Title: Sedation protocols to reduce duration of mechanical ventilation in the ICU: a Cochrane Systematic Review

Running head: Sedation protocol CSR

Author details:
Leanne M AITKEN
Professor of Critical Care Nursing
NHMRC Centre for Research Excellence in Nursing; Centre for Health Practice Innovation; Menzies Health Institute Queensland; Griffith University; Brisbane; Australia
Intensive Care Unit; Princess Alexandra Hospital; Woolloongabba; Australia
School of Health Sciences; City University London; London; UK
RN; PhD
Email: l.aitken@griffith.edu.au
Ph: +61 7 3735 5115

Tracey BUCKNALL
Professor of Nursing; Associate Head of School (Research)
Centre for Quality and Patient Safety, School of Nursing and Midwifery; Faculty of Health; Deakin University; Melbourne; Australia
Director of Nursing Research, Alfred Health
RN; PhD

Bridie KENT
Professor of Nursing
School of Nursing and Midwifery; Plymouth University; Plymouth; UK
RN; PhD

Marion Mitchell
Associate Professor of Nursing
NHMRC Centre for Research Excellence in Nursing; Centre for Health Practice Innovation; Menzies Health Institute Queensland; Griffith University; Brisbane; Australia
Intensive Care Unit; Princess Alexandra Hospital; Woolloongabba; Australia
RN; PhD

Elizabeth Burmeister
Nurse Researcher
Centre for Health Practice Innovation; Menzies Health Institute Queensland; Griffith University; Brisbane; Australia
Princess Alexandra Hospital; Woolloongabba; Australia
RN; MSc

Samantha Keogh
Senior Research Fellow
NHMRC Centre for Research Excellence in Nursing; Centre for Health Practice Innovation; Menzies Health Institute Queensland; Griffith University; Brisbane; Australia

RN; PhD

Acknowledgements: We would like to thank Jane Cracknell (Managing Editor, Cochrane Anaesthesia Review Group) and Karen Hovhannisyan (Trials Search Co-ordinator, Cochrane Anaesthesia Review Group) for their assistance in the preparation of the protocol and review. We would also like to thank Harald Herkner (content editor), Nathan Pace (statistical editor), and John P Kress, Bronagh Blackwood and HS Jeffrey Mann (peer reviewers) and Janet Wale (CARG consumer editor) for their help and editorial advice during the preparation of this systematic review. We also thank Maria Isabel Castillo and Cesar Caramo for assistance with translating a Spanish language manuscript. The National Health and Medical Research Council (NHMRC) has provided funding for this review from its Centre of Research Excellence scheme, which funds one or more of the authors.

Conflict of interest statement: No conflict of interest has been declared by the author(s).

Funding statement: The National Health and Medical Research Council (NHMRC) has provided funding for this review from its Centre of Research Excellence scheme, which funds one or more of the authors. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors

ABSTRACT:

Aims: Assess the effects of protocol-directed sedation management on the duration of mechanical ventilation and other relevant patient outcomes in mechanically ventilated intensive care unit patients.

Background: Sedation is a core component of critical care. Sub-optimal sedation management incorporates both under-and over-sedation and has been linked to poorer patient outcomes.

Design: Cochrane systematic review of randomised controlled trials.

Data Sources: Cochrane Central Register of Controlled trials, MEDLINE, EMBASE, CINAHL, Database of Abstracts of Reviews of Effects, LILACS, Current Controlled Trials and US National Institutes of Health Clinical Research Studies (1990 – November 2013), and reference lists of articles were used.

Review Methods: Randomised controlled trials conducted in intensive care units comparing management with and without protocol-directed sedation were included. Two authors screened titles, abstracts and full-text reports. Potential risk of bias was assessed. Clinical, methodological and statistical heterogeneity were examined and the random-effects model used for meta-analysis where appropriate. Mean difference for duration of mechanical ventilation and risk ratio for mortality, with 95% confidence intervals, were calculated.

Results: Two eligible studies with 633 participants comparing protocol-directed sedation delivered by nurses versus usual care were identified. There was no evidence of differences in duration of mechanical ventilation or hospital mortality. There was significant heterogeneity between studies for duration of mechanical ventilation.

Conclusions: There is insufficient evidence to evaluate the effectiveness of protocol-directed sedation as results from the two randomised controlled trials were conflicting.

SUMMARY STATEMENT:

Why is this research or review needed?

- Equivocal evidence from international studies
- Increasing focus on sub-optimal sedation management
- Implications of sedation and ventilation management highlighted in ICU recovery research

What are the key findings?

- Limited RCTs to evaluate the effectiveness; both studies had limitations and contrasting results
- Heterogeneity limited interpretation
- Insufficient evidence to assess the impact of protocol-directed sedation on relevant patient outcomes

How should the findings be used to influence policy / practice / research / education?

- Limitations of the research should be addressed in a longitudinal cluster randomised trial, with follow to assess patient outcomes

INTRODUCTION

Sedation management of critically ill patients is a core component of critical care; these patients are often treated with invasive and difficult-to-tolerate procedures and treatments. Ensuring comfort throughout this process assists recovery and ensures humane treatment (Mehta *et al.* 2009). To promote this, appropriate sedation is essential for all critically ill patients, as is associated pain relief and anxiolysis. To support this practice, a systematic review of randomised controlled trials (RCTs) that examined the effectiveness of nurse-directed sedation protocols was undertaken and published as a Cochrane systematic review (anon); this current paper presents a summarised version of that review.

Growing evidence suggests that sedation is poorly managed; one systematic review of 36 studies found a substantial incidence of sub-optimal sedation (Jackson *et al.* 2009). The detrimental impact of poor sedation practices extends from under-sedation to over-sedation. Under-sedation has the potential to lead to agitated patients with compromised long-term psychological recovery, while over-sedation may lead to increased intensive care unit (ICU) and hospital lengths of stay and poor long-term recovery (Mehta *et al.* 2009). There is some evidence to suggest links between short-term measures (such as intensive care and hospital lengths of stay) (Jackson *et al.* 2010, Kollef *et al.* 1998, Schweickert and Kress 2008), adverse events (such as self extubation) (Girard *et al.* 2008), and longer-term outcomes such as ICU memory recall and psychological recovery (Jackson *et al.* 2010, Ringdal *et al.* 2006, Samuelson *et al.* 2006).

Sedation refers to the administration of pharmacological agents designed primarily to induce a sedative effect in patients. Sedation does not include pharmacological agents administered primarily for other reasons, such as analgesics, even though these agents might have some secondary sedative effect. Internationally there is a range of different methods of managing patients' sedation needs.

Various strategies have been proposed to improve sedation management of critically ill patients: sedation assessment instruments (Curley *et al.* 2006, Ely *et al.* 2003, Riker *et al.* 1999); sedation guidelines, algorithms or protocols to guide assessment and therapy (Jacobi *et al.* 2002, Sessler and Pedram 2009); implementation of daily sedation interruptions (Kress *et al.* 2000); targeting minimal levels of sedation and regular assessment of sedation and analgesia requirements (Schweickert and Kress 2008). Despite a core component of many of these recommendations being the use of an algorithm or protocol, there is evidence to suggest that sedation guidelines remain poorly implemented, with less than 50% of critical care units in Canada, USA and Denmark indicating such use (Sessler and Pedram 2009). This lack of implementation may be due to the inconsistent results in the studies examining the effect of protocol-directed sedation (Brook *et al.* 1999, Bucknall *et al.* 2008, De Jonghe *et al.* 2005, Quenot *et al.* 2007, Elliott *et al.* 2006). Protocol-directed sedation is ordered by a physician, contains guidance regarding sedation management, and is

implemented by nurses, pharmacists or other members of the healthcare team. Selection of the most appropriate sedative agent, as well as when to commence, increase, decrease or cease administration of the agent, is based on patient assessment, usually with the aid of a sedation scale. Protocols may include an analgesic component (Brook *et al.* 1999). Protocol-directed sedation is distinct from, but related to, protocol-directed weaning, which is specifically directed towards limiting the duration of mechanical ventilation (Blackwood *et al.* 2014).

Use of a protocol may improve sedation by incorporating regular patient assessment with planned changes to sedative or analgesic agents, or both. There is widespread evidence of international variation in sedation assessment and management practices (Mehta *et al.* 2009, O'Connor *et al.* 2009). The potential to reduce the individual clinician variation is significant, with management based on standardised assessment practices. Despite widespread use of sedation protocols there is mixed evidence as to their effectiveness.

THE REVIEW

Aims

To assess the effects of protocol-directed sedation management on the duration of mechanical ventilation and other relevant patient outcomes (see Table 1) in mechanically ventilated ICU patients.

<Insert Table 1>

Design

RCTs and quasi-randomised controlled trials published in any language were included. An RCT was defined as a study in which patients were allocated to treatment groups based on a random or quasi-random method (e.g. using random number tables, hospital number, date of birth).

All ICU patients who were mechanically ventilated (via endotracheal or tracheostomy tube) were included. If eligible studies had included both patients who met the above criteria and those who did not, data were excluded unless the subpopulations were reported, or able to be obtained.

The target intervention was protocol-directed sedation management which was compared with non-protocol-directed sedation management. Protocol-directed sedation was defined as sedation directed by a protocol or algorithm that was ordered by a medical officer, contained guidance regarding sedation management, and was implemented by nurses, pharmacists or other members of the healthcare team with sedation increased or decreased based on patient assessment. The guidance regarding sedation management consisted of a series of decision points or decision algorithms that assisted clinicians to make decisions regarding increasing, decreasing or maintaining current sedation levels. Protocols included provision for

administration of analgesics in addition to sedative agents. Medical officers may have continued to be involved in sedation assessment and management beyond the point of ordering the sedation protocol, but any protocol that required physician approval for changes in amounts of sedation was excluded. The essential element of protocol-directed sedation was that other members of the healthcare team could alter the level of sedation being administered without consulting with a medical officer. Usual care was defined as physician-led sedation management of mechanically ventilated patients according to local practice where no specific strategies were implemented to change the level of sedation. Sedative agents may or may not have been different to those used in the intervention; importantly the intervention was not about the agents that were used but how they were used.

The Cochrane Central Register of Controlled trials (CENTRAL) (2013, Issue 11), MEDLINE (OvidSP; from 1990 to November 2013), EMBASE (OvidSP; from 1990 to November 2013), CINAHL (BIREME host; from 1990 to November 2013), Database of Abstracts of Reviews of Effects (DARE) (from 1990 to November 2013), LILACS (1990 to November 2013), Current Controlled Trials and US National Institutes of Health Research Studies (from 1990 to November 2013) were searched. An example of the search strategy is provided in Supplementary Table 1. The search was re-run in October 2014 and any studies of interest will be dealt with when the review is updated. The MEDLINE search strategy was combined with the Cochrane highly sensitive search strategy, as detailed in Higgins and Green (2011) and was adapted for searching all other databases. Relevant critical care journals, reference lists of identified published trials, abstracts of relevant conference proceedings and the reference lists of relevant articles were hand-searched to identify further clinical trials. Relevant trial authors were contacted to identify any additional studies. We searched specific websites for relevant ongoing trials:

1. International Clinical trials registry (www.who.int/ trialsearch);
2. International Standard Randomized Controlled Trials (www.controlled-trials.com/isrctn);
3. Country specific trial websites for the UK, South Africa, India, Hong Kong, China, and Australia and New Zealand.

No language restriction was imposed.

Quality appraisal

Two authors (LA and TB or MM) independently assessed the methodological quality of each eligible trial as per the Cochrane Collaboration guidelines (Higgins and Green 2011); disagreements were resolved by discussion. Where potential conflicts of interest existed, the relevant author was excluded from the process. Seven domains were assessed to determine risk of bias (Table 2); we considered a trial as having a high risk of bias if one or more of the assessment domains was rated as high risk or unclear.

<Insert Table 2>

We assessed clinical heterogeneity for key participant and sedation protocol characteristics. Study cohorts were considered sufficiently similar for participant and intervention characteristics to suggest data could potentially be pooled for statistical analysis. We assessed statistical heterogeneity using the I^2 statistic. Where this analysis suggested statistical heterogeneity was moderate or greater, we have noted that care should be taken when interpreting the results for that outcome. In the absence of sufficient homogeneity between the studies, we provided a descriptive presentation of the results. We did not undertake meta-regression due to insufficient studies and appropriate homogeneity; similarly there were insufficient studies (less than 10) to construct a funnel plot to explore the symmetry of the intervention effects to assess for publication bias.

Data abstraction

Two authors (LA and TB) independently reviewed all titles and decided on the inclusion of studies based on selection criteria, then extracted standardised data from each study. We resolved differences and avoided conflicts by consulting a third author (MM). If a study had insufficient data to complete data extraction or if we required data clarification, we contacted the authors of the study. We considered the studies to have sufficient data if at least one of the listed outcomes (either primary or secondary) was reported.

Synthesis

Subject to the absence of clinical heterogeneity, we undertook an analysis using Review Manager 5 software (RevMan 2013). For continuous data, the mean difference (MD), or standardized mean difference (SMD), and 95% confidence interval (CI) for summary statistics (hospital and ICU length of stay, duration of mechanical ventilation) was used wherever possible. We found the data to be skewed and, due to the unavailability of source data related to one study, we were unable to transform the data for analysis. For dichotomous data, we used risk ratio (RR) and 95% CI.

We used the results of intention-to-treat (ITT) analyses for all analyses so all data extracted reflected the original allocation group. There was no evidence of multiple observations or outcome measurements in either of the included studies and all outcome measurements were taken at the same time point in both studies. The duration of mechanical ventilation was measured on the same group of patients throughout their ICU stay. Both included studies had a small number (less than 4%) of participants who were recruited into the studies despite not meeting inclusion criteria (re-admission to ICU, patient awaiting rapid transfer to another ICU) and we excluded these patients from all analyses. Published study reports identified complete data for all included participants, indicating there were no drop-outs in either study.

If studies were sufficiently homogenous, we planned to conduct a meta-analysis using a fixed-effect model or where heterogeneity existed, a random-effects model. We conducted meta-analyses for all outcomes where possible, although the meta-analyses for many of the outcomes should be interpreted with caution due to the presence of substantial heterogeneity (duration of mechanical ventilation, length of ICU stay and incidence of tracheostomy). Analyses were considered significant at the alpha = 0.05 level. Estimates of precision were assessed by interpretation of CIs, such as widths, overlapping and inclusion of the null hypothesis.

Intensive care patients were a heterogeneous group. Given the small number of studies and limited variation in the included participants and methods, we could not undertake sub-group or sensitivity analyses.

We used the principles of the GRADE system to assess the quality of the body of evidence associated with outcomes reported (Guyatt *et al.* 2008). The GRADE approach appraises the quality of evidence based on the extent to which one can be confident that an estimate of effect or association reflects the item being assessed. The quality of a body of evidence considers within-study risk of bias (methodological quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias.

RESULTS

The results of the search and selection of studies are summarised in the PRISMA study flow diagram (see Figure 1). After exclusion of duplicates we identified 2041 records, with 21 full text articles retrieved. We excluded 13 of these as they did not address our research question, for example they answered different questions or provided a review of the topic, and we excluded six studies as, although they addressed the question of our review, they did not use a randomised or quasi-randomised design (Elliott *et al.* 2006, De Jonghe *et al.* 2005, Quenot *et al.* 2007, Arias-Rivera *et al.* 2008, Brattebo *et al.* 2002, Tobar *et al.* 2008). We identified two studies of interest (Brook *et al.* 1999, Bucknall *et al.* 2008). We re-ran the search in October 2014. We identified a further 482 records after removing duplicates; we identified one study of interest and we will report this study when we update the review.

<Insert Figure 1>

We included two studies (Brook *et al.* 1999, Bucknall *et al.* 2008). The studies were similar in design and examined the impact of protocol-directed sedation on a range of outcomes including duration of mechanical ventilation, mortality, ICU and hospital length of stay, and some adverse events (see Table 2).

<Insert Table 2>

Brook *et al.* (1999) enrolled 332 participants from a single 19-bed medical ICU within a university-affiliated urban teaching hospital in the USA, with data collected in 1997 to 1998. In contrast, Bucknall *et al.* (2008) enrolled 316 participants from a 24-bed mixed ICU in a major Australian metropolitan university-associated teaching hospital. Participants were adults who were mechanically ventilated. Both studies were single-centre RCTs. The interventions were similar, with Bucknall *et al.* (2008) indicating they modelled their intervention on that reported by Brook *et al.* (1999). In both studies, nurses used a structured approach for assessment to determine whether analgesics or sedatives (or both) were required by the patient, then administered pre-specified medications according to their ongoing assessment. Differences in the medications used existed, with Brook *et al.* (1999) using diazepam, midazolam, fentanyl and morphine, while Bucknall *et al.* (2008) used midazolam, propofol and morphine.

The most important difference between the two studies was the usual method of providing sedation-related aspects of care to patients in each of the two study sites. In the USA study, all aspects of sedation were ordered by the treating physicians and nurses could not make changes without a physician's written or verbal order (Brook *et al.* 1999). In the Australian study, ICU medical staff prescribed the type of sedation medication and dose limits for infusion and boluses, with each patient's ICU nurse free to assess, titrate and manage sedation, including the ceasing of sedation, within those limits (Bucknall *et al.* 2008).

Risk of bias in included studies

We analysed seven domains of potential risk of bias. We rated both studies the same for risk of bias for five of the seven domains (see Table 2). Of note, usual care was not described well by Brook *et al.* (1999), except for the number of participants and duration of chemical paralysis. It was unclear if standard management practices (mode of mechanical ventilation, physiotherapy, suctioning, re-positioning, investigations outside ICU, need for physical restraints) or nurse:patient ratios were equally applied to both groups. While Bucknall *et al.* (2008) provided a description of usual care for general management and specific sedation management, some associated aspects of care, such as physiotherapy, suctioning, re-positioning, investigations outside ICU and need for physical restraints, were not provided. a potential for contamination between the two groups existed as participants in both studies were cared for in the same ICU at the same time and care of control group participants was directed by physicians in line with usual local practice and individual preferences (Brook *et al.* 1999, Bucknall *et al.* 2008). It is possible that the principles of protocol-directed care could have been partially applied to the control group.

Effects of interventions

<u>Duration of mechanical ventilation</u>

Both included studies reported duration of mechanical ventilation. When we pooled data to analyse the MD receiving mechanical ventilation (MD -5.74 hours, 95% CI -62.01 to 50.53) comparing management with protocol-directed sedation with usual care, the test of heterogeneity was substantial (Tau^2 = 1416.10; Chi^2 = 7.08, degrees of freedom (df) = 1; P value = 0.008; I^2 = 86%). Such high heterogeneity suggested that the two studies were dissimilar, and may reflect the differing nurse:patient ratios present in usual care within the study environments. Interpretation of these results related to duration of mechanical ventilation should proceed with caution given this high level of statistical heterogeneity.

Intensive care unit and hospital mortality

One study reported ICU mortality data (RR 1.04, 95% CI 0.67 to 1.61) (Bucknall *et al.* 2008) whereas both reported hospital mortality data. The combined hospital mortality outcome, with 633 patients, was not significantly different between the protocol-directed sedation and usual care groups (RR 0.96, 95% CI 0.71 to 1.31; heterogeneity Tau^2 = 0.02; Chi^2 = 1.50, df = 1; P value = 0.22; I^2 = 33%) (Figure 2).

<Insert Figure 2>

Length of intensive care unit stay

Both included studies reported length of ICU stay. Pooled data to analyse the MD in length of ICU stay (MD -0.62 days, 95% CI -2.97 to 1.73) comparing management with protocol-directed sedation with usual care, showed the test of heterogeneity was substantial (Tau^2 = 2.35; Chi^2 = 5.43, df = 1; P value = 0.02; I^2 = 82%). Again, such high heterogeneity suggested that the two studies were dissimilar, and interpretation of these results should proceed with caution.

Hospital length of stay

Both included studies reported hospital length of stay. The combined MD in hospital length of stay, with 633 patients, was not significantly different between the protocol-directed sedation and usual care groups (MD -3.78 days, 95% CI -8.54 to 0.97) (heterogeneity Tau^2 = 4.83; Chi^2 = 1.67, df = 1; P value = 0.20; I^2 = 40%; Figure 3).

<Insert Figure 3>

Adverse events

The studies reported few adverse event data. One study reported re-intubation rates (RR 0.65, 95% CI 0.35 to 1.24) (Brook *et al.* 1999) while the other study reported self extubation data (RR 2.08, 95% CI 0.19 to 22.69) (Bucknall *et al.* 2008). In clinical practice, some patients who self extubate will not require re-intubation, therefore self extubation rates would normally be higher than re-intubation rates. In these two studies, Bucknall *et al.* (2008) reported self extubation rates of only 1% in each

group, while Brook *et al.* (1999) reported reintubation rates of 6% to 13% in their two groups.

Incidence of tracheostomy

The incidence of tracheostomy was reported in both included studies. When we pooled data to analyse the frequency of tracheostomy (RR 0.77, 95% CI 0.31 to 1.89) comparing management with protocol-directed sedation with usual care, the test of heterogeneity was substantial ($Tau^2 = 0.32$; Chi2 = 4.16, df = 1; P value = 0.04; $I^2 = 76\%$). Such high heterogeneity suggested that the two studies were dissimilar, and interpretation of these results should proceed with caution.

No studies were identified where the outcomes of total dose of sedation, incidence of delirium, memory function, psychological recovery, cognitive recovery or quality of life were addressed.

DISCUSSION

Summary of main results

A systematic search of databases identified 2041 potential records, 21 potential studies and ultimately 2 eligible studies, with 633 participants, for review and analysis of the impact of protocol-directed sedation on duration of mechanical ventilation and mortality. Brook *et al.* (1999) reported a significant reduction in duration of mechanical ventilation and no difference in mortality with protocol-directed sedation in the USA study, while Bucknall *et al.* (2008) reported no difference in either outcome in the Australian study. When we pooled data, hospital mortality did not differ between participants who received protocol-directed sedation and participants who received usual care. Significant heterogeneity suggested the cohorts were dissimilar for the outcome of duration of mechanical ventilation, therefore interpretation of results should proceed with caution.

Secondary outcomes that were reported in both studies included ICU and hospital length of stay as well as incidence of tracheostomy. There was no difference in duration of hospital length of stay between participants who received protocol-directed sedation and participants who received usual care. Significant heterogeneity suggested the cohorts were very dissimilar for the outcomes of ICU length of stay and incidence of tracheostomy, therefore interpretation of results should proceed with caution.

Overall completeness and applicability of evidence

The two studies included in this systematic review both reported our primary outcomes; however, only a few of our secondary outcomes were reported. Neither study examined the relationship between protocol directed sedation and post-ICU outcomes such as memory function, psychological and cognitive recovery, and quality of life. Despite this, there is increasing recognition that sedation practices are

likely to influence these long-term outcomes (Barr *et al.* 2013). Despite similar participant and intervention characteristics, substantial heterogeneity existed for most outcomes, limiting our ability to interpret the meta-analyses in a meaningful way. This heterogeneity may be the result of one study being conducted in the USA in the 1990s (Brook *et al.* 1999), while the other study was conducted in Australia approximately 10 years later (Bucknall *et al.* 2008). These differences in geographic location and time may have resulted in substantial differences in important related areas of practice such as usual sedation practices and agents, patterns and modes of mechanical ventilation, mobilisation practices and other aspects of intensive care that affect the identified outcomes. One aspect of critical care organisation that differed between the two settings was the usual nurse:patient ratio, with each nurse caring for two or three patients in the USA setting (confirmed with study investigators), while each nurse cared for one mechanically ventilated patient in the Australian setting; this has the potential to affect aspects of care such as how much patient agitation might be tolerated. Details regarding usual care are essential in the publication of studies that deal with a complex area of practice, as there are many variations that are essential to understand in order to determine transferability of evidence.

Quality of the evidence

The methodological quality of the studies was moderate, but the quality of the overall evidence was low. We only included two studies and they had conflicting results resulting in wide CIs for some outcomes. Furthermore, although we rated studies as having a low risk of detection and attrition bias and some aspects of selection bias, one or both studies had unclear or high risks of bias related to other aspects of selection, reporting and performance. Due to the nature of the intervention, it was not possible to blind participants or clinicians. Inclusion of alternative grades of evidence, for example non-randomised experimental studies may help to provide a more complete picture of the evidence, but is precluded under some Cochrane review group guidelines. Further, synthesis of qualitative studies may be beneficial in identifying the characteristics of patients and context where nurse-directed sedation protocols are beneficial, and how benefit might be enhanced in the future.

Potential biases in the review process

Clearly described procedures were followed to minimise potential bias in the review process. We conducted a systematic and rigorous literature search, and used transparent and reproducible methods. Where a review author was involved in any included study, she was removed from the process of analysing relevant information.

Agreements and disagreements with other studies or reviews

The effect of the use of protocol-directed sedation on patient outcomes has been of interest for several years and, while it has not been the subject of any other reviews, it has been the subject of additional, non-randomised studies. Consistent with the

findings of the two studies included in this review (Brook *et al.* 1999, Bucknall *et al.* 2008), findings from non-randomised studies have generally been conflicting. One non-randomised study conducted in Australia found no benefit and, in fact, an increase in the duration of ICU length of stay with the implementation of protocol-directed sedation (Elliott *et al.* 2006), while non-randomised studies conducted in Europe identified mixed results. One Spanish study reported no difference in duration of mechanical ventilation (Arias-Rivera *et al.* 2008), one Norwegian study reported a reduction in duration of mechanical ventilation but no difference in ICU length of stay (Brattebo *et al.* 2002) and two French studies identified a reduction in duration of mechanical ventilation (De Jonghe *et al.* 2005, Quenot *et al.* 2007). These mixed results are likely to be influenced by multiple behavioural factors within the study sites, particularly the role of nurses in contributing to sedation management during usual care.

One systematic review of observational and controlled studies examined multiple aspects of sedation practice to determine the impact of changes on economic and patient safety outcomes (Jackson *et al.* 2010). When considering a broad methodological range of studies, the overall conclusion was that the introduction of guidelines and protocols generally improved outcomes. Furthermore, in one related systematic review of the effect of daily sedation interruption, there was no strong evidence of benefit from the intervention although individual studies reported inconsistent results (Burry *et al.* 2014). The reasons for these inconsistencies are likely to be multidimensional; however, they may include factors such as nurse:patient ratios, proportion of speciality specific postgraduate educated nurses, sedative agents used during usual care and other related aspects such as ventilation and mobilisation practices. It is also possible that the sedation protocols resulted in different practices of sedation administration that were not identified in the outcomes assessed in this review. Both included studies measured doses of sedative agents but few differences were noted and no total dose of sedation was available to enable comparisons (Brook *et al.* 1999, Bucknall *et al.* 2008). It is unlikely that any meaningful comparison of sedative agents could be made given the effect of factors such as patient weight, and renal and liver function on drug metabolism. Although inconsistencies in the effects of various interventions have been identified, there is strong agreement that the principle of reducing sedation, both in terms of depth and duration, should be a goal of care given it's link with both short and long term outcome (need ref). Achievement of this goal is likely to be optimised with consistent use of validated assessment instruments, identification of clear sedation targets, and examination of various interventions within local contexts.

CONCLUSION

Currently limited evidence from RCTs is available to evaluate the effectiveness of protocol-directed sedation on patient outcomes. The two included RCTs reported conflicting results whilst heterogeneity limited the interpretation of results for many of the outcomes. Notably, the clinical context and practice roles of ICU clinicians should

be considered prior to implementation of protocol-directed sedation management. There was no evidence to draw conclusions on the efficacy and safety of protocol-directed sedation, although there was general agreement that validated sedation assessment instruments should be used in all critical care settings and strategies to minimise sedation should be implemented (Barr *et al.* 2013). The trend towards sedation minimisation has been ongoing since the mid- 2000s and is likely to continue, particularly in the context of related strategies to optimise early mobilisation and reduce complications of intensive care such as delirium, and ongoing cognitive and psychological compromise (Needham *et al.* 2012).

Implications for research

Further research needs to be undertaken to ascertain the effect of protocol-directed sedation on patient outcomes. In particular, studies need to be conducted in a variety of clinical contexts to determine whether there are specific practice environments where benefit is more likely. The issue of whether a study randomised at the level of the individual can be conducted without contamination needs to be considered; it may be that a design such as cluster randomisation is required. Given there are multiple different strategies that have been developed in recent years to reduce the detrimental impact of sedation, the interaction between protocol-directed sedation and other sedation minimisation strategies should also be examined. It is vital that a detailed description of both the experimental care process and usual care is provided. Furthermore, a range of both process and outcome measures should be incorporated into the design, with outcome measures extending beyond confines of ICU or the acute care hospital and incorporating physical, cognitive and psychological health, as well as cost-effectiveness (Needham *et al.* 2012).

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Table 1: Primary and secondary outcomes for systematic review

Primary outcomes
1. Duration of mechanical ventilation measured in hours for the entire duration of the first ICU stay for each patient 2. ICU and hospital mortality
Secondary outcomes
1. ICU length of stay 2. Hospital length of stay 3. Total dose of sedation 4. Adverse events (e.g. non-planned extubation) 5. Incidence of delirium 6. Memory function 7. Psychological recovery 8. Cognitive recovery 9. Quality of life 10. Incidence of tracheostomy

ICU=Intensive care unit

Table 2 Characteristics, strengths and limitations of included studies

	Brook et al 1999	**Bucknall et al 2008**
Characteristics (see Supplementary table 2 for more detail)	RCT, 322 patients in a closed medical ICU in a university affiliated teaching hospital in USA.	RCT, 316 patients in a closed general ICU in a metropolitan teaching hospital in Australia.
Intervention (see Supplementary table 2 for more detail)	Protocol-directed sedation vs. non-protocol-directed sedation (usual care). Sedation protocol required nurses to determine type, method of administration and dosage analgesics and sedatives after assessing using the Ramsay Scale.	Protocol-directed sedation vs. non-protocol-directed sedation. Sedation protocol required nurses to determine the type, method of administration, dosage of sedation or analgesia after assessing using the Sedation-Agitation Scale.
Outcomes measured (see Supplementary table 2 for more detail)	Primary outcome - duration of mechanical ventilation. Secondary outcomes - ICU and hospital LOS, hospital mortality, rates of organ failure, re-intubation and tracheostomy.	Primary outcome – duration of mechanical ventilation. Secondary outcomes - ICU and hospital LOS, ICU and hospital mortality, rates of self extubation and tracheostomy
Assessment of bias (see Supplementary Table 3 for more detail)	Generally low risk of bias with the exception of the following: - Unclear risk of selection bias due to randomisation process - High risk of performance bias due to inability to blind participants and personnel - Unclear risk of other bias due to lack of description of usual care	Generally low risk of bias with the exception of the following: - High risk of performance bias due to inability to blind participants and personnel - Unclear risk of other bias due to lack of description of some aspects of usual care

RCT – randomised controlled trial; ICU – intensive care unit; LOS – length of stay

Supplementary Table 1 CENTRAL search strategy

#1 MeSH descriptor Algorithms explode all trees
#2 MeSH descriptor Guidelines as Topic explode all trees
#3 MeSH descriptor Clinical Protocols explode all trees
#4 MeSH descriptor Medication Therapy Management explode all trees
#5 (protocol* or non? protocol* or directed or guide* or algorithm* or manage* or ((standar* or regular*) near assess*)):ti,ab
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Conscious Sedation explode all trees
#8 MeSH descriptor Analgesia, Patient-Controlled explode all trees
#9 MeSH descriptor Analgesics explode all trees
#10 MeSH descriptor Hypnotics and Sedatives explode all trees
#11 (sedat* or analge*):ti,ab
#12 (#7 OR #8 OR #9 OR #10 OR #11)
#13 MeSH descriptor Intensive Care explode all trees
#14 MeSH descriptor Intensive Care Units explode all trees
#15 MeSH descriptor Critical Care explode all trees
#16 MeSH descriptor Critical Illness explode all trees
#17 MeSH descriptor Respiration, Artificial explode all trees
#18 MeSH descriptor Ventilator Weaning explode all trees
#19 MeSH descriptor Length of Stay explode all trees
#20 (#13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19)
#21 (#6 AND #12 AND #20)

MeSH= Medical subject heading

Supplementary Table 2: Key characteristics of included studies

Brook et al. (1999)	
Methods	Randomized, controlled clinical trial
Participants	*Setting:* University-affiliated urban teaching hospital in USA; closed medical ICU (19 beds); nurse : patient ratio - 2 : 1 to 3 : 1 *Participants:* 332 patients requiring mechanical ventilation were randomized; 4 patients were randomized twice (their second study admission was excluded) and 7 surgical patients were awaiting transfer to the surgical ICU (and therefore met the exclusion criteria). 321 patients were included in the analysis *Participant characteristics:* Mean age: 58 years in both groups; gender: 51%men (protocol group), 47% men (usual care group); APACHE II score: 23 in both groups; common diagnoses: pneumonia (21% protocol group, 30% usual care group), COPD or asthma (17% protocol group, 15% usual care group), sepsis (17% protocol group, 15% usual care group)
Interventions	Protocol-directed sedation vs. non-protocol-directed sedation (usual care). Sedation protocol required nurses to determine whether analgesics (morphine, fentanyl), sedatives (diazepam, midazolam, lorazepam), or both were needed to provide optimal patient care. The type of sedation administration (i.e. bolus vs. continuous) as well as the dosage were determined by the nursing staff with reference to the Ramsay Scale. Weaning or withdrawal from sedation was also guided by protocol. Treating physicians could deviate patient management from the protocol, including using non-protocol sedatives. Non protocol- directed sedation was ordered by the treating physician; nurses were only able to make changes with a physician's written or verbal order
Outcomes	Primary outcome: duration of mechanical ventilation. Secondary outcomes: ICU and hospital lengths of stay, hospital mortality, rates of development of organ system derangements, re-intubation and tracheostomy.
Bucknall et al. (2008)	
Methods	Randomized controlled trial
Participants	*Setting:* metropolitan teaching hospital in Australia; closed general ICU (24 beds); nurse: patient ratio 1 : 1

	Participants: 316 mechanically ventilated ICU patients were randomized in the study. Four patients were excluded from final analysis due to inappropriate re-enrolment into the study following re-admission to ICU. 312 patients were included in the final analysis *Participants characteristics:* mean age: 58 years in protocol group, 56 years in usual care group; gender: 64% men (protocol group), 58% men (usual care group); APACHE II score: 19 in protocol group, 20 in usual care group; diagnostic groups: medical (69% protocol group, 59% usual care group), surgical (12% protocol group, 17% usual care group), trauma (19% protocol group, 24% usual care group).
Interventions	Protocol-directed sedation vs. non-protocol-directed sedation. Within the protocol-directed sedation group, physicians prescribed the medications contained within the protocol. Nurses determined the type and dosage of sedation (midazolam, propofol) or analgesia (morphine) (or both) and the method of administration (infusion or intermittent dose). Sedation was guided by assessment using the Sedation-Agitation Scale. The protocol was sufficiently flexible to allow the de-escalation of sedation dose every 2 hours to avoid over-sedation. Non-protocol sedation type and dose limits for both infusion and boluses were prescribed by ICU medical staff with nurses able to assess, titrate and manage within those orders, including complete cessation of sedation. Nurses could communicate with any member of the ICU medical team if they believed changes to the written sedation orders were needed.
Outcomes	Primary outcome: time from commencement of mechanical ventilation in the ICU to successful weaning from mechanical ventilation Secondary outcomes: duration of ICU and hospital length of stay, ICU and hospital mortality, rates of self extubation and tracheostomy

ICU=Intensive care unit

Supplementary Table 3: Summary of risk of bias assessment for included studies

	Brook et al. (1999)	Bucknall et al. (2008)
Selection bias: Random sequence generation	**Unclear** Blocked randomization was used, but no detail was provided regarding how the randomization sequence was generated.	**Low risk** Randomization using a simple 1:1 randomization sequence. Randomization sequence was computer generated.
Selection bias: Allocation concealment	**Low risk** Opaque sealed envelopes that were opened each time a participant was enrolled; unclear if envelopes were sequentially numbered.	**Low risk** Participants were randomized to protocol or non-protocol sedation by the senior nurse on duty, who chose the next serially numbered sealed opaque envelope.
Performance bias: Blinding of participants and personnel	**High risk** No blinding of participants or personnel was undertaken, this would have been difficult to achieve, but may have influenced processes of care. Performance bias (personnel) was unclear, as treating physicians were able to deviate from the protocol, and physicians in the physician directed control group could alter their practices as desired.	**High risk** Participants and personnel were not blinded, this would have been difficult to achieve given the nature of the intervention, but may have influenced processes of care. All ICU nurses were required to attend an education session on the implementation of the study and the sedation protocol. No comment regarding deviation from the protocol by medical staff was provided, although non-protocol drugs were administered to participants in the protocol group.
Detection bias:	**Low risk**	**Low risk**

Blinding of outcome assessment	There was no blinding of outcome assessors; however, given all outcomes were objectively measured, the risk of biasing results was low	ICU research nurses collected outcomes data, no information was provided as to whether they were blinded to group allocation. However, given the objective nature of the outcomes (duration of mechanical ventilation, ICU & hospital length of stay, mortality, self extubation, tracheostomy rates), the potential for this knowledge to bias outcome measurement was low
Attrition bias: Incomplete outcome data	**Low risk** 11 patients were randomized but not included in the analysis: 4 were randomized twice (the second randomization was excluded) and 7 were randomized while they were waiting for transfer to the surgical ICU (and therefore met exclusion criteria). Intention-to-treat analysis was conducted on a sample of 321 patients. Incomplete data from 106 participants who died and were not successfully waned from mechanical ventilation - data from these participants were labelled as censored data. Censored data were included in all univariate analysis (primary and secondary outcomes) with removal of censored data from pre-specified post-hoc analysis	**Low risk** 316 participants were enrolled and randomized in the study, 4 participants were excluded from analysis due to inappropriate re-enrolment during a re-admission to ICU. Outcome data were provided for the remaining 312 participants and included in final analysis
Reporting bias:	**Unclear**	**Low**

Selective reporting	No registration of study or publication of study protocol; however, all primary and secondary outcomes results and pre-specified analyses were reported according to the aims stated in the publication.	Prospectively registered on a clinical trial registry; all primary and secondary outcomes and all pre-specified analyses were reported according to the aims stated in the publication.
Other bias:	**Unclear** Usual care was not described, except for the number of participants and duration of chemical paralysis. Unclear if standard management practices (mode of mechanical ventilation, physiotherapy, suctioning, re-positioning, investigations outside ICU, need for physical restraints) or nurse:patient ratios were equally applied to both groups. If standard management practices differed between groups, there was a risk of bias. Baseline participant characteristics were described as similar between groups, with variables of interest tabulated in the report and no statistically significant differences found, including the indication for mechanical ventilation and severity of illness scores (APACHE II, predicted mortality).However, control group had a higher trend for the number of participants with pneumonia (34 participants in protocol group vs. 47 participants in usual care group,	**Unclear** A description of usual care for general management and specific sedation management was provided, although some associated aspects of care such as physiotherapy, suctioning, re-positioning, investigations outside ICU and need for physical restraints were not provided. If standard management practices differed between groups, there was a risk of bias.

	P value = 0.077) Potential for contamination between the two groups existed as participants were cared for in the same ICU at the same time and care of usual care group participants was directed by individual physician preferences, so the principles of protocol-directed care may have been partially applied to the control group.	

ICU= Intensive care unit

Figure 1. Study flow diagram.

Figure 2: Forest plot comparing protocol directed sedation versus non-protocol directed sedation to effect hospital mortality

Review: Protocol-directed sedation versus non-protocol-directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients

Comparison: 1 Protocol-directed sedation management compared with usual care

Outcome: 2 Hospital mortality

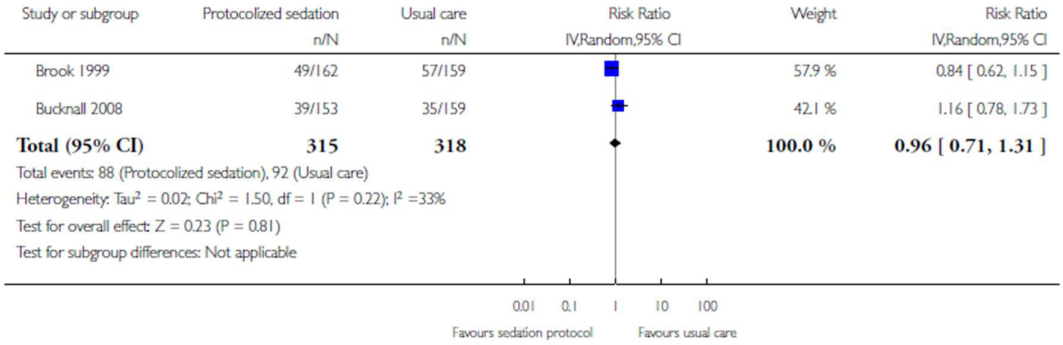

Figure 3: Forest plot comparing protocol directed sedation versus non-protocol directed sedation to effect hospital length of stay

Review: Protocol-directed sedation versus non-protocol-directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients

Comparison: 1 Protocol-directed sedation management compared with usual care

Outcome: 4 Hospital length of stay