form-36; SGRQ = St George's Respiratory Questionnaire; SIMV = Synchronized intermittent mechanical ventilation; SOFA = Sequential organ failure assessment; TBI = Traumatic brain injury; TISS = Therapeutic intervention scoring system; VAP = Ventilator-associated pneumonia.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beuret 2002	The primary reason for use of mechanical ventilation in this cohort of patients was brain injury causing reduced level of consciousness (Glasgow Coma Scale of 9 or less). Such patients require intubation airway protection and mechanical ventilation to maintain target P_aCO_2. Brain injury in this study was as a result of trauma, intracranial haemorrhage, Ischaemic stroke, anoxic encephalopathy, intracranial infection and other miscellaneous causes of coma. Randomization to ventilation in the prone position was investigated as a means of prevention of hypoxaemic respiratory failure (as stated in the title of the study) and not as a treatment. Mean PaO_2/FIO_2 quotient exceeded 40 kPa (300 mmHg) in both groups which does not meet the criteria for even mild ARDS by The Berlin Criteria (ARDS definition workforce 2012). This study has been incorporated into three systematic reviews of prone positioning (Abroug 2008; Sud 2008;Sud 2010). Total hours prone for duration of study = 24 (4 hours for 6.0 days)
Cao 2014	No mention of randomization in text.
Charron 2011	Not a randomized controlled trial (retrospective analysis of database) but reconsidered because it was incorporated in to the cumulative meta-analysis of Yue et al (Yue 2017).
Cheng 2016	No mention of randomization in text. Primarily reports on physiological results from PiCCO monitor and some data derived from ventilator
Curley 2005	This study has been incorporated into other meta-analyses. However, the study population (n = 102) predominantly consisted of very young children, with 49% ≤ 2 years of age and 73% ≤ 8 years of age. Our protocol specifically excluded children (Bloomfield 2009) for several reasons listed in the text.
Demory 2007	Non-conventional ventilation employed: 12 hours of high-frequency oscillatory ventilation (HFOV) following 12 hours of conventional ventilation in the prone or the supine position. Non-conventional ventilation was specifically excluded from our protocol. Treatment interaction could not be excluded, as not a factorial design (Fleiss 1986; Friedman 1998). Total hours prone in study = 12 (12 hours prone for 1 day)
Li G 2015	The study is a retrospective analysis.
Li J 2015	Percussion/vibration was used as an intervention for prone position patients only. There is no indication of randomization, no mention how they performed prone position, how long, how often etc.
Papazian 2005	Non-conventional ventilation employed: comparison of non-conventional mechanical ventilation vs high-frequency oscillatory ventilation (HFOV) used in 12-hour protocol only Non-conventional ventilation was specifically excluded from our protocol. Treatment interaction could not be exclud-

Study	Reason for exclusion
	ed, as not a factorial design (Fleiss 1986; Friedman 1998). Total hours prone = 12 (12 hours prone for 1 day only)
Peng 2018	RCT with 2 interventions and 4 study limbs but short term physiological intervention with no mortality outcomes presented. We also note large baseline imbalances between groups (eg age and APACHE scores).
Wang 2015	Randomization is not mentioned in the text of this large study of 73 obstetric patients at high altitude who suffered severe pneumonia and underwent Caesarean Section (CS). The study was excluded because randomization is not specified.Thirty four patients received prone positioning.Mechanical ventilation occurred after the CS. Blood gas analysis and respiratory mechanics are reported as are duration of mechanical ventilation (6.3 days for prone position group and 10.2 days in control group) and the ICU length of stay (10.6 days in prone position group and 14.8 days in control group).
Watanabe 2002	Infusion of muscle relaxants given to prone participants only; this co-intervention has been associated with improved survival in patients with lung injury in some studies (Papazian 2010). Mortality outcomes not published
Yan 2015	Randomisation is not mentioned in text. There are no descriptions regarding prone positioning. Blood-gas analyses were their primary outcome.
Zhou 2014	RCT but supine positioning alone is compared with prone positioning together with an additional respiratory intervention (recruitment manoeuvres). Different sedation regime (bolus and infusions of midazolam) and neuromuscular blockers (vecuronium) employed in the prone position group during prone positioning.

HFOV = High-frequency oscillatory ventilation; n = number.

Characteristics of ongoing studies *[ordered by study ID]*

NCT03891212

Study name	The Effect of Prone Position Drainage on the Efficacy of Severe Pneumonia, a Multicenter Randomized Controlled Trial
Methods	Randomized controlled trial
Participants	Estimated number of participants = 500 **Inclusion Criteria:** • Age ≥18 years and ≤75 years, male or female • Weight ≥40 kg and ≤100 kg • Meet the diagnostic criteria for SP • Need invasive mechanical ventilation • Provide signed informed consent **Exclusion Criteria:** • Contraindication for prone positioning：a. Intracranial pressure >30 mm Hg or cerebral perfusion pressure <60 mmHg;b. Massive hemoptysis requiring an immediate surgical or interventional radiology procedure; c. Tracheal surgery or sternotomy during the previous 15 days;d. Serious facial trauma or facial surgery during the previous 15 days;e. Deep venous thrombosis treated for less than 2 days; f. Cardiac pacemaker inserted in the last 2 days;g. Unstable spine, femur, or pelvic fractures;h. Mean arterial pressure lower than 65 mm Hg;i. Pregnant women; j. Single anterior chest tube with air leaks.

NCT03891212 *(Continued)*

- Respiratory reason：a. Inhaled nitric oxide (NOi) or almitrine bismesylate use before inclusion;b. Use of extracorporeal membrane oxygenation (ECMO) before inclusion.
- Clinical context：a. Lung transplantation;b. Burns on more than 20 % of the body surface;c. Chronic respiratory failure requiring oxygen therapy or non-invasive ventilation(NIV);d. Underlying disease with a life expectancy of less than one year;e. NIV delivered for more than 24 hours before inclusion.
- Other non-inclusion criteria ：a. End-of-life decision before inclusion;b. Inclusion in another research protocol in the previous 30 days with mortality as the main end-point;c. Prone positioning before inclusion;d. Subject deprived of freedom, minor, subject under a legal protective measure;e. Opposition from next of kin.

Interventions	**Experimental:** Placed in prone position for at least 16 consecutive hours a day; **Control:** Placed in supine position for at least 16 consecutive hours
Outcomes	1. The changes in C-reactive protein [Time Frame: On the tenth day after hospitalization] 2. The changes in procalcitonin [Time Frame: On the tenth day after hospitalization] 3. The changes in d-dimer [Time Frame: On the tenth day after hospitalization] 4. Chest x-ray changes [Time Frame: On the tenth day after hospitalization] 5. Mortality rate after 28 days [Time Frame: 28 days after admission] 6. The time of total duration of ICU stay [Time Frame: 28 day] 7. The time of mechanical ventilation [Time Frame: 28 day] 8. mortality [Time Frame: 28 day] 9. The time of antibiotic use [Time Frame: 28 day] 10.The time of bacterial cultures becoming negative [Time Frame: 28 day] 11.Daily sputum drainage [Time Frame: On the tenth day after hospitalization]
Starting date	Not reported
Contact information	Pinhua Pan: pinhuapan668@126.com
Notes	

NCT04139733

Study name	Early Use of Prone Position in ECMO for Severe ARDS
Methods	Randomized single-blind parallel trial
Participants	Estimated number of participants = 110 Age: 18 years to 75 years **Inclusion Criteria:** 1. met the diagnostic criteria of Berlin definition for ARDS; 2. the cause of ARDS was determined as pneumonia； 3. patients had one of following criteria despite optimum mechanical ventilation (tidal volume 6ml/kg of PBM, PEEP≥10cmH2O, and FiO2≥0.8) and use of various rescue therapies (corticosteroids, recruitment manoeuvres, prone position, neuromuscular blockade, and high-frequency oscillatory ventilation): ratio of partial pressure of arterial oxygen (PaO2) to FiO2≤80 mm Hg, or an arterial blood pH <7.20 with a partial pressure of arterial carbon dioxide (PaCO2)>60mmHg, with respiratory rate increased to 35 breaths/min and keep a Pplat ≤30 cmH2O. **Exclusion Criteria:** 1. spinal instability；

NCT04139733 *(Continued)*

	2. elevated intracranial pressure; 3. facial/neck trauma; 4. recent sternotomy; 5. large ventral surface burn; 6. multiple trauma with unstabilized fractures; 7. severe hemodynamic instability; 8. massive hemoptysis; 9. high risk of requiring CPR or defibrillation;
Interventions	**Experimental:** Prone position within 6 hours after randomization. Prone position for at least conservative hours per days during a minimum number of days; **Control:** Conventional supine position ventilation, no prone position.
Outcomes	**Primary Outcome Measures:** 1. VV-ECMO duration time [Time Frame: After patients randomized grouping 30 days] a. From VV-ECMO establishment to weaning **Secondary Outcome Measures:** 1. 60-day mortality [Time Frame: After patients randomized grouping 60 days] a. Mortality after patients randomized grouping 60 days
Starting date	3 September 2020
Contact information	Rui Wang, Dr.; +8618601342030; xuanben1985@163.com
Notes	

NCT04607551

Study name	PRONing to Facilitate Weaning From ECMO in Patients With Refractory Acute Respiratory Distress Syndrome (PRONECMO)
Methods	Randomized open-label parallel assignment trial
Participants	Estimated number of participants = 170 Age: 18 Years to 75 Years **Inclusion Criteria:** 1. Severe ARDS refractory to conventional therapy placed on VV-ECMO support in the preceding 48h. 2. Obtain informed consent from a close relative or surrogate. According to the specifications of emergency consent, randomization without the close relative or surrogate consent could be performed.Close relative/surrogate/family consent will be asked as soon as possible. The patient will be asked to give his/her consent for the continuation of the trial when his/her condition will allow. 3. Social security registration **Exclusion Criteria:** 1. Age <18 and >75 2. Pregnancy and breastfeeding woman 3. Initiation of VV-ECMO >48 h 4. Resuscitation >10 minutes before ECMO 5. Irreversible neurological pathology 6. End-stage chronic lung disease

NCT04607551 *(Continued)*

7. ARDS secondary to an abdominal surgery
8. Contraindications for PP
9. Irreversible ARDS with no hope for lung function recovery
10. Patient moribund on the day of randomization, SAPS II >90
11. Liver cirrhosis (Child B or C)
12. Chronic renal failure requiring hemodialysis
13. Lung transplantation
14. Burns on more than 20 % of the body surface

Interventions	**Experimental:** Prone positioning - 4 to 5 persons required for the procedure, one of them being dedicated to the management of the head of the patient, the endotracheal tube, the jugular ECMO cannula and the ventilator lines and another dedicated to the femoral ECMO cannula. The person at the head of the bed will coordinate the steps. The other persons will stand at each side of the bed. The direction of the rotation will be decided giving priority to the side of the central venous lines. The length of vascular and ventilator lines will be checked for appropriateness, the endotracheal tube and gastric tube will be secured, and the patient's knees, forehead, chest, and iliac crests will be protected using adhesive pads. The patient will be then moved along the horizontal plane to the opposite side of the bed selected for the direction of rotation. Patients will be proned at least four times during the first days on ECMO. Each prone session will stand for at least 16 hours; **Control:** Supine position- Patients assigned to supine will remain in a semi-recumbent position.
Outcomes	**Primary Outcome Measures:** 1. Time to successful ECMO weaning within the 60 days following randomization [Time Frame: Day 60] a. ECMO weaning will be considered successful only if the patient survives without ECMO, or lung transplantation 30 days after ECMO removal. Thus all ECMO weaning from randomization to 60 days after randomization will be considered, and the qualification for successful ECMO weaning will need 30 days of follow-up after ECMO removal (thus until day 90 after randomization for an ECMO weaning performed on day 60 after randomization). b. Patients still under ECMO 60 days after randomization will be censored. c. A protocolized management regarding weaning of VV-ECMO will be applied to both groups d. The planned analysis will model the risk of successful ECMO ablation in the presence of competing risk (death and weaning failure). **Secondary Outcome Measures:** 1. Mortality [Time Frame: Day 7, Day 14, Day 30, Day 60, Day 90] 2. Total duration of ECMO support [Time Frame: Between inclusion visit (day 1) and day 60, Between inclusion visit and day 90,] 3. Number of ECMO-free days [Time Frame: Between day 1 and Day 60/Day 90] 4. Duration of ICU stay [Time Frame: Between day 1 and Day 60/Day 90] 5. Duration of hospitalization [Time Frame: Between day 1 and Day 60/Day 90] 6. Time to improvement in respiratory respiratory system compliance [Time Frame: Through study completion] 7. Time to get a respiratory system compliance > 30 mL/cmH2O [Time Frame: Between day 1 and Day 60/Day 90] 8. Number of days with organ failure [Time Frame: Between day 1 and Day 60] a. defined by SOFA score 9. Number of days alive without organ failure [Time Frame: Between day 1 and Day 60] a. defined by SOFA score 10. Number of ventilator assist pneumonia, bacteriemia, and cannula infection episodes [Time Frame: Through study completion] 11. Number of days with hemodynamic support with catecholamines [Time Frame: Between day 1 and Day 60] 12. Number of days alive without hemodynamic support with catecholamines [Time Frame: Between day 1 and Day 60]

NCT04607551 *(Continued)*	13.Number of days with mechanical ventilation [Time Frame: Between day 1 and Day 60] 14.Number of days alive without mechanical ventilation [Time Frame: Between day 1 and Day 60] 15.Acute core pulmonale diagnosis [Time Frame: Between day 1 and D60] a. by echocardiography 16.Need for VA ECMO [Time Frame: Between day 1 and Day 60/Day 90] 17.Incidence of intervention side effects [Time Frame: Between day 1 and Day 60] a. (accidental decannulation, non-scheduled extubation during the procedure, hemoptysis, endotracheal tube obstruction, cardiac arrest, pressure sore, and death 18.Occurrence of refractory hypoxemia on ECMO [Time Frame: Through study completion, an average of 3 months]
Starting date	November 2020
Contact information	Matthieu SCHMIDT, MD; + 33 1 42 16 29 37; matthieu.schmidt@aphp.fr
Notes	

DATA AND ANALYSES

Comparison 1. Mortality

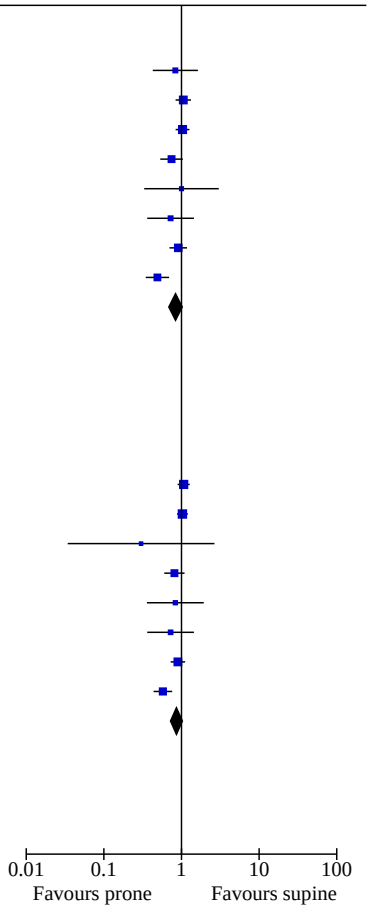
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Mortality	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1.1 Short-term mortality	8	2117	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.69, 1.02]
1.1.2 Longer-term mortality	8	2140	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.72, 1.03]
1.2 Sub-group analysis (SGA) of mortality < 16 hours/d prone	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2.1 Short-term mortality	2	1095	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.89, 1.21]
1.2.2 Longer-term mortality	3	1135	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.92, 1.17]
1.3 SGA of mortality prone ≥ 16 hours/d	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.3.1 Short-term mortality	6	1022	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.58, 0.93]
1.3.2 Longer-term mortality prone	5	1005	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.61, 0.99]
1.4 SGA of mortality: enrolled ≤ 48 hours after entry criteria met/ventilation	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4.1 Short-term mortality	5	1000	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.56, 0.93]
1.4.2 Longer-term mortality	5	1024	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.59, 0.94]
1.5 SGA of mortality: enrolled > 48 hours after entry criteria met/ ventilation	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.5.1 Short-term mortality	3	1117	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.89, 1.21]
1.5.2 Longer-term mortality	3	1116	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.17]
1.6 SGA of severe hypoxaemia at entry	8		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.6.1 Short-term mortality	6	744	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.70, 0.95]
1.6.2 Longer-term mortality	7	977	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.65, 0.92]
1.7 SGA of less severe hypoxaemia at entry	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.7.1 Short-term mortality	4	1095	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.87, 1.21]
1.7.2 Longer-term mortality	6	1108	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.93, 1.21]
1.8 SGA of SAPS II ≤ 49/≥ 50: short-term mortality	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.8.1 SAPS II ≤ 49	2	327	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.45, 1.60]
1.8.2 SAPS II ≥ 50	2	113	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.25, 1.40]
1.9 SGA of low tidal volume (mean 6 to 8 mL/kg IBW)	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.9.1 Short-term mortality	3	830	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.43, 1.20]
1.9.2 Longer-term mortality	5	911	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.55, 0.96]
1.10 SGA of high tidal volume (> 8 mL/kg IBW)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.10.1 Short-term mortality	3	1231	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.86, 1.14]
1.10.2 Longer-term mortality	3	1231	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.90, 1.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.11 SGA of ARDS only	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.11.1 Short-term mortality	7	1326	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.63, 1.00]
1.11.2 Longer-term mortality	8	1758	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.71, 1.01]

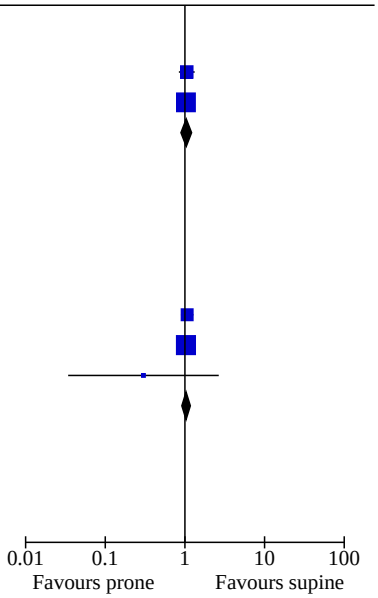
Analysis 1.1. Comparison 1: Mortality, Outcome 1: Mortality

Study or Subgroup	Prone group Events	Prone group Total	Supine group Events	Supine group Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Short-term mortality						
Leal 1997	5	8	6	8	6.5%	0.83 [0.43 , 1.63]
Gattinoni 2001	77	152	73	152	18.7%	1.05 [0.84 , 1.32]
Guerin 2004	134	413	119	378	19.6%	1.03 [0.84 , 1.26]
Mancebo 2006	33	76	35	60	14.6%	0.74 [0.53 , 1.04]
Chan 2007	4	11	4	11	2.9%	1.00 [0.33 , 3.02]
Fernandez 2008	8	21	10	19	6.2%	0.72 [0.36 , 1.45]
Taccone 2009	64	168	73	174	17.4%	0.91 [0.70 , 1.18]
Guerin 2013	38	237	75	229	14.2%	0.49 [0.35 , 0.69]
Subtotal (95% CI)		**1086**		**1031**	**100.0%**	**0.84 [0.69 , 1.02]**
Total events:	363		395			
Heterogeneity: Tau² = 0.04; Chi² = 17.29, df = 7 (P = 0.02); I² = 60%						
Test for overall effect: Z = 1.74 (P = 0.08)						
1.1.2 Longer-term mortality						
Gattinoni 2001	96	152	90	152	20.3%	1.07 [0.89 , 1.28]
Guerin 2004	179	413	159	377	21.1%	1.03 [0.87 , 1.21]
Voggenreiter 2005	1	21	3	19	0.6%	0.30 [0.03 , 2.66]
Mancebo 2006	38	76	37	60	14.7%	0.81 [0.60 , 1.10]
Chan 2007	5	11	6	11	3.7%	0.83 [0.36 , 1.94]
Fernandez 2008	8	21	10	19	5.2%	0.72 [0.36 , 1.45]
Taccone 2009	79	168	91	174	18.6%	0.90 [0.73 , 1.11]
Guerin 2013	56	237	94	229	15.7%	0.58 [0.44 , 0.76]
Subtotal (95% CI)		**1099**		**1041**	**100.0%**	**0.86 [0.72 , 1.03]**
Total events:	462		490			
Heterogeneity: Tau² = 0.03; Chi² = 18.05, df = 7 (P = 0.01); I² = 61%						
Test for overall effect: Z = 1.67 (P = 0.10)						



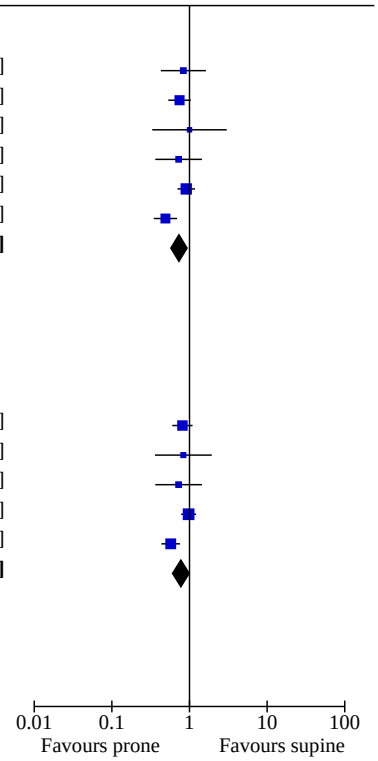
Analysis 1.2. Comparison 1: Mortality, Outcome 2: Sub-group analysis (SGA) of mortality < 16 hours/d prone

Study or Subgroup	Prone group Events	Total	Supine group Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Short-term mortality						
Gattinoni 2001	77	152	73	152	37.0%	1.05 [0.84 , 1.32]
Guerin 2004	134	413	119	378	63.0%	1.03 [0.84 , 1.26]
Subtotal (95% CI)		**565**		**530**	**100.0%**	**1.04 [0.89 , 1.21]**
Total events:	211		192			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.50 (P = 0.62)						
1.1.2 Longer-term mortality						
Gattinoni 2001	96	152	90	152	34.7%	1.07 [0.89 , 1.28]
Guerin 2004	179	413	159	378	64.1%	1.03 [0.88 , 1.21]
Voggenreiter 2005	1	21	3	19	1.2%	0.30 [0.03 , 2.66]
Subtotal (95% CI)		**586**		**549**	**100.0%**	**1.03 [0.92 , 1.17]**
Total events:	276		252			
Heterogeneity: Chi² = 1.35, df = 2 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						



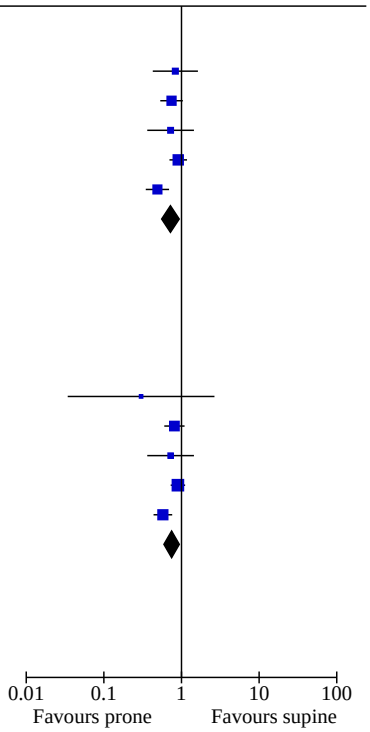
Analysis 1.3. Comparison 1: Mortality, Outcome 3: SGA of mortality prone ≥ 16 hours/d

Study or Subgroup	Prone group Events	Total	Supine group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Short-term mortality						
Leal 1997	5	8	6	8	10.0%	0.83 [0.43 , 1.63]
Mancebo 2006	33	76	35	60	23.9%	0.74 [0.53 , 1.04]
Chan 2007	4	11	4	11	4.3%	1.00 [0.33 , 3.02]
Fernandez 2008	8	21	10	19	9.5%	0.72 [0.36 , 1.45]
Taccone 2009	64	168	73	174	29.2%	0.91 [0.70 , 1.18]
Guerin 2013	38	237	75	229	23.2%	0.49 [0.35 , 0.69]
Subtotal (95% CI)		**521**		**501**	**100.0%**	**0.73 [0.58 , 0.93]**
Total events:	152		203			
Heterogeneity: Tau² = 0.03; Chi² = 8.49, df = 5 (P = 0.13); I² = 41%						
Test for overall effect: Z = 2.56 (P = 0.01)						
1.1.2 Longer-term mortality prone						
Mancebo 2006	38	76	37	60	25.5%	0.81 [0.60 , 1.10]
Chan 2007	5	11	6	11	7.1%	0.83 [0.36 , 1.94]
Fernandez 2008	8	21	10	19	9.7%	0.72 [0.36 , 1.45]
Taccone 2009	79	168	84	174	30.8%	0.97 [0.78 , 1.22]
Guerin 2013	56	237	94	228	27.0%	0.57 [0.43 , 0.76]
Subtotal (95% CI)		**513**		**492**	**100.0%**	**0.77 [0.61 , 0.99]**
Total events:	186		231			
Heterogeneity: Tau² = 0.04; Chi² = 8.89, df = 4 (P = 0.06); I² = 55%						
Test for overall effect: Z = 2.04 (P = 0.04)						



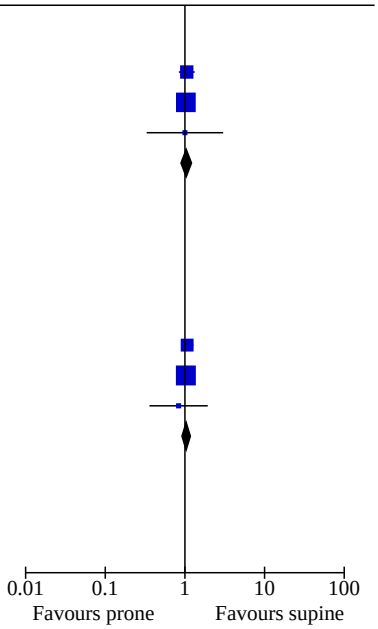
Analysis 1.4. Comparison 1: Mortality, Outcome 4: SGA of mortality: enrolled ≤ 48 hours after entry criteria met/ventilation

Study or Subgroup	Prone group Events	Prone group Total	Supine group Events	Supine group Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Short-term mortality						
Leal 1997	5	8	6	8	11.1%	0.83 [0.43 , 1.63]
Mancebo 2006	33	76	35	60	24.8%	0.74 [0.53 , 1.04]
Fernandez 2008	8	21	10	19	10.6%	0.72 [0.36 , 1.45]
Taccone 2009	64	168	73	174	29.5%	0.91 [0.70 , 1.18]
Guerin 2013	38	237	75	229	24.1%	0.49 [0.35 , 0.69]
Subtotal (95% CI)		**510**		**490**	**100.0%**	**0.72 [0.56 , 0.93]**
Total events:	148		199			
Heterogeneity: Tau² = 0.04; Chi² = 8.21, df = 4 (P = 0.08); I² = 51%						
Test for overall effect: Z = 2.47 (P = 0.01)						
1.1.2 Longer-term mortality						
Voggenreiter 2005	1	21	3	19	1.1%	0.30 [0.03 , 2.66]
Mancebo 2006	38	76	37	60	26.7%	0.81 [0.60 , 1.10]
Fernandez 2008	8	21	10	19	8.9%	0.72 [0.36 , 1.45]
Taccone 2009	79	168	91	174	34.6%	0.90 [0.73 , 1.11]
Guerin 2013	56	237	94	229	28.7%	0.58 [0.44 , 0.76]
Subtotal (95% CI)		**523**		**501**	**100.0%**	**0.75 [0.59 , 0.94]**
Total events:	182		235			
Heterogeneity: Tau² = 0.03; Chi² = 7.37, df = 4 (P = 0.12); I² = 46%						
Test for overall effect: Z = 2.52 (P = 0.01)						



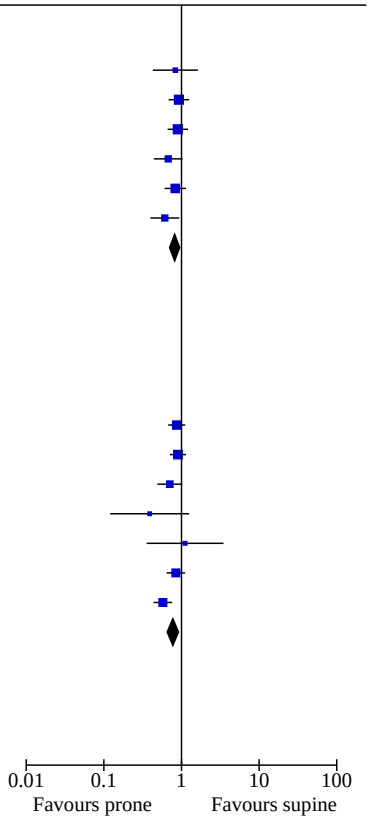
Analysis 1.5. Comparison 1: Mortality, Outcome 5: SGA of mortality: enrolled > 48 hours after entry criteria met/ventilation

Study or Subgroup	Prone group Events	Prone group Total	Supine group Events	Supine group Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Short-term mortality						
Gattinoni 2001	77	152	73	152	36.3%	1.05 [0.84 , 1.32]
Guerin 2004	134	413	119	378	61.7%	1.03 [0.84 , 1.26]
Chan 2007	4	11	4	11	2.0%	1.00 [0.33 , 3.02]
Subtotal (95% CI)		**576**		**541**	**100.0%**	**1.04 [0.89 , 1.21]**
Total events:	215		196			
Heterogeneity: Chi² = 0.03, df = 2 (P = 0.99); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.62)						
1.1.2 Longer-term mortality						
Gattinoni 2001	96	152	90	152	34.3%	1.07 [0.89 , 1.28]
Guerin 2004	179	413	159	377	63.4%	1.03 [0.87 , 1.21]
Chan 2007	5	11	6	11	2.3%	0.83 [0.36 , 1.94]
Subtotal (95% CI)		**576**		**540**	**100.0%**	**1.04 [0.92 , 1.17]**
Total events:	280		255			
Heterogeneity: Chi² = 0.37, df = 2 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.58 (P = 0.56)						



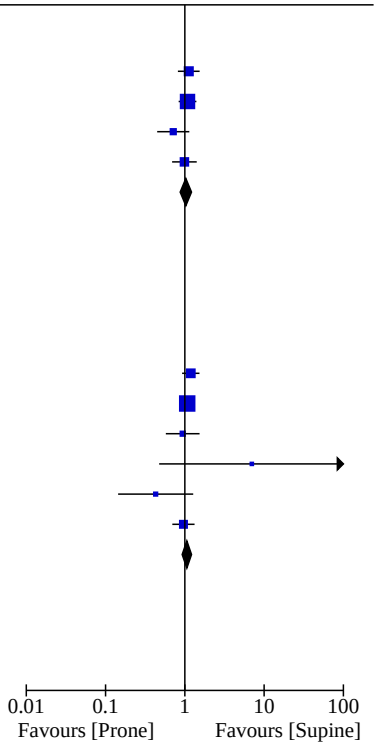
Analysis 1.6. Comparison 1: Mortality, Outcome 6: SGA of severe hypoxaemia at entry

Study or Subgroup	Prone group Events	Total	Supine group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Short-term mortality						
Leal 1997	5	8	6	8	5.0%	0.83 [0.43 , 1.63]
Gattinoni 2001	32	53	30	46	24.3%	0.93 [0.68 , 1.25]
Guerin 2004	43	90	40	75	24.4%	0.90 [0.66 , 1.21]
Mancebo 2006	19	43	19	29	12.2%	0.67 [0.44 , 1.03]
Taccone 2009	34	74	42	76	21.9%	0.83 [0.60 , 1.14]
Guerin 2013	25	121	41	121	12.2%	0.61 [0.40 , 0.94]
Subtotal (95% CI)		**389**		**355**	**100.0%**	**0.82 [0.70 , 0.95]**
Total events:	158		178			
Heterogeneity: Tau² = 0.00; Chi² = 3.70, df = 5 (P = 0.59); I² = 0%						
Test for overall effect: Z = 2.67 (P = 0.008)						
1.1.2 Longer-term mortality						
Gattinoni 2001	35	53	35	46	21.2%	0.87 [0.67 , 1.12]
Guerin 2004	53	90	49	75	22.3%	0.90 [0.71 , 1.14]
Mancebo 2006	22	43	21	29	13.7%	0.71 [0.49 , 1.02]
Chan 2007	2	6	6	7	2.0%	0.39 [0.12 , 1.25]
Fernandez 2008	5	9	2	4	2.1%	1.11 [0.36 , 3.48]
Taccone 2009	39	73	48	76	19.5%	0.85 [0.64 , 1.11]
Guerin 2013	56	237	94	229	19.3%	0.58 [0.44 , 0.76]
Subtotal (95% CI)		**511**		**466**	**100.0%**	**0.77 [0.65 , 0.92]**
Total events:	212		255			
Heterogeneity: Tau² = 0.02; Chi² = 9.81, df = 6 (P = 0.13); I² = 39%						
Test for overall effect: Z = 2.99 (P = 0.003)						



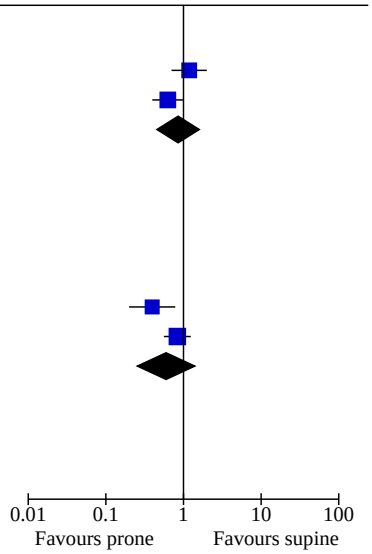
Analysis 1.7. Comparison 1: Mortality, Outcome 7: SGA of less severe hypoxaemia at entry

Study or Subgroup	Prone group Events	Total	Supine group Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Short-term mortality						
Gattinoni 2001	45	99	43	106	23.0%	1.12 [0.82 , 1.54]
Guerin 2004	91	323	79	303	45.1%	1.08 [0.84 , 1.40]
Mancebo 2006	18	43	17	29	11.2%	0.71 [0.45 , 1.14]
Taccone 2009	36	94	38	98	20.6%	0.99 [0.69 , 1.41]
Subtotal (95% CI)		**559**		**536**	**100.0%**	**1.03 [0.87 , 1.21]**
Total events:	190		177			
Heterogeneity: Chi² = 2.83, df = 3 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.35 (P = 0.73)						
1.1.2 Longer-term mortality						
Gattinoni 2001	57	95	52	103	21.7%	1.19 [0.92 , 1.53]
Guerin 2004	126	323	110	302	49.5%	1.07 [0.88 , 1.31]
Mancebo 2006	16	33	16	31	7.2%	0.94 [0.58 , 1.53]
Chan 2007	3	4	0	4	0.2%	7.00 [0.47 , 103.27]
Fernandez 2008	3	12	7	12	3.0%	0.43 [0.14 , 1.28]
Taccone 2009	40	93	43	96	18.4%	0.96 [0.70 , 1.33]
Subtotal (95% CI)		**560**		**548**	**100.0%**	**1.06 [0.93 , 1.21]**
Total events:	245		228			
Heterogeneity: Chi² = 5.93, df = 5 (P = 0.31); I² = 16%						
Test for overall effect: Z = 0.84 (P = 0.40)						



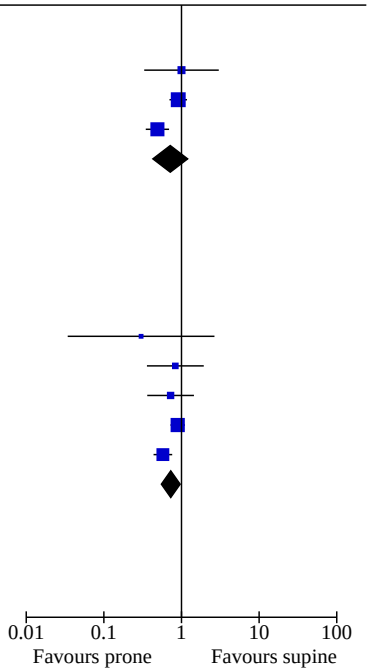
Analysis 1.8. Comparison 1: Mortality, Outcome 8: SGA of SAPS II ≤ 49/≥ 50: short-term mortality

Study or Subgroup	Prone group Events	Total	Supine group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 SAPS II ≤ 49						
Gattinoni 2001	23	105	22	119	48.1%	1.18 [0.70 , 2.00]
Mancebo 2006	18	54	26	49	51.9%	0.63 [0.40 , 1.00]
Subtotal (95% CI)		**159**		**168**	**100.0%**	**0.85 [0.45 , 1.60]**
Total events:	41		48			
Heterogeneity: Tau² = 0.14; Chi² = 3.26, df = 1 (P = 0.07); I² = 69%						
Test for overall effect: Z = 0.50 (P = 0.62)						
1.1.2 SAPS II ≥ 50						
Gattinoni 2001	9	47	16	33	44.7%	0.39 [0.20 , 0.78]
Mancebo 2006	15	22	9	11	55.3%	0.83 [0.56 , 1.24]
Subtotal (95% CI)		**69**		**44**	**100.0%**	**0.60 [0.25 , 1.40]**
Total events:	24		25			
Heterogeneity: Tau² = 0.30; Chi² = 4.68, df = 1 (P = 0.03); I² = 79%						
Test for overall effect: Z = 1.19 (P = 0.24)						



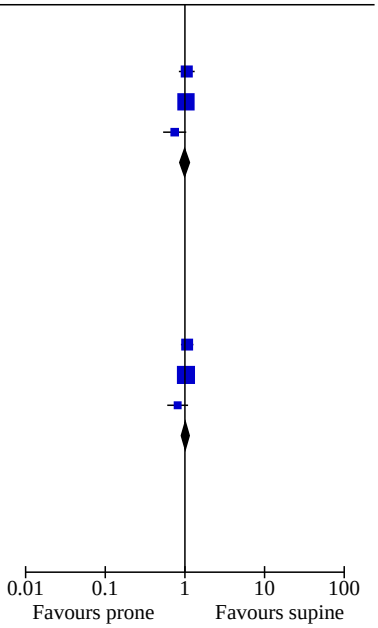
Analysis 1.9. Comparison 1: Mortality, Outcome 9: SGA of low tidal volume (mean 6 to 8 mL/kg IBW)

Study or Subgroup	Prone group Events	Total	Supine group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Short-term mortality						
Chan 2007	4	11	4	11	15.1%	1.00 [0.33 , 3.02]
Taccone 2009	64	168	73	174	44.2%	0.91 [0.70 , 1.18]
Guerin 2013	38	237	75	229	40.7%	0.49 [0.35 , 0.69]
Subtotal (95% CI)		**416**		**414**	**100.0%**	**0.72 [0.43 , 1.20]**
Total events:	106		152			
Heterogeneity: Tau² = 0.14; Chi² = 8.35, df = 2 (P = 0.02); I² = 76%						
Test for overall effect: Z = 1.27 (P = 0.20)						
1.1.2 Longer-term mortality						
Voggenreiter 2005	1	21	3	19	1.6%	0.30 [0.03 , 2.66]
Chan 2007	5	11	6	11	9.1%	0.83 [0.36 , 1.94]
Fernandez 2008	8	21	10	19	12.5%	0.72 [0.36 , 1.45]
Taccone 2009	79	169	91	174	41.3%	0.89 [0.72 , 1.11]
Guerin 2013	56	237	94	229	35.5%	0.58 [0.44 , 0.76]
Subtotal (95% CI)		**459**		**452**	**100.0%**	**0.73 [0.55 , 0.96]**
Total events:	149		204			
Heterogeneity: Tau² = 0.04; Chi² = 7.05, df = 4 (P = 0.13); I² = 43%						
Test for overall effect: Z = 2.25 (P = 0.02)						



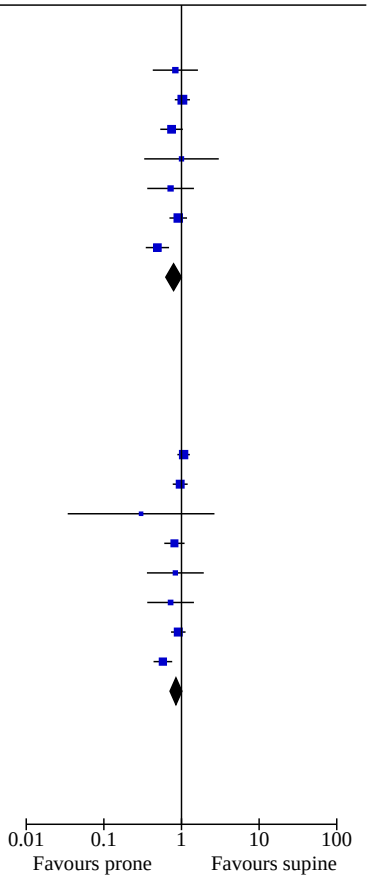
Analysis 1.10. Comparison 1: Mortality, Outcome 10: SGA of high tidal volume (> 8 mL/kg IBW)

Study or Subgroup	Prone group Events	Total	Supine group Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Short-term mortality						
Gattinoni 2001	77	152	73	152	30.9%	1.05 [0.84 , 1.32]
Guerin 2004	134	413	119	378	52.6%	1.03 [0.84 , 1.26]
Mancebo 2006	33	76	35	60	16.5%	0.74 [0.53 , 1.04]
Subtotal (95% CI)		**641**		**590**	**100.0%**	**0.99 [0.86 , 1.14]**
Total events:	244		227			
Heterogeneity: Chi² = 3.25, df = 2 (P = 0.20); I² = 38%						
Test for overall effect: Z = 0.13 (P = 0.90)						
1.1.2 Longer-term mortality						
Gattinoni 2001	96	152	90	152	30.3%	1.07 [0.89 , 1.28]
Guerin 2004	179	413	159	378	55.8%	1.03 [0.88 , 1.21]
Mancebo 2006	38	76	37	60	13.9%	0.81 [0.60 , 1.10]
Subtotal (95% CI)		**641**		**590**	**100.0%**	**1.01 [0.90 , 1.13]**
Total events:	313		286			
Heterogeneity: Chi² = 2.47, df = 2 (P = 0.29); I² = 19%						
Test for overall effect: Z = 0.19 (P = 0.85)						



Analysis 1.11. Comparison 1: Mortality, Outcome 11: SGA of ARDS only

Study or Subgroup	Prone group Events	Total	Supine group Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Short-term mortality						
Leal 1997	5	8	6	8	8.4%	0.83 [0.43 , 1.63]
Gattinoni 2001	77	152	75	152	22.8%	1.03 [0.82 , 1.29]
Mancebo 2006	33	76	35	60	18.1%	0.74 [0.53 , 1.04]
Chan 2007	4	11	4	11	3.8%	1.00 [0.33 , 3.02]
Fernandez 2008	8	21	10	19	8.0%	0.72 [0.36 , 1.45]
Taccone 2009	64	168	73	174	21.3%	0.91 [0.70 , 1.18]
Guerin 2013	38	237	75	229	17.6%	0.49 [0.35 , 0.69]
Subtotal (95% CI)		**673**		**653**	**100.0%**	**0.79 [0.63 , 1.00]**
Total events:	229		278			
Heterogeneity: Tau² = 0.05; Chi² = 13.90, df = 6 (P = 0.03); I² = 57%						
Test for overall effect: Z = 2.00 (P = 0.05)						
1.1.2 Longer-term mortality						
Gattinoni 2001	92	148	87	149	20.9%	1.06 [0.88 , 1.28]
Guerin 2004	98	230	81	183	19.0%	0.96 [0.77 , 1.20]
Voggenreiter 2005	1	21	3	19	0.6%	0.30 [0.03 , 2.66]
Mancebo 2006	38	76	37	60	15.1%	0.81 [0.60 , 1.10]
Chan 2007	5	11	6	11	3.7%	0.83 [0.36 , 1.94]
Fernandez 2008	8	21	10	19	5.2%	0.72 [0.36 , 1.45]
Taccone 2009	79	168	91	176	19.3%	0.91 [0.73 , 1.13]
Guerin 2013	56	237	94	229	16.2%	0.58 [0.44 , 0.76]
Subtotal (95% CI)		**912**		**846**	**100.0%**	**0.85 [0.71 , 1.01]**
Total events:	377		409			
Heterogeneity: Tau² = 0.03; Chi² = 15.84, df = 7 (P = 0.03); I² = 56%						
Test for overall effect: Z = 1.85 (P = 0.07)						



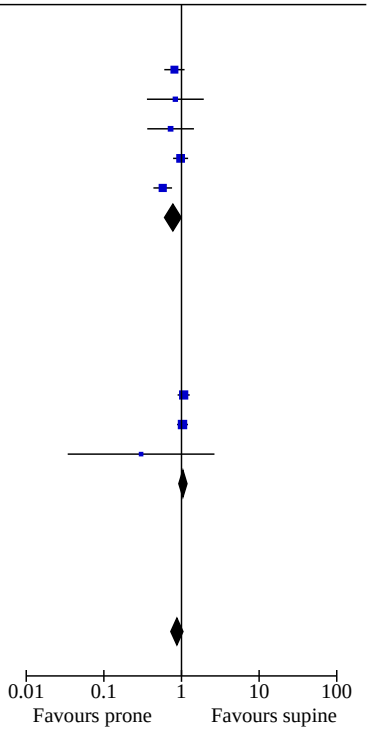
Comparison 2. Intervention comparisons and interactions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Longer duration vs shorter duration of proning: longer-term mortality	8	2140	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.73, 1.04]
2.1.1 > 16 hours	5	1005	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.61, 0.99]
2.1.2 ≤ 16 hours prone	3	1135	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.92, 1.18]
2.2 Early enrolment vs later enrolment to intervention: longer-term mortality	8	2140	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.72, 1.03]
2.2.2 Late enrolment > 48 hours	3	1116	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.92, 1.17]
2.2.3 Early enrolment ≤ 48 hours	5	1024	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.59, 0.94]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 Severe vs less-severe hypoxaemia: longer-term mortality	7	2085	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.03]
2.3.1 Severe hypoxaemia	7	977	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.65, 0.92]
2.3.2 Less severe hypoxaemia	6	1108	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.92, 1.26]
2.4 Lower tidal volume (TV) ventilation vs higher TV ventilation: longer-term mortality	8	2183	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.72, 1.01]
2.4.1 Lower TV - mean 6 to 8 mL/kg IBW	5	911	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.55, 0.96]
2.4.2 High TV - mean > 8 mL/kg IBW	4	1272	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.88, 1.12]

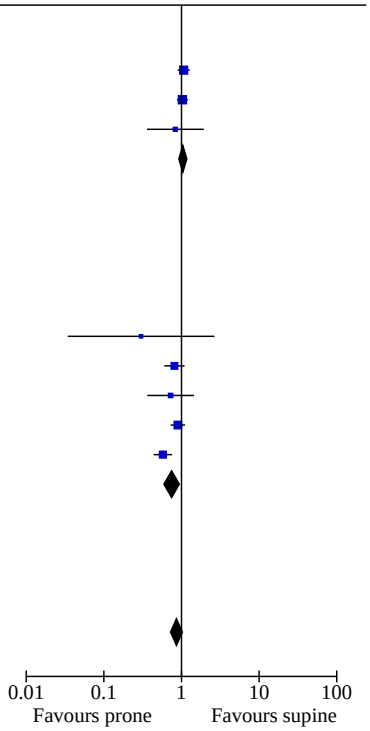
Analysis 2.1. Comparison 2: Intervention comparisons and interactions, Outcome 1: Longer duration vs shorter duration of proning: longer-term mortality

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 > 16 hours						
Mancebo 2006	38	76	37	60	14.8%	0.81 [0.60 , 1.10]
Chan 2007	5	11	6	11	3.8%	0.83 [0.36 , 1.94]
Fernandez 2008	8	21	10	19	5.3%	0.72 [0.36 , 1.45]
Taccone 2009	79	168	84	174	18.3%	0.97 [0.78 , 1.22]
Guerin 2013	56	237	94	228	15.8%	0.57 [0.43 , 0.76]
Subtotal (95% CI)		**513**		**492**	**58.1%**	**0.77 [0.61 , 0.99]**
Total events:	186		231			
Heterogeneity: Tau² = 0.04; Chi² = 8.89, df = 4 (P = 0.06); I² = 55%						
Test for overall effect: Z = 2.04 (P = 0.04)						
2.2.2 ≤ 16 hours prone						
Gattinoni 2001	96	152	90	152	20.2%	1.07 [0.89 , 1.28]
Guerin 2004	179	413	159	378	21.0%	1.03 [0.88 , 1.21]
Voggenreiter 2005	1	21	3	19	0.7%	0.30 [0.03 , 2.66]
Subtotal (95% CI)		**586**		**549**	**41.9%**	**1.04 [0.92 , 1.18]**
Total events:	276		252			
Heterogeneity: Tau² = 0.00; Chi² = 1.35, df = 2 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**1099**		**1041**	**100.0%**	**0.87 [0.73 , 1.04]**
Total events:	462		483			
Heterogeneity: Tau² = 0.03; Chi² = 18.48, df = 7 (P = 0.010); I² = 62%						
Test for overall effect: Z = 1.49 (P = 0.13)						
Test for subgroup differences: Chi² = 4.54, df = 1 (P = 0.03), I² = 78.0%						



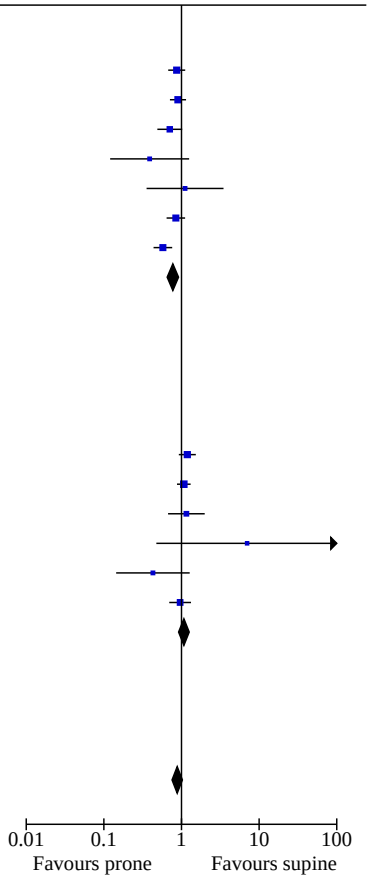
Analysis 2.2. Comparison 2: Intervention comparisons and interactions, Outcome 2: Early enrolment vs later enrolment to intervention: longer-term mortality

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.2 Late enrolment > 48 hours						
Gattinoni 2001	96	152	90	152	20.3%	1.07 [0.89 , 1.28]
Guerin 2004	179	413	159	377	21.1%	1.03 [0.87 , 1.21]
Chan 2007	5	11	6	11	3.7%	0.83 [0.36 , 1.94]
Subtotal (95% CI)		**576**		**540**	**45.2%**	**1.04 [0.92 , 1.17]**
Total events:	280		255			
Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 2 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.65 (P = 0.52)						
2.2.3 Early enrolment ≤ 48 hours						
Voggenreiter 2005	1	21	3	19	0.6%	0.30 [0.03 , 2.66]
Mancebo 2006	38	76	37	60	14.7%	0.81 [0.60 , 1.10]
Fernandez 2008	8	21	10	19	5.2%	0.72 [0.36 , 1.45]
Taccone 2009	79	168	91	174	18.6%	0.90 [0.73 , 1.11]
Guerin 2013	56	237	94	229	15.7%	0.58 [0.44 , 0.76]
Subtotal (95% CI)		**523**		**501**	**54.8%**	**0.75 [0.59 , 0.94]**
Total events:	182		235			
Heterogeneity: Tau² = 0.03; Chi² = 7.37, df = 4 (P = 0.12); I² = 46%						
Test for overall effect: Z = 2.52 (P = 0.01)						
Total (95% CI)		**1099**		**1041**	**100.0%**	**0.86 [0.72 , 1.03]**
Total events:	462		490			
Heterogeneity: Tau² = 0.03; Chi² = 18.05, df = 7 (P = 0.01); I² = 61%						
Test for overall effect: Z = 1.67 (P = 0.10)						
Test for subgroup differences: Chi² = 6.43, df = 1 (P = 0.01), I² = 84.4%						



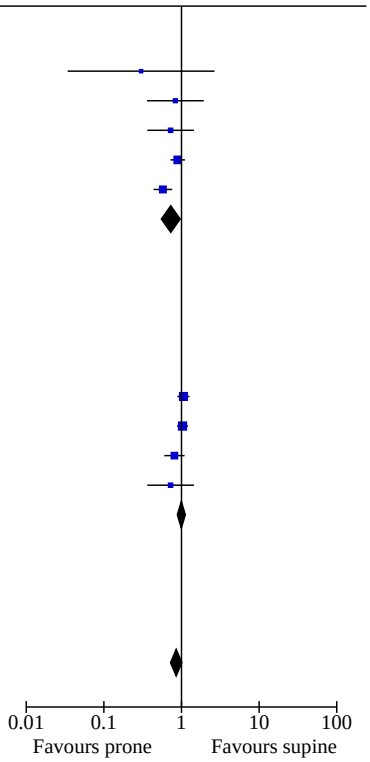
Analysis 2.3. Comparison 2: Intervention comparisons and interactions, Outcome 3: Severe vs less-severe hypoxaemia: longer-term mortality

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Severe hypoxaemia						
Gattinoni 2001	35	53	35	46	11.7%	0.87 [0.67 , 1.12]
Guerin 2004	53	90	49	75	12.1%	0.90 [0.71 , 1.14]
Mancebo 2006	22	43	21	29	8.6%	0.71 [0.49 , 1.02]
Chan 2007	2	6	6	7	1.6%	0.39 [0.12 , 1.25]
Fernandez 2008	5	9	2	4	1.6%	1.11 [0.36 , 3.48]
Taccone 2009	39	73	48	76	11.1%	0.85 [0.64 , 1.11]
Guerin 2013	56	237	94	229	11.0%	0.58 [0.44 , 0.76]
Subtotal (95% CI)		**511**		**466**	**57.8%**	**0.77 [0.65 , 0.92]**
Total events:	212		255			
Heterogeneity: Tau² = 0.02; Chi² = 9.81, df = 6 (P = 0.13); I² = 39%						
Test for overall effect: Z = 2.99 (P = 0.003)						
2.2.2 Less severe hypoxaemia						
Gattinoni 2001	57	95	52	103	11.7%	1.19 [0.92 , 1.53]
Guerin 2004	126	323	110	302	13.2%	1.07 [0.88 , 1.31]
Mancebo 2006	16	33	13	31	5.4%	1.16 [0.67 , 1.99]
Chan 2007	3	4	0	4	0.3%	7.00 [0.47 , 103.27]
Fernandez 2008	3	12	7	12	1.8%	0.43 [0.14 , 1.28]
Taccone 2009	40	93	43	96	9.8%	0.96 [0.70 , 1.33]
Subtotal (95% CI)		**560**		**548**	**42.2%**	**1.07 [0.92 , 1.26]**
Total events:	245		225			
Heterogeneity: Tau² = 0.01; Chi² = 5.74, df = 5 (P = 0.33); I² = 13%						
Test for overall effect: Z = 0.89 (P = 0.37)						
Total (95% CI)		**1071**		**1014**	**100.0%**	**0.88 [0.76 , 1.03]**
Total events:	457		480			
Heterogeneity: Tau² = 0.04; Chi² = 26.60, df = 12 (P = 0.009); I² = 55%						
Test for overall effect: Z = 1.63 (P = 0.10)						
Test for subgroup differences: Chi² = 7.79, df = 1 (P = 0.005), I² = 87.2%						



Analysis 2.4. Comparison 2: Intervention comparisons and interactions, Outcome 4: Lower tidal volume (TV) ventilation vs higher TV ventilation: longer-term mortality

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Lower TV - mean 6 to 8 mL/kg IBW						
Voggenreiter 2005	1	21	3	19	0.6%	0.30 [0.03 , 2.66]
Chan 2007	5	11	6	11	3.4%	0.83 [0.36 , 1.94]
Fernandez 2008	8	21	10	19	4.7%	0.72 [0.36 , 1.45]
Taccone 2009	79	169	91	174	17.8%	0.89 [0.72 , 1.11]
Guerin 2013	56	237	94	229	14.9%	0.58 [0.44 , 0.76]
Subtotal (95% CI)		**459**		**452**	**41.4%**	**0.73 [0.55 , 0.96]**
Total events:	149		204			
Heterogeneity: Tau² = 0.04; Chi² = 7.05, df = 4 (P = 0.13); I² = 43%						
Test for overall effect: Z = 2.25 (P = 0.02)						
2.2.2 High TV - mean > 8 mL/kg IBW						
Gattinoni 2001	96	153	90	152	19.6%	1.06 [0.89 , 1.27]
Guerin 2004	179	413	159	378	20.4%	1.03 [0.88 , 1.21]
Mancebo 2006	38	76	37	60	13.9%	0.81 [0.60 , 1.10]
Fernandez 2008	8	21	10	19	4.7%	0.72 [0.36 , 1.45]
Subtotal (95% CI)		**663**		**609**	**58.6%**	**1.00 [0.88 , 1.12]**
Total events:	321		296			
Heterogeneity: Tau² = 0.00; Chi² = 3.24, df = 3 (P = 0.36); I² = 7%						
Test for overall effect: Z = 0.08 (P = 0.94)						
Total (95% CI)		**1122**		**1061**	**100.0%**	**0.85 [0.72 , 1.01]**
Total events:	470		500			
Heterogeneity: Tau² = 0.03; Chi² = 18.34, df = 8 (P = 0.02); I² = 56%						
Test for overall effect: Z = 1.85 (P = 0.06)						
Test for subgroup differences: Chi² = 4.15, df = 1 (P = 0.04), I² = 75.9%						



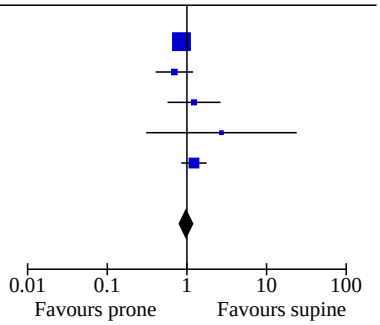
Comparison 3. Pneumonia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Pneumonia	5	1473	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.80, 1.18]

Analysis 3.1. Comparison 3: Pneumonia, Outcome 1: Pneumonia

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Guerin 2004	85	413	91	378	58.8%	0.85 [0.66 , 1.11]
Voggenreiter 2005	10	21	13	19	8.5%	0.70 [0.40 , 1.20]
Mancebo 2006	14	76	9	60	6.2%	1.23 [0.57 , 2.64]
Fernandez 2008	3	21	1	19	0.7%	2.71 [0.31 , 23.93]
Ayzac 2016	52	237	41	229	25.8%	1.23 [0.85 , 1.77]
Total (95% CI)		**768**		**705**	**100.0%**	**0.97 [0.80 , 1.18]**
Total events:	164		155			

Heterogeneity: Chi² = 5.14, df = 4 (P = 0.27); I² = 22%
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable



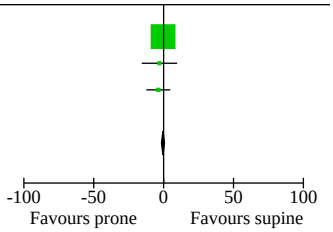
Comparison 4. Duration of mechanical ventilation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Duration of mechanical ventilation	3	871	Mean Difference (IV, Fixed, 95% CI)	-0.47 [-1.53, 0.59]

Analysis 4.1. Comparison 4: Duration of mechanical ventilation, Outcome 1: Duration of mechanical ventilation

Study or Subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Fixed, 95% CI
Guerin 2004	13.7	7.8	413	14.1	7.6	378	97.8%	-0.40 [-1.47 , 0.67]
Voggenreiter 2005	30	17	21	33	23	19	0.7%	-3.00 [-15.64 , 9.64]
Fernandez 2008	11.9	9.2	21	15.7	16.9	19	1.5%	-3.80 [-12.36 , 4.76]
Total (95% CI)			**455**			**416**	**100.0%**	**-0.47 [-1.53 , 0.59]**

Heterogeneity: Chi² = 0.75, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 0.87 (P = 0.38)
Test for subgroup differences: Not applicable



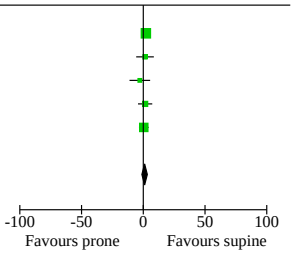
Comparison 5. Length of stay (LOS)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 ICU LOS	5	1775	Mean Difference (IV, Fixed, 95% CI)	1.06 [-1.13, 3.26]

Analysis 5.1. Comparison 5: Length of stay (LOS), Outcome 1: ICU LOS

Study or Subgroup	Experimental Mean [days]	Experimental SD [days]	Experimental Total	Control Mean [days]	Control SD [days]	Control Total	Weight	Mean Difference IV, Fixed, 95% CI [days]
Guerin 2004	26.6	29.6	413	24.5	21.9	378	37.1%	2.10 [-1.51 , 5.71]
Mancebo 2006	20.5	18.2	76	19.1	23.1	60	9.5%	1.40 [-5.73 , 8.53]
Fernandez 2008	14.7	9.7	21	17.5	16.1	19	6.9%	-2.80 [-11.14 , 5.54]
Taccone 2009	17.5	29.7	168	16	24.3	174	14.6%	1.50 [-4.26 , 7.26]
Guerin 2013	21.7	21.8	237	21.3	21.1	229	31.9%	0.40 [-3.50 , 4.30]
Total (95% CI)			**915**			**860**	**100.0%**	**1.06 [-1.13 , 3.26]**

Heterogeneity: Chi² = 1.28, df = 4 (P = 0.86); I² = 0%
Test for overall effect: Z = 0.95 (P = 0.34)
Test for subgroup differences: Not applicable

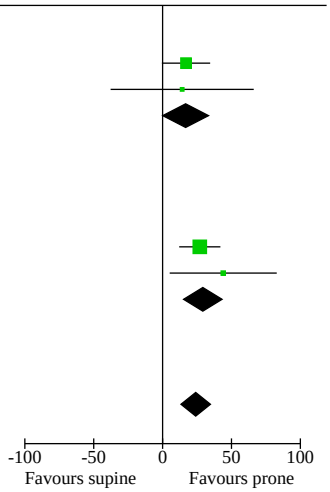


Comparison 6. Mean change in PaO_2/FIO_2 quotient (mmHg)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Mean increase in PaO_2/FIO_2 quotient (mmHg) at 7 or 10 days	4	827	Mean Difference (IV, Fixed, 95% CI)	24.03 [13.35, 34.71]
6.1.1 Change data provided	2	268	Mean Difference (IV, Fixed, 95% CI)	16.71 [0.11, 33.32]
6.1.2 Calculated change data	2	559	Mean Difference (IV, Fixed, 95% CI)	29.19 [15.24, 43.14]

Analysis 6.1. Comparison 6: Mean change in PaO_2/FIO_2 quotient (mmHg), Outcome 1: Mean increase in PaO_2/FIO_2 quotient (mmHg) at 7 or 10 days

Study or Subgroup	Prone Mean	Prone SD	Prone Total	Supine Mean	Supine SD	Supine Total	Weight	Mean Difference IV, Fixed, 95% CI
6.6.1 Change data provided								
Gattinoni 2001	63	66.8	114	46	68.2	114	37.2%	17.00 [-0.52 , 34.52]
Voggenreiter 2005	80.7	77.3	21	66.5	89.1	19	4.2%	14.20 [-37.74 , 66.14]
Subtotal (95% CI)			**135**			**133**	**41.4%**	**16.71 [0.11 , 33.32]**
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%								
Test for overall effect: Z = 1.97 (P = 0.05)								
6.6.2 Calculated change data								
Guerin 2004	78	91	254	51	78	238	51.1%	27.00 [12.05 , 41.95]
Mancebo 2006	67	80	35	23	82	32	7.6%	44.00 [5.15 , 82.85]
Subtotal (95% CI)			**289**			**270**	**58.6%**	**29.19 [15.24 , 43.14]**
Heterogeneity: Chi² = 0.64, df = 1 (P = 0.42); I² = 0%								
Test for overall effect: Z = 4.10 (P < 0.0001)								
Total (95% CI)			**424**			**403**	**100.0%**	**24.03 [13.35 , 34.71]**
Heterogeneity: Chi² = 1.92, df = 3 (P = 0.59); I² = 0%								
Test for overall effect: Z = 4.41 (P < 0.0001)								
Test for subgroup differences: Chi² = 1.27, df = 1 (P = 0.26), I² = 21.4%								

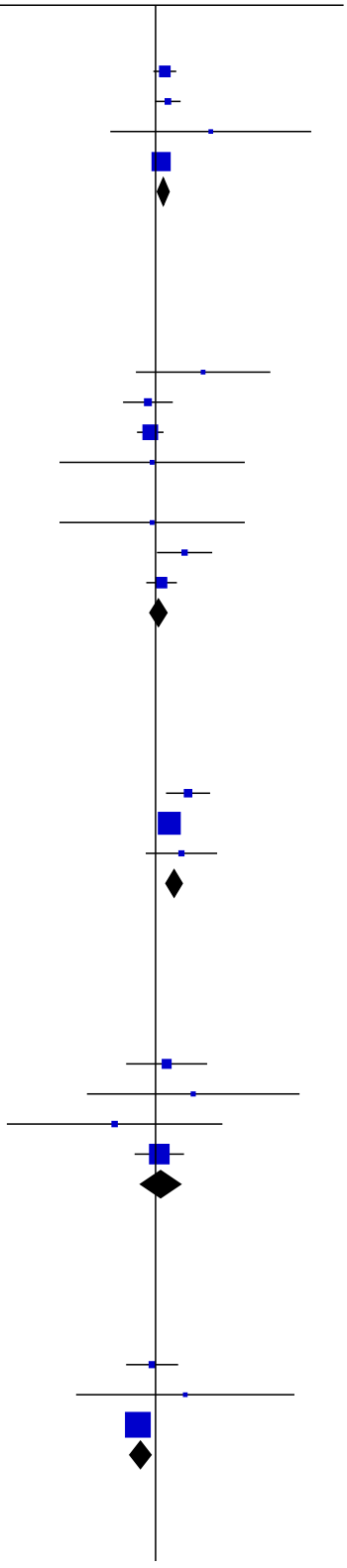


Comparison 7. Adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Adverse events	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1.1 Pressure ulcers	4	823	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.06, 1.48]
7.1.2 Tracheal tube displacement	8	2021	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.85, 1.39]
7.1.3 Tracheal tube obstruction	3	1597	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [1.35, 2.18]
7.1.4 Pneumothorax	4	664	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.65, 2.08]
7.1.5 Arrhythmias	3	642	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.47, 0.87]

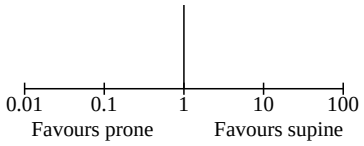
Analysis 7.1. Comparison 7: Adverse events, Outcome 1: Adverse events

Study or Subgroup	Prone Events	Prone Total	Supine Events	Supine Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.7.1 Pressure ulcers						
Gattinoni 2001	55	152	42	152	29.7%	1.31 [0.94 , 1.83]
Voggenreiter 2005	19	21	12	19	8.9%	1.43 [0.99 , 2.07]
Chan 2007	2	11	0	11	0.4%	5.00 [0.27 , 93.55]
Girard 2014	103	232	85	225	61.0%	1.18 [0.94 , 1.47]
Subtotal (95% CI)		**416**		**407**	**100.0%**	**1.25 [1.06 , 1.48]**
Total events:	179		139			
Heterogeneity: Chi² = 1.75, df = 3 (P = 0.63); I² = 0%						
Test for overall effect: Z = 2.58 (P = 0.010)						
7.7.2 Tracheal tube displacement						
Leal 1997	4	8	1	8	0.9%	4.00 [0.56 , 28.40]
Gattinoni 2001	12	152	15	152	14.2%	0.80 [0.39 , 1.65]
Guerin 2004	44	413	47	378	46.5%	0.86 [0.58 , 1.26]
Voggenreiter 2005	1	21	1	19	1.0%	0.90 [0.06 , 13.48]
Chan 2007	0	11	0	11		Not estimable
Fernandez 2008	1	21	1	19	1.0%	0.90 [0.06 , 13.48]
Taccone 2009	18	168	8	174	7.4%	2.33 [1.04 , 5.21]
Guerin 2013	37	237	30	229	28.9%	1.19 [0.76 , 1.86]
Subtotal (95% CI)		**1031**		**990**	**100.0%**	**1.09 [0.85 , 1.39]**
Total events:	117		103			
Heterogeneity: Chi² = 7.48, df = 6 (P = 0.28); I² = 20%						
Test for overall effect: Z = 0.65 (P = 0.52)						
7.7.3 Tracheal tube obstruction						
Guerin 2004	34	413	12	376	16.6%	2.58 [1.36 , 4.91]
Taccone 2009	85	168	59	174	76.7%	1.49 [1.16 , 1.93]
Guerin 2013	11	237	5	229	6.7%	2.13 [0.75 , 6.02]
Subtotal (95% CI)		**818**		**779**	**100.0%**	**1.72 [1.35 , 2.18]**
Total events:	130		76			
Heterogeneity: Chi² = 2.85, df = 2 (P = 0.24); I² = 30%						
Test for overall effect: Z = 4.44 (P < 0.00001)						
7.7.4 Pneumothorax						
Mancebo 2006	7	76	4	60	22.6%	1.38 [0.42 , 4.50]
Chan 2007	1	11	0	11	2.5%	3.00 [0.14 , 66.53]
Fernandez 2008	0	21	1	19	8.0%	0.30 [0.01 , 7.02]
Guerin 2013	15	237	13	229	66.9%	1.11 [0.54 , 2.29]
Subtotal (95% CI)		**345**		**319**	**100.0%**	**1.16 [0.65 , 2.08]**
Total events:	23		18			
Heterogeneity: Chi² = 1.16, df = 3 (P = 0.76); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.62)						
7.7.5 Arrhythmias						
Voggenreiter 2005	8	21	8	19	10.8%	0.90 [0.42 , 1.93]
Mancebo 2006	1	76	0	60	0.7%	2.38 [0.10 , 57.32]
Guerin 2013	42	237	68	229	88.5%	0.60 [0.43 , 0.84]
Subtotal (95% CI)		**334**		**308**	**100.0%**	**0.64 [0.47 , 0.87]**
Total events:	51		76			
Heterogeneity: Chi² = 1.61, df = 2 (P = 0.45); I² = 0%						
Test for overall effect: Z = 2.81 (P = 0.005)						



Analysis 7.1. (Continued)

Heterogeneity: Chi² = 1.61, df = 2 (P = 0.45); I² = 0%
Test for overall effect: Z = 2.81 (P = 0.005)



APPENDICES

Appendix 1. Search strategy for updated review

The following strategies were used for this update.

Database: Ovid MEDLINE(R) ALL <1946 to May 01, 2020>

1 exp Respiratory Insufficiency/

2 (respiratory adj2 (insufficien* or failure* or depression)).mp.

3 Respiratory Distress Syndrome, Adult/

4 exp Severe Acute Respiratory Syndrome/

5 (ards or sars or respiratory distress syndrome* or acute respiratory syndrome*).mp.

6 ((acute or adult) adj2 respiratory distress).mp.

7 exp Lung Injury/

8 lung injur*.mp.

9 exp Pneumonia/

10 pneumon*.mp.

11 exp Pulmonary Embolism/

12 ((pulmonary or lung) adj2 embolism).mp.

13 Pulmonary Edema/

14 (Pulmonary adj2 (oedema* or edema*)).mp.

15 Shock, Cardiogenic/

16 left ventricular failure*.mp.

17 exp Heart Failure/

18 ((cardiac or heart) adj2 failure*).mp.

19 exp coronavirus/ or exp Coronavirus Infections/ or (coronavirus* or corona-virus* or 2019-nCoV or nCoV or COVID-19 or Covid19 or SARS-CoV* or SARSCov* or ncov* or Pandemi*2).mp.

20 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

21 (prone* or proning or pronation).mp.

22 Prone Position/

23 positioning in.mp.

24 face down.mp.

25 ventral position*.mp.

26 21 or 22 or 23 or 24 or 25

27 20 and 26

28 (2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020*).dt,ez,yr,dp,ed.

29 27 and 28

30 ((randomized controlled trial or controlled clinical trial).pt. or randomi?ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)

31 29 and 30

Database: Embase <1974 to 2020 May 01>

1 exp respiratory failure/

2 (respiratory adj2 (insufficien* or failure* or depression)).mp.

3 adult respiratory distress syndrome/

4 severe acute respiratory syndrome/

5 (ards or sars or respiratory distress syndrome* or acute respiratory syndrome*).mp.

6 ((acute or adult) adj2 respiratory distress).mp.

7 exp lung injury/

8 lung injur*.mp.

9 exp pneumonia/

10 pneumon*.mp.

11 lung embolism/

12 ((pulmonary or lung) adj2 embolism).mp.

13 lung edema/

14 ((Pulmonary or lung) adj2 (oedema* or edema*)).mp.

15 cardiogenic shock/

16 left ventricular failure*.mp.

17 exp heart failure/

18 ((cardiac or heart) adj2 failure*).mp.

19 exp coronavirinae/

20 exp coronaviridae infection/

21 (coronavirus* or corona-virus* or 2019-nCoV or nCoV or COVID-19 or Covid19 or SARS-CoV* or SARSCov* or ncov* or Pandemi*2).mp.

22 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21

23 (prone* or proning or pronation).mp.

24 prone position/

25 positioning in.mp.

26 face down.mp.

27 ventral position*.mp.

28 23 or 24 or 25 or 26 or 27

29 exp intensive care/

30 exp intensive care unit/

31 exp Respiration, Artificial/

32 critical illness/

33 (ICU or ICUs or ITU or CCU or ((intensive or critical) adj3 (care or unit*)) or (critical* adj3 ill*)).mp.

34 (artificial* adj3 respirat*).mp.

35 ventilat*.mp.

36 29 or 30 or 31 or 32 or 33 or 34 or 35

37 22 and 28 and 36

38 (2014* or 2015* or 2016* or 2017* or 2018* or 2019* or 2020*).dc,dp,yr.

39 37 and 38

40 (randomized controlled trial/ or controlled clinical study/ or random$.ti,ab. or randomization/ or intermethod comparison/ or placebo.ti,ab. or (compare or compared or comparison).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. or (open adj label).ti,ab. or ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. or double blind procedure/ or parallel group$1.ti,ab. or (crossover or cross over).ti,ab. or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. or (assigned or allocated).ti,ab. or (controlled adj7 (study or design or trial)).ti,ab. or (volunteer or volunteers).ti,ab. or human experiment/ or trial.ti.) not (((random$ adj sampl$ adj7 (cross section$ or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)) or (cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)) or (((case adj control$) and random$) not randomi?ed controlled).ti,ab. or (Systematic review not (trial or study)).ti. or (nonrandom$ not random$).ti,ab. or Random field$.ti,ab. or (random cluster adj3 sampl$).ti,ab. or ((review.ab. and review.pt.) not trial.ti.) or (we searched.ab. and (review.ti. or review.pt.)) or update review.ab. or (databases adj4 searched).ab. or ((rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/) or (Animal experiment/ not (human experiment/ or human/)))

41 39 and 40

Central
Cochrane Database of Systematic Reviews: Issue 5 of 12, May 2020

#1 MeSH descriptor: [Respiratory Insufficiency] explode all trees

#2 (respiratory near/2 (insufficien* or failure* or depression))

#3 MeSH descriptor: [Respiratory Distress Syndrome, Adult] explode all trees

#4 MeSH descriptor: [Severe Acute Respiratory Syndrome] explode all trees

#5 (ards or sars or (respiratory next distress next syndrome*) or (acute next respiratory next syndrome*))

#6 ((acute or adult) near/2 (respiratory next distress))

#7 MeSH descriptor: [Lung Injury] explode all trees

#8 lung next injur*

#9 MeSH descriptor: [Pneumonia] explode all trees

#10 pneumon*

#11 MeSH descriptor: [Pulmonary Embolism] explode all trees

#12 ((pulmonary or lung) near/2 embolism)

#13 MeSH descriptor: [Pulmonary Edema] explode all trees

#14 (Pulmonary near/2 (oedema* or edema*))

#15 MeSH descriptor: [Shock, Cardiogenic] explode all trees

#16 left next ventricular next failure*

#17 MeSH descriptor: [Heart Failure] explode all trees

#18 ((cardiac or heart) near/2 failure*)

#19 MeSH descriptor: [Coronavirus] explode all trees

#20 MeSH descriptor: [Coronavirus Infections] explode all trees

#21 (coronavirus* or corona-virus* or corona next virus* or 2019 next nCoV or nCoV or COVID next 19 or Covid19 or SARS next CoV* or SARSCov* or ncov* or Pandemi next 2)

#22 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21

#23 MeSH descriptor: [Prone Position] explode all trees

#24 prone* or proning or pronation

#25 positioning next in

#26 face next down

#27 ventral next position*

#28 #23 or #24 or #25 or #26 or #27

#29 #22 and #28

#30 #29 with Cochrane Library publication date Between Jan 2014 and Dec 2020, in Trials

Cinahl

S1 (MH "Respiratory Failure+")

S2 TX (respiratory N2 (insufficien* or failure* or depression))

S3 (MH "Respiratory Distress Syndrome, Acute")

S4 (MH "Severe Acute Respiratory Syndrome")

S5 TX (ards or sars or (respiratory distress syndrome*) or (acute respiratory syndrome*))

S6 TX ((acute or adult) N2 respiratory distress)

S7 (MH "Lung Injury+")

S8 (MH "Acute Lung Injury+")

S9 TX (lung injur*)

S10 (MH "Pneumonia+")

S11 TX (pneumon*)

S12 (MH "Pulmonary Embolism")

S13 TX ((pulmonary or lung) N2 embolism)

S14 (MH "Pulmonary Edema+")

S15 TX (Pulmonary N2 (oedema* or edema*))

S16 (MH "Shock, Cardiogenic")

S17 TX (left ventricular failure*)

S18 (MH "Heart Failure+")

S19 TX ((cardiac or heart) N2 failure*)

S20 (MH "Coronavirus+") OR (MH "Coronavirus Infections+")

S21 (coronavirus* or corona-virus* or corona virus or 2019-nCoV or nCoV or COVID-19 or Covid19 or SARS-CoV* or SARSCov* or ncov* or Pandemi*2)

S22 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21

S23 (MH "Prone Position")

S24 TX (prone* or proning or pronation)

S25 TX (positioning in)

S26 TX (face down)

S27 TX (ventral position*)

S28 S23 OR S24 OR S25 OR S26 OR S27

S29 S22 AND S28

S30 S22 AND S28 Published Date: 20140101-20201231

S31 (MH (randomized controlled trials) OR MH (double-blind studies) OR MH (single-blind studies) OR MH (random assignment) OR MH (pretest-posttest design) OR MH (cluster sample) OR TI

(randomised OR randomized) OR AB (random*) OR TI (trial) OR (MH (sample size) AND AB (assigned OR allocated OR control)) OR MH (placebos) OR PT (randomized controlled trial) OR

AB (control W5 group) OR MH (crossover design) OR MH (comparative studies) OR AB (cluster W3 RCT)) NOT ((MH (animals+) OR MH (animal studies) OR TI (animal model*)) NOT MH (human))

S32 S30 AND S31

LILACS

(ARDS or respiratory distress syndrome or Pneumonia or Pneumonitis or Respiratory failure or Respiratory insufficiency or Respiratory depression or Pulmonary edema or Pulmonary oedema or Pulmonary embolism or corona virus or coronavirus or covid19 or covid 19 or SARSCov or ncov) [Words] and (prone or proning or pronation) [Words] 2014-2020

Cochrane Covid 19 register

Filtered by: prone* or proning or pronation:

Appendix 2. Original data extraction form

DATA EXTRACTION FORM – PRONE POSITION FOR ACUTE RESPIRATORY FAILURE IN ADULTS

(CARG 038)

Reviewer name
Study author & date

(Continued)

Journal, volume, pages & MEDLINE ID
Title
Location of study
Enrolment finished (month & year)
Period of study

Verification of study eligibility:

	Yes/No	Query or comments
Is this a randomized controlled trial?		
All patients are adults and required mechanical ventilation for acute respiratory failure?		
Relevant clinical outcomes?		

Study population:

Population description
Inclusion criteria
Exclusion criteria

PARTICIPANTS:

Number of eligible participants	Number enrolled in study
Number of males	Number of females

STUDY POPULATION:

Baseline characteristics	Intervention group	Control group	Overall
Number for which data are given			
Sex			
Age (range, mean, SD)			
SAPS II score			
Other severity score (specify)			
Number of organ dysfunctions			
Organ dysfunction score (specify)			
PaO_2			
FIO_2			
PaO_2/FIO_2			
$PaCO_2$			
PEEP			
PIP			
Plat Press			
Vt (mL/kg) Unspecified mode - MV Volume controlled Pressure controlled			
ALI (%)			
ARDS (%)			
Pulmonary cause			
Extrapulmonary cause			
Pneumonia			
Shock			
Aspiration			

(Continued)

Septic shock
Acute on chronic RF
Coma
Postoperative
Non-pulmonary sepsis
Acute cardiogenic pulmonary oedema (%)
NIV before MV
Number of participants with vasopressors
Planned duration (dose) of prone ventilation (< 18 hours vs > 18 hours/d)
Duration (days) of interventions
Early randomization to prone vs undefined OR late
Severity of process (PaO_2/FIO_2, oxygenation index OR LIS)
CO-INTERVENTIONS
Inhaled nitric oxide
Renal replacement therapy
Packed red cells/participant (units)
Pulmonary artery catheter

Quality of concealment of random allocation:

Allocation was not concealed (e.g. quasi-randomization)	D
Allocation concealment was inadequate	C
Methods of concealment were unclear	B
Concealment was adequate (e.g. numbered, sealed opaque envelopes drawn NON-consecutively)	A
Inclusion and exclusion criteria were not clearly defined in the text	
Outcomes of participants who withdrew or were excluded after allocation were NEITHER detailed separately NOR included in an intention-to-treat analysis	

(Continued)

Outcomes of participants who withdrew or were excluded after allocation were EITHER detailed separately OR included in an intention-to-treat analysis OR the text stated there were no withdrawals
Treatment and control groups were NOT adequately described at entry
Treatment and control groups were adequately described at entry. A minimum of 4 admission details were described

METHODS:

	Yes	No	Unclear
Subject - blinded (N/A – sedated)	----------	----------	----------
Physician - blinded (N/A - impossible to achieve, as body position cannot be concealed)	----------	----------	----------
Outcome assessor - blinded			

Modified Jadad quality assessment tool (see Appendix for guidance*):

	Yes/No (Y = 1)	Points
1. Was the study described as randomized?		
2. Was the study described as blinded for assessments?		
3. Was there a description of withdrawals?		
Additional point if study randomization appropriate*		
Deducted point if study randomization inappropriate*		

Total points _____

*Give **one additional point** if: For question 1, the method used to generate the sequence was described, and it was appropriate (table of random numbers, computer-generated, etc.)

Deduct one point if: For question 1, the method used to generate the sequence of randomization was described, and it was inappropriate (participants were allocated alternately or according to date of birth, hospital number, etc.)

RESULTS AND OUTCOMES:

	Intervention group	Control group	Overall
10-Day mortality			
ICU mortality			
28-Day mortality			
Hospital mortality			
90-Day mortality			
Duration of MV			
Time to extubation			
ICU length of stay			
Hospital LOS			
Days with ARDS			
Days with ALI			
Days with LIS > 2			
VAP rate			
Percentage of participants with VAP/Prevalence of pneumonia			
Days on vasopressors			
FIO_2 d4			
PaO_2 d4			
PaO_2/FIO_2 d4			
$PaCO_2$ d4			
Vt d4			
FIO_2 d10			
PaO_2 d10			
PaO_2/FIO_2 d10			

(Continued)

$PaCO_2$ d10
Vt d10
Economic evaluation

COMPLICATIONS:

	Intervention group	Control group	Overall
New pressure sores			
Arrhythmias			
Pneumothorax			
Unplanned extubation/"Displacement" of tracheal tube/Obstruction			
Intracranial hypertension			
Total number of complications documented for both groups			

SUB-GROUP ANALYSES:

	Intervention group	Control group	Overall
10-Day mortality/SAPS > 49			
ICU mortality SAPS > 49			
ICU mortality SAPS ≤ 49			
ICU or 10-day mortality according to SAPS cutoffs			
Vt ≥ 12 mL/kg			
PaO_2/FIO_2 ≤ 88			

WHAT'S NEW

Date	Event	Description
24 November 2020	Amended	An updated search of databases was run in May 2020. No new trials were included in this rapid update. Review text was updated in the context of advances in knowledge since the original review and based on the availability of some secondary analyses from already included studies. There was no change to the conclusions. An updated search of trial registries was run in November 2020. Three ongoing studies were identified.

HISTORY

Protocol first published: Issue 4, 2009
Review first published: Issue 11, 2015

Date	Event	Description
13 December 2018	Amended	Editorial team changed to Cochrane Emergency and Critical Care

CONTRIBUTIONS OF AUTHORS

Conceiving of the review: Roxanna Bloomfield (RB), David W. Noble (DWN).
Co-ordinating the review: RB, DWN.
Undertaking manual searches: RB, DWN.
Screening search results: RB, DWN.
Organizing retrieval of papers: RB, DWN.
Screening retrieved papers against inclusion criteria: RB, DWN.
Appraising quality of papers: RB, DWN, Alexis Sudlow (AS).
Abstracting data from papers: RB, DWN, AS.
Writing to authors of papers for additional information: DWN.
Providing additional data about papers:
Obtaining and screening data on unpublished studies: RB, DWN.
Managing data for the review: RB, DWN.
Entering data into Review Manager (RevMan 5.40): RB, DWN, AS.
Analysing RevMan statistical data: DWN.
Performing other statistical analyses not using RevMan: DWN
Performing double entry of data: (data entered by person one: RB; data entered by person two: DWN).
Interpreting data: RB, DWN, AS.
Making statistical inferences: RB, DWN.
Writing the review: RB, DWN, AS.
Securing funding for the review:
Performing previous work that served as the foundation of the present study:
Serving as guarantor for the review (one review author): DWN.
Taking responsibility for reading and checking the review before submission: AS.

DECLARATIONS OF INTEREST

Roxanna Bloomfield: none known.

David W Noble: none known.

Alexis Sudlow: none known.

SOURCES OF SUPPORT

Internal sources

- NHS Grampian, UK

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the protocol (Bloomfield 2009).

- We replaced Nigel Webster, who had insufficient time to assist with the review process, with Alexis Sudlow.
- We added references and Background text.
- We made the definition of tidal volume more specific for the purpose of identifying studies that employed "lung-protective ventilation" (i.e. tidal volume should be expressed in mL per kg of *ideal* body weight.
- Risk of bias methods for a Cochrane review have changed since protocol publication, and we reanalysed data for the new format.
- The GRADE-based summary of findings table has been introduced since protocol publication, and we have therefore retrospectively chosen the analyses displayed.
- We did not employ the Q-partitioning method (Deeks 2011) in exploring heterogeneity and used the I^2 approach recommended instead.
- We made minor modifications to search strategies for Ovid MEDLINE, EMBASE, CENTRAL, CINAHL and LILACS to better suit their updated search engines.
- We changed the cutoff for prolonged duration of prone positioning from 18 or more hours per day to 16 or more hours per day. This placed the last published study (Guerin 2013) in the more biologically appropriate category for analysis. (The mean duration of proning in the short-duration proning group was 8.3 hours per day, and for the long-duration proning group 18.1 hours per day, and one study aiming for 20 hours per day actually achieved 17 hours per day (Mancebo 2006). The study of Guerin et al (Guerin 2013) also achieved proning for a mean of 17 hours per day.)

NOTES

The present interim amendment includes an updated search (May 2020, no new trials identified), and search of trial registries (November 2020, 3 ongoing studies identified). Review text was updated to reflect advances in knowledge since the original review and the availability of new data from secondary analyses; however, a complete update of this review is pending.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Hypoxia [etiology] [mortality] [therapy]; Patient Positioning [*methods] [mortality]; *Prone Position; Randomized Controlled Trials as Topic; Respiration, Artificial [*methods] [mortality]; Respiratory Distress Syndrome [mortality] [*therapy]; Respiratory Insufficiency [mortality] [*therapy]

MeSH check words

Adult; Humans; Middle Aged