Appendix 1 (as supplied by the authors): Amendments to previously described protocol for the systematic review of randomized controlled trials (RCTs) comparing the effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome (ARDS)

Original protocol[1]	Amendments	Rationale
Inclusion criteria: All RCTs of prone position v. supine position during mechanical ventilation, regardless of whether protective lung ventilation was used	We limited the primary mortality analysis to RCTs that used protective lung ventilation (tidal volume < 8 mL/kg of predicted or actual body weight)	Protective lung ventilation is now the standard of care for patients with ARDS; studies that used higher tidal volumes are less relevant to current clinical practice
Primary outcome: Hospital (or longest follow-up) mortality stratified according to the severity of hypoxemia at baseline (as assessed by the PaO_2/FIO_2 ratio at baseline)	Hospital mortality (or longest follow-up mortality) in studies which used protective lung ventilation (see above)	More recent trials that used lower tidal volumes also enrolled patients with more severe hypoxemia; the previous analysis had decreased external validity because they included trials that used higher than currently recommended tidal volumes and less severely hypoxemic patients; we retained the subgroup analysis stratified according to severity of hypoxemia as a secondary outcome
Secondary outcomes: Duration of mechanical ventilation and ventilator-free days	We did not examine the duration of mechanical ventilation or ventilator-free days	These outcomes are not patient centered; interpreting duration of mechanical ventilation is problematic, because interventions that prolong survival may increase duration of mechanical ventilation; ventilator-free days is a composite outcome of duration of mechanical ventilation and mortality (the latter is the outcome important to patients)
Risk of bias: We qualitatively assessed risk of bias after reviewing for possible selection, reporting and attrition bias	We used the Cochrane risk-of-bias instrument to assess risk of bias	Since our previous review, the Cochrane risk-of-bias tool has been developed and validated as a reliable instrument for the assessment of risk of bias
Methodologic quality: We subjectively assessed quality of evidence	We used GRADE methodology to assess the quality of evidence. We used GradeProfiler 3.2.2 to generate summary of evidence tables to summarize the quality and strength of evidence	The GRADE approach is a recently developed objective, reproducible and transparent method of grading the quality of evidence and strength of recommendations for systematic reviews and clinical practice guidelines

Note: GRADE = Grading of Recommendations Assessment, Development and Evaluation, PaO_2/FIO_2 ratio = ratio of partial pressure of arterial oxygen to fraction of inspired oxygen.

Reference

1. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. *Intensive Care Med* 2010;36:585-99.

Appendix to: Sud S, Friedrich JO, Adhikari NKJ, et al. Effect of prone positioning during mechanical ventilation on mortality among patients with acute respiratory distress syndrome: a systematic review and meta-analysis. *CMAJ* 2014. DOI:10.1503/cmaj.140081.