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Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients (Review)

Blackwood B, Burns KEA, Cardwell CR, O'Halloran P

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[Intervention Review]

Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

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ABSTRACT

Background

This is an update of a review last published in Issue 5, 2010, of *The Cochrane Library*. Reducing weaning time is desirable in minimizing potential complications from mechanical ventilation. Standardized weaning protocols are purported to reduce time spent on mechanical ventilation. However, evidence supporting their use in clinical practice is inconsistent.

Objectives

The first objective of this review was to compare the total duration of mechanical ventilation of critically ill adults who were weaned using protocols versus usual (non-protocolized) practice.

The second objective was to ascertain differences between protocolized and non-protocolized weaning in outcomes measuring weaning duration, harm (adverse events) and resource use (intensive care unit (ICU) and hospital length of stay, cost).

The third objective was to explore, using subgroup analyses, variations in outcomes by type of ICU, type of protocol and approach to delivering the protocol (professional-led or computer-driven).

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2014), MEDLINE (1950 to January 2014), EMBASE (1988 to January 2014), CINAHL (1937 to January 2014), LILACS (1982 to January 2014), ISI Web of Science and ISI Conference Proceedings (1970 to February 2014), and reference lists of articles. We did not apply language restrictions. The original search was performed in January 2010 and updated in January 2014.

Selection criteria

We included randomized controlled trials (RCTs) and quasi-RCTs of protocolized weaning versus non-protocolized weaning from mechanical ventilation in critically ill adults.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. We performed a priori subgroup and sensitivity analyses. We contacted study authors for additional information.

Main results

We included 17 trials (with 2434 patients) in this updated review. The original review included 11 trials. The total geometric mean duration of mechanical ventilation in the protocolized weaning group was on average reduced by 26% compared with the usual care group (N = 14 trials, 95% confidence interval (CI) 13% to 37%, P = 0.0002). Reductions were most likely to occur in medical, surgical and mixed ICUs, but not in neurosurgical ICUs. Weaning duration was reduced by 70% (N = 8 trials, 95% CI 27% to 88%, P = 0.009); and ICU length of stay by 11% (N = 9 trials, 95% CI 3% to 19%, P = 0.01). There was significant heterogeneity among studies for total duration of mechanical ventilation (I^2 = 67%, P < 0.0001) and weaning duration (I^2 = 97%, P < 0.00001), which could not be explained by subgroup analyses based on type of unit or type of approach.

Authors' conclusions

There is evidence of reduced duration of mechanical ventilation, weaning duration and ICU length of stay with use of standardized weaning protocols. Reductions are most likely to occur in medical, surgical and mixed ICUs, but not in neurosurgical ICUs. However, significant heterogeneity among studies indicates caution in generalizing results. Some study authors suggest that organizational context may influence outcomes, however these factors were not considered in all included studies and could not be evaluated. Future trials should consider an evaluation of the process of intervention delivery to distinguish between intervention and implementation effects. There is an important need for further development and research in the neurosurgical population.

PLAIN LANGUAGE SUMMARY

The usefulness of weaning protocols for reducing the time critically ill adult patients spend on mechanical ventilation

Review question: We reviewed the evidence about the effect of weaning protocols (guidelines) used by clinicians on reducing the time that critically ill patients spent on a breathing machine.

Background: Helping patients to breathe with the use of a mechanical ventilator can be life saving. Yet the longer someone stays on a ventilator, the greater the likelihood of harmful effects including infection of the lungs and complications of prolonged immobility such as blood clots in the legs or lungs. It is important, therefore, to recognize early on when patients are ready to breathe for themselves so they can gradually come off the ventilator (this is called weaning). Usually, weaning is left to the judgement of clinicians, but recently protocols for weaning have been found to be safe for patients and useful for clinicians. Some studies said protocols led to better practice, but there was no clear evidence that using them actually produced beneficial results for patients.

Search date: The evidence is current to January 2014.

Study characteristics: This updated Cochrane review included 17 studies involving 2434 critically ill men and women who were being cared for in medical, surgical, neurosurgical and mixed medical/surgical intensive care units (ICUs). The studies compared the use of protocols to wean patients from the ventilator against usual practice. They were conducted in ICUs in America, Europe, Asia and Australia. The ICUs cared for patients with heart conditions, breathing difficulties, head injuries, trauma and following major surgery. In 13 studies, clinicians used weaning protocols to guide them to reduce the ventilator support. In four studies ventilator support was reduced automatically by programmed computers following a protocol.

Results: In comparison with usual practice without protocols, the average total time spent on the ventilator was reduced by 26%. The duration of weaning was reduced by 70% and length of stay in the ICU reduced by 11%. Using protocols did not result in any additional harms. We found considerable variation in the types of protocols used, the criteria for considering when to start weaning, the medical conditions of the patients and usual practice in weaning. This means that we cannot say exactly which protocols will work best for particular patients, but we do know they have not been beneficial in neurosurgical patients.

Quality of evidence: We graded the quality of the available evidence as moderate for duration of ventilation and harmful effects, and low for the duration of weaning and ICU length of stay. The reasons for our grading were that results were not consistent across the studies, and studies lacked sufficient detail about usual care practices.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Patient or population: mechanically ventilated adult patients
Settings: intensive care units
Intervention: protocolized weaning
Comparison: non-protocolized weaning

Outcomes	Illustrative comparative risks* (95% CI)		Effect Estimates (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk non-protocolized weaning	Corresponding risk protocolized weaning			
Total duration of mechanical ventilation (hours)	Mean 96 hours[1]	Mean 71 hours (60.5 to 83.5 hours)	Geometric mean difference -26% (-37% to -13%)	2205 [14 studies]	+++O moderate[2]
Weaning duration (hours)	Mean 24 hours[1]	Mean 7 hours (2.8 to 17.5 hours)	Geometric mean difference -70% (-88% to -27%)	989 [8 studies]	++OO low[3]
ICU length of stay (days)	Mean 8 days[1]	Mean 7 days (6.5 to 7.8 days)	Geometric mean difference -11% (-19% to -3%)	1378 [9 studies]	++OO low[4]
ICU mortality	31%[1]	30% (20% to 42%)	OR 0.97 (0.57 to 1.63)	651 [6 studies]	+++O moderate[5]
Reintubation	10%[1] (*followingdeliberateextubation*)	8% (5% to 12%)	OR 0.74 (0.44 to 1.23)	1487 [11 studies]	++OO moderate[6]

*The basis for the **assumed risk** (e.g. the mean control group risk) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **effect estimate** of the intervention (and its 95% CI).

CI: Confidence interval; ICU: intensive care unit; OR: Odds 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 (+++0): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality (++00): 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 (+000): We are very uncertain about the estimate.

[1] The assumed risk is derived from the median reported in a large epidemiological study of characteristics and outcomes in patients (N = 4968) receiving mechanical ventilation by Esteban 2008. The reported medians were used as an approximation for the means used for illustrative comparisons of all continuous variables. The table shows the mean duration of mechanical ventilation, weaning and ICU length of stay if patients are not weaning by protocol (non-protocolized weaning) and what would be expected with protocolized weaning based on the effect estimates from our review.

[2] There was considerable variability in effect estimates (I^2 = 67%) that could not be explained by subgroup analysis although variability was lower than the previous review. The confidence interval was narrower in this review and the difference at the lower limit would still be clinically significant.

[3] There was considerable variability in effect estimates (I^2 = 97%) and the wide confidence intervals indicate imprecision in results. The lower limit suggests a one hour difference in weaning that is not clinically significant.

[4] There was no heterogeneity among trials effects estimates, but wide confidence intervals indicate imprecision in results.

[5] There was moderate variability in effect estimates (I^2 = 50%).

[6] There was moderate variability in effect estimates (I^2 = 43%).

BACKGROUND

Prolonged mechanical ventilation for critically ill patients is associated with adverse clinical outcomes, including physiological and psychological experiences. Consequently, in an effort to reduce morbidity and mortality associated with mechanical ventilation, clinical and research attention, over the last 20 years, has been focused on reducing the duration of mechanical ventilation, by improving the processes of ventilator weaning. For approximately 77% of patients, resuming spontaneous, unassisted breathing is accomplished easily (Esteban 2008); for others it is more difficult. Patients who experience difficulty in discontinuing mechanical ventilation present significant challenges to clinicians involved in their care. These patients frequently require longer hospital stays and generally have a higher morbidity, including ventilator-associated pneumonia, ventilator-associated lung injury and mortality (Boles 2007). Moreover, ventilator-dependent patients generally remain in an intensive care unit (ICU) setting, as they require specialized care and frequent monitoring. In the current climate of limited ICU bed availability, maximizing use of limited ICU resources (including nursing and equipment costs) is an important goal of providing care to critically ill patients. Thus, timely and safe discontinuation of mechanical ventilation is a desirable outcome for patients and clinicians alike.

Description of the condition

The process leading to discontinuation of mechanical support is known as 'weaning' and has been classically defined as follows. "Weaning from mechanical ventilation represents the period of transition from total ventilatory support to spontaneous breathing" (Mancebo 1996). However, there are many interpretations of the 'period of transition' and the endpoint of 'spontaneous breathing'.

The transition period may take many forms, ranging from abrupt to gradual withdrawal from ventilatory support (Alia 2000). Some clinicians do not view abrupt withdrawal as weaning and suggest the term 'discontinuation' as a better descriptor, with 'weaning' being used to describe the more gradual withdrawal process (Cook 2000; Hess 2011). There are differing schools of thought regarding this gradual process of weaning. Some clinicians maintain that the transition should be initiated gradually right from the outset of mechanical ventilation, with as much of the breathing workload transferred to the patient as tolerated; which obscures the onset of weaning. Other clinicians believe that the transition should only be attempted when the condition that indicated the need for respiratory support has significantly resolved. Another view is to provide full support during an initial period and then attempt to transfer the breathing workload to the patient when the patient's condition shows early signs of improvement (Marini 1995). The work of Levine and colleagues (Levine 2008) showing marked atrophy of diaphragmatic myofibrils after less than three days of ventilation would support strategies that lead to some early spontaneous breathing during the phase of mechanical ventilatory support. Gradually transferring the breathing workload requires titrating ventilatory support to the needs of the patient. Titration may mean increasing or decreasing support and may be so gradual that it leads to problems in defining the time when weaning commenced.

The end of the weaning process can be defined as the cessation of mechanical ventilation, which implies the return of spontaneous breathing, but the term spontaneous breathing is ambiguous. All forms of spontaneous breathing involve the initiation of each breath by the patient, and contraction of the respiratory muscles. If the patient is free from all respiratory support (disconnected from the ventilator and extubated, or disconnected but still intubated and breathing through a T-piece circuit), the depth or size of the patient's breath will depend upon the strength and duration of respiratory muscle contraction, airways resistance and lung compliance. If the patient is still connected to a ventilator, the patient-initiated breath may be augmented by mechanical (albeit minimal) assistance from the ventilator. Both these situations are considered to be spontaneous breathing. Furthermore, some clinicians view the end of the weaning process as extubation without the need for (i) reintubation and (ii) ventilatory support within the following 48 to 72 hours (MacIntyre 2001).

Identifying when the patient is ready to wean, and deciding on the most appropriate method of weaning is influenced by the judgement and experience of the clinician (Sahn 1973). In some cases, clinicians tend to underestimate the probability of successful discontinuation of mechanical ventilation (Strickland 1993) and predictions, based on judgement alone, have low sensitivity (ability to predict success) and specificity (ability to predict failure) (Stroetz 1995). Until recently, there have been few standards of care in this area based on scientifically sound data. As a result, variation exists in weaning practice. There are several options, or weaning methods, for decreasing support. They include intermittent T-piece trials involving short time periods of spontaneous breathing through a T-piece circuit; synchronized intermittent mechanical ventilation (SIMV) involving gradual reductions in the ventilator rate, by increments of 1 to 4 breaths/min; pressure support ventilation (PSV) involving the gradual reduction of pressure by increments of 2 to 6 cmH_2O; spontaneous breathing through a ventilator circuit with the application of continuous positive airway pressure (CPAP), and combinations of these and newer options, such as bi-level, positive airway pressure. The evidence is equivocal as to which method is superior, although it has been suggested that SIMV is the least effective method (Brochard 1994; Esen 1992; Esteban 1995).

Description of the intervention

A weaning protocol is a structured guide for reducing, or discontinuing, or both, mechanical ventilatory support, and it generally

contains three components. The first component is a list of objective criteria based on general clinical factors used to help decide if a patient is ready to breathe without the help of a ventilator, often referred to as 'readiness to wean' criteria (such as that used by Ely 1996). The second component consists of structured guidelines for reducing ventilatory support. This may be abrupt (for example spontaneous breathing trials) or gradual by using a stepwise reduction in support to achieve discontinuation (for example SIMV or PSV), such as used by Brochard 1994, Esteban 1995, Kollef 1997, and Marelich 2000. The third component consists of a list of criteria for deciding if the patient is ready for extubation (such as that used by Hendrix 2006). In many ICUs, protocols are presented as written guides or algorithms and ventilator settings are manually adjusted by healthcare professionals. More recently, progress in ventilator microprocessor technology has enabled the development of computer-assisted management of ventilation and weaning. Computer ventilatory management adapts the ventilator output to the patient's needs using closed loop systems. These systems measure and interpret respiratory data in real time and provide continual adjustment of the level of assistance within targeted values. It is suggested that through enabling 'interaction' between the patient and the ventilator, the closed loop systems may improve mechanical ventilation tolerance and reduce the work of breathing (Burns 2008). Multiple, commercial computerized ventilation and weaning programs have been developed, including adaptive support ventilation, proportional assist ventilation and PSV(SmartCare^{TM}/pressure support) (Rose 2007).

How the intervention might work

Clinicians have different experiences, skills and weaning philosophies, thus there is potential for variation. As a result, there has been increasing interest in establishing more consistent practice in ICUs by developing and using weaning protocols that provide structured guidance. Protocols are based on the principle that the collective knowledge of a group is usually better than that of an individual. Protocols are intended to reduce variation, to improve efficiency of practice by reducing the influence of subjectivity of judgement and experience, and by seeking to apply objectivity (Murtagh 2007). Furthermore, they can empower the nurse and respiratory therapist to initiate the process of early weaning from the ventilator by identifying patients who are ready.

Why it is important to do this review

Our initial review of 11 trials concluded that weaning protocols are safe and effective in reducing the time spent on mechanical ventilation. Notwithstanding, we found considerable heterogeneity in results reporting total duration of ventilation and weaning duration. The variability may reflect the fact that protocols differ in more ways than in composition alone. While many protocols include readiness to wean criteria and guidelines for reducing ventilator support, the criteria applied and guidance used varied. Trials of protocolized weaning are continuing (Roh 2012) and the adoption of weaning protocols is growing. Surveys show reported use in ICUs of 8% in Greece, 56% in Italy, Denmark and Norway, 61% in the UK, 68% in Switzerland and the Netherlands (Rose 2011), 22% in Poland (Kubler 2013), and 71% in Canada (Ellis 2012). For these reasons. it is important that findings from recent trials are synthesized to guide future practice.

In addition to weaning protocols, another key feature in the management of weaning is the use of sedation and analgesia. Mechanical ventilation is generally accompanied by administration of high doses of sedative medications, and sedative management is known to influence the duration of mechanical ventilation. Recent clinical trials evaluating sedation management strategies (Bucknall 2008; Girard 2008; Mehta 2008; Mehta 2012) have all reported effects on the duration of mechanical ventilation and ICU stay. A systematic review of the effectiveness of protocol-directed sedation on duration of mechanical ventilation is underway (Aitken 2012); therefore this review does not include sedation protocols.

OBJECTIVES

The first objective of this review was to compare the total duration of mechanical ventilation of critically ill adults who were weaned using protocols versus usual (non-protocolized) practice.

The second objective was to ascertain differences between protocolized and non-protocolized weaning in outcomes measuring weaning duration, harm (adverse events) and resource use (intensive care unit (ICU) and hospital length of stay, cost).

The third objective was to explore, using subgroup analyses, variations in outcomes by type of ICU, type of protocol and approach to delivering the protocol (professional-led or computer-driven).

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs) and quasi-RCTs that compared protocolized with non-protocolized (usual) weaning practices.

Types of participants

We included critically ill adults (at least 18 years of age and over) receiving invasive mechanical ventilation with either a nasotracheal or an orotracheal tube. We excluded studies involving children, those exploring non-invasive ventilation as a weaning strategy and studies of tracheotomized patients only.

Types of interventions

We compared two strategies to achieve discontinuation from invasive mechanical ventilation: protocolized weaning and non-protocolized weaning (or usual practice). For the purpose of this review, discontinuation was defined as the time when mechanical ventilatory support was discontinued and the patient was breathing spontaneously through a T-piece circuit or following extubation. In addition, protocolized weaning was defined as a method of limiting the duration of invasive ventilation that includes at least the first two of the following three components.

1. A list of objective criteria based on general clinical factors for deciding if a patient is ready to tolerate discontinuation of mechanical ventilation.
2. Structured guidelines for reducing ventilatory support, such as a spontaneous breathing trial or a stepwise reduction in support to achieve discontinuation (e.g. synchronized intermittent mechanical ventilation (SIMV) or pressure support ventilation (PSV)).
3. A list of criteria for deciding if the patient is ready for extubation.

We did not exclude studies that did not include formal extubation criteria as not all studies included this component; and delay in extubation may be caused by organizational factors and not necessarily by delays in weaning. Usual weaning practice was defined as the usual practice in an ICU (as stated by the authors) where no written guides were applied. Where possible, usual practice was described in the review.

Types of outcome measures

Primary outcomes

1. Total duration of mechanical ventilation (time in hours, from mechanical ventilation initiation to discontinuation).

Secondary outcomes

1. Mortality (as stated by the study authors).
2. Number of patients experiencing the adverse events: reintubation; self extubation; tracheostomy; requirement for protracted mechanical ventilation (greater than 21 days).
3. Quality of life (as stated by the authors).
4. Weaning duration (time, as stated by the authors, from identification of weaning readiness to mechanical ventilation discontinuation).
5. ICU length of stay.
6. Hospital length of stay.
7. Cost.

Search methods for identification of studies

The search was performed by the Trials Search Co-ordinator (Karen Hovhannisyan) using the standard strategy of the Cochrane Anaesthesia Review Group of The Cochrane Collaboration.

Electronic searches

In this updated review, we searched the current issue of the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* Issue 1, 2014), MEDLINE (1950 to January 2014), EMBASE (1988 to January 2014), CINAHL (1937 to January 2014), ISI Web of Science (to February 2014) and LILACS (to January 2014). The search strategies for each database can be found in the appendices (Appendix 1: MEDLINE; Appendix 2: EMBASE; Appendix 3: LILACS; Appendix 4: CINAHL; Appendix 5: CENTRAL; Appendix 6: ISI Web of Science). The original search was performed in January 2010 (Blackwood 2010).

Searching other resources

In addition, we searched the reference lists of all identified study reports; we contacted authors for further information on ongoing trials; and we searched the meta-register of controlled trials web site at http://www.controlled-trials.com.

Data collection and analysis

BB entered the data into Review Manager 5 software (RevMan 2014) and POH checked data entry.

Selection of studies

Two authors (BB, POH) independently scanned the titles and abstracts identified by electronic searching, manual searches and contact with experts. Two authors (BB, POH) retrieved and evaluated the full text versions of potentially relevant studies.

Data extraction and management

Two authors (BB, KB) independently extracted data using a modified paper version of the Cochrane Anaesthesia Review Group's data extraction form (Appendix 7). We extracted information pertaining to the study design, method of randomization, study use of allocation concealment; and reporting of the study setting and participants, inclusion and exclusion criteria, interventions and

outcomes. We contacted the authors of included studies if sufficient information was unavailable in the publications, and to obtain raw data. There were no disagreements requiring consultation with a third author.

Assessment of risk of bias in included studies

BB and KB used The Cochrane Collaboration's domain-based evaluation tool for assessing the risk of bias in included studies (Higgins 2011a), in the following seven domains.

1. Random sequence generation

Random allocation sequence generation included any method that used an unpredictable sequence of allocating participants to groups, such as a random table; computer-generated random numbers; throwing dice; or shuffling envelopes.

2. Allocation concealment

Adequate allocation concealment included central randomization (for example allocation by a central office unaware of participant characteristics); on-site computer system combined with allocation kept in a locked unreadable computer file accessed only after the characteristics of an enrolled participant were entered; sequentially numbered, sealed, opaque envelopes or other similar approaches that ensured the person who generated the allocation scheme did not administer it.

3. Blinding of participants and personel

We report any attempts to blind up until the point of randomization.

4. Blinding of outcome assessment

We ascertained if study outcome assessors were independent from the clinical personnel delivering or supervising the assigned intervention.

5. Incomplete outcome data

6. Selective reporting

7. Other bias

Within each study we described what was reported for each domain and contacted the authors for additional information, where necessary. We evaluated the risk of bias for each domain as follows.

Low risk: criteria appropriately applied and described in the report or ascertained in communication with the primary author of the study.

Unclear: criteria not described and impossible to acquire from or clarify with the author.

High risk: criteria inappropriately applied.

Blinding of study personnel (domain 3) is impossible in these trials and, as a result, all studies were assessed as high risk of bias in this domain. Therefore, we amended the previous version of classification of included studies as follows.

A - Low risk of bias: all criteria met, except domain 3.

B - Moderate risk of bias: domain 3 not met, and one or more criteria unclear.

C- High risk of bias: two or more criteria not applied or met.

At each stage, BB and KB compared results.

Measures of treatment effect

We expressed treatment effect using the odds ratio (OR) for dichotomous data and mean difference (MD) for continuous data.

Unit of analysis issues

There were no cross over studies and randomization was by patient, therefore there were no unit of analysis issues.

Dealing with missing data

We contacted authors for clarification where data were missing or unclear.

Assessment of heterogeneity

We informally evaluated the degree of statistical heterogeneity by visual inspection of forest plots and more formally by measuring the impact of heterogeneity using the I^2 statistic (I^2 > 50%: significant heterogeneity); we tested it using the Chi^2 statistic (P < 0.05) (Higgins 2002).

We evaluated clinical heterogeneity (differences in the studies in relation to type of ICU, clinician(s) involved in weaning and the protocol used to guide the weaning process) using clinical judgement. We calculated pooled summary estimates of effect only in the absence of clinical heterogeneity.

Assessment of reporting biases

We constructed funnel plots (trial effect versus standard error) to assess possible publication bias when sufficient (at least five) studies were identified (Egger 1997).

Data synthesis

For continuous variables (duration of mechanical ventilation, duration of weaning, ICU and hospital length of stay) the data were skewed; therefore, these data were log transformed for the primary analyses. In three studies the authors provided the means and standard deviations on the log scale (Ely 1996; Navalesi 2008; Rose 2008). In three studies the authors provided raw data (Ogica 2007; Reardon 2011; Roh 2012) for log transformation. In five studies where only means and standard deviations of the unlogged data were available (de Carvalho Oliveira 2002; Kollef 1997; Piotto 2011; Simeone 2002; Strickland 1993) approximations were used to calculate the mean and standard deviation on the log scale using Method 1 in Higgins (Higgins 2008). In five studies we could only obtain outcomes reported as the median and interquartile range (Chaiwat 2010; Krishnan 2004; Marelich 2000; Namen 2001; Stahl 2009): we approximated the mean using the median as suggested previously (Hozo 2005) and approximate standard deviation estimates were calculated from the interquartile range on the log scale as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). The difference between

the treatment and control groups in the mean of a variable on the log scale was exponentiated to give the ratio of geometric means of the variable on the unlogged scale. This was generally reported as a percentage increase (or reduction) in geometric mean in the treatment group compared with the control group for ease of understanding (see Bland 1996 for more details). One study (Fan 2013) reported the mean with no standard deviation for duration of mechanical ventilation, duration of weaning, ICU length of stay and cost; we excluded this study from meta-analyses of these outcomes. We undertook meta-analyses for similar comparisons and the same outcomes across studies. We calculated pooled estimates of the difference in means using either the fixed-effect model or the random-effects model, depending on the degree of heterogeneity.

Subgroup analysis and investigation of heterogeneity

We planned to perform subgroup analyses to assess the impact of type of ICU, type of protocol and approach to delivering the protocol (physician-led, non-physician led or computer-driven) on the total duration of mechanical ventilation and weaning duration. We performed subgroup analyses for type of ICU (medical, surgical, mixed, neurosurgical) and approach (professional-led and computer-driven) on duration of mechanical ventilation. We were unable to complete the other subgroup analyses due to the small number of studies in some subgroups and lack of clarity in studies on protocol delivery.

Sensitivity analysis

A priori, we planned a sensitivity analysis to assess the impact of excluding studies with a high risk of bias (that is those in which there was a high risk of bias in two or more of the six domains) on the total duration of mechanical ventilation and weaning duration. In addition, we conducted a further sensitivity analysis to show the results using the unlogged data.

Summary of findings

We used the principles of the GRADE system (Guyatt 2008) to assess the quality of the body of evidence in our review associated with five main specific outcomes (total duration of mechanical ventilation, weaning duration, ICU length of stay, ICU mortality, and reintubation). BB and POH independently graded the evidence prior to agreement and construction of the 'Summary of findings' table using the GRADE software (Higgins 2011b). We appraised the quality of evidence based on the extent to which we were confident that an estimate of effect reflected the outcome assessed. In doing this we considered study risk of bias, directness of the evidence, heterogeneity of the data, precision of the effect estimates, and risk of publication bias.

RESULTS

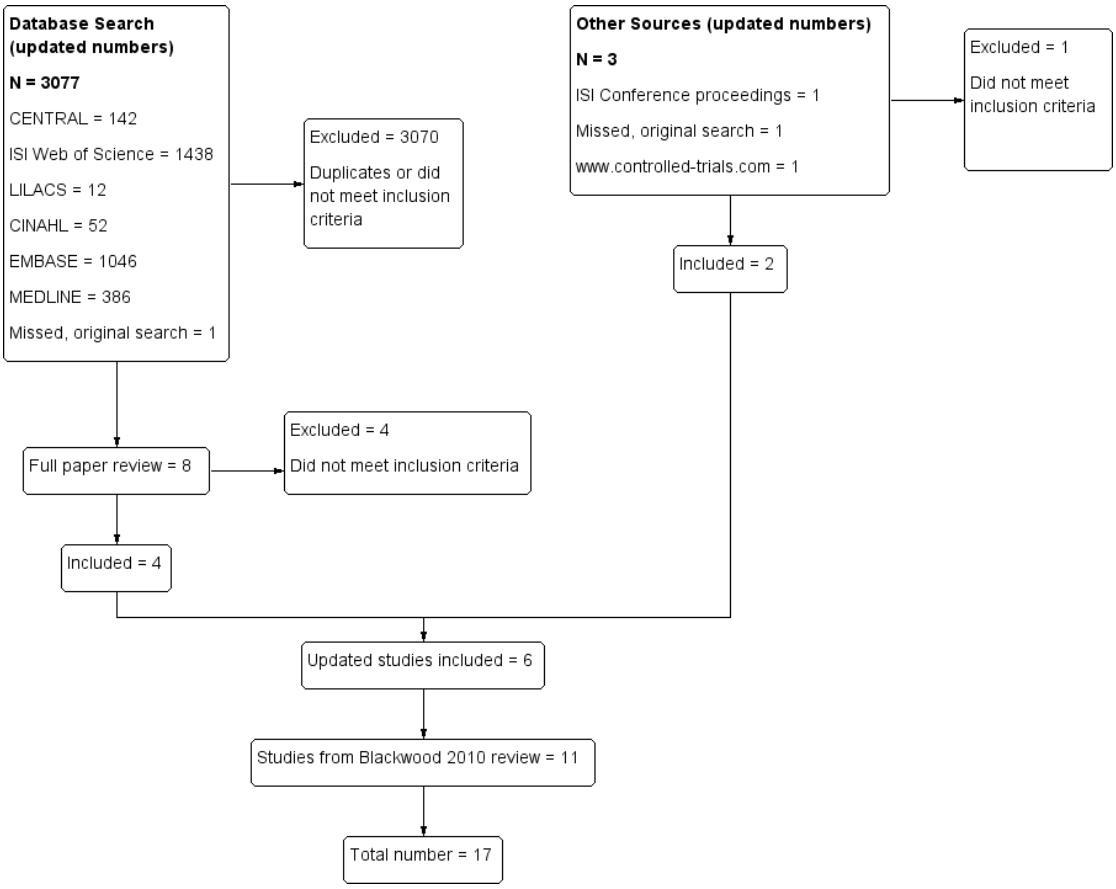
Description of studies

The studies were RCTs or quasi-RCTs conducted on mechanically ventilated adult patients in intensive care units (ICUs). The intervention groups were weaned following written or automated weaning protocols delivered by healthcare professionals or computer systems. The control groups were weaned according to the subjective judgement of healthcare professionals without the use of written, formal guidelines.

Results of the search

The original search resulted in 11 studies being included in our review (Blackwood 2010). As a result of our updated search we retrieved a total of 3080 citations: 3077 references from the database search, including one reference missed in the original search; three relevant references from web-based sources, including one abstract missed in the previous search. After reviewing the titles and abstracts, we identified and retrieved for review eight database references in full text, and obtained further information on three unpublished trials located on the controlled trials web site and conference proceedings (see Figure 1). We excluded four database references (Gnanapandithan 2011; Liu 2013; Ma 2010a; Ma 2010b) and one conference abstract (Vaschetto 2011) that did not meet our inclusion criteria. We included six studies with 463 participants (Chaiwat 2010; de Carvalho Oliveira 2002; Fan 2013; Ogica 2007; Reardon 2011; Roh 2012) following this search, bringing the total number included in this review to 17 studies with 2434 participants.

Figure 1. Updated study flow diagram.



Included studies

The 17 studies included in this updated review are described in the Characteristics of included studies tables. The individual studies involved sample sizes of 15 to 357 participants and took place in ICUs. Studies were conducted in four continents: nine American studies from the US (Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000; Namen 2001; Reardon 2011; Strickland 1993) and Brazil (de Carvalho Oliveira 2002; Piotto 2011); four European studies from Italy (Navalesi 2008; Simeone 2002), Germany (Stahl 2009) and Romania (Ogica 2007); three Asian studies from China (Fan 2013), South Korea (Roh 2012) and Thailand (Chaiwat 2010); and one study from Australia (Rose 2008). Participants were recruited from a variety of ICUs, including medical (Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000; Reardon 2011; Roh 2012; Strickland 1993); coronary (Ely 1996; Piotto 2011); surgical (Chaiwat 2010; Kollef 1997; Stahl 2009); surgical and trauma (Marelich 2000); mixed (including medical, surgical and trauma patients) (de Carvalho Oliveira 2002; Rose 2008); neurosurgical (Fan 2013; Namen 2001; Navalesi 2008); cardiac surgical units (Simeone 2002); and two were not reported (Fan 2013; Ogica 2007). One study specified the population (neurosurgical) rather than the unit (Namen 2001). Three studies were conducted in multiple ICUs (Ely 1996; Kollef 1997; Marelich 2000), and the remaining studies were conducted in single sites.

The reported time of randomizing patients to weaning protocol or usual practice groups varied among trials. In six trials this was either not reported (de Carvalho Oliveira 2002; Fan 2013; Krishnan 2004; Ogica 2007; Piotto 2011; Simeone 2002) or reported as 'on enrolment', but the timing of enrolment was unclear (Ely 1996; Navalesi 2008). Seven trials randomized patients when they met weaning criteria (Marelich 2000; Namen 2001; Reardon 2011; Roh 2012; Rose 2008; Stahl 2009; Strickland 1993), and two trials randomized on ICU admission (Chaiwat 2010; Kollef 1997).

Five studies provided details of the ventilatory modes used as 'usual practice' in the control group; these were the four computer-led studies (Reardon 2011; Rose 2008; Stahl 2009; Strickland 1993)

and one professional-led study (Piotto 2011). Usual practice involved a reduction in respiratory rate in synchronized intermittent mechanical ventilation (SIMV) and a reduction in pressure support (Piotto 2011; Strickland 1993); a reduction in positive end expiratory pressure (PEEP) and pressure support (Rose 2008); a reduction in pressure support (Stahl 2009); and a reduction in pressure support followed by a spontaneous breathing trial (SBT). The remaining 12 studies described usual practice as weaning according to the physician's discretion but did not describe what this constituted. A printed standard approach to ventilatory management was used to guide usual practice in the surgical and trauma unit in the Marelich 2000 study; the author was unable to provide further information on the ventilatory mode used or compliance with its use.

The weaning protocol was professional-led in 13 studies and computer-led in four studies. Professional-led weaning was delivered by registered nurse and respiratory therapist (Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000); by registered nurse (Chaiwat 2010; Roh 2012); by respiratory therapist (Namen 2001); by physician, registered nurse and respiratory therapist (Navalesi 2008); and unclear or not stated in five studies (de Carvalho Oliveira 2002; Fan 2013; Ogica 2007; Piotto 2011; Simeone 2002). Computer-led weaning was delivered by Draeger EvitaXL ventilator with SmartCare^{TM}/pressure support software that titrated pressure support and initiated SBTs (Reardon 2011; Rose 2008; Stahl 2009) or an early computer prototype (Supersport model 2) that titrated respiratory rate and pressure support (Strickland 1993).

All studies, except Ogica 2007 (reported in an abstract) and Fan 2013, reported readiness to wean criteria for protocol entry. Criteria ranged from a list of five to 19, and parameters were inconsistent. Fourteen studies included criteria that measured oxygenation; namely PaO_2 and FiO_2 (Chaiwat 2010; de Carvalho Oliveira 2002; Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000; Namen 2001; Navalesi 2008; Piotto 2011; Reardon 2011; Rose 2008; Simeone 2002; Stahl 2009; Strickland 1993), and may or may not have included criteria relating to cardiovascular, neurological, inflammatory response, medication or other factors (see Table 1). Sedation scores were not reported as a readiness to wean criterion in any study, although awake and conscious/rousable was reported in four studies (Chaiwat 2010; Kollef 1997; Piotto 2011; Simeone 2002) and a Glasgow Coma Scale was reported in six studies with variable parameters (de Carvalho Oliveira 2002; Marelich 2000; Navalesi 2008; Piotto 2011; Rose 2008; Reardon 2011). The frequency of assessing readiness to wean was reported as twice daily (Marelich 2000); daily (Chaiwat 2010; Ely 1996; Fan 2013; Krishnan 2004; Namen 2001; Navalesi 2008; Piotto 2011; Reardon 2011); not reported (de Carvalho Oliveira 2002; Ogica 2007; Roh 2012); or only when the patient entered the study (Kollef 1997; Simeone 2002; Rose 2008; Stahl 2009; Strickland 1993).

In addition to the wide variety in ways of assessing readiness to wean, there were considerable differences in weaning methods (see Table 2). Eleven studies used a protocolized weaning intervention that included a SBT (Chaiwat 2010; de Carvalho Oliveira 2002; Ely 1996; Fan 2013; Krishnan 2004; Marelich 2000; Namen 2001; Navalesi 2008; Ogica 2007; Piotto 2011; Roh 2012). In addition, Marelich 2000 used a stepwise reduction in PEEP, SIMV and pressure support prior to the SBT in patients ventilated for more than 72 hours, and Roh 2012 used a Continuous Positive Airway Pressure (CPAP) trial followed by gradual reduction of pressure support prior to the SBT. One trial used a weaning protocol consisting of stepwise reductions in SIMV and pressure support with extubation (Simeone 2002). Kollef 1997 implemented different protocols in four ICUs: SBT and extubation; SIMV reduction and extubation; and pressure support reduction and extubation. Weaning parameters varied among trials. SBTs ranged from 30 to 120 minutes, delivered through a T-tube or ventilator circuit with CPAP ranging from 2 to 5 cmH_2O with or without pressure support of 6 or 7 cmH_2O. In pressure support weaning protocols, the pressure support was reduced to levels ranging from 4 to 8 cmH_2O prior to extubation. In SIMV weaning protocols, respiratory rates were reduced to between 0 and 6 breaths/minute prior to a SBT or extubation. In automated weaning protocols, the pressure support was reduced to levels between 5 or 7 cmH_2O prior to a SBT.

All studies, with the exception of Reardon 2011 and Strickland 1993, reported on the review's primary outcome measure, total duration of mechanical ventilation. Strickland's data collection was limited to 48 hours because the trial tested a computerized protocol and only one computer system was available for the study. Only one study reported time from discontinuation from mechanical ventilation to extubation (Piotto 2011), and no study reported quality of life.

Excluded studies

We excluded 14 studies. Eight studies (Beale 2008; Donglemans 2009; Lellouche 2006; Liu 2013; Ma 2010b; NCT00502489; NCT00445289; Taniguchi 2009) compared automated (computerized) protocolized weaning with standardized weaning guidelines as opposed to 'no guidelines'. Gnanapandithan 2011 compared two different weaning protocols. Ma 2010a compared the efficacy of a SBT prior to extubation; the weaning method was the same in both groups. Vaschetto 2011 included tracheotomized patients only. In addition, East 1999 and McKinley 2001 evaluated automated (computerized) protocolized weaning in a population of adult respiratory distress syndrome patients using a cluster-RCT. From the papers, we were unable to identify the comparator or the weaning outcomes, and we were unable to contact the authors to obtain further information. One registered trial was not completed due to recruitment problems, and the data were unobtainable (NCT00157287). See the Characteristics of excluded studies tables.

Risk of bias in included studies

We used The Cochrane Collaboration's domain-based evaluation table provided in Review Manager 5 (RevMan 2014) to assess included trials for risk of selection, performance, detection, attrition, reporting and other bias (see Figure 2 and Figure 3).

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

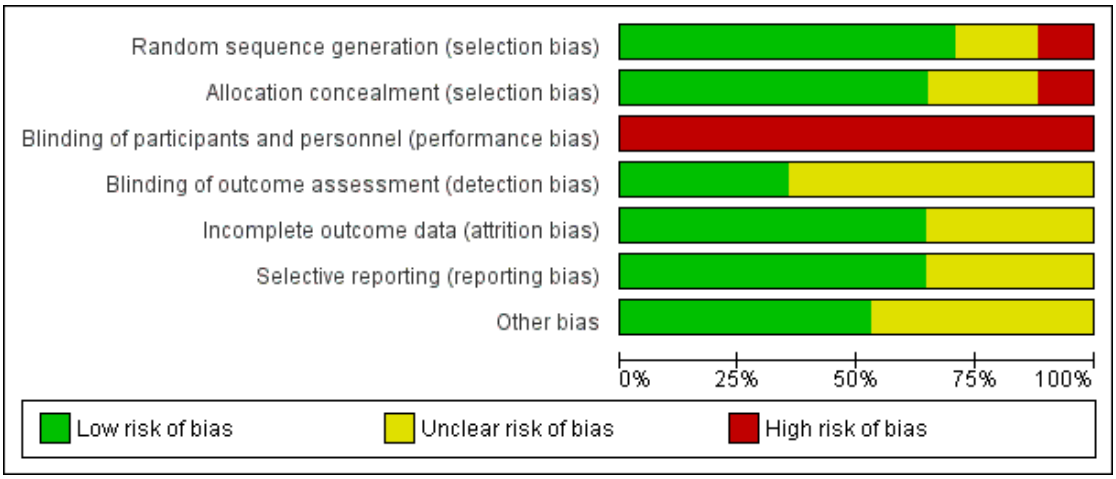
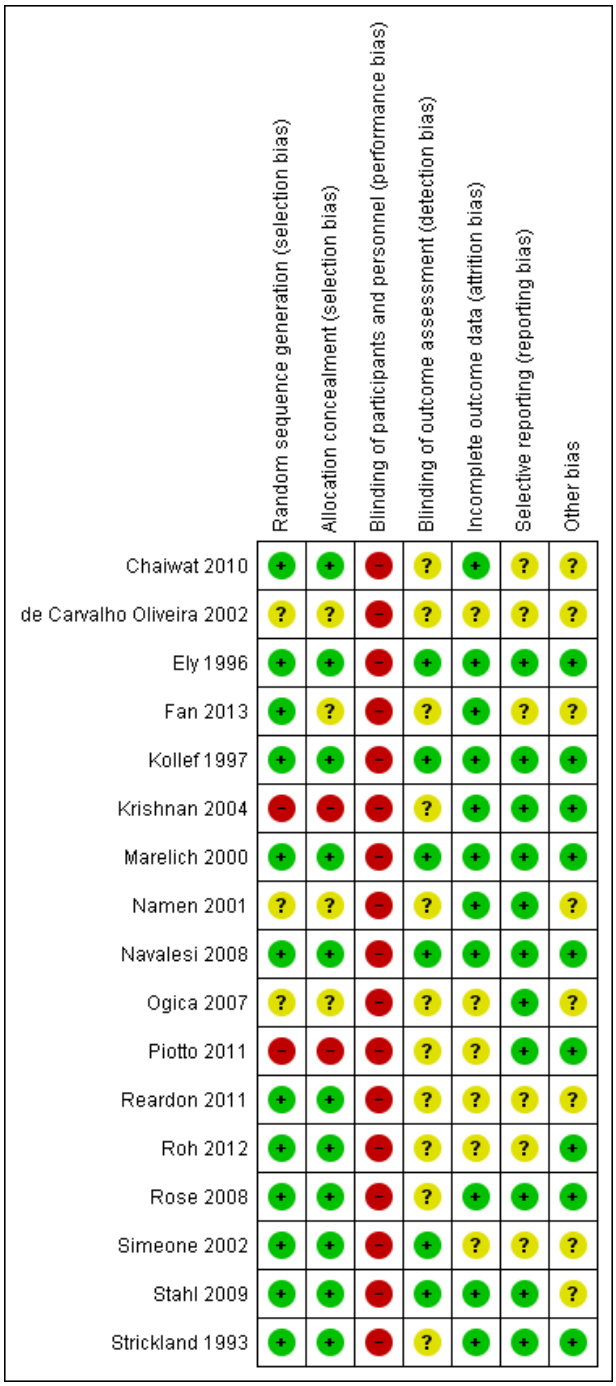


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Allocation

In 11 (69%) studies, we assessed risk of selection bias as low because the allocation and concealment of participants to groups was adequately conducted (Chaiwat 2010; Ely 1996; Kollef 1997; Marelich 2000; Navalesi 2008; Reardon 2011; Roh 2012; Rose 2008; Simeone 2002; Stahl 2009; Strickland 1993). Three studies (de Carvalho Oliveira 2002; Namen 2001; Ogica 2007) did not report their methods and two studies used inadequate methods: Krishnan 2004 allocated using odd and even hospital numbers; and Piotto 2011 allocated sequentially on recruitment. One study (Fan 2013) used a random numbers table to generate the sequence, but it was unclear how allocation was concealed.

Blinding

Blinding of study participants and personnel from intervention allocations after inclusion of participants was not possible in these studies, thus we assessed the risk of performance bias as high for all studies. Eleven (65%) studies were assessed as being at unclear risk because they did not report if outcome assessors were blinded (Chaiwat 2010; de Carvalho Oliveira 2002; Fan 2013; Krishnan 2004; Namen 2001; Ogica 2007; Piotto 2011; Reardon 2011; Roh 2012; Rose 2008; Simeone 2002) and the remaining six studies had low risk of detection bias.

Incomplete outcome data

Eleven (65%) studies reported complete outcome data (Chaiwat 2010; Ely 1996; Fan 2013; Kollef 1997; Krishnan 2004; Marelich 2000; Namen 2001; Navalesi 2008; Rose 2008; Stahl 2009; Strickland 1993) and the remaining six studies reported insufficient information on the recruitment, attrition and exclusion numbers to permit a judgement (de Carvalho Oliveira 2002; Ogica 2007; Piotto 2011; Reardon 2011; Roh 2012; Simeone 2002).

Selective reporting

Eleven studies provided a description or algorithm for their intervention, ventilator weaning protocol (Chaiwat 2010; de Carvalho Oliveira 2002; Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000; Namen 2001; Navalesi 2008; Piotto 2011; Roh 2012; Strickland 1993) and three described the automated computer system (Reardon 2011; Rose 2008; Stahl 2009). Eleven (63%) studies reported prespecified outcomes and we assessed these at low risk of reporting bias. We assessed six studies (Chaiwat 2010; de Carvalho Oliveira 2002; Fan 2013; Reardon 2011; Roh 2012; Simeone 2002) at unclear risk because they did not prespecify outcomes, or did not report usual outcomes of interest in protocolized weaning trials (duration of mechanical ventilation, mortality, ICU length of stay).

Other potential sources of bias

Nine studies appeared free from 'other sources of bias' as determined in The Cochrane Collaboration's domain-based evaluation (Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000; Navalesi 2008; Piotto 2011; Roh 2012; Rose 2008; Strickland 1993). Four studies were stopped early for futility (Chaiwat 2010; Namen 2001; Reardon 2011; Stahl 2009); Simeone 2002 reported unsubstantiated findings; Fan 2013 reported insufficient information to permit judgement; and the Ogica 2007 study was published as an abstract so there was insufficient information to permit judgement.

Effects of interventions

See: **Summary of findings for the main comparison**

All trials presented data suitable for inclusion in the meta-analyses. All study authors were contacted to confirm and supplement, where needed, information related to study methods and data. Fourteen study authors responded (Ely 1996; de Carvalho Oliveira 2002; Kollef 1997; Krishnan 2004; Marelich 2000; Namen 2001; Navalesi 2008; Ogica 2007; Piotto 2011; Reardon 2011; Roh 2012; Rose 2008; Simeone 2002; Stahl 2009), although not all were able to supply information. Three study authors could not be contacted (Chaiwat 2010; Fan 2013; Strickland 1993). We converted all reported durations of mechanical ventilation and weaning to hours; ICU and hospital length of stay are reported in days. Fan 2013 reported the mean only for these outcomes; these data were not included in meta-analyses and are reported in the text. We present the results in three sections. In section one, we present the primary analysis for total duration of mechanical ventilation, weaning duration, ICU and hospital length of stay using log-transformed data due to the skewed distribution of these outcomes. We also present subgroup analyses for type of ICU and approach on the durations of mechanical ventilation and weaning. In section two, we present a sensitivity analysis of the logged data for duration of mechanical ventilation and weaning duration that excludes studies judged at high risk of bias (Krishnan 2004; Piotto 2011). In section three, we present a further sensitivity analysis using the mean and standard deviation prior to log-transformation for total duration of mechanical ventilation, weaning duration, ICU and hospital length of stay for all studies. We present this sensitivity analysis to show the effects without log-transformation.

Section 1. Primary analysis: comparison of protocolized versus non-protocolized weaning

Total duration of mechanical ventilation

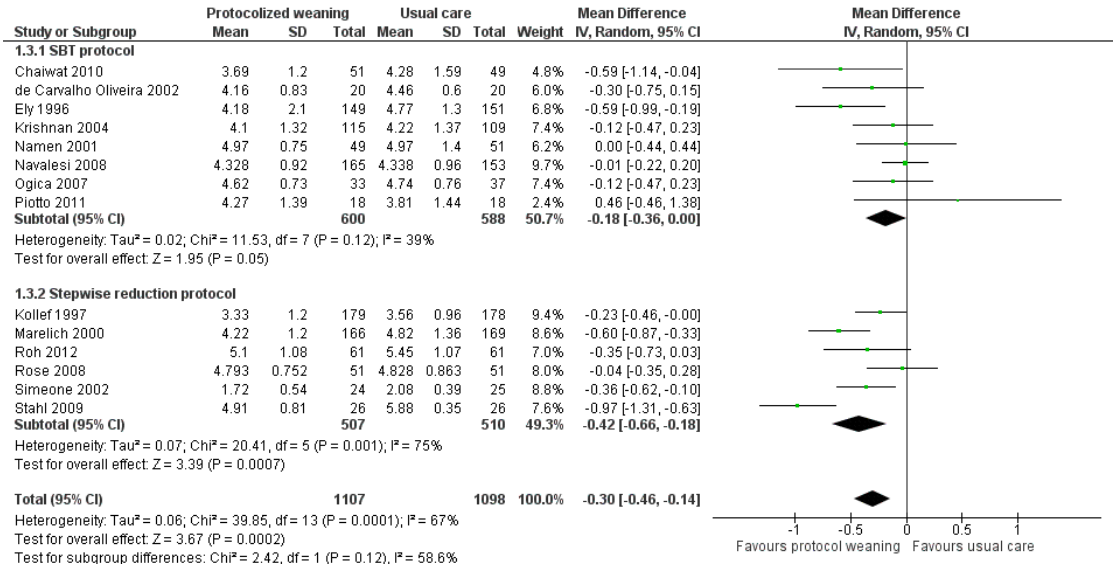
Fourteen trials reported the total duration of mechanical ventilation and we included them in the meta-analysis (Chaiwat 2010; de Carvalho Oliveira 2002; Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000; Namen 2001; Navalesi 2008; Ogica 2007; Piotto 2011; Roh 2012; Rose 2008; Simeone 2002; Stahl 2009). Strickland 1993 did not measure this outcome as the trial duration was 48 hours for each individual patient, and Reardon 2011 did not report the outcome. Pooled data, using the random-effects model because of significant (P < 0.0001) and substantial heterogeneity (I^2 = 67%), showed a significant reduction in duration of mechanical ventilation in the protocolized weaning group (mean log -0.30, 95% confidence interval (CI) -0.46 to -0.14, P = 0.0002) equivalent to a reduction of 26% (95% CI 13% to 37%) in the geometric mean. Fan 2013 reported a non-significant reduction of 151.52 hours for the protocolized weaning group (mean 272.01 versus 423.53, P = 0.20).

We performed a subgroup analysis to assess the impact of type of ICU on the total duration of mechanical ventilation. The ICU subgroups included: mixed ICUs that incorporated medical, surgical and trauma patients (de Carvalho Oliveira 2002; Kollef 1997; Marelich 2000; Ogica 2007; Piotto 2011; Rose 2008); neurosurgical ICUs (Namen 2001; Navalesi 2008); surgical ICUs (Chaiwat 2010; Simeone 2002; Stahl 2009); and medical ICUs (Ely 1996; Krishnan 2004; Roh 2012). Pooled data from the neurosurgical subgroup showed no difference in duration of mechanical ventilation (mean log -0.01, 95% CI -0.2 to 0.18, P = 0.93; equivalent to a 1% reduction, 95% CI 20% reduction to 18% increase in geometric mean). Pooled data in the other three subgroups showed a significant reduction in duration of mechanical ventilation in the protocolized weaning arm: mixed ICU subgroup (N = 6 trials, mean log -0.23, 95% CI -0.44 to -0.02, P = 0.03, equivalent to a 21% 95% CI 2% to 36% reduction in geometric mean); surgical ICU subgroup (N = 3 trials, mean log -0.63, 95% CI -1.05 to -0.22, P = 0.003 equivalent to a 47%, 95% CI 20% to 65% reduction in geometric mean); and medical ICU subgroup (N = 3, mean log -0.34, 95% CI -0.61 to -0.07, P = 0.01 equivalent to a 29%, 95% CI 7% to 46% reduction in geometric mean). There was evidence of a difference in estimates between the four subgroups (P for subgroup differences = 0.02). See Analysis 1.1.

We performed a subgroup analysis to assess the impact of type of approach: professional-led or computer-driven. Pooled data from 12 studies using a professional-led approach (Chaiwat 2010; de Carvalho Oliveira 2002; Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000; Namen 2001; Navalesi 2008; Ogica 2007; Piotto 2011, Roh 2012; Simeone 2002) showed a significant reduction in duration of mechanical ventilation favouring the protocolized weaning arm (mean log -0.27, 95% CI -0.40 to -0.13, P = 0.0002 equivalent to a 24% 95% CI 12% to 49%) reduction in the geometric mean; there was significant moderate heterogeneity (P = 0.03, I^2 = 48%). Pooled data from the computer-driven subgroup (Rose 2008; Stahl 2009) showed no difference in duration of mechanical ventilation (mean log -0.5, 95% CI -1.42 to 0.42, P = 0.28; equivalent to 39% reduction, 95% CI 52% reduction to 76% increase in geometric mean). There was no evidence of a difference in estimates between subgroups (P = 0.62 for subgroup differences). See Analysis 1.2.

The larger number of trials included in this updated review allowed us to perform a subgroup analysis on type of protocol (Figure 4). Protocol subgroups were a spontaneous breathing trial (SBT) (comprising daily assessment of readiness to wean followed by SBT) and stepwise reduction (comprising a gradual reduction in either intermittent mandatory ventilation or pressure support ventilation (PSV) with or without a SBT). We included automated systems in this latter subgroup as these involved stepwise reductions in support. Eight trials evaluated a SBT protocol (Chaiwat 2010; de Carvalho Oliveira 2002; Ely 1996; Krishnan 2004; Namen 2001; Navalesi 2008; Ogica 2007; Piotto 2011). Pooled data indicated a trend towards reduced duration of ventilation in the SBT subgroup with low heterogeneity (39%), but was not significant (mean log -0.18, 95% CI -0.36 to 0.00, P =0.05; equivalent to a 16%, 95% CI 0% to 30% reduction in geometric mean). Six trials evaluated a stepwise reduction protocol (Kollef 1997; Marelich 2000; Roh 2012; Rose 2008; Simeone 2002; Stahl 2009). There was a significant reduction in duration of ventilation in this protocol group (mean log -0.42, 95% CI -0.66 to -0.18, P = 0.0007; equivalent to a 34%, 95% CI 16% to 48% reduction in geometric mean); there was also significant heterogeneity in effect estimates (I^2 = 75%, P = 0.001). See Analysis 1.3.

Figure 4. Forest plot of comparison: 1 Primary analysis: protocolized versus non-protocolized weaning, outcome: 1.3 Total duration of mechanical ventilation by type of protocol [log hours].



Mortality

Fourteen trials reported ICU, or hospitality mortality, or both. Pooled data from eight trials (Ely 1996; Kollef 1997; Krishnan 2004; Marelich 2000; Namen 2001; Reardon 2011; Roh 2012; Stahl 2009) showed no difference in hospital mortality (odds ratio (OR) 1.04, 95% CI 0.82 to 1.32, P = 0.74). Pooled data from seven trials (de Carvalho Oliveira 2002; Fan 2013; Navalesi 2008; Ogica 2007; Piotto 2011; Rose 2008; Stahl 2009) showed no difference in ICU mortality (OR 0.93, 95% CI 0.58 to 1.48, P = 0.75) (Analysis 1.4).

Adverse events

Adverse events were reported in 11 trials and the OR was not significant between groups. Reintubation was reported in 11 trials (Chaiwat 2010; de Carvalho Oliveira 2002; Ely 1996; Kollef 1997; Namen 2001; Navalesi 2008; Piotto 2011; Reardon 2011; Rose 2008; Simeone 2002; Stahl 2009) with an 11% (158/1484) event rate. The pooled result was not statistically significant (OR 0.74, 95% CI 0.44 to 1.23, P = 0.25) (Analysis 1.5). Self extubation was reported in three trials (Ely 1996; Namen 2001; Reardon 2011). There was a 3% (14/433) event rate and the pooled result was not statistically significant (OR 0.43, 95% CI 0.14 to 1.34, P = 0.15) (Analysis 1.6). Tracheostomy was reported in eight trials (Ely 1996; Marelich 2000; Namen 2001; Navalesi 2008; Reardon 2011; Roh 2012; Piotto 2011; Rose 2008) with an 11% (148/1346) event rate. The pooled effect was not statistically significant (OR 0.85, 95% CI 0.51 to 1.40, P = 0.51) (Analysis 1.7). Four trials reported the requirement for protracted mechanical ventilation at three different time points: > 21 days, > 14 days and > 7 days. Ely 1996 showed a significantly reduced likelihood of protracted mechanical ventilation (> 21 days) in the protocolized group (OR 0. 42, 95% CI 0.19 to 0.96, P = 0.04). Namen 2001 showed no difference in protracted mechanical ventilation (> 21 days) (OR 0.18, 95% CI 0.02 to 1.63, P = 0.21). Rose 2008 showed no difference in protracted mechanical ventilation (> 14 days) (OR 0.68, CI 0.20 to 2.31, P = 0.54); and Kollef 1997 showed no difference in protracted weaning (> 7 days) (OR 0.63, 95% CI 0.35 to 1.15, P = 0.13).

Quality of life

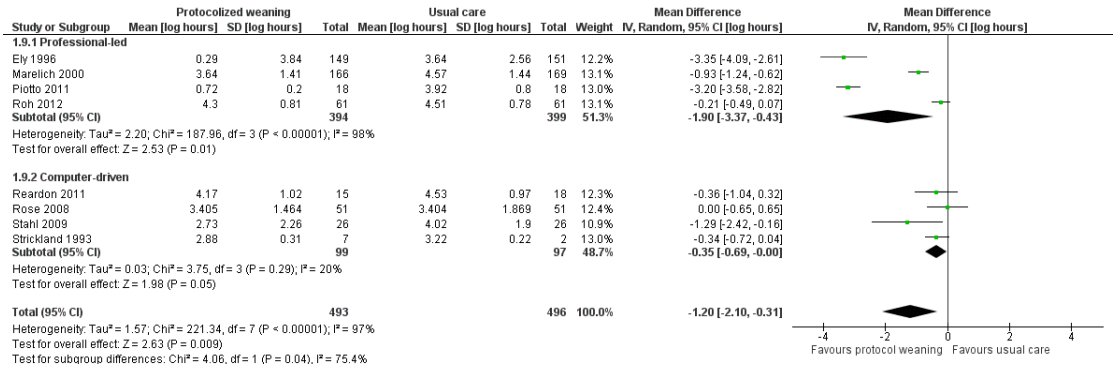
None of the trial authors reported on quality of life.

Weaning duration (hours)

In the meta-analysis, we included weaning duration reported in eight trials (Ely 1996; Marelich 2000; Piotto 2011; Reardon 2011; Roh 2012; Rose 2008; Stahl 2009; Strickland 1993). The pooled result, using the random-effects model because of significant (P < 0.00001) and considerable heterogeneity (I^2 = 97%), showed a significant reduction in the mean log for the protocolized weaning group (mean log -1.20, 95% CI -2.10 to -0.31, P < 0.009), which corresponds to a reduction of 70% (95% CI 27% to 88%) in the geometric mean (Analysis 1.8). Subgroups by type of ICU were

small and subgroup analyses showed no evidence of a difference in estimates (P for subgroup differences = 0.92). However, there was evidence of a significant difference among type of approaches (P for subgroup differences = 0.04) (Figure 5). Pooled results for the professional-led approach showed a significant mean log reduction for protocolized weaning (mean log -1.90, 95% CI -3.37 to -0.43, P = 0.01) corresponding to an 85% reduction (95% CI 35% to 97%) in the geometric mean. The computer-driven approach showed less of an effect (mean log -0.35, 95% CI -0.69 to -0.00, representing a reduction of 30%, 95% CI 0% to 50%, P = 0.05) that may be attributed to the small number of trials in this subgroup (Analysis 1.9).

Figure 5. Forest plot of comparison: 1 Primary analysis: protocolized versus non-protocolized weaning, outcome: 1.9 Weaning duration by type of approach [log hours].



There was evidence of a difference in estimates between the two protocol subgroups (P for subgroup differences < 0.00001). Weaning duration was significantly reduced in the stepwise reduction protocol group (mean log -0.46, 95% CI -0.81 to -0.12, P = 0.009, equivalent to a 37% reduction in geometric mean, 95% CI 11% to 56%). The effect on weaning duration was, expectedly, stronger in the SBT protocol subgroup (mean log -3.23, 95% CI -3.57 to -2.89, P < 0.00001; equivalent to a 96% reduction in geometric mean, 95% CI 94% to 97%) (Analysis 1.10).

Fan 2013 reported a significant reduction of 188.04 hours in weaning duration in the protocolized group (55.91 versus 243.95 hours, P < 0.01).

ICU length of stay (hours)

We entered data in the meta-analysis for ICU length of stay reported in nine trials (Ely 1996; Namen 2001; Krishnan 2004; Navalesi 2008; Piotto 2011; Roh 2012; Rose 2008; Simeone 2002; Stahl 2009). There was no statistical heterogeneity among studies (I^2 = 0%). Two trials (Krishnan 2004; Simeone 2002) showed a significant reduction in ICU stay in the protocolized weaning group and the others did not, but the pooled estimate was statistically significant (Analysis 1.11) (mean log -0.12, 95% CI -0.21 to -0.03, P = 0.01). This corresponds to an average percentage reduction in geometric mean in the protocolized weaning group of 11% (95% CI 3% to 19%). Fan 2013 reported a non-significant reduction of 205 hours in the protocolized weaning group (611.03 versus 816.03, P = 0.212).

Hospital length of stay (days)

Protocolized weaning produced no significant reduction (mean log -0.01, 95% CI -0.11 to 0.09, P = 0.84) in mean hospital length of stay in five trials (Ely 1996; Kollef 1997; Namen 2001; Roh 2012; Rose 2008). There was no heterogeneity (I^2 = 0%) (Analysis 1.12). This corresponded to an average percentage reduction in geometric mean of 1% (95% CI 9% reduction to 10% increase).

Economic costs

Four trials reported costs; three in the US (Ely 1996; Kollef 1997; Namen 2001) and one in China (Fan 2013). Ely 1996 and Namen 2001 reported no significant differences between groups in ICU costs (Analysis 1.13) (mean difference (MD) USD 3.37k, 95% CI -15.02 to 21.76, P = 0.72); and Ely 1996, Kollef 1997 and Namen 2001 reported no difference in hospital costs (Analysis 1.14) (MD USD 0.59k, 95% CI -4.67 to 3.49, P = 0.78). Fan 2013 reported a non-significant reduction of CNY 29,346.21 (CNY 101,642.74 versus CNY 130,988.95, P = 0.305), but it was unclear if this referred to hospital or ICU costs.

Section 2. Sensitivity analysis: comparison of protocolized versus non-protocolized weaning excluding high risk of bias studies

This sensitivity analysis explored the effects of the intervention when high risk of bias studies (Krishnan 2004; Piotto 2011) were excluded. Excluding these studies did not change the effects observed in the primary analysis. Pooled results showed that protocolized weaning significantly reduced the mean log duration of mechanical ventilation by an average of 0.33 (Analysis 2.1) (mean log -0.33, 95% CI -0.50 to -0.16, P = 0.0001), which corresponds to a reduction of 28% (95% CI 15% to 39%) in the geometric mean; there was significant heterogeneity (I^2 = 70%, P < 0.0001). Additionally, protocolized weaning significantly reduced the mean log weaning duration by an average of 1.64 (Analysis 2.2) (mean log -1.64, 95% CI -3.18 to -0.1, P = 0.04), which corresponds to a reduction of 81% (95% CI 10% to 96%) in the geometric mean; there was significant heterogeneity (I^2 = 97%, P < 0.00001).

Section 3. Sensitivity analysis: protocolized versus non-protocolized weaning for all studies, unlogged data

This sensitivity analysis explored the effects of the intervention on the data prior to log-transformation. In 11 studies we obtained the mean and standard deviation from the authors or the published papers (de Carvalho Oliveira 2002; Ely 1996; Kollef 1997; Navalesi 2008; Ogica 2007; Piotto 2011; Reardon 2011; Roh 2012; Rose 2008, Simeone 2002; Strickland 1993). In five studies where outcomes were reported as median and interquartile ranges (Chaiwat 2010; Krishnan 2004; Marelich 2000; Namen 2001; Stahl 2009), we approximated the mean and standard deviation as described in the methods.

The pooled result for duration of mechanical ventilation, using the random-effects model (because of significant heterogeneity) (I^2 = 48 %, P = 0.02), showed that protocolized weaning significantly reduced the total duration of mechanical ventilation by an average of 20.26 hours (Analysis 3.1) (MD -20.26 hours, 95% CI -5.24 to -35.28 hours, P = 0.008).

The pooled result for weaning duration, using the random-effects model (because of significant heterogeneity) (I^2 = 80 %, P < 0.0001), showed that protocolized weaning significantly reduced the weaning duration by an average of 39.35 hours (Analysis 3.2) (N = 7 trials, MD -39.35 hours, 95% CI -11.32 to -67.38 hours, P = 0.006).

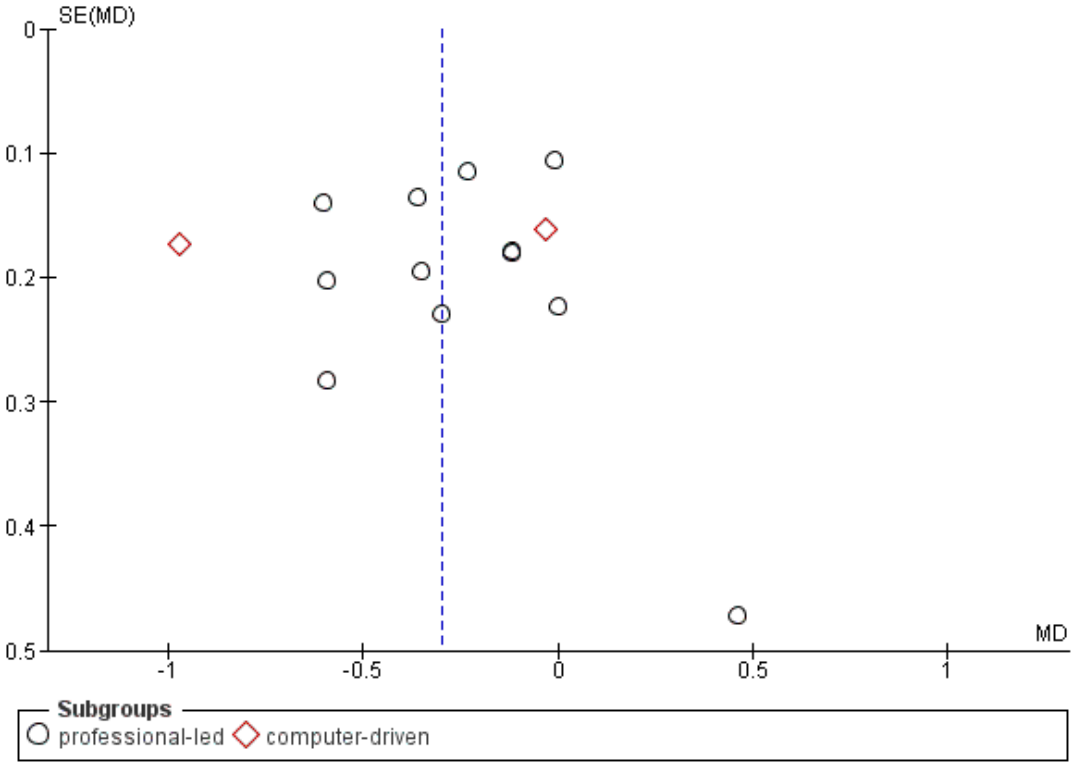
ICU length of stay was significantly reduced in the protocol group by an average of 9 hours (Analysis 3.3) (N = 9 trials, MD -9.08 hours, 95% CI -2.30 to -15.85, P = 0.009).

Pooled results for hospital length of stay showed no difference between groups (Analysis 3.4) (N = 5 trials, MD -1.32 days, 95% CI -3.09 to 0.44 days, P = 0.14).

Funnel plots

Although funnel plots did not conform to the expected shape, there was little evidence of asymmetry. As we were able to obtain published and unpublished data from studies reporting both significant and non-significant statistical differences in the primary outcome measure, we concluded that there was no evidence of publication or reporting bias. The non-conformity to expected shape may be due to small sample and effect sizes in some studies (see Figure 6).

Figure 6. Funnel plot of comparison: 1 Primary analysis: protocolized versus non-protocolized weaning, outcome: 1.2 Total duration of MV by type of approach [log hours].



DISCUSSION

The conclusions of our updated review remain the same as the original (Blackwood 2010). In comparison with usual (non-protocolized) weaning practice, protocolized weaning significantly reduced the total duration of ventilation, weaning duration and intensive care unit (ICU) length of stay without impacting on mortality or adverse events. There is significant heterogeneity among effect sizes. The evidence from trials of protocolized weaning to reduce the duration of mechanical ventilation in critically ill adults is derived from 17 trials which have a variety of settings, participants, interventions and outcome measures. The main outcome, duration of mechanical ventilation, was reported in 15 trials and data were available for seven out of eight secondary outcomes. The methodological quality of the studies varied from low to high. Fifteen trials were randomized and two were quasi-randomized.

Summary of main results

Impact on ventilation duration

In comparison with usual (non-protocolized) weaning practice, protocolized weaning significantly impacted on ventilation durations, reducing the total duration of mechanical ventilation by an average of 26% in geometric mean and weaning duration by 70%. However, substantial heterogeneity among study effect estimates (67% and 97% respectively) indicated that findings should be interpreted with caution. Subgroup analysis of total duration of mechanical ventilation by type of ICU, showed a significant difference in effect estimates between subgroups. In comparison with usual weaning practice, protocolized weaning significantly reduced the duration of ventilation in surgical (47% reduction in geometric mean), medical (29%) and mixed ICUs (21%), but not neurological ICUs (1%). There were no significant differences between subgroup effect estimates for type of delivery (professional and automated) and type of protocol (spontaneous breathing trial (SBT) and stepwise reduction). However, protocolized weaning delivered by professionals significantly reduced the geometric mean dura-

tion of mechanical ventilation (23%), as did protocols consisting of stepwise reductions in ventilator support (34%). For weaning duration, there was no evidence of a difference in effect estimates for type of ICU subgroups, but there were significant differences in effects for the type of delivery and type of protocol subgroups. Protocols delivered by professionals significantly reduced weaning duration by 85%, and although automated systems showed a 29% reduction in geometric mean, this did not reach significance. The SBT protocol group showed an unsurprising reduction in geometric mean (96%) (unsurprising because the SBT duration is generally fixed at 2 hours duration), while protocols comprising stepwise reductions in support, also showed a significant, albeit smaller, reduction (37%).

Impact on mortality and adverse events

Protocolized weaning did not impact on ICU or hospital mortality. Neither did it impact on adverse events such as reintubation, self extubation, tracheostomy, or protracted weaning at 7, 14 and 21 days.

Impact on resource utilisation

Protocolized weaning significantly reduced the mean geometric length of stay in ICUs by 11%, but with no impact on overall hospital length of stay. Basic costing exercises undertaken in four trials showed no statistically significant differences between groups in either ICU or hospital costs. However, these fail to provide a full understanding of the true impact of protocolized weaning, including costs associated with training. A cost-effectiveness analysis would be beneficial in enabling policymakers to compare the costs associated with protocolized weaning with the benefits gained.

Overall completeness and applicability of evidence

We are confident that our search strategy obtained all available updated studies and, through contact with experts, we were also able to obtain additional studies that did not appear in the previous search. The majority of trials evaluated spontaneous breathing trials (SBTs) or stepwise reduction in pressure support ventilation (PSV) protocols and thus provide a clear reflection of the evidence applicable to current weaning practice.

It is not easy to isolate the reasons for heterogeneity because weaning from ventilation is a complex process. It is plausible that heterogeneity may be due to contextual factors (differences in patient populations and usual practice within units); intervention factors (differences in determining readiness to wean and weaning protocols, trial fidelity); or inconsistency in measuring ventilation outcomes. A Cochrane synthesis review is in progress exploring the contribution of these factors in the trials included in this review, and on protocolized weaning in general, and may help explain the heterogeneity demonstrated in this review (Jordan 2012).

In contrast to the original review, this updated review showed a significant impact for protocolized weaning in mixed and medical ICU groups: previously protocols only impacted favourably in the surgical group. There was one additional study in a neurological intensive care unit (ICU), but as we could not include this in the meta-analysis it is difficult to assess a change in impact. Another important contextual factor, and one that causes controversy in ICU studies of non-pharmacological interventions, is the use of the 'usual care' group as a control in trials (Thompson 2007). Usual care in ICUs may encompass a wide variety of styles. For example usual care may be standardized around high level evidence and thus represent best practice, but it may also be highly variable and include unfavourable practice (Thompson 2007). Consequently, if the culture of an ICU is such that usual care is a standardized high level approach to weaning, albeit not formally laid out in guidelines, then it may not differ greatly from that delivered in a weaning protocol. Thus in a trial of effectiveness, the gap between usual care and protocolized weaning may be too narrow to show a significant difference between groups. For example, the Marelich 2000 study was conducted in one medical and one surgical and trauma ICU, and the authors reported variable practice between units. The medical ICU had no standardized approach to weaning whereas the surgical ICU had a standardized approach to ventilatory management, although extubation was based on subjective decisions. Thus, while combined data from both units demonstrated a reduction in the duration of mechanical ventilation time, when data were analysed separately for each unit, the reduction in mechanical ventilation was only statistically significant in the medical ICU, where there was variability in weaning practice. Similarly, the study by Rose 2008 attributed their lack of effect between computer-directed weaning and non-protocolized weaning to usual practice in their ICU. They reported unlimited assessment of weaning and readiness to wean by experienced and relatively autonomous critical care nurses, a one-to-one nurse-to-patient ratio supported by 24-hour medical staff and twice-daily intensivist rounds. These examples suggest that one might not find any further beneficial effect from using weaning protocols in comparison with standardized high level approaches to weaning. Twelve of the 17 trials included in this review did not describe usual care in their control group; as a result it is impossible to determine if this was a cause of heterogeneity and, further, it limits generalizability of findings.

This review has highlighted inconsistency in defining outcome measures that may have contributed to heterogeneity in effects. The review noted variation in defining the start time of randomization (unreported in 44% of included studies) and criteria for determining readiness to wean. Furthermore, although readiness to wean criteria usually involved similar indicators of oxygenation, factors such as positive end expiratory pressure (PEEP) varied from 5 to 8: as a consequence, the leniency or restrictiveness of crite-

ria may have contributed to differences in effects across studies. Substantial variation in the selection and definition of ventilation outcomes is an ongoing issue that was highlighted in a recent review of trials published from 2007 to 2012 in eight main critical care journals. From 66 trials measuring duration of mechanical ventilation, 75% did not define start and endpoint measures, and prompted the authors to call for establishment of a core outcome set (Blackwood 2014).

Weaning of sedation is an important accompanying feature in ventilation weaning, yet only two trials included minimal sedation as a criterion for weaning, making it difficult to ascertain if sedation management impacted on outcomes. Concerning the weaning protocols themselves, although they mainly included gradual reductions in pressure support, or SBT, or both, reflecting contemporary weaning practice, only two studies used an identical weaning protocol (Ely 1996; Namen 2001). Even so, they reported conflicting results in the duration of mechanical ventilation and weaning that could reflect differences in the type of patient population (medical and neurosurgical) and unreported usual practice within the units.

A limitation of the review is that outcome data for duration of mechanical ventilation and weaning duration were skewed: this is likely why some authors reported median and interquartile ranges. In our primary analysis, the estimates were based on approximations of the data presented (as described in the methods) and this may have impacted on our analysis. However, we feel this is likely to have had negligible impact as we conducted a sensitivity analysis of the unlogged data and this had little effect on the main findings. Similarly, when high risk studies were removed from the analysis, heterogeneity and effect estimates were similar to those from the primary analysis, indicating that high risk of bias studies did not adversely impact on overall results.

Quality of the evidence

Overall, the quality of the evidence was low for weaning duration and ICU length of stay due to substantial variability in effect estimates for weaning duration and wide confidence intervals. The quality of evidence was moderate for duration of mechanical ventilation, mortality and reintubation. We rated the majority of trials as low risk of bias across all six domains with the exception of performance bias. The nature of protocolized weaning means it is not possible to blind clinicians involved in the weaning process. Only four studies fully reported the trial sufficiently to enable a clear rating of risk of bias in all domains.

Potential biases in the review process

We adhered closely to our protocol which outlined our procedures for minimising bias in the review: these included independent screening for trial inclusion, data extraction and assessment of risk of bias by two review authors. With assistance from the Cochrane Anaesthesia Group's Search Trials Co-ordinator and an experienced librarian, we conducted a thorough search strategy, and believe we have identified all relevant studies.

Agreements and disagreements with other studies or reviews

Automated computerized systems are increasingly being employed in an attempt to improve the adaptation of mechanical support to the needs of patients. Computers can continuously monitor changes in ventilation, interpret real time physiological changes and adapt ventilation in response to these changes. This is evident from the automated weaning studies included in this review (Reardon 2011; Rose 2008; Stahl 2009; Strickland 1993). However, in comparison with usual care of non-protocolized weaning, their efficacy in reducing the duration of mechanical ventilation has yet to be demonstrated. It should be noted that the practice of protocolized weaning has increased to the point where it is 'usual practice' in many units. As one might expect, we are beginning to see studies that compare automated weaning with protocolized weaning practice and a review of automated versus non-automated systems summarises the findings from these trials (Rose 2013). Similar to this review, automated systems also impact favourably on the duration of mechanical ventilation and weaning without causing harm, but with significant heterogeneity in effect estimates.

A review of protocolized weaning in children (Blackwood 2013) highlighted the paucity of trials in the paediatric population. Three trials reported findings from three different interventions. Only one large trial was adequately powered to detect an effect, therefore the benefits and harms of protocolized weaning on children could not be determined.

The paediatric review and this updated review of protocolized weaning are being augmented by a systematic review of qualitative evidence to identify contextual factors and processes that might explain the observed heterogeneity (Jordan 2012). The qualitative review will enhance these reviews by synthesizing trial-related qualitative evidence to help explain the observed heterogeneity. It will extend the reviews by undertaking a specific search for and synthesis of evidence from relevant qualitative research to address questions raised by the review. These questions concern the contextual factors (for example, ICU culture, organization, staffing levels and extent of collaboration), and their interplay, that may impact on the effective use of weaning protocols in mechanical ventilation. Both the enhancing and extending reviews of qualitative evidence will add value to the reviews of protocolized weaning by exploring questions to do with the development, delivery, uptake, implementation, experience and evaluation of weaning protocols.

AUTHORS' CONCLUSIONS

Implications for practice

There are several important implications for practice arising from our systematic review and meta-analysis. First, the use of protocolized weaning may result in decreased total duration of mechanical ventilation, weaning duration, and intensive care unit (ICU) length of stay. The reduction in the duration of mechanical ventilation and weaning may be due to consistent application of objective criteria for determining early readiness to wean, and a guided approach to reducing support. Similarly, the reduction in ICU stay may be attributable to the reduction in mechanical ventilation. However, in ICUs where objective criteria and guided approaches are already standard weaning practice, further beneficial effects of protocolized weaning may not be gained on these outcomes. There are insufficient studies in neurological ICUs, and studies comparing automated systems with standard practice to determine effects.

Implications for research

Studies included in this review varied considerably in reporting details of their intervention groups, the implementation of their intervention, and outcome measures. In many studies neither usual practice nor organizational context (for example staffing ratios and frequency of medical rounds) were described in sufficient detail. Thus it is difficult to ascertain the extent to which weaning practice differed between the intervention and control groups in the individual studies. It is important that future trials fully report the details of weaning protocols, usual practice and the context into which weaning protocols are introduced, as this would enable clinicians to gain a more accurate picture of the potential impact of weaning protocols in their own environment. From a methodological perspective, it is also important that future trials report key outcomes using standardized definitions. This will enable the effects of interventions reported in different trials to be compared in an unbiased, reliable and robust manner.

Given that protocolized weaning is a complex intervention with multiple interrelated and interdependent components (Blackwood 2006), future research should take into account the contextual and intervention factors that are likely to impact on protocolized weaning. These need to be described in sufficient detail to enable clinicians to more readily generalize findings to their particular ICUs. We strongly recommend that trials fully evaluate the components of this complex intervention by following a framework that incorporates process evaluation (such as that advocated by the Medical Research Council; MRC 2008). This will enable an understanding of how the clinical context influences outcome, as well as provide insights to aid implementation in other settings, and an ability to separate effectiveness of the intervention from effectiveness of implementation.

In addition, an economic evaluation taking into consideration the cost-effectiveness of protocolized weaning, not only from the payer's perspective, but also from that of service users and society as a whole, would be useful for decision makers.

Further research into development and testing of protocolized weaning to aid early detection of readiness and safe weaning is required in the neurological population.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Chaiwat 2010

Methods	Randomized controlled trial
Participants	Setting: Bangkok, Thailand; academic hospital; surgical ICU 14 beds; physician staffing included one senior attending certified for critical care medicine or anaesthesia board; one junior attending. Additionally, 5-6 trainees working 24 hours in ICU. Nurse staffing not reported, but stated they were under staffed Participants: 100 adults (51 intervention group, 49 control group) Conditions: general, urological, gynaecological or obstetric intra-abdominal surgery Inclusion: Intra-abdominal surgical patients; intubated and receiving MV > 24 hours; ASA class I - III. Exclusion: < 18 years; brain death; inability to obtain informed consent; mental retardation; perioperative myocardial infarction; morbid obesity
Interventions	Intervention: daily screen for readiness; SBT on PS 7 cmH_2O and 5 cmH_2O PEEP for 120 minutes; if successful ask attending for approval to extubate Control: Weaning at the discretion of the managing physician
Outcomes	1. Duration of MV (primary) from tracheal intubation to discontinuation of MV or continued need for MV at day 21 after randomization 2. Reintubation within 72 hours after extubation 3. Need for MV > 21 days
Notes	Protocol registration not reported. ITT not reported. Sample size calculation based on 80% power to detect a mean (SD) difference in duration of MV between the two groups of 36 (120) hours, α 0.05, 176 patients per group. Four interim analyses planned at 4, 6, 8 months and end of study. Study terminated after the 6 month interim analysis (100 patients recruited) Informed consent obtained

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Block randomization, size 4 and 6. Each assignment of weaning method was indicated on a data form, folded & sealed in opaque envelope, opened only after informed consent obtained"
Allocation concealment (selection bias)	Low risk	Sealed in opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported, but impossible to blind personnel to the intervention groups

Chaiwat 2010 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	472 patients screened and 372 excluded due to exclusion criteria or not obtaining informed consent (no details reported)
Selective reporting (reporting bias)	Unclear risk	There was no protocol and ICU length of stay and mortality were not reported which would be usual in these studies
Other bias	Unclear risk	The paper reported that a priori interim analyses were planned and the study was terminated at 6 months by an independent committee. However the discussion states "The authors did the 1^{st} and 2^{nd} analyses of 100 patients & found significant outcomes so the authors decided to stop the present study earlier" P 934. For this reason we assessed the risk as unclear

de Carvalho Oliveira 2002

Methods	Randomized controlled trial
Participants	Setting: Sao Paulo, Brazil; single combined medical/surgical unit. Physician and nurse staffing not reported Participants: 40 adults (20 intervention group, 20 control group) Conditions: Not reported Inclusion: medically fit - decision of multidisciplinary team; receiving MV > 24 hours; APACHE II < 25. Exclusion: < 18 years; tracheostomy
Interventions	Intervention: algorithm that included readiness to wean criteria and a SBT on PS 7 cmH_2O with PEEP 5 cmH_2O for 120 minutes; if successful, extubated Control: "Weaning without obeying strict procedures or criteria"
Outcomes	1. Weaning success (primary), no requirement for reintubation within 48 hours after extubation 2. Use of NIV postextubation 3. Total duration of MV 4. Weaning duration 5. Death
Notes	Protocol registration not reported. ITT not reported. Sample size calculation and ethical approval not reported

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

de Carvalho Oliveira 2002 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind personnel to the intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Unclear risk	There was no protocol, although usual outcomes for weaning studies reported
Other bias	Unclear risk	Appears to be free of other sources of bias

Ely 1996

Methods	Randomized controlled trial
Participants	Setting: USA; 806-bed university medical centre. One medical and one coronary ICU. "Closed units staffed by intensivists". Staffing - 3.5 physician hours/bed/day (Krishnan 2004). NURSE/RT staffing not reported Participants: 300 adults (149 intervention, 151 control) Conditions: CHF; heart disease; COPD/asthma; pneumonia; ARDS/MSOF; GI and liver disease; cancer/leukaemia; overdose/ketoacidosis; neurologic emergency Inclusion:18 years and older; intubated and mechanically ventilated. Exclusions: 18 years; lack of informed consent; extubation order at time of evaluation; dependence on MV 2 weeks before recruitment
Interventions	Intervention: protocol delivered by RNs and RTs consisting of daily screening of readiness to wean using 5 criteria; a 2-hour SBT; and notification of the physician of successful SBT Control: usual practice consisting of weaning according to physician judgement
Outcomes	1. Total duration of mechanical ventilation (primary) 2. Weaning duration (time from successful screening test to discontinuation of MV) (primary) 3. ICU length of stay (primary) 4. Adverse events (reintubation; self-extubation; tracheostomy; MV > 21 days) 5. Cost of respiratory care, intensive care and hospitalisation 6. Hospital length of stay 7. Mortality

Ely 1996 (*Continued*)

Notes	ITT analysis performed. Sample size calculation not reported. Study approved by hospital Institutional Review Board and informed consent required. The primary author supplied additional data

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized randomization
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind personnel to the intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"All of the data were collected by research personnel not involved in the patients' care"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented. Analyses performed using ITT principle
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Appears to be free of other sources of bias

Fan 2013

Methods	Randomized controlled trial
Participants	Setting; China, neurosurgical ICU in an academic hospital Participants: 65 enrolled (intervention 32; control 33). 5 withdrawn following randomization, group attrition numbers not reported Inclusion: Respiratory or pulmonary failure; age 18-85 years; mechanically ventilated >/ = 24 hours Exclusion: motor neuron disease of other nervous system disease; mechanically ventilated > 2 weeks; patients who gave up ventilation; patients not expected to survive > 6 months
Interventions	Intervention: Patients were assessed by screening test once per day. The patients who did not pass the test were treated with mechanical ventilation and continued screening test. The patients who passed the test were assessed by 30 minute spontaneous breathing trial. The patients who passed the SBT would withdraw from mechanical ventilation. The patients who did not pass the SBT would be ventilated by SIMV + PSV, and ventilator parameters were gradually reduced every 4 hours; the respiratory frequency was decreased 2/breaths every 4 hours, until 4/breaths; the pressure support was decreased 2 cmH_2O every 4 hours, until 7 cmH_2O. SBT was conducted once per day. The patients who passed

Fan 2013 (*Continued*)

	the SBT or when the respiratory frequency was maintained as 4/breaths and pressure support was maintained as 7 cmH_2O would withdraw from mechanical ventilation Control: usual practice by physicians, not described
Outcomes	1. Total duration of mechanical ventilation 2. Weaning duration 3. ICU length of stay 4. Cost 5. ICU mortality 6. VAP incidence 7. Weaning success
Notes	Paper was translated from Chinese to English. Authors were contacted (in Chinese) to supply standard deviations, but we received no response

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table used
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not reported, but not possible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition numbers reported in both groups
Selective reporting (reporting bias)	Unclear risk	Insufficient information
Other bias	Unclear risk	Insufficient information

Kollef 1997

Methods	Randomized controlled trial
Participants	Setting: USA, 2 medical and 2 surgical ICUs in 2 university affiliated teaching hospitals (900 and 450-beds). Nurse to patient ratio 1:2 and 4.0 physician hours/bed/day (Krishnan 2004) Participants: 357 adults (intervention 179, control 178) Conditions: postoperative; trauma; pneumonia; COPD/asthma; pulmonary oedema; respiratory failure; drug overdose; cardiac arrest/cardiogenic shock

Kollef 1997 (*Continued*)

	Inclusion: mechanically ventilated. Exclusions: head/facial burns or trauma; transfer from other hospital with prior MV; brain death
Interventions	Intervention: protocol entry criteria assessed, then protocol delivered by RNs and RTs consisting of: a) ICUs 1 and 4 - daily SBTs through ventilator circuit with CPAP $\leq$ 5 cmH_20 and PS $\leq$ 6 cmH_20 for 30-60 minutes then extubation b) ICU 2 - stepwise reductions of 2 cmH_20 in PSV until 6 cmH_20 then extubation c) ICU 3 - on PEEP $\leq$ 5 cmH_20, PS $\leq$ 6 cmH_20, stepwise IMV reductions of 2 breaths/min until $\leq$4 breaths/min, then 0 breaths for 30-60 minutes, then extubation Control: usual practice consisting of weaning according to physician judgement
Outcomes	1. Total duration of mechanical ventilation from intubation until discontinuation of MV 2. Reintubation 3. Length of hospital stay 4. Hospital mortality rate 5. Hospital costs 6. MV time prior to weaning 7. Requiring MV for > 7 days
Notes	Protocol registration not reported. Sample size calculation based on 80% power to detect a difference in weaning time of 1 (SD 3) days, α 0.05, 145 patients needed per group. Study approved by University Human Studies Committee and hospital Institutional Review Board - both waived requirement for informed consent

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Seperate blocked randomization schedules
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind personnel to the intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors were independent from the individuals administering/supervising the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data.Recruitment & attrition data presented. Analyses performed using ITT principle
Selective reporting (reporting bias)	Low risk	Weaning protocol is available; all prespecified outcomes reported

Kollef 1997 (*Continued*)

Other bias	Low risk	Appears to be free of other sources of bias. Sample size calculation stated (based on 80% power to detect a 1 day difference in weaning time, α 0.05, 145 required for each group)

Krishnan 2004

Methods	Quasi-randomized controlled trial
Participants	Setting: USA, 1000-bed hospital. 14 bed medical ICU; nurse to patient ratio 1:2; 9.5 physician hours/bed/day. 1-2 RTs. Daily bedside rounds Medical cover at night Participants: 299 adults (intervention 154, control 145) Conditions: cardiopulmonary arrest; pneumonia/acute lung injury; COPD/asthma; cardiogenic pulmonary oedema; neurologic emergency Inclusion: mechanically ventilated > 24 hours Exclusions: previous participants; enrolled in other studies; transferred from other facilities intubated
Interventions	Intervention: protocol delivered by RNs and RTs consisting of daily screening of readiness to wean using 5 criteria; a 1-hour SBT on CPAP 5 cmH_20; and notification of the physician of successful SBT Control: usual practice consisting of weaning according to physician judgement
Outcomes	1. Total duration of MV (time from start of MV to beginning of SBT that ended with successful discontinuation of MV) 2. Duration of SBT that preceded MV discontinuation 3. ICU length of stay 4. Location after ICU discharge 5. ICU and hospital mortality 6. Reinstitution of MV (< 48 hours & > 48 hours)
Notes	Protocol registration not reported. Successful discontinuation was unassisted breathing for 48 hours. Analyses based on ITT. The sample size (? post hoc) provided 82% power to detect a difference in duration of MV of 1 day, α 0.05. Study approved by Institutional Review Board - waived requirement for informed consent

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Assigned by hospital number (odd versus even)
Allocation concealment (selection bias)	High risk	Case record number
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind personnel to the intervention groups

Krishnan 2004 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear whether outcome assessors were independent from those making decisions. RNs and RTs recorded results of screening and SBTs on case report forms. Study coordinator documented other data
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented. ITT analysis performed
Selective reporting (reporting bias)	Low risk	Weaning protocol is available; all prespecified outcomes reported
Other bias	Low risk	Appears to be free of other sources of bias

Marelich 2000

Methods	Randomized controlled trial
Participants	Setting: USA, 1 university medical centre. 3 ICUs with medical and trauma/surgical services; RT to ventilator ratio 1:7; nurse to patient ratio 1:1 or 1:2; 4.7 physician hours/bed/day Participants: 335 adults (intervention 166, control 169) Conditions: postoperative trauma; non-operative trauma; pneumonia; neurologic emergency; poisoning; GI bleed/liver; COPD/asthma; respiratory failure; metabolic/renal; CHF Inclusion: mechanically ventilated. Exclusions: pregnancy; < 18 years; mentally disabled; prisoners
Interventions	Intervention: protocol delivered by RNs and RTs consisting of twice daily screening of readiness to wean; a 30-minute SBT (< 72 hours ventilated) or stepwise reduction in PEEP, PS and IMV (> 72 hours ventilated); and notification of the physician of successful SBT Control: usual practice consisting of weaning according to physician judgement on MICU; and a standardized MD approach on trauma services consisting of gradual reductions in IMV, then PS, then SBTs administered (but extubation was based on subjective opinion)
Outcomes	1. Total duration of MV (primary) 2. Incidence of VAP (primary) 3. Weaning duration (duration of MV from study entry to discontinuation of ventilator support) 4. Duration of MV from initiation of mechanical support to meeting discontinuation criteria 5. Ventilator discontinuation failure rate 6. Tracheostomy 7. Hospital mortality

Marelich 2000 (*Continued*)

Notes	Protocol registration not reported. Sample size calculation based on 80% power to detect a difference in time to ventilator discontinuation of 1.5 days, α 0.05, but patient numbers required not reported. Study approved by University Human Subjects Review Committee - requirement for informed consent waived

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified according to medical or surgical, put into envelopes and shuffled
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind personnel to the intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors independent from those involved in intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented
Selective reporting (reporting bias)	Low risk	Weaning protocol is available; all prespecified outcomes reported
Other bias	Low risk	Appears to be free of other sources of bias

Namen 2001

Methods	Randomized controlled trial
Participants	Setting: USA. Hospital and units not specified. Staffing ratios not stated Participants: 100 neurosurgical adult patients (intervention 49, control 51) Conditions: head trauma; subarachnoid haemorrhage; intracerebral haemorrhage/arteriovenous malformation; tumour; spinal trauma Inclusion: mechanically ventilated. Exclusions not stated
Interventions	Intervention: RT-focused protocol consisting of daily screening of readiness to wean; a 2-hour SBT; and notification of the physician of successful SBT Control: not stated
Outcomes	1. Total duration of MV (primary) 2. ICU length of stay (primary) 3. Time to successful extubation (primary) 4. Adverse events (reintubation; self-extubation; tracheostomy, MV exceeding 21 days)

Namen 2001 (*Continued*)

	5. Costs of MV, respiratory and ICU care & overall hospitalisation 6. Hospital length of stay 7. Mortality 8. Existence of pneumonia
Notes	Protocol registration not reported. ITT analysis performed. Study powered for 188 patients (80% power, α 0.05) to detect a 20% difference in duration of MV. Study approved by hospital Institutional Review Board and informed consent required

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind personnel to the intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented. ITT analysis performed
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	Trial stopped early for futility. Study powered for 188 patients. Planned interim analysis at 12-months showed lack of efficacy, study stopped at 100 patients

Navalesi 2008

Methods	Randomized controlled trial
Participants	Setting: Italy, 1200 bed hospital. Closed neuro-ICU, 9 bed unit. Nurse to patient ratio 1:2; 24-hour physicians certified and trained in anaesthesiology and critical care. 1 RT Participants: 318 adult neurosurgical and neurological patients (165 intervention group; 153 control group) Conditions: subarachnoid haemorrhage, intracerebral haemorrhage; head trauma; cerebral tumour; spinal trauma Inclusion: mechanically ventilated adults between 18 and 80 years; not already intubated or transferred from other ICU; mechanically ventilated >12 hours; no continuous sedation infusion; not on controlled mechanical ventilation; ability to trigger the ventilator;

	no tracheostomy; no surgery scheduled for 72 hours. Exclusion: lesion affecting upper airway; pre-existing decision to limit life support
Interventions	ICU staff trained and piloted the protocol during a 3-month run in period Intervention: daily readiness to wean criteria (GCS =/> 8; cough present; tracheal suctioning =/< 2/hour; normal sodium blood values; Temperature < 38.5°C; pH ≥ 7.35 and $PaCO_2$ ≤ 50 mmHg; PaO_2/FiO_2 ratio ≥ 200 with PEEP ≤ 5 cmH_2O; FiO_2 ≤ 0.4; Heart rate ≤ 125 b/min; SBP ≥ 90 mmHg without vasoactive medication); followed by a 1-hour SBT through ventilator circuit with 2 - 3 cmH_2O CPAP and FiO_2 0.4. Extubation criteria: respiratory rate/tidal volume ratio ≤105, $PaO_2/FiO2$ ≥200, pH ≥7.35 and $PaCO_2$ ≤ 50 mmHg Control: usual care that was daily evaluation by attending physician, weaning and extubation using their own clinical judgement
Outcomes	1. Rate of extubation within 48 hours (primary) 2. Duration of mechanical ventilation (days) 3. Length of ICU stay (mean/SD) 4. Length of hospital stay (mean/SD) 5. ICU Mortality N(%) 6. Rate of tracheostomy N(%)
Notes	Trial protocol was registered. ITT analysis performed. A priori power analysis showed that a recruitment of 280 patients (140 each group) over a 21 month period would detect a decrease in reintubation rate from 15% to 5% with 80% power at 5% two-sided level of significance. Ethics committee approval; requirement for informed consent waived

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A computer-generated randomisation sequence was drawn up. We used a simple randomisation without blocks"
Allocation concealment (selection bias)	Low risk	"We utilised the same PC used to register the patient in the ICU, which was located in the office of the chief nurse. As soon as the patient was eligible, a person (the chief nurse from Monday to Friday) not involved in the study (i.e. not one of the authors) communicated to the attending physician the group of assignment"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind personnel to the intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, staff and research personnel unblinded to the intervention, "however the analysis of data were performed by two investigators not involved either in the clinical management of patients and in data acquisition

Navalesi 2008 (*Continued*)

		and report"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition and exclusions reported
Selective reporting (reporting bias)	Low risk	All a priori outcomes reported
Other bias	Low risk	Appears to be free of other sources of bias. Sample size calculation stated (based on 80% power, α 0.05, 140 patients in each group)

Ogica 2007

Methods	Randomized controlled trial
Participants	Setting: Bucharest, Romania. Centre for bone marrow, liver and renal transplant (web site information), ICU and staffing not reported Participants: 103 participants (51 intervention group, 52 control group) Conditions: Surgical (abdominal) and myasthenia gravis Inclusion: Not reported Exclusion: Not reported
Interventions	Intervention: Readiness to wean criteria and SBT (communication) Control: Not reported (classical ventilator disconnection)
Outcomes	1. Duration of MV 2. ICU length of stay 3. Reintubation 4. Mortality
Notes	Protocol registration not reported. The study was reported in a conference abstract and details on ITT, sample size calculation, ethics and trials methods are not reported. We were unable to contact the primary author for details, but managed to contact a co-author who sent a data file, but could not elaborate further on study details Data entered into the meta-analyses were calculated from the raw data sent by a co-author

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Ogica 2007 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind personnel to the intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	No study protocol, but usual outcomes reported
Other bias	Unclear risk	Abstract lacks detail to confirm

Piotto 2011

Methods	Quasi-randomized controlled trial
Participants	Setting: Brazil, hospital not described. One coronary care unit. Staffing ratios not stated Participants: 36 coronary care patients (intervention 18, control 18) Conditions: myocardial revascularization; valve surgery; acute coronary syndrome; CHF; pulmonary thromboembolism Inclusion: mechanically ventilated > 24 hours. Exclusion: conditions that might result in difficulty understanding informed consent; lack of consent; end-stage diseases; dependence on MV
Interventions	Predetermined protocol entry criteria specified. After resolution of cause for MV resolved, all patients underwent a daily clinical evaluation according to prespecified criteria Intervention: SBT 120 minutes delivered by RT then extubation Control: weaning according to physician and RT judgement, typically gradual reduction in ventilatory support (RR and PS) and in some cases SBT without evaluation of clinical criteria
Outcomes	1. Reintubation rate during hospitalization (primary) 2. Length of CCU stay 3. Time from intubation to start of weaning 4. Time from start of weaning to extubation 5. Time from SBT to extubation 6. Presence of respiratory infection in patients requiring reintubation 7. Mortality of patients requiring reintubation
Notes	Protocol registration not reported. Sample size calculation based on 80% power to detect a difference in reintubation rate of 15% in the intervention group and 60% in the control group, 17 patients per group. Informed consent required: ethical approval obtained
Risk of bias	

Piotto 2011 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	1st recruited patient into experimental group, 2nd into control group, thereafter alternated
Allocation concealment (selection bias)	High risk	Not concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind personnel to the intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Recruitment and attrition data not reported
Selective reporting (reporting bias)	Low risk	Study protocol is available; all prespecified outcomes reported
Other bias	Low risk	Sample size calculation based on 80% power to detect a difference in reintubation of 15% in experimental group and 60% in control group, α 0.05, 17 patients in each group. Ethics Committee approval obtained

Reardon 2011

Methods	Randomized controlled trial
Participants	Setting: US; single, academic, urban, tertiary medical centre with closed medical ICU Participants: 33 adult participants (15 intervention group; 18 control group) Conditions: Respiratory insufficiency Inclusion:18 years and older; mechanically ventilated via endotracheal tube; requiring mechanical ventilation for > 48 hours Exclusion: do not resuscitate status; tracheostomy; cardiac arrest > 5 minutes with poor neurological prognosis; pregnancy; transfer from another institution; baseline $PaCO_2$ > 60 mmHg
Interventions	Intervention: computer-driven weaning program - Drager Evita Smartcare System Control: usual care weaning that was SBT or PS (10 cmH_2O or less with PEEP 5 cmH_2O) for 30-120 minutes
Outcomes	1. Duration of weaning (primary) 2. Duration of ICU stay 3. Duration of mechanical ventilation 4. Duration of hospitalization

Reardon 2011 (*Continued*)

	5. Mortality 6. Sedation requirements 7. No. of SBTs prior to extubation 8. Complications (mortality during weaning; VAP; self extubation; reintubation rate)
Notes	Study was not published. Information obtained from the trial registration site. Trial started January 2007 and stopped May 2010 prior to reaching recruitment target because of slow recruitment and inadequate resources. ITT analyses. Sample size calculation based on 80% power to detect a difference in weaning time of 1.5 (SD 4) days, α 0.05, 220 patients. Protocol approved by Boston University Institutional Review Board

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization was performed utilizing an online random number generator with permuted blocks of four, stratified by etiology of respiratory failure ..."
Allocation concealment (selection bias)	Low risk	"...and revealed through opening of opaque envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind personnel to the intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear from the trial register
Selective reporting (reporting bias)	Unclear risk	Some outcomes not reported: total duration of MV; ICU length of stay
Other bias	Unclear risk	Trial started January 2007 and stopped May 2010 prior to reaching recruitment target because of slow recruitment and inadequate resources

Roh 2012

Methods	Randomized controlled trial
Participants	Setting: Asan Medical Center, a tertiary academic hospital with 2680 beds in Seoul, Korea. Medical ICU, a closed ICU with 28 beds staffed by 3 attending physicians; 2 ICU fellows; and 6 medical residents in their 2nd or 3rd years. Physicians work in 3 teams each with 3/4 physicians. All physicians attend structured twice daily bedside rounds lastly approximately 2 hours. Decisions about management of mechanically ventilated patients

	are based on electronic templates and medical records that cover each major physiologic system and completed daily by house staff and charge nurses. Most physicians remain in the ICU for their entire working hours, and 2 house officers stay overnight. All nurses are registered nurses, and the nurse-to patient ratio was 1:2.5, plus 4 additional senior nurses. Two respiratory therapists were involved in the management of mechanically ventilated patients Participants: 122 enrolled (61 intervention group, 61 control group) Conditions: acute exacerbation of COPD; postoperative; pulmonary oedema; pneumonia; sepsis Inclusion: PaO2/FIO2 > 200 mm Hg; minute ventilation <15 L/min; age 18 to 90 years; pH > 7.3; serum potassium 3 to 5 mmol/L; serum sodium 128 to 150 mmol/L; Hemoglobin > 7 g/dL Exclusion: do-not-resuscitate order; ventilatory support less than 12 hours or greater than 14 days; on non-invasive ventilation; active bleeding; known or suspected increased intracranial pressure
Interventions	Intervention: Nurse-directed protocol with an algorithm outlining steps that included stepwise reductions in FiO2 to >/= 0.4 and PEEP to </= 5 cmH_2O; followed by screening for readiness to wean and CPAP trial at 5 cmH_2O for 5 minutes; then gradual PS weaning to 5 cmH_2O; followed by SBT via T-piece for 30 minutes. If successful, screen for extubation and if ready notify physician Control: Weaning at the discretion of the medical resident physicians (blinded to the weaning protocol used in the intervention group)
Outcomes	1. Weaning time (primary) - defined as the time from enrolment and randomization, to successful discontinuation of mechanical ventilation Classified as successfully weaned if able to breathe unassisted for 48 hours at their first spontaneous breathing trial 2. Overall duration of mechanical ventilation 3. Duration of stay in the ICU 4. Duration of hospitalization 5. Frequency of complications (tracheostomy, failure of discontinuation, death)
Notes	Protocol registration not reported. ITT analysis performed. Sample size calculation was based on the difference in weaning times in pilot study, sample size had 80% power to detect a significant effect, assuming 2-sided type I error of 0.05 and the rate of the failure of discontinuation was 30%. Institutional review board of hospital approved the study protocol. Data entered into the meta-analyses were calculated from the raw data sent by the authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A computerized randomization scheme was used
Allocation concealment (selection bias)	Low risk	A computerized randomization scheme used for group assignment at enrolment, and each assignment was indicated on a data form that was folded and sealed in

		an opaque envelope. The envelope was opened only after written informed consent, mostly provided by relatives because the patients were sedated. The charge nurse screened mechanically ventilated patients in the medical ICU every morning, and eligible patients were randomly assigned to the intervention or control group
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind personnel to the intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	122 enrolled, but duration of weaning and mechanical ventilation only reported for 93. Attrition not reported
Selective reporting (reporting bias)	Unclear risk	No registered protocol; reintubation is a common outcome, but not reported
Other bias	Low risk	None apparent

Rose 2008

Methods	Randomized controlled trial
Participants	Setting: Australia, 390 bed acute tertiary referral hospital with 100,000 admissions/annum. 24-bed mixed medical/surgical/trauma ICU. Nurse to patient ratio 1:1, 9 intensivists providing twice-daily structured rounds and supported by 26 hospital medical officers providing 24-hour care Participants: 102 adult patients (51 intervention group; 51 control group) Conditions: trauma; coma; postoperative; pneumonia; sepsis; heart failure Inclusion: 24-hour mandatory ventilation; a ventilator with SmartCare/PS software ready for use; PEEP $\leq$ 8 cmH_2O; PaO_2/FiO_2 ratio >150 or $SaO_2 \geq$ 90% with FiO_2 0.5; Plateau Pressure $\leq$ 30 cmH_2O; haemodynamic stability; temperature 36-39 C; GCS > 4; no anticipated requirement for transport or surgery; successful completion of 30-min SBT using max 20 cmH_20 PS to achieve VT > 200mL Exclusion: ventilator with software unavailable; CNS disorder with anticipated poor outcome
Interventions	Intervention: automated computerized protocol delivered by Draeger EvitaXL ventilator with SmartCare^{TM}/PS software version 1.1. Programme monitors patient's respiratory status every 2 to 5 minutes and adjusts PS accordingly. When PS reduced to 7 cmH_2O (or 5 cmH_2O for tracheostomy), PEEP was reduced to 5 cmH_2O and following a 1-hour monitoring period patient assigned as having ventilator "separation potential" Control: weaning of PS and PEEP according to usual local practice in the absence of formal guidelines. When PS reduced to 7 cmH_2O (or 5 cmH_2O for tracheostomy) , PEEP was reduced to 5 cmH_2O and following a 1-hour monitoring period patient

	assigned as having ventilator "separation potential"
Outcomes	1. Time to separation (immediately following successful 30-minute PS SBT [randomization] to declaring "separation potential") in hours 2. Total duration of weaning (randomization to successful extubation) 3. Time from intubation to first extubation 4. Time from intubation to successful extubation 5. Length of ICU stay 6. Length of hospital stay 7. ICU Mortality 8. Rate of successful extubation 9. Rate of reintubation 10. Rate of use of non-invasive ventilation postextubation 11. Tracheostomy 12. Prolonged mechanical ventilation > 14 days
Notes	Protocol registration not reported. ITT analysis. Sample size calculation not reported. Ethical approval. Required written informed consent from next-of-kin and later patients (when competent)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated block randomization (block size 4)
Allocation concealment (selection bias)	Low risk	Administered through a sequential opaque envelope technique
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind personnel to the intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition and exclusions reported
Selective reporting (reporting bias)	Low risk	All a priori outcomes reported
Other bias	Low risk	Appears to be free of other sources of bias

Simeone 2002

Methods	Randomized controlled trial
Participants	Setting: Italy, hospital not described. One cardiac surgical ICU. Staffing ratios not stated Participants: 49 patients > 15 years of age (intervention 24, control 25) Conditions: elective coronary, aortic and mitral valve surgery Inclusion: low or medium Higgins risk score Exclusion: FiO_2 > 0.5%; PEEP > 10 cmH_2O to achieve O_2 sat > 90%; PEEP > 10 cmH_2O; excessive respiratory secretions; uncontrolled arrhythmias; high inotropic support; bleeding > 250 mLs in first hour; contraindications to steroid administration
Interventions	Intervention: protocol consisting of reduction in SIMV and 2 cmH_2O stepwise reduction in PSV until SIMV 0 and PS 4 cmH_2O, then extubation Control: weaning according to physician's subjective clinical judgement without the aid of the measured indexes
Outcomes	1. Total duration of mechanical ventilation (intubation time) 2. ICU length of stay 3. Number of complications recorded (cardiac tamponade; myocardial ischaemia; increased creatinine level; aphasia; disorientation; paralysis; postoperative bleeding; reintubation due to epileptic crisis)
Notes	Protocol registration not reported. ITT not reported. Sample size calculation not reported. Patients assessed 3rd/4th hour after admission. Predetermined protocol entry criteria specified. Ethical committee approval gained and informed consent required

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Used a random numbers table generated by a software program on a PC
Allocation concealment (selection bias)	Low risk	Each random number was associated with either 'control' or 'experimental' & was inserted into a black sealed envelope
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind personnel to the intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"The fellows were involved in collecting the data, not in weaning the patient" - communication
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Outcomes were not prespecified. Recruitment and attrition data absent. ITT not stated
Selective reporting (reporting bias)	Unclear risk	Outcomes were not prespecified

Simeone 2002 (*Continued*)

Other bias	Unclear risk	No data to support following statements; "...Patients that underwent a longer cardiopulmonary bypass time required prolonged MV support...". (Baseline showed patients in the control group had longer cardiopulmonary bypass times.) "...a weaning protocol allows early identification of patients ready for spontaneous breathing, thus reducing MV dependence." (This outcome - early identification or MV time prior to weaning - was not measured.) Data produced from a Fast Track Recovery study for comparison with weaning group data, but no information provided on this group of patients (nos., characteristics etc) Sample size calculation not stated

Stahl 2009

Methods	Randomized controlled trial
Participants	Setting: University Hospital in Germany. Surgical ICU. Staffing ratios not stated Participants: 60 patients, (intervention 30, control 30) Conditions: abdominal, vascular, thoracic & trauma/orthopaedic surgery Inclusion: 18-80 years, mechanically ventilated via endotracheal tube or tracheostomy for at least 24 hours; breathing spontaneously; Ramsay sedation score ≤ 3; $paO_2 > 75$ cmH_2O or $SaO_2 > 90\%$ at $FiO_2 \leq 0.5$; 18-80 years; body weight 35 kg-200 kg Exclusion: PEEP > 10 cmH_2O; haemodynamic instability with demand for catecholamines; rectal temperature > 39^oC; haemoglobin < 7 g/dl; pH > 7.2
Interventions	Intervention: computerized automated weaning of CPAP/ASB mode (SmartCare ^{TM}/PS) Control: physician-directed weaning using no strict protocol, but PSV should be gradually reduced in single steps of no more than 15 cmH_2O Extubation criteria: respiratory rate, 30/minute; paO_2 >75 cmH_2O or $SaO_2 > 90\%$; sufficient airway protection; haemodynamic stability
Outcomes	1. Duration of ventilator weaning in days (time from switching controlled to assisted breathing (CPAP/ASB mode) until extubation or disconnection (if tracheostomy)) 2. Total duration of MV until successful extubation 3. ICU length of stay 4. Reintubation within 48 hours 5. Physician workload (quantity of PSV, FiO_2 and PEEP settings/hour) 6. Nursing workload (frequency of alarm "clean CO_2 cuvette"/hour) 7. ICU and hospital mortality
Notes	Protocol registration not reported. ITT analysis. Sample size calculation based on 80% power to detect a difference of 2 days in weaning time, α 0.05, 54 patients each group. Local ethics committee approval; signed informed consent from patients or relatives

Stahl 2009 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomization list generated using RITA version 1.13a. Stratified randomization with age and duration of MV prior to weaning
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants, staff and research personnel were unblinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	On contact, authors stated that "outcome assessors were independent from those managing patient care"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All a priori outcomes reported. ITT analysis performed
Selective reporting (reporting bias)	Low risk	Appears to be free of other sources of bias
Other bias	Unclear risk	Sample size calculation stated (based on 80% power to detect a difference of 2 days in weaning time, α 0.05, 54 patients each group). Unplanned interim analysis was undertaken because of low recruitment after 1 year: sample size and significance levels were recalculated (N = 60 patients) and after the 60th patient the trial was stopped for futility

Strickland 1993

Methods	Randomized controlled trial
Participants	Setting: USA, Medical ICU. Hospital description and staffing ratios not stated Participants: 15 adult patients (intervention 9, control 6) Conditions: COPD/asthma; septic shock; ARDS; pulmonary oedema Inclusion: mechanically ventilated; judged ready to wean by physicians and meeting prespecified inclusion criteria Exclusion: postoperative patients < 3 days
Interventions	Intervention: protocol delivered by a computer-controlled weaning system (Supersport model 2, Zenith Data Systems) consisting of stepwise reductions in SIMV and PSV responsive to tidal volume & respiratory rate sampling (computer-directed algorithm) Control: weaning with SIMV and PS reduction as judged appropriate by the patient's physician

Strickland 1993 (*Continued*)

Outcomes	1. Time spent with RR < 8 or > 30 2. Time spent with tidal volume < 5 mL/kg 3. No. of arterial blood gases drawn during weaning 4. Weaning duration 5. MV prior to weaning
Notes	Protocol registration not reported. ITT performed. No sample size calculation performed. Study period and data collection were limited to 48 hours because only one computer system was available for the study. Study approved by hospital Institutional Review Board and informed consent required

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Impossible to blind personnel to the intervention groups
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcome assessors were independent from the individuals administering/supervising the intervention
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. Recruitment and attrition data presented
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	Appears to be free of other sources of bias. No sample size calculation stated

ARDS - acute respiratory distress syndrome; ASB - assisted spontaneous breathing; CPAP - continuous positive airway pressure; CHF - congestive heart failure; COPD - chronic obstructive pulmonary disease; GI - gastrointestinal; ICU - intensive care unit; IMV - intermittent mandatory ventilation; ITT - intention to treat; MD - medical doctor; MSOF - multi-system organ failure; MV - mechanical ventilation; NIV = non-invasive ventilation; PC - personal computer; PEEP - positive end expiratory pressure; PS - pressure support; PSV - pressure support ventilation; RN - registered nurse; RR - respiratory rate; RT - respiratory therapist; SBT- spontaneous breathing trial; SD -standard deviation; VAP - ventilator-associated pneumonia.

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

Study	Reason for exclusion
Beale 2008	Compared an automated protocol with protocol guided weaning. The comparator did not fulfil our inclusion criteria
Donglemans 2009	Intervention group was weaned using a computer protocol and compared with a control group where weaning was undertaken using standardized guidelines. Control group did not meet the review inclusion criteria (i.e. was not 'non-protocolized' according to our definition)
East 1999	The authors evaluated automated (computerized) protocolized weaning in a population of acute respiratory distress syndrome patients using a cluster randomized controlled trial. From the papers, we were unable to identify the comparator or the weaning outcomes and we were unable to contact the authors to obtain further information
Gnanapandithan 2011	Compared two weaning protocols involving gradual pressure support reduction with or without a spontaneous breathing trial. The comparator did not fulfil our inclusion criteria
Lellouche 2006	Intervention group was weaned using a computer protocol and compared with a control group where weaning was undertaken using standardized guidelines. Control group did not meet the review inclusion criteria (i.e. was not 'non-protocolized' according to our definition)
Liu 2013	Compared computer-driven automated weaning system with a local protocol based on local written weaning guidelines
Ma 2010a	Compared the use of a spontaneous breathing trial (SBT) prior to extubation versus no SBT prior to extubation when both groups met weaning readiness criteria. The intervention does not fulfil the definition of a weaning protocol
Ma 2010b	Compared an automated protocol with a standard weaning protocol. The comparator did not fulfil our inclusion criteria
McKinley 2001	The authors evaluated automated (computerized) protocolized weaning in a population of acute respiratory distress syndrome patients using a cluster randomized controlled trial. From the papers, we were unable to identify the comparator or the weaning outcomes and we were unable to contact the authors to obtain further information
NCT00157287	This was a cluster randomized controlled trial comparing an evidence based protocol with standard practice (no guidelines). The study was stopped due to recruitment problems and we were unable to obtain sufficient data to include it in the review
NCT00445289	Compared an automated protocol with a standard weaning protocol. The comparator did not fulfil our inclusion criteria
NCT00502489	Control group weaning is not 'non-protocolized' according to our definition
Taniguchi 2009	Intervention group was weaned using a computer protocol and compared with a control group where weaning was undertaken using standardized guidelines. Control group did not meet the review inclusion criteria (i.e. was not 'non-protocolized' according to our definition)

(*Continued*)

Vaschetto 2011	Types of participants were tracheotomized patients only. Did not meet our study inclusion criteria

DATA AND ANALYSES

Comparison 1. Primary analysis: protocolized versus non-protocolized weaning

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total duration of MV by type of unit	14	2205	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.46, -0.14]
1.1 Mixed ICUs	6	940	Mean Difference (IV, Random, 95% CI)	-0.23 [-0.44, -0.02]
1.2 Neuro ICUs	2	418	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.20, 0.18]
1.3 Surgical ICUs	3	201	Mean Difference (IV, Random, 95% CI)	-0.63 [-1.05, -0.22]
1.4 Medical ICUs	3	646	Mean Difference (IV, Random, 95% CI)	-0.34 [-0.61, -0.07]
2 Total duration of MV by type of approach	14	2205	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.46, -0.14]
2.1 professional-led	12	2051	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.40, -0.13]
2.2 computer-driven	2	154	Mean Difference (IV, Random, 95% CI)	-0.50 [-1.42, 0.42]
3 Total duration of MV by type of protocol [log hours]	14	2205	Mean Difference (IV, Random, 95% CI)	-0.30 [-0.46, -0.14]
3.1 SBT protocol	8	1188	Mean Difference (IV, Random, 95% CI)	-0.18 [-0.36, 0.00]
3.2 Stepwise reduction protocol	6	1017	Mean Difference (IV, Random, 95% CI)	-0.42 [-0.66, -0.18]
4 Mortality	14	2234	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.82, 1.26]
4.1 Hospital mortality	8	1523	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.82, 1.32]
4.2 ICU mortality	7	711	Odds Ratio (M-H, Fixed, 95% CI)	0.93 [0.58, 1.48]
5 Reintubation	11	1487	Odds Ratio (M-H, Random, 95% CI)	0.74 [0.44, 1.23]
6 Self extubation	3	433	Odds Ratio (M-H, Random, 95% CI)	0.43 [0.14, 1.34]
7 Tracheostomy	8	1346	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.51, 1.40]
8 Weaning duration by type of ICU	8	989	Mean Difference (IV, Random, 95% CI)	-1.20 [-2.10, -0.31]
8.1 Surgical ICUs	1	52	Mean Difference (IV, Random, 95% CI)	-1.29 [-2.42, -0.16]
8.2 Mixed ICUs	3	473	Mean Difference (IV, Random, 95% CI)	-1.39 [-3.17, 0.39]
8.3 Medical ICUs	4	464	Mean Difference (IV, Random, 95% CI)	-1.02 [-2.08, 0.03]
9 Weaning duration by type of approach	8	989	Mean Difference (IV, Random, 95% CI)	-1.20 [-2.10, -0.31]
9.1 Professional-led	4	793	Mean Difference (IV, Random, 95% CI)	-1.90 [-3.37, -0.43]
9.2 Computer-driven	4	196	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.69, -0.00]
10 Weaning duration by type of protocol [log hours]	8	989	Mean Difference (IV, Random, 95% CI)	-1.20 [-2.10, -0.31]
10.1 SBT protocol	2	336	Mean Difference (IV, Random, 95% CI)	-3.23 [-3.57, -2.89]
10.2 Stepwise reduction protocol	6	653	Mean Difference (IV, Random, 95% CI)	-0.46 [-0.81, -0.12]
11 ICU length of stay	9	1378	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.21, -0.03]
12 Hospital length of stay	5	977	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.11, 0.09]
13 ICU costs	2	400	Mean Difference (IV, Random, 95% CI)	3.37 [-15.02, 21.76]
14 Hospital costs	3	757	Mean Difference (IV, Random, 95% CI)	-0.59 [-4.67, 3.49]

Comparison 2. Sensitivity analysis: protocolized versus non-protocolized weaning excluding high risk of bias studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total duration of MV	12	1945	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.50, -0.16]
2 Weaning duration	5	499	Mean Difference (IV, Random, 95% CI)	-1.64 [-3.18, -0.10]

Comparison 3. Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total duration of MV	14	2205	Mean Difference (IV, Random, 95% CI)	-20.26 [-35.28, -5.24]
2 Weaning duration	7	739	Mean Difference (IV, Random, 95% CI)	-39.35 [-67.38, -11.32]
3 ICU length of stay	9	1378	Mean Difference (IV, Fixed, 95% CI)	-9.08 [-15.85, -2.30]
4 Hospital length of stay	5	977	Mean Difference (IV, Fixed, 95% CI)	-1.32 [-3.09, 0.44]

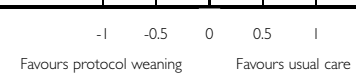
Analysis 1.1. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 1 Total duration of MV by type of unit.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 1 Total duration of MV by type of unit

Study or subgroup	Protocolized weaning N	Protocolized weaning Mean(SD)[log hours]	Usual care N	Usual care Mean(SD)[log hours]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 Mixed ICUs							
de Carvalho Oliveira 2002	20	4.16 (0.83)	20	4.46 (0.6)		6.0 %	-0.30 [-0.75, 0.15]
Kollef 1997	179	3.33 (1.2)	178	3.56 (0.96)		9.4 %	-0.23 [-0.46, 0.00]
Marelich 2000	166	4.22 (1.2)	169	4.82 (1.36)		8.6 %	-0.60 [-0.87, -0.33]
Ogica 2007	33	4.62 (0.73)	37	4.74 (0.76)		7.4 %	-0.12 [-0.47, 0.23]
Piotto 2011	18	4.27 (1.39)	18	3.81 (1.44)		2.4 %	0.46 [-0.46, 1.38]
Rose 2008	51	4.793 (0.752)	51	4.83 (0.863)		8.0 %	-0.04 [-0.35, 0.28]
Subtotal (95% CI)	**467**		**473**			**41.8 %**	**-0.23 [-0.44, -0.02]**
Heterogeneity: Tau² = 0.03; Chi² = 10.91, df = 5 (P = 0.05); I² =54%							
Test for overall effect: Z = 2.14 (P = 0.032)							
2 Neuro ICUs							
Namen 2001	49	4.97 (0.75)	51	4.97 (1.4)		6.2 %	0.0 [-0.44, 0.44]
Navalesi 2008	165	4.328 (0.92)	153	4.34 (0.96)		9.7 %	-0.01 [-0.22, 0.20]
Subtotal (95% CI)	**214**		**204**			**15.8 %**	**-0.01 [-0.20, 0.18]**
Heterogeneity: Tau² = 0.0; Chi² = 0.00, df = 1 (P = 0.97); I² =0.0%							
Test for overall effect: Z = 0.09 (P = 0.93)							
3 Surgical ICUs							
Chaiwat 2010	51	3.69 (1.2)	49	4.28 (1.59)		4.8 %	-0.59 [-1.14, -0.04]
Simeone 2002	24	1.72 (0.54)	25	2.08 (0.39)		8.8 %	-0.36 [-0.62, -0.10]
Stahl 2009	26	4.91 (0.81)	26	5.88 (0.35)		7.6 %	-0.97 [-1.31, -0.63]
Subtotal (95% CI)	**101**		**100**			**21.2 %**	**-0.63 [-1.05, -0.22]**
Heterogeneity: Tau² = 0.10; Chi² = 7.72, df = 2 (P = 0.02); I² =74%							
Test for overall effect: Z = 2.98 (P = 0.0029)							
4 Medical ICUs							
Ely 1996	149	4.18 (2.1)	151	4.77 (1.3)		6.8 %	-0.59 [-0.99, -0.19]
Krishnan 2004	115	4.1 (1.32)	109	4.22 (1.37)		7.4 %	-0.12 [-0.47, 0.23]
Roh 2012	61	5.1 (1.08)	61	5.45 (1.07)		7.0 %	-0.35 [-0.73, 0.03]
Subtotal (95% CI)	**325**		**321**			**21.1 %**	**-0.34 [-0.61, -0.07]**



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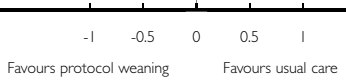
Study or subgroup	Protocolized weaning N	Mean(SD)[log hours]	Usual care N	Mean(SD)[log hours]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Heterogeneity: Tau² = 0.02; Chi² = 3.03, df = 2 (P = 0.22); I² =34%							
Test for overall effect: Z = 2.50 (P = 0.012)							
Total (95% CI)	**1107**		**1098**			**100.0 %**	**-0.30 [-0.46, -0.14]**
Heterogeneity: Tau² = 0.06; Chi² = 39.85, df = 13 (P = 0.00015); I² =67%							
Test for overall effect: Z = 3.67 (P = 0.00024)							
Test for subgroup differences: Chi² = 9.35, df = 3 (P = 0.02), I² =68%							



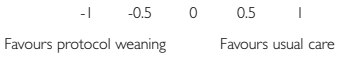
Analysis 1.2. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 2 Total duration of MV by type of approach.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 2 Total duration of MV by type of approach

Study or subgroup	Protocolized weaning N	Mean(SD)[log hours]	Usual care N	Mean(SD)[log hours]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
1 professional-led							
Chaiwat 2010	51	3.69 (1.2)	49	4.28 (1.59)		4.8 %	-0.59 [-1.14, -0.04]
de Carvalho Oliveira 2002	20	4.16 (0.83)	20	4.46 (0.6)		6.0 %	-0.30 [-0.75, 0.15]
Ely 1996	149	4.18 (2.1)	151	4.77 (1.3)		6.8 %	-0.59 [-0.99, -0.19]
Kollef 1997	179	3.33 (1.2)	178	3.56 (0.96)		9.4 %	-0.23 [-0.46, 0.00]
Krishnan 2004	115	4.1 (1.32)	109	4.22 (1.37)		7.4 %	-0.12 [-0.47, 0.23]
Marelich 2000	166	4.22 (1.2)	169	4.82 (1.36)		8.6 %	-0.60 [-0.87, -0.33]
Namen 2001	49	4.97 (0.75)	51	4.97 (1.4)		6.2 %	0.0 [-0.44, 0.44]
Navalesi 2008	165	4.328 (0.92)	153	4.34 (0.96)		9.7 %	-0.01 [-0.22, 0.20]
Ogica 2007	33	4.62 (0.73)	37	4.74 (0.76)		7.4 %	-0.12 [-0.47, 0.23]



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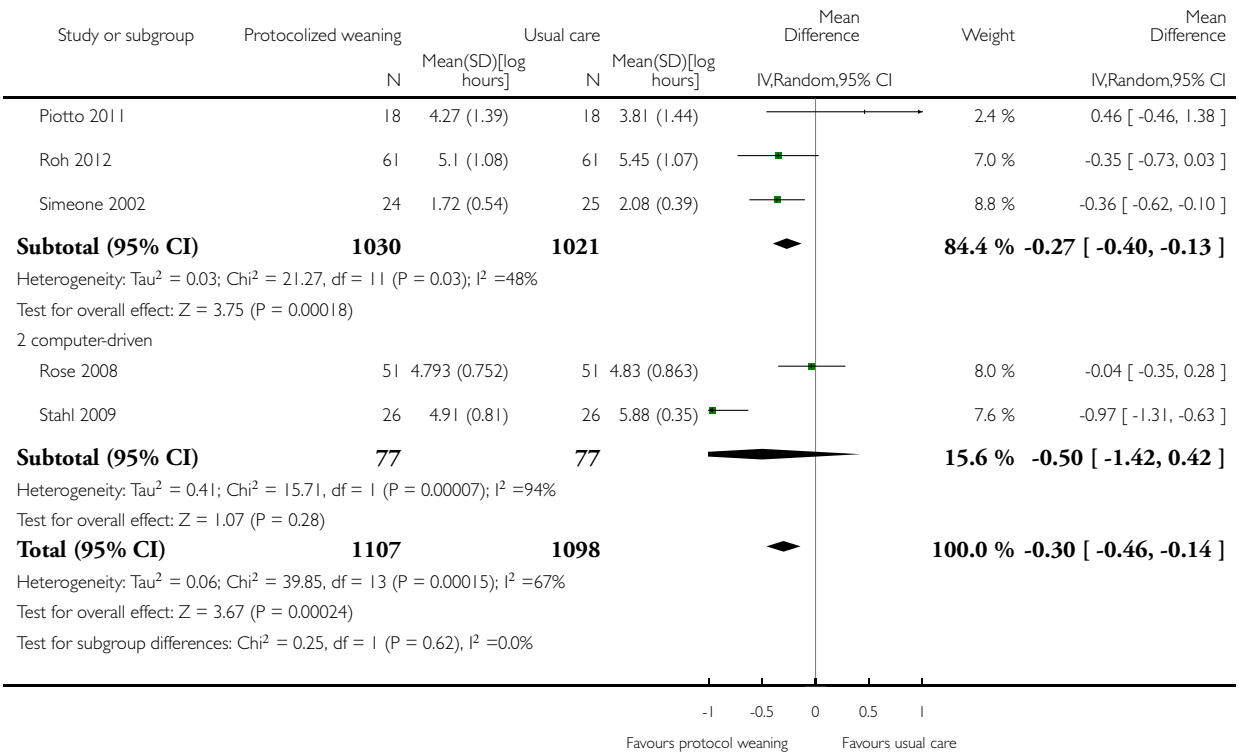
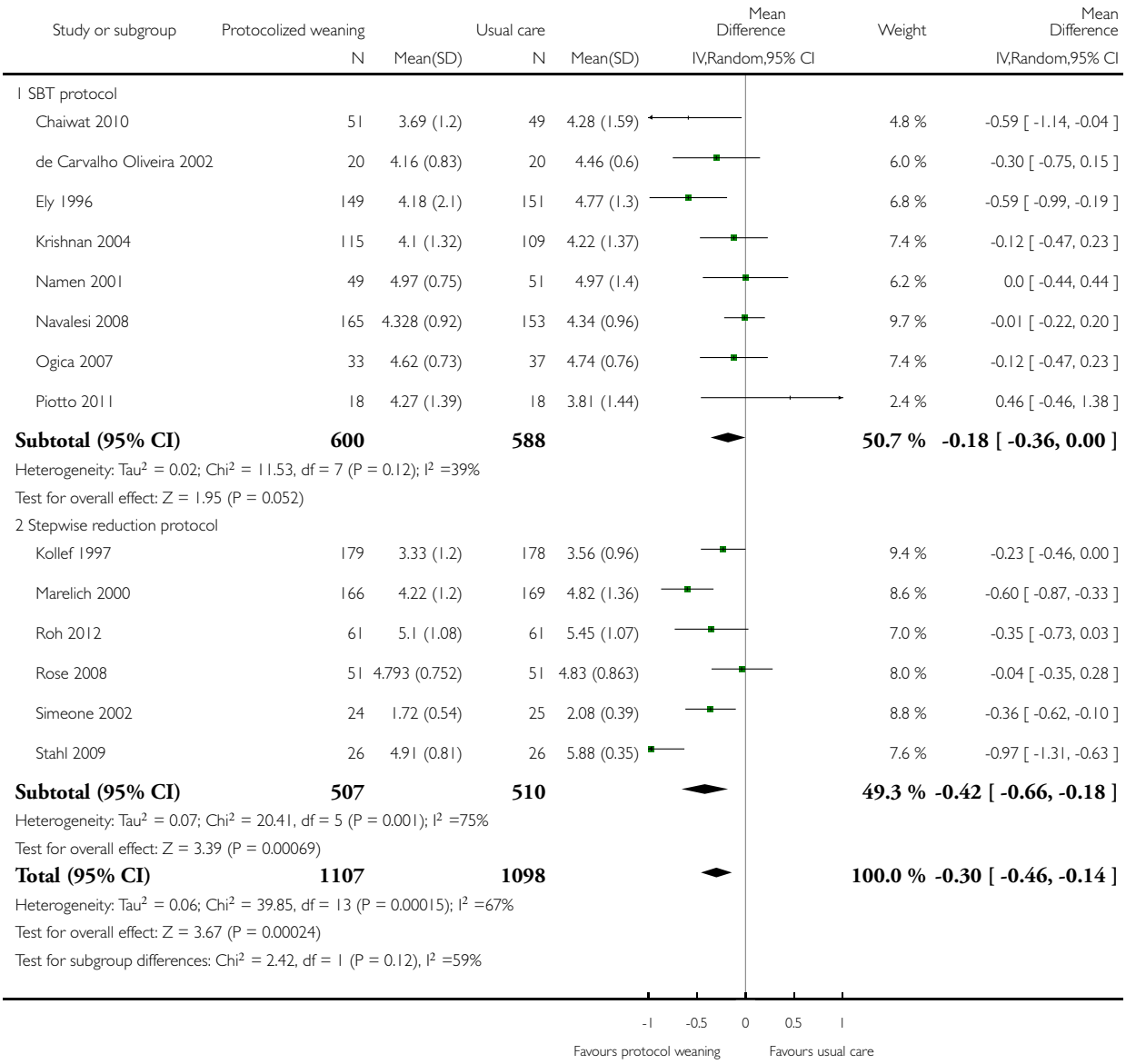


Analysis 1.3. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 3 Total duration of MV by type of protocol [log hours].

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 3 Total duration of MV by type of protocol [log hours]

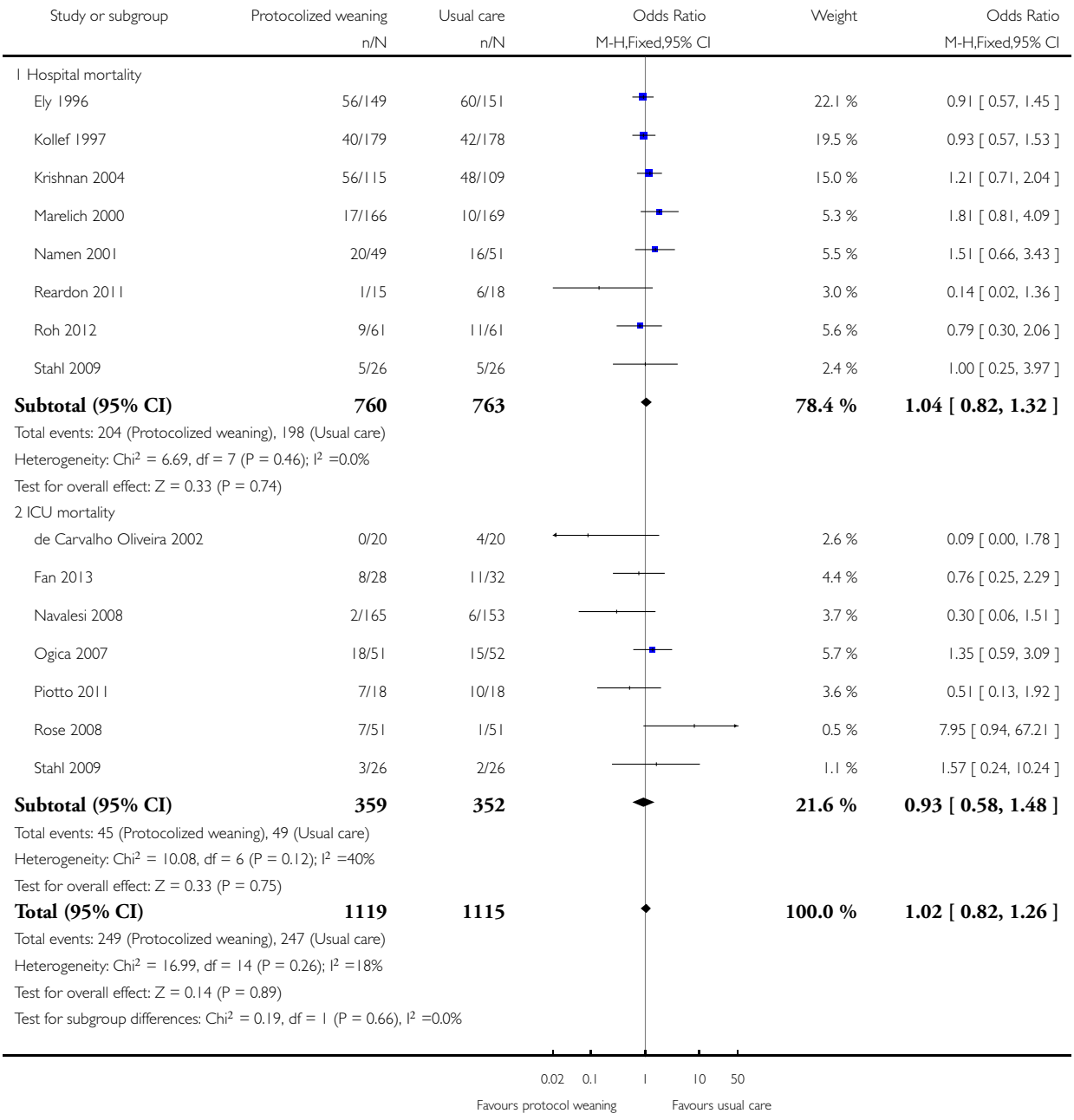


Analysis 1.4. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 4 Mortality.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 4 Mortality



Analysis 1.5. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 5 Reintubation.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 5 Reintubation

Study or subgroup	Protocolized weaning n/N	Usual care n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Chaiwat 2010	2/51	3/49		5.8 %	0.63 [0.10, 3.92]
de Carvalho Oliveira 2002	1/20	3/20		3.9 %	0.30 [0.03, 3.15]
Ely 1996	5/149	12/151		11.6 %	0.40 [0.14, 1.17]
Kollef 1997	23/179	18/178		17.1 %	1.31 [0.68, 2.52]
Namen 2001	10/49	6/51		11.3 %	1.92 [0.64, 5.77]
Navalesi 2008	9/165	18/153		14.5 %	0.43 [0.19, 0.99]
Piotto 2011	2/18	11/18		6.3 %	0.08 [0.01, 0.46]
Reardon 2011	4/15	5/18		7.5 %	0.95 [0.20, 4.41]
Rose 2008	5/51	6/51		9.7 %	0.82 [0.23, 2.86]
Simeone 2002	1/24	0/25		2.2 %	3.26 [0.13, 83.90]
Stahl 2009	8/26	6/26		9.9 %	1.48 [0.43, 5.10]
Total (95% CI)	**747**	**740**		**100.0 %**	**0.74 [0.44, 1.23]**

Total events: 70 (Protocolized weaning), 88 (Usual care)

Heterogeneity: $Tau^2 = 0.29$; $Chi^2 = 17.50$, df = 10 (P = 0.06); $I^2 = 43\%$

Test for overall effect: Z = 1.15 (P = 0.25)

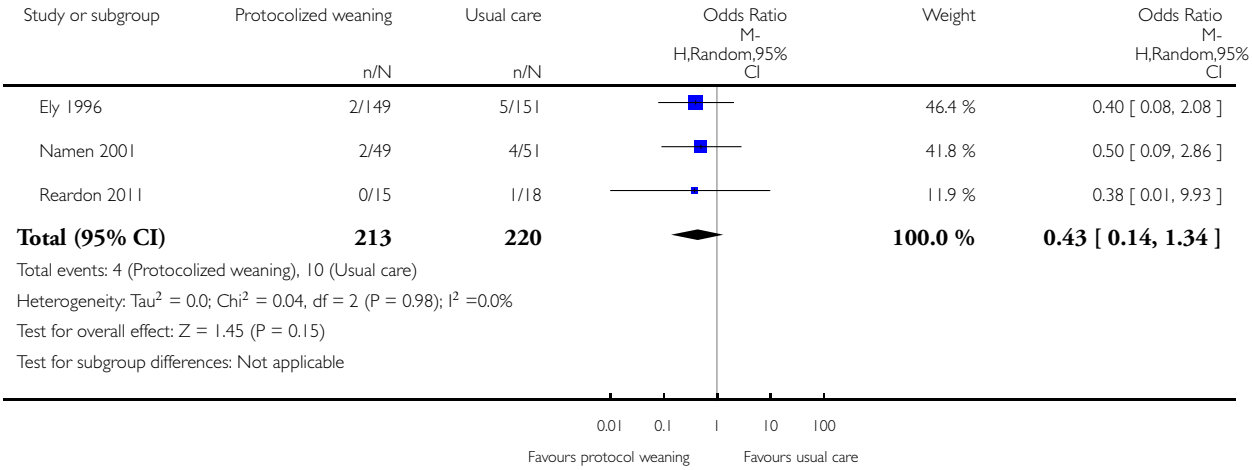
Test for subgroup differences: Not applicable

Analysis 1.6. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 6 Self extubation.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 6 Self extubation



Analysis 1.7. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 7 Tracheostomy.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 7 Tracheostomy

Study or subgroup	Protocolized weaning n/N	Usual care n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Ely 1996	13/149	22/151		19.9 %	0.56 [0.27, 1.16]
Marelich 2000	13/166	21/169		19.9 %	0.60 [0.29, 1.24]
Namen 2001	14/49	15/51		17.0 %	0.96 [0.40, 2.28]
Navalesi 2008	5/165	11/153		13.2 %	0.40 [0.14, 1.19]
Piotto 2011	8/18	2/18		6.7 %	6.40 [1.12, 36.44]
Reardon 2011	2/15	0/18		2.4 %	6.85 [0.30, 154.61]
Roh 2012	5/61	3/61		8.6 %	1.73 [0.39, 7.57]
Rose 2008	6/51	8/51		12.4 %	0.72 [0.23, 2.24]
Total (95% CI)	**674**	**672**		**100.0 %**	**0.85 [0.51, 1.40]**

Total events: 66 (Protocolized weaning), 82 (Usual care)

Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 11.60$, df = 7 (P = 0.11); $I^2 = 40\%$

Test for overall effect: Z = 0.66 (P = 0.51)

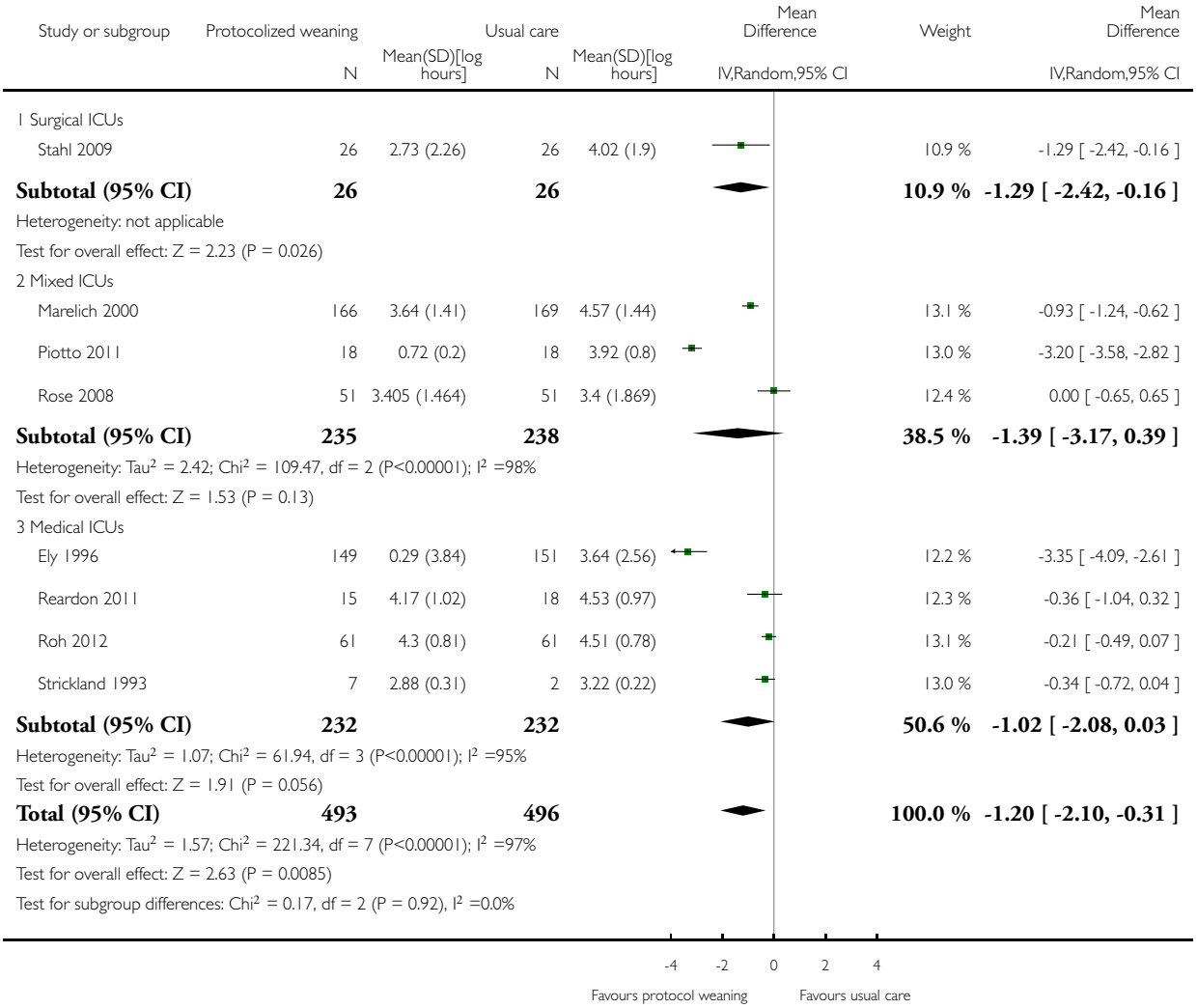
Test for subgroup differences: Not applicable

Analysis 1.8. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 8 Weaning duration by type of ICU.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 8 Weaning duration by type of ICU

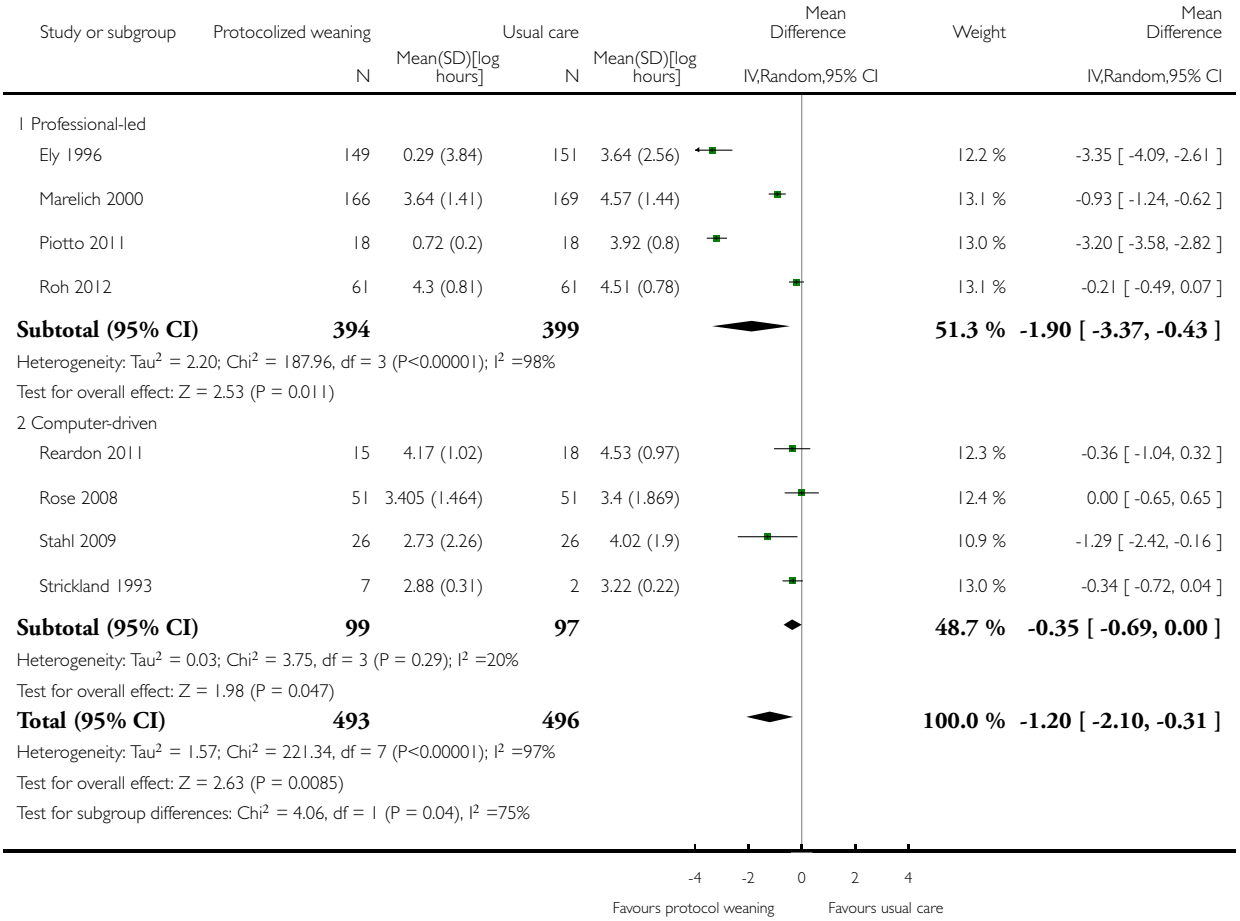


Analysis 1.9. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 9 Weaning duration by type of approach.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 9 Weaning duration by type of approach

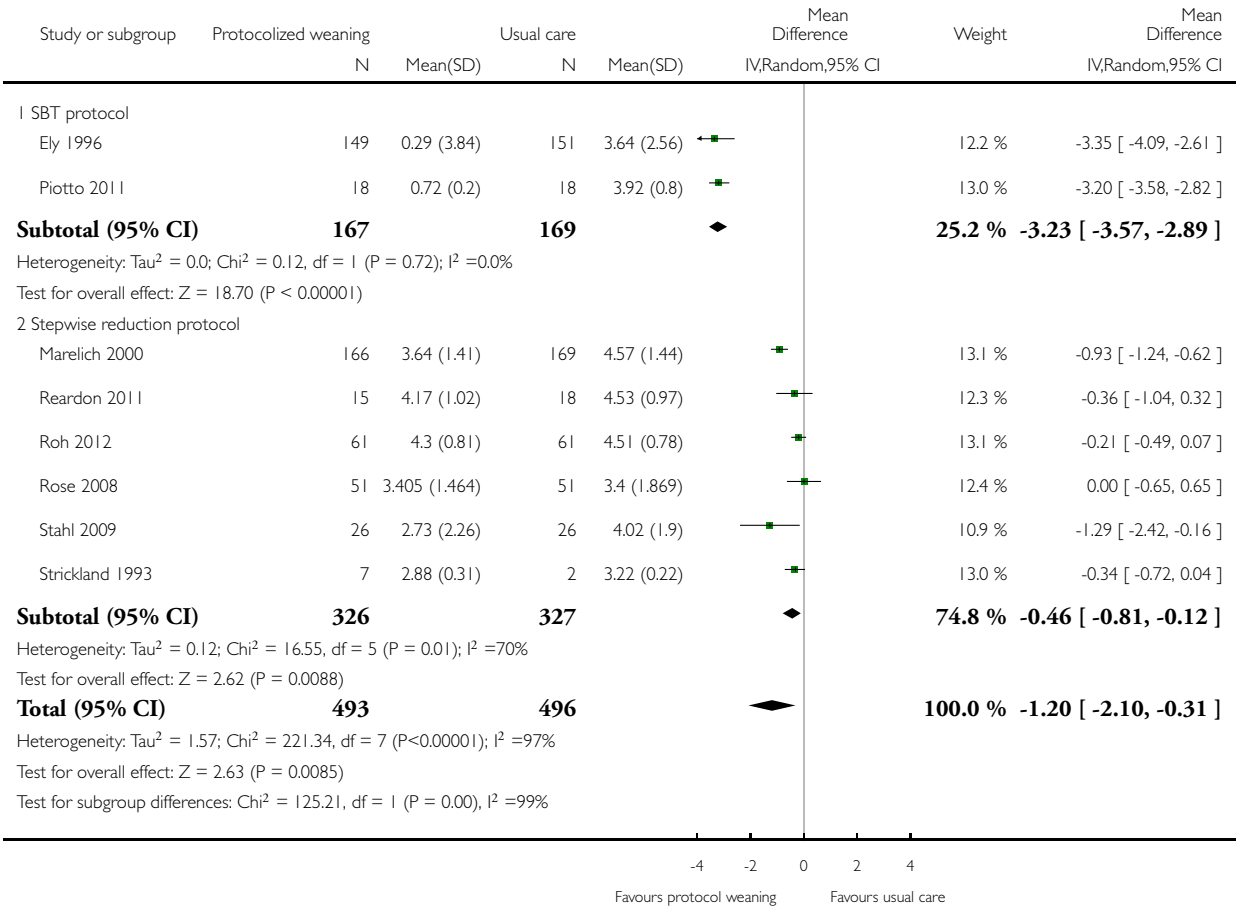


Analysis 1.10. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 10 Weaning duration by type of protocol [log hours].

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 10 Weaning duration by type of protocol [log hours]



Analysis 1.11. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 11 ICU length of stay.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

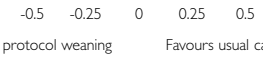
Outcome: 11 ICU length of stay

Study or subgroup	Protocolized weaning		Usual care		Mean Difference	Weight	Mean Difference
	N	Mean(SD)[log days]	N	Mean(SD)[log days]	IV,Fixed,95% CI		IV,Fixed,95% CI
Ely 1996	149	3.72 (2.4)	151	3.78 (2.1)		3.2 %	-0.06 [-0.57, 0.45]
Krishnan 2004	154	4.74 (1.01)	145	4.98 (0.95)		17.0 %	-0.24 [-0.46, -0.02]
Namen 2001	49	5.89 (0.42)	51	5.82 (0.79)		13.8 %	0.07 [-0.18, 0.32]
Navalesi 2008	165	4.93 (0.8)	153	5.04 (0.79)		27.4 %	-0.11 [-0.28, 0.06]
Piotto 2011	18	6.06 (0.72)	18	6.15 (0.66)		4.1 %	-0.09 [-0.54, 0.36]
Roh 2012	61	2.64 (0.78)	61	2.82 (0.74)		11.5 %	-0.18 [-0.45, 0.09]
Rose 2008	51	5.09 (0.67)	51	5.18 (0.79)		10.4 %	-0.09 [-0.37, 0.19]
Simeone 2002	24	3.24 (0.51)	25	3.61 (0.66)		7.7 %	-0.37 [-0.70, -0.04]
Stahl 2009	26	6.26 (0.78)	26	6.16 (0.74)		4.9 %	0.10 [-0.31, 0.51]
Total (95% CI)	**697**		**681**			**100.0 %**	**-0.12 [-0.21, -0.03]**

Heterogeneity: Chi^2 = 7.02, df = 8 (P = 0.53); I^2 =0.0%

Test for overall effect: Z = 2.58 (P = 0.0098)

Test for subgroup differences: Not applicable



Analysis 1.12. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 12 Hospital length of stay.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

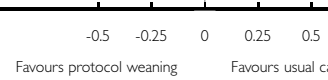
Outcome: 12 Hospital length of stay

Study or subgroup	Protocolized weaning N	Mean(SD)[log days]	Usual care N	Mean(SD)[log days]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Ely 1996	149	5.82 (0.79)	151	5.92 (1.2)		17.8 %	-0.10 [-0.33, 0.13]
Kollef 1997	179	5.58 (0.66)	178	5.58 (0.72)		45.8 %	0.0 [-0.14, 0.14]
Namen 2001	49	6.87 (0.62)	51	6.64 (0.9)		10.3 %	0.23 [-0.07, 0.53]
Roh 2012	58	3.61 (0.76)	60	3.64 (0.74)		12.8 %	-0.03 [-0.30, 0.24]
Rose 2008	51	2.89 (0.68)	51	2.98 (0.69)		13.3 %	-0.09 [-0.36, 0.18]
Total (95% CI)	**486**		**491**			**100.0 %**	**-0.01 [-0.11, 0.09]**

Heterogeneity: $Chi^2 = 3.41$, df = 4 (P = 0.49); $I^2 = 0.0\%$

Test for overall effect: Z = 0.20 (P = 0.84)

Test for subgroup differences: Not applicable



Analysis 1.13. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 13 ICU costs.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 13 ICU costs

Study or subgroup	Protocolized weaning N	Mean(SD)[USD (k)]	Usual care N	Mean(SD)[USD (k)]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Ely 1996	149	15.74 (18.64)	151	20.89 (19.31)		54.8 %	-5.15 [-9.44, -0.86]
Namen 2001	49	57.7 (28.2)	51	44 (34.07)		45.2 %	13.70 [1.46, 25.94]
Total (95% CI)	**198**		**202**			**100.0 %**	**3.37 [-15.02, 21.76]**

Heterogeneity: $Tau^2 = 155.77$; $Chi^2 = 8.11$, df = 1 (P = 0.004); $I^2 = 88\%$

Test for overall effect: Z = 0.36 (P = 0.72)

Test for subgroup differences: Not applicable

Analysis 1.14. Comparison 1 Primary analysis: protocolized versus non-protocolized weaning, Outcome 14 Hospital costs.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 1 Primary analysis: protocolized versus non-protocolized weaning

Outcome: 14 Hospital costs

Study or subgroup	Protocolized weaning		Usual care		Mean Difference	Weight	Mean Difference
	N	Mean(SD)[USD (k)]	N	Mean(SD)[USD (k)]	IV,Random,95% CI		IV,Random,95% CI
Ely 1996	149	26.23 (28.18)	151	29.05 (29.52)		39.1 %	-2.82 [-9.35, 3.71]
Kollef 1997	179	27.7 (26.8)	178	27.4 (25.9)		55.8 %	0.30 [-5.17, 5.77]
Namen 2001	49	64.5 (44.6)	51	57.7 (47.9)		5.1 %	6.80 [-11.33, 24.93]
Total (95% CI)	**377**		**380**			**100.0 %**	**-0.59 [-4.67, 3.49]**

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.19$, df = 2 (P = 0.55); $I^2 = 0.0\%$

Test for overall effect: Z = 0.28 (P = 0.78)

Test for subgroup differences: Not applicable

Analysis 2.1. Comparison 2 Sensitivity analysis: protocolized versus non-protocolized weaning excluding high risk of bias studies, Outcome 1 Total duration of MV.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 2 Sensitivity analysis: protocolized versus non-protocolized weaning excluding high risk of bias studies

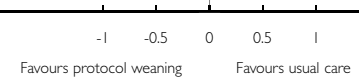
Outcome: 1 Total duration of MV

Study or subgroup	Protocolized weaning N	Mean(SD)[log hours]	Usual care N	Mean(SD)[log hours]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Chaiwat 2010	51	3.69 (1.2)	49	4.28 (1.59)		5.4 %	-0.59 [-1.14, -0.04]
de Carvalho Oliveira 2002	20	4.16 (0.83)	20	4.46 (0.6)		6.7 %	-0.30 [-0.75, 0.15]
Ely 1996	149	4.18 (2.1)	151	4.77 (1.3)		7.5 %	-0.59 [-0.99, -0.19]
Kollef 1997	179	3.33 (1.2)	178	3.56 (0.96)		10.4 %	-0.23 [-0.46, 0.00]
Marelich 2000	166	4.22 (1.2)	169	4.82 (1.36)		9.5 %	-0.60 [-0.87, -0.33]
Namen 2001	49	4.97 (0.75)	51	4.97 (1.4)		6.9 %	0.0 [-0.44, 0.44]
Navalesi 2008	165	4.328 (0.92)	153	4.34 (0.96)		10.7 %	-0.01 [-0.22, 0.20]
Ogica 2007	33	4.62 (0.73)	37	4.74 (0.76)		8.3 %	-0.12 [-0.47, 0.23]
Roh 2012	61	5.1 (1.08)	61	5.43 (1.07)		7.7 %	-0.33 [-0.71, 0.05]
Rose 2008	51	4.793 (0.752)	51	4.83 (0.863)		8.8 %	-0.04 [-0.35, 0.28]
Simeone 2002	24	1.72 (0.54)	25	2.08 (0.39)		9.7 %	-0.36 [-0.62, -0.10]
Stahl 2009	26	4.91 (0.81)	26	5.88 (0.35)		8.4 %	-0.97 [-1.31, -0.63]
Total (95% CI)	**974**		**971**			**100.0 %**	**-0.33 [-0.50, -0.16]**

Heterogeneity: $Tau^2 = 0.06$; $Chi^2 = 36.38$, df = 11 (P = 0.00015); $I^2 = 70\%$

Test for overall effect: Z = 3.84 (P = 0.00012)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Sensitivity analysis: protocolized versus non-protocolized weaning excluding high risk of bias studies, Outcome 2 Weaning duration.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 2 Sensitivity analysis: protocolized versus non-protocolized weaning excluding high risk of bias studies

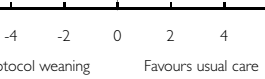
Outcome: 2 Weaning duration

Study or subgroup	Protocolized weaning		Usual care		Mean Difference	Weight	Mean Difference
	N	Mean(SD)[log hours]	N	Mean(SD)[log hours]	IV,Random,95% CI		IV,Random,95% CI
Ely 1996	149	0.29 (3.84)	151	3.64 (2.56)		19.9 %	-3.35 [-4.09, -2.61]
Marelich 2000	18	0.72 (0.2)	18	3.92 (0.8)		20.6 %	-3.20 [-3.58, -2.82]
Rose 2008	51	3.405 (1.464)	51	3.4 (1.869)		20.1 %	0.00 [-0.65, 0.65]
Stahl 2009	26	2.73 (2.26)	26	4.02 (1.9)		18.8 %	-1.29 [-2.42, -0.16]
Strickland 1993	7	2.88 (0.31)	2	3.22 (0.22)		20.6 %	-0.34 [-0.72, 0.04]
Total (95% CI)	**251**		**248**			**100.0 %**	**-1.64 [-3.18, -0.10]**

Heterogeneity: $Tau^2 = 2.97$; $Chi^2 = 154.11$, df = 4 ($P<0.00001$); $I^2 = 97\%$

Test for overall effect: Z = 2.08 (P = 0.037)

Test for subgroup differences: Not applicable

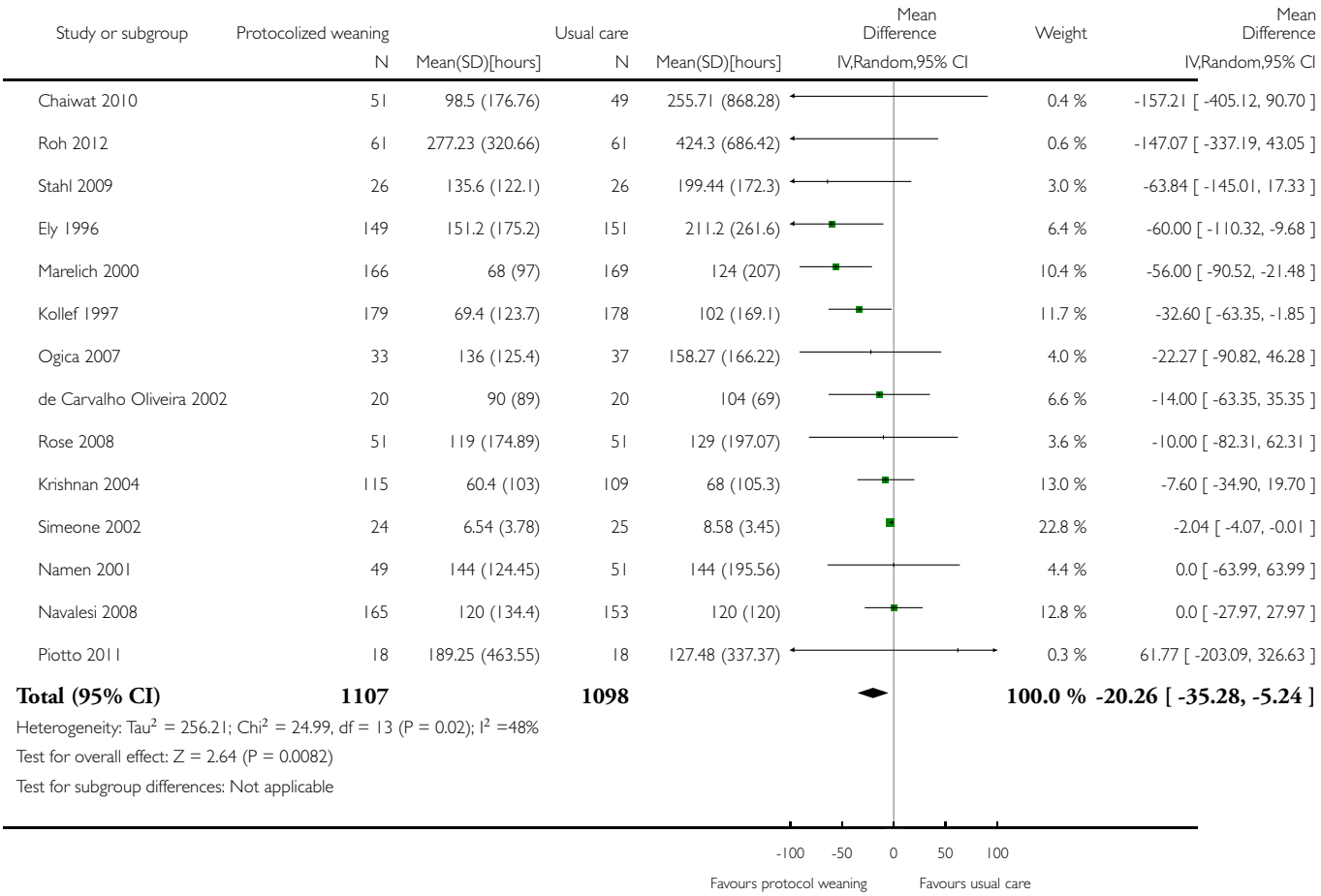


Analysis 3.1. Comparison 3 Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data, Outcome 1 Total duration of MV.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 3 Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data

Outcome: 1 Total duration of MV



Analysis 3.2. Comparison 3 Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data, Outcome 2 Weaning duration.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 3 Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data

Outcome: 2 Weaning duration

Study or subgroup	Protocolized weaning N	Mean(SD)[hours]	Usual care N	Mean(SD)[hours]	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Ely 1996	149	108 (124.56)	15	144 (142.32)		8.7 %	-36.00 [-110.75, 38.75]
Marelich 2000	166	38 (66.67)	169	97 (135.56)		19.7 %	-59.00 [-81.82, -36.18]
Piotto 2011	18	2.1 (0.424)	18	69.5 (65.36)		17.9 %	-67.40 [-97.59, -37.21]
Reardon 2011	15	109.22 (148.48)	18	148.04 (184.98)		4.8 %	-38.82 [-152.61, 74.97]
Rose 2008	51	69.89 (95.48)	51	98.08 (141.15)		13.9 %	-28.19 [-74.96, 18.58]
Stahl 2009	30	15.4 (98.13)	30	55.92 (105.25)		12.8 %	-40.52 [-92.01, 10.97]
Strickland 1993	7	18.7 (5.9)	2	25.6 (5.6)		22.2 %	-6.90 [-15.81, 2.01]
Total (95% CI)	**436**		**303**			**100.0 %**	**-39.35 [-67.38, -11.32]**

Heterogeneity: $Tau^2 = 902.64$; $Chi^2 = 29.89$, df = 6 (P = 0.00004); $I^2 = 80\%$

Test for overall effect: Z = 2.75 (P = 0.0059)

Test for subgroup differences: Not applicable

Analysis 3.3. Comparison 3 Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data, Outcome 3 ICU length of stay.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 3 Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data

Outcome: 3 ICU length of stay

Study or subgroup	Protocolized weaning N	Mean(SD)[hours]	Usual care N	Mean(SD)[hours]	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Ely 1996	149	192 (248.88)	151	216 (10.9)		2.9 %	-24.00 [-64.00, 16.00]
Krishnan 2004	154	115 (209.37)	145	146 (155.56)		2.6 %	-31.00 [-72.65, 10.65]
Namen 2001	49	360 (160)	51	336 (266.67)		0.6 %	24.00 [-61.81, 109.81]
Navalesi 2008	165	194.4 (172.8)	153	211.2 (175.2)		3.1 %	-16.80 [-55.09, 21.49]
Piotto 2011	18	554.4 (458.2)	18	564 (373.4)		0.1 %	-9.60 [-282.66, 263.46]
Roh 2012	61	18.56 (14.8)	61	23.38 (29.09)		68.5 %	-4.82 [-13.01, 3.37]
Rose 2008 (1)	51	205.37 (157.17)	51	243.73 (218.57)		0.8 %	-38.36 [-112.25, 35.53]
Simeone 2002	24	29 (15.8)	25	46.1 (33.9)		21.2 %	-17.10 [-31.82, -2.38]
Stahl 2009	26	522.72 (352.2)	26	471.6 (338.86)		0.1 %	51.12 [-136.74, 238.98]
Total (95% CI)	**697**		**681**			**100.0 %**	**-9.08 [-15.85, -2.30]**

Heterogeneity: $Chi^2 = 5.50$, df = 8 (P = 0.70); $I^2 = 0.0\%$

Test for overall effect: Z = 2.62 (P = 0.0087)

Test for subgroup differences: Not applicable

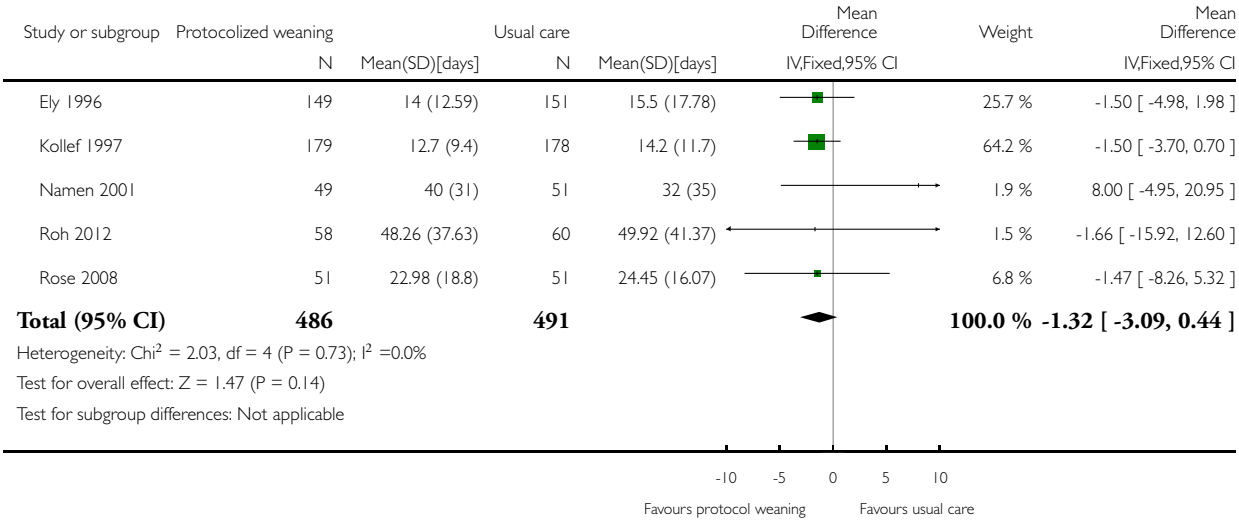
(1) Hours

Analysis 3.4. Comparison 3 Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data, Outcome 4 Hospital length of stay.

Review: Protocolized versus non-protocolized weaning for reducing the duration of mechanical ventilation in critically ill adult patients

Comparison: 3 Sensitivity analysis: protocolized versus non-protocolized weaning, unlogged data

Outcome: 4 Hospital length of stay



ADDITIONAL TABLES

Table 1. Readiness to wean criteria

Study	Assessment frequency	Oxygenation	Other respiratory factors	Cardiovascular	Neurological	Inflammatory response	Medication	Other
Chaiwat 2010	Daily screen	PaO_2/FiO_2 >/= 200 on FiO_2 </= 0.4 SpO_2 >/= 94%	PEEP </= 5 Respiratory rate < 35 Rapid Shallow breathing index </= 105 Static lung compliance >/= 25 mL/ cmH_2O Minute vol-	HR < 120 b/min	Awake and easily rousable	Not included	Dopamine </= 5 ug/kg/min Noradrenaline </= 5 ug/kg/min	Pain score < 4

Table 1. Readiness to wean criteria (*Continued*)

			ume </= 10L/min					
de Carvalho Oliveira 2002	Not reported	PaO_2 < 90 on FiO_2 </= 0.4	PEEP < 5 Pimax < - 25 cm H_2O	Not included	GCS > 8	Not included	No sedation No vasopressors	Cause of MV resolved No planned surgery
Ely 1996	Daily screen	PaO_2/FiO_2 > 200	PEEP </= 5 f/VT </= 105	Not included	Not included	Not included	No vasopressors or sedation	Adequate cough
Fan 2013	Daily screen	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Kollef 1997	Protocol entry criteria	PaO_2/FiO_2 > 200	PEEP </= 5 RR </= 35 b/min	HR < 140 b/min	Awake and orientated	Not included	No vasoactive or inotropic agents	Not included
Krishnan 2004	Daily screen	SpO_2 >/= 92% FiO_2 </= 0.5	PEEP </=5	Stable CAD HR < 140 b/min	No raised ICP	Not included	No paralytics	Cough and gag reflex present Responsive to stimuli
Marelich 2000	x 2 daily screen	PaO_2/FiO^2 >/= 200	Not included	MAP >/= 60 mmHg	GCS >/= 10 or tracheostomy	Not included	No vasopressors Dopamine </= 5 ug/kg/min	Adequate cough not limited by pain
Namen 2001	Daily screen	PaO_2/FiO_2 > 200	PEEP </= 5 f/VT </= 105	Not included	Not included	Not included	No vasopressors or sedation	Adequate cough
Navalesi 2008	Daily screen	PaO_2/FiO_2 > 200 FiO_2 </= 0.4 pH >/= 7.35 $PaCO_2$ </= 50 mmHg	PEEP </= 5	HR </= 125 b/min SBP >/= 90 mmHg	GCS >/= 8	T < 38.5°C	No vasopressors Dopamine </= 5 ug/kg/min	Adequate cough Suctioning < 2/hr Normal Na blood values
Ogica 2007	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Table 1. Readiness to wean criteria (*Continued*)

Piotto 2011	Daily screen	PaO_2/FiO_2 150-300 FiO_2 </= 0.4 PaO_2 >/= 60 mmHg Hb = 8 - 10 g/L	Not included	MAP >/= 60 mmHg HR </= 140 b/min	Awake GCS >/= 9	T < 37.8^oC	Minimum sedation No or low vasopressors	Cause of MV resolved Effective cough Metabolic stability No hydro-electrolyte disorders
Reardon 2011	Daily screen	SaO_2 > 90% or PaO_2 > 60 mmHg on FiO_2 </= 0.5	Respiratory rate < 35 pH > 7.20 Triggering breaths	SBP > 90 and < 180 HR > 50 and < 130 No cardiac ischaemia	GCS > 8	Not included	Minimal pressure requirements	Improving condition Absence of excessive secretions Suctioning < hourly Deemed ready to wean
Roh 2012	Not reported	FiO_2 </= 0.5	RR </= 35 PEEP </= 8 Triggering breaths	SBP >/= 90 mmHg HR </= 150 b/min	Not included	Not included	No paralytics No vasopressors Dopamine </= 5 ug/kg/min Noradrenaline </= 5 ug/kg/min	Not included
Rose 2008	Inclusion criteria	PaO_2/FiO_2 > 150 or SaO_2 >/= 90% on FiO_2 0.5	PEEP </= 8 Plateau pressure </= 30 cmH_2O Successful 30 min SBT using PS 20 cm H_2O to achieve TV > 200 mL	Haemodynamically stable	GCS > 4	T = 36 - 39 ^oC	Not included	No surgery anticipated MV > 24 hr
Simeone 2002	Inclusion criteria	PaO_2/FiO_2 >/= 200	PEEP < 4 RR < 35 b/	Haemodynamically	Awake and conscious	T > 35 < 38 ^oC	Not included	Urine output > 100

Table 1. Readiness to wean criteria (*Continued*)

		FiO_2 < 0.5 pH 7.3 - 7.5 PaO_2 30 - 50 mmHg SaO_2 > 90% Hb > 8 mg/dL Pulse oximeter oxygenation stable Cardiopulmonary bypass time < 150 min	min Dynamic compliance > 22 mL/cmH_2O Compliance statica >33 mL/cmH_2O Vital capacity >10 mL/kg MIP >/= -15 cmH_2O	stable				mL/hr Normal CXR
Stahl 2009	Inclusion criteria	FiO_2 </= 0.5 PaO_2 > 75 mmHg or SaO_2 > 90% pH </= 7.2 Hb >/= 7g/dL	PEEP </= 10	Haemodynamically stable	Not included	Not included	Dopamine </= 5 ug/kg/min	MV > 24 hr Breathing spontaneously Ramsey sedation score =/< 3
Strickland 1993	Inclusion criteria	FiO_2 </= 0.4 pH >/= 7.3 </= 7.5 PCO_2 >/= 30 </= 50 SaO_2 >/= 90% on SIMV rate 6 - 10 PS 20 cmH_2O	NIF </= - 20 cmH_2O FVC >/= 10 mL/kg TV 10 - 15 mL/kg	Haemodynamically stable	Not included	T </= 37^oC	Not included	Judged ready to wean by physician Feeding - parenteral or tube Stable renal function Normal electrolytes

CAD = coronary artery diease; CXR = chest X-ray; GCS = Glasgow Coma Scale; FVC = forced vital capacity; Hb = haemoglobin; HR - heart rate; MAP = mean arterial pressure; MIP = maximal inspiratory pressure; MV = mechanical ventilation; NIF = negative inspiratory force; PEEP = positive end expiratory pressure; Pimax = maximal inspiratory mouth pressure; PS = pressure support; RR = respiratory rate; SBP = systolic blood pressure; SIMV = synchronized intermittent mechanical ventilation; T = temperature; TV = tidal volume; f/VT = ratio of respiratory frequency to tidal volume.

Table 2. Weaning protocol differences

Study	Time of randomization	Intervention protocol	Extubation criteria	Comparator (usual practice)
Chaiwat 2010	ICU admission	SBP on PS 7 cmH_2O, PEEP 5 cmH_2O for 2 hours	Notify MD	Not reported
de Carvalho Oliveira 2002	Not reported	SBP on PS 7 cmH_2O, PEEP 5 cmH_2O for 2 hours	Yes	Not reported
Ely 1996	Enrolment, time not reported	SBT 2 hour on CPAP 5 cmH_2O	Notify MD	Not reported
Fan 2013	Not reported	a) SBT 30 minutes and extubation if passed b) If failed, daily SBT and stepwise reduction in SIMV and PS until 4 breaths/min and PS 7 cmH_2O	Not reported	Not reported
Kollef 1997	ICU admission	a) SBT 30 to 60 min on CPAP 5 cmH_2O, PS 6 cmH_2O b) PS stepwise reduction to 6 cmH_2O c) IMV stepwise reduction to 0 breaths/min, on PEEP 5 cmH_2O and PS 6 cmH_2O for 30 to 60 min	a) Yes b) Yes c) Yes	Not reported
Krishnan 2004	Not reported	SBT 1 hour on CPAP 5 cmH_2O	Notify MD	Not reported
Marelich 2000	On meeting weaning criteria	a) < 72-hour admissions: SBT 30 min on PS </= 8 cmH_2O & PEEP </= 8 cmH_2O b) > 72-hour admissions: PEEP, IMV and PS stepwise reductions to achieve FiO_2 0.5, PEEP </= 8 cmH_2O, IMV </= 6 breaths/min, PS </= 8 cmH_2O then SBT as above	a) Notify MD b) Notify MD	Not reported

Table 2. Weaning protocol differences (*Continued*)

Namen 2001	On meeting weaning criteria	SBT 2 hours on CPAP 5 cmH_2O	Notify MD	Not reported
Navalesi 2008	Enrolment, time not reported	SBT 1 hour on CPAP 2 to 3 cmH_2O, FiO_2 0.4	Yes	Not reported
Ogica 2007	Not reported	SBT (details not reported)	Not reported	Not reported
Piotto 2011	Not reported	SBT 2 hours on PS 7 cmH_2O, PEEP 5 cmH_2O, FiO_2 0.4, RR 1 breath/min	Yes	Stepwise reduction in PS and IMV
Reardon 2011	On meeting weaning criteria	Computer automated SmartCare^{TM}/PS with stepwise reductions to PS 7 cmH_2O and PEEP 5 cmH_2O	Notify MD	Stepwise reduction in PS and SBT
Roh 2012	On meeting weaning criteria	CPAP trial on 5 cmH_2O, then stepwise reductions in PS to 5 cmH_2O, then SBT on T-piece for 30 minutes	Yes	Not reported
Rose 2008	On meeting weaning criteria	Computer automated SmartCare^{TM}/PS with stepwise reductions to PS 7 cmH_2O and PEEP 5 cmH_2O	No	Stepwise reduction in PS and PEEP
Simeone 2002	Not reported	SIMV and PS stepwise reductions to SIMV 0 breath/min and PS 4 cmH_2O	Yes	Not reported
Stahl 2009	On meeting weaning criteria	Computer automated SmartCare^{TM}/PS stepwise reductions to PS	Yes	Spepwise reduction in PS and CPAP
Strickland 1993	On meeting weaning criteria	Computer automated Supersport model 2 stepwise reductions in SIMV and PS to RR 2 breaths/min and PS 5 cmH_2O	Not reported	Stepwise reduction in IMV and PS

CPAP = continuous positive airway pressure; IMV = intermittent mechanical ventilation; MD = Medical Doctor; PEEP = positive end expiratory pressure; PS = pressure support; SBT = spontaneous breathing trial; SIMV =synchronized intermittent mechanical ventilation; RR = respiratory rate.

APPENDICES

Appendix 1. Ovid MEDLINE(R) in-process and other non-indexed citations and Ovid MEDLINE(R) (1950 to week 04 January 2014)

#1 exp Ventilator Weaning/
#2 mechanical ventilat$ weaning.mp.
#3 mechanical ventilation.mp.
#4 (protocol$ adj weaning).mp.
#5 (ventilat$ adj weaning).mp.
#6 exp Ventilators, Mechanical/
#7 exp Ventilators, Negative-Pressure/
#8 (mechanical adj ventilat$).mp.
#9 (mechanical adj weaning).mp.
#10 ventilat$.ab,ti.
#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 protocol$.mp.
#13 exp Clinical Protocols/
#14 exp Patient Care Management/
#15 Practice Guidelines/
#16 #12 or #13 or #14 or #15
#17 #11 and #16
#18 clinical trial.pt.
#19 randomized.ab.
#20 placebo.ab.
#21exp Clinical Trials/
#22 randomly.ab.
#23 trial.ti.
#24 #18 or #19 or #20 or #21 or #22 or #23
#25 Animals/
#26 Humans/
#27 #25 not (#25 and #26)
#28 #24 not #27
#29 #17 and #28

Appendix 2. EMBASE (1988 to week 04 January 2014)

#1 exp Ventilator Weaning/
#2 mechanical ventilat$ weaning.mp.
#3 mechanical ventilation.mp.
#4 (protocol$ adj weaning).mp.
#5 (ventilat$ adj weaning).mp.
#6 exp Ventilators, Mechanical/
#7 exp Ventilators, Negative-Pressure/
#8 (mechanical adj ventilat$).mp.
#9 (mechanical adj weaning).mp.
#10 ventilat$.ab,ti.
#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
#12 protocol$.mp.
#13 exp Clinical Protocols/
#14 exp Patient Care Management/
#15 Practice Guidelines/
#16 #12 or #13 or #14 or #15
#17 #11 and #16
#18 clinical trial.pt.
#19 randomized.ab.
#20 placebo.ab.
#21exp Clinical Trials/
#22 randomly.ab.
#23 trial.ti.
#24 #18 or #19 or #20 or #21 or #22 or #23
#25 Animals/
#26 Humans/
#27 #25 not (#25 and #26)
#28 #24 not #27
#29 #17 and #28

Appendix 3. LILACS (via BIREME interface) (1982 to January 2014)

1 "WEANING" or "MECHANICAL VENTILATION" or "VENTILATOR" or "NEGATIVE-PRESSURE" [Words] or "ventilat* weaning" or "mechanical ventilator*" or "destetar mecánico" or "desmamar mecânico" [Words]

Appendix 4. CINAHL Plus EBSCO host (1937 to January 2014)

#1 (MM "Ventilators, Mechanical") or (MM "Ventilator Weaning") or (MH"Respiration, artificial+")
#2 ("mechanical ventilat$ weaning") or ("MH Ventilator Weaning") or (MH "Mechanical Ventilatory Weaning (Iowa NIC)") or (MH "Ventilatory Weaning Impairment (Saba CCC)")
#3 "mechanical ventilation"
#4 "weaning protocol"
#5 #1 or #2 or #3 or #4
#6 ("protocol$") or (MM "Nursing Protocols+")
#7 (MM "Practice Guidelines")
#8 #6 or #7
#9 #5 and #8
#10 (MM "Clinical Trials+")
#11 (MH "Random Assignment")
#12 "randomly"

#13 “trial”
#14 #10 or #11 or #12 or #13
#15 #9 and #14

Appendix 5. CENTRAL (*The Cochrane Library* Issue 1, 2014)

#1 MeSH descriptor Ventilator Weaning explode all trees
#2 mechanical ventilat* weaning
#3 protocol* near weaning
#4 ventilat* near weaning
#5 MeSH descriptor Ventilators, Mechanical explode all trees
#6 MeSH descriptor Ventilators, Negative-Pressure explode all trees
#7 (mechanical ventilat*):ab
#8 mechanical near weaning
#9 ventilat*:ti
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)
#11 protocol*:ti,ab
#12 MeSH descriptor Clinical Protocols explode all trees
#13 MeSH descriptor Patient Care Management explode all trees
#14 MeSH descriptor Practice Guidelines explode all trees
#15 (#11 OR #12 OR #13 OR #14)
#16 (#10 AND #15)

Appendix 6. ISI Web of Science with Conference Proceedings (1970 to February 2014)

#1 TS=mechanical ventilat*
#3 TS=(ventilat* SAME weaning)
#2 TS=(protocol* SAME weaning)
#4 TS=Ventilator* Negative-Pressure
#5 TS=(mechanical SAME weaning)
#6 TS=ventilat*
#7 #6 OR #5 OR #4 OR #3 OR #2 OR #1
#8 TS=protocol*
#9 TS=(Care SAME Manag*)
#10 TS=(Patient* SAME Management)
#11 TS=(Practice Guideline*)
#12 #11 OR #10 OR #9 OR #8
#13 #12 AND #7
#14 TS=clinical trial*
#15 TS=random*
#16 TS=placebo*
#17 #16 OR #15 OR #14
#18 #17 AND #13

Appendix 7. Data extraction form

Study Selection, Quality Assessment & Data Extraction Form
Name of author extracting data: .....
Date form completed: .....
Study ID

Title	
Study ID for RevMan (Family name of first author and year of publication + letter if more than one per year, e.g. Smith2001b)	
Are there other articles of same study? (YES, NO, Unclear. If Yes, write Study IDs)	

Study Eligibility

	(please circle)	
Type of study Can the study be described as randomized?	**Yes, Unclear, No**	
Participants 1. Were the participants adults (at least 18 years & over) and in ICUs? 2. Were participants intubated (naso/oro-tracheal) and receiving invasive mechanical ventilation (MV)?	**Yes, Unclear, No** **Yes, Unclear, No**	
Interventions 1. Was one group weaned using a formal weaning protocol[1]? 2. Was the other group weaned without reference to a formal protocol?	**Yes, Unclear, No** **Yes, Unclear, No**	
Outcomes: Did the study report any one of - 1. Total duration of MV (time from initiation of MV to MV discontinuation)? 2. Weaning duration (time from identification of weaning readiness to MV discontinuation)? 3. ICU length of stay	**Yes, Unclear, No** **Yes, Unclear, No** **Yes, Unclear, No**	

Conclusion: Do not proceed if any of the above answers are 'No'.
If study to be 'included' or 'excluded & listed in excluded table', record below the information to be inserted into tables
If included - continue to page 2
Included, or

(*Continued*)

Excluded and should be listed in the excluded table **More information needed before inclusion decision (specify):** **Record for tables:**

[1]Protocol = a written set of rules, criteria, guidelines or algorithm for deciding if a patient is ready to tolerate MV discontinuation & for reducing ventilatory support.

PARTICIPANTS			
Inclusion/Exclusion Criteria			
INTERVENTION		**CONTROL**	
Number randomized			
Number analyzed			
Age, mean (SD) med (IQR)		Age, mean (SD) med (IQR)	
Male n (%)		Male n (%)	
Name severity of illness measure (e.g. APACHE, SAPS, PELOD) mean (SD) med (		Name severity of illness measure (e.g. APACHE, SAPS, PELOD) mean (SD) med (IQR)	

Setting	Participating site country(ies):			
	Academic hospital	Non-teaching hospital	Not reported	
	Any other information about hospital (e.g. number of beds)			
	Number of ICUs and types (e.g. medical; surgical; mixed; neuro. Include number of beds if reported)			

(*Continued*)

	Closed ICU structure	Open ICU structure			Not reported	
Nurse staffing for vent patients	1:1	1:2	1:3	1:4	Not reported	
Physician staffing (describe) Not reported						
INTERVENTION						
Describe weaning protocol and, if appropriate, who delivered it (verbatim)						
Describe sedation strategies in intervention arm (tick all that apply):						
sedation score	sedation protocol	daily interruption			not reported	
CONTROL						
Describe usual/standard weaning (verbatim)						
Describe sedation strategies in control arm (tick all that apply): as above						
sedation score	sedation protocol	daily interruption			not reported	

Outcomes (list & provide descriptors if they were described in the paper)

Primary	
Secondary	

Domain	**Description (verbatim)**	**Judgement**
Sequence generation Was the allocation sequence adequately generated?		Yes No Unclear
Allocation concealment Was allocation adequately concealed?		Yes No Unclear

(*Continued*)

Blinding (participants, personnel, outcome) Was knowledge of the allocated intervention adequately prevented during the study?		Yes No Unclear
Incomplete outcome data Were incomplete outcome data adequately addressed? State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons	Total duration of mechanical ventilation (initiation of mechanical ventilation to discontinuation)	Not measured Yes No Unclear
	Weaning duration (identification of weaning to mechanical ventilation discontinuation)	Not measured Yes No Unclear
	Mechanical ventilation time prior to weaning (initiation of mechanical ventilation to identification of weaning)	Not measured Yes No Unclear
	Time from mechanical ventilation discontinuation to extubation	Not measured Yes No Unclear
	ICU length of stay	Not measured Yes No Unclear
	Hospital length of stay	Not measured Yes No Unclear
	Cost	Not measured Yes No Unclear
	Mortality	Not measured Yes No Unclear
	Reintubation	Not measured Yes No Unclear

(*Continued*)

	Selfextubation	Not measured Yes No Unclear
	Postextubation NIV	Not measured Yes No Unclear
	≥ 21 days vented	Not measured Yes No Unclear
	Tracheostomy	Not measured Yes No Unclear
Selective outcome reporting. Are reports of the study free of suggestion of selective outcome reporting?		Yes No Unclear
Other sources of bias. Study free from other bias?		Yes No Unclear

Outcomes - Continuous Data

Outcomes	**Unit measurement**	**Intervention group**			**Control group**				**95% CI or any further details if outcome only described in text**
		n	**Mean (SD)**	**Median (IQR)**	**n**	**Mean (SD)**	**Median (IQR)**	**P-value**	
Total duration of mechanical ventilation (initiation of mechanical ventilation to discontinuation)									

(*Continued*)

Weaning duration (identification of weaning to mechanical ventilation discontinuation)									
Mechanical ventilation time prior to weaning (initiation of mechanical ventilation to identification of weaning)									
Time from mechanical ventilation discontinuation to extubation									
ICU length of stay									
Hospital length of stay									
Cost (state, hospital or ICU)									

Outcomes - Dichotomous Data

Outcomes	Intervention group (n =)	Control group (n =)	P value	Any further information
Reintubation				
Self extubation				
Tracheostomy				
Mechanical ventilation > 21 days				
Mortality				
Postextubation NIV				

Please specify number of patients in each group experiencing the specified outcomes.
Other information which you feel is relevant to the results:

Indicate if: any data were obtained from the primary author; if results were estimated from graphs etc; or calculated by you using a formula (this should be stated and the formula given)
In general if results not reported in paper(s) are obtained this should be made clear here to be cited in review

WHAT'S NEW

Last assessed as up-to-date: 30 January 2014.

Date	Event	Description
6 November 2014	New citation required but conclusions have not changed	In general, our review reaches the same conclusions as the Blackwood 2010 review. However, because we included more trials we have more precise estimates on duration of mechanical ventilation
6 November 2014	New search has been performed	This is an update of the previous Cochrane systematic review (Blackwood 2010) published in Issue 5, 2010 that included 11 randomized controlled trials. We ran the search until 30 January 2014 and found six new trials

HISTORY

Protocol first published: Issue 1, 2008

Review first published: Issue 5, 2010

Date	Event	Description
6 June 2011	Amended	We have amended the flow chart and corrected minor errors in the text We have updated RevMan and Cochrane Handbook references.
7 March 2011	Amended	Contact details updated.
7 June 2010	Amended	We have corrected the geometric confidence intervals (CI) for hospital length of stay. Previously it read: -1% (95% CI -2% to -10%), it now reads -1% (95% CI -11% to 10%) We have been informed that the previously unpublished paper by Stahl 2009 has now been published (Stahl 2009).
29 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: B Blackwood (BB)

Co-ordinating the review: BB

Undertaking manual searches: BB, P O'Halloran (POH)

Organizing retrieval of papers: BB, POH

Screening retrieved papers against inclusion criteria: BB, POH

Appraising quality of papers: BB, KEA Burns (KB)

Abstracting data from papers: BB, KB

Writing to authors of papers for additional information: BB

Providing additional data about papers: BB

Obtaining and screening data on unpublished studies: BB, KB

Data management for the review: BB

Entering data into Review Manager (RevMan 2014): BB

Review Manager statistical data: BB, CR Caldwell (CC)

Other statistical analysis not using Review Manager: BB, CC

Checking entry of data: (data entered by person one: BB; data checked by person two: POH)

Interpretation of data: CC, BB, POH, KB

Statistical analysis: CC, BB

Writing the review: BB, POH, KB, CC

Performing previous work that was the foundation of the present study: BB

Guarantor for the review (one author): BB

Person responsible for reading and checking review before submission: BB

DECLARATIONS OF INTEREST

Bronagh Blackwood: none known.

Karen EA Burns: holds a CAD 5000 travel bursary from Draeger Medical Inc. (Canada) for the purpose of conducting site visits to participating centres in the WEAN Study. The WEAN study is not included in this Cochrane review. (The WEAN Study is an investigator-initiated trial comparing SmartCare™ and protocolized weaning, for which the co-principal investigator (Dr Burns) obtained funding from peer review, non-industry sources for implementation. Draeger Medical Inc. provided ventilators and ventilator upgrades for the WEAN study and a central randomization system using electronic mail correspondence (Draeger Medical, Germany). Draeger Medical was not involved in any aspects of study design and oversight, data management or data analysis).

Chris R Cardwell: none known.

Peter O'Halloran: none known.

SOURCES OF SUPPORT

Internal sources

- Critical Care Translational Research Group, Northern Ireland, UK.

External sources

- Research and Development Office, Northern Ireland and the Health Research Board, Ireland.

Cochrane Fellowship

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

There are four differences between the published protocol (Blackwood 2008) and this updated review.

1. We included quasi-randomized controlled trials, that is trials that prospectively assigned patients to groups using a quasi-random method such as alternation or hospital number. We included these studies because we felt that the rule-based system reduced investigator bias to a certain degree. Nevertheless, we assessed risk of bias in a similar manner to randomized controlled trials and conducted a sensitivity analysis excluding quasi-randomized trials.

2. We used The Cochrane Collaboration's new domain-based evaluation to assess the validity and quality of the included studies because this was released after publication of the protocol.

3. We included neurosurgical units in the subgroup analysis of type of unit as there are specific differences in weaning this group of patients because of their neurological impairment.

4. We included one further sensitivity analysis to explore the impact on the findings before log transforming the variables to approximate normality.

INDEX TERMS

Medical Subject Headings (MeSH)

*Critical Illness; Clinical Protocols [standards]; Intensive Care Units [utilization]; Length of Stay; Randomized Controlled Trials as Topic; Respiration, Artificial [adverse effects; *utilization]; Time Factors; Ventilator Weaning [adverse effects; *methods]

MeSH check words

Adult; Humans