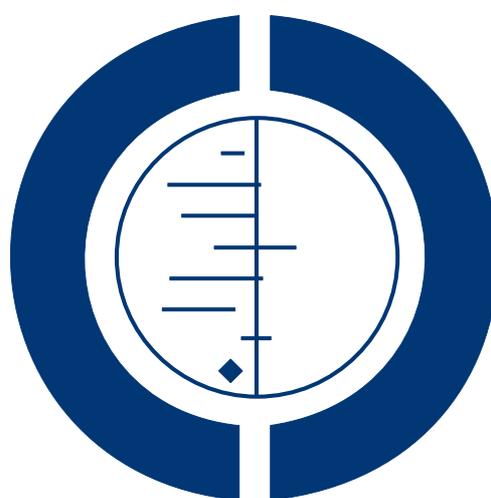


# Protocol directed sedation versus non-protocol directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients (Protocol)

Aitken LM, Bucknall T, Kent B, Mitchell M, Burmeister E, Keogh SJ



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[Intervention Protocol]

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

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## ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of protocol directed sedation management on the duration of mechanical ventilation and other relevant patient outcomes in mechanically ventilated ICU patients. We will look at various outcomes, conduct subgroup and sensitivity analyses and examine the role of bias in order to examine the level of evidence for this intervention.

## BACKGROUND

### Description of the condition

The sedation needs of critically ill patients are a core component of critical care. Intensive care patients are often treated with invasive and difficult-to-tolerate procedures and treatments. Ensuring comfort throughout this process is considered to assist recovery and ensure humane treatment (Mehta 2009). While appropriate sedation is essential for all patients it is paramount for those receiving muscle relaxants. In association with sedation management, it is essential that adequate pain relief and anxiolysis are provided to all critically ill patients. There is growing evidence to suggest that sedation requirements are not optimally managed; a systematic review of 36 studies found a substantial incidence of suboptimal sedation, ranging from 1% to more than 50% of either sedation time or number of patients (Jackson 2009).

The detrimental impact of poor sedation practices is beginning to be understood and 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 and hospital lengths of stay and also poor long term recovery (Mehta 2009). There is some evidence to suggest links between short term measures (such as intensive care and hospital lengths of stay) (Jackson 2010; Kollef 1998; Schweickert 2008), adverse events (such as self-extubation) (Girard 2008) and longer term aspects such as recall of time spent in the intensive care unit (ICU) and long term psychological recovery (Jackson 2010; Ringdal 2006; Samuelson 2006).

Sedation refers to the administration of pharmacological agents designed primarily to induce a sedative effect in patients. It includes benzodiazepines, for example diazepam, midazolam; sedative-hypnotic agents, for example propofol; and other specific sedative agents such as dexmedetomidine. Sedation does not include pharmacological agents administered primarily for other reasons, such as analgesic agents, even though these agents might have some secondary sedative effect. Internationally there are a range of different methods of managing patients' sedation needs. Common elements in this process include the prescription (order) of sedation, including details such as drug and route, made by the physician or nurse practitioner; and use of a formal sedation scale to determine how sedated the patient is, although many different scales are in use. Less consistent elements include whether a target of how awake the patient should be (this may be a descriptor of a score on a sedation scale) is specified, whether nurses or other healthcare professionals can titrate the sedative administration rate, including ceasing it, and whether daily interruptions are used.

### Description of the intervention

Various strategies have been proposed as methods to improve sedation management of critically ill patients. These strategies have

included use of an appropriate sedation assessment instrument (Curley 2006; Ely 2003; Riker 1999); use of a sedation guideline, algorithm or protocol to guide assessment and therapy (Jacobi 2002; Sessler 2009); implementation of daily sedation interruptions (Kress 2000); use of minimal levels of sedation and regular assessment of sedation and analgesia requirements (Schweickert 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 (Schweickert 2008). This lack of implementation may be due to the inconsistent results that have been identified in the studies examining the effect of protocol directed sedation (Brook 1999; Bucknall 2008; De Jonghe 2005; Elliott 2006; Quenot 2007).

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 1999). Protocol directed sedation is distinct from, but related to, protocol directed weaning, which is specifically directed towards limiting the duration of mechanical ventilation; this topic is the subject of a separate review (Blackwood 2010).

### How the intervention might work

Use of a protocol to guide sedation 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 2009; O'Connor 2009). The potential to reduce the individual clinician variation is significant, with management based on standardized assessment practices.

### Why it is important to do this review

Use of sedation protocols has been proposed as a potential strategy to improve sedation practices in intensive care with resultant reduced duration of mechanical ventilation and ICU length of stay. Despite widespread support there is mixed evidence as to their effectiveness.

## OBJECTIVES

To assess the effects of protocol directed sedation management on the duration of mechanical ventilation and other relevant patient

outcomes in mechanically ventilated ICU patients. We will look at various outcomes, conduct subgroup and sensitivity analyses and examine the role of bias in order to examine the level of evidence for this intervention.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include randomized and quasi-randomized controlled trials published in any language. We define a randomized controlled trial as a study in which patients are allocated to treatment groups on the basis of a random or quasi-random method (for example using random number tables, hospital number, date of birth).

#### Types of participants

We will include all ICU patients who are mechanically ventilated (via endotracheal or tracheostomy tube). Where studies include both patients who meet the above criteria and those who do not, we will only include the data if we are able to consider separately the subset that is of interest to this review.

#### Types of interventions

The target intervention will be protocol directed sedation management. We will compare this to non-protocol directed sedation management.

We define protocol directed sedation as sedation directed by a protocol or algorithm that is ordered by a medical officer, contains guidance regarding sedation management, and is 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 consists of a series of decision points or decision algorithms that assist clinicians to make decisions regarding increasing, decreasing, or maintaining current sedation levels. Protocols may include provision for administration of analgesic agents in addition to sedative agents. Medical officers may continue to be involved in sedation assessment and management beyond the point of ordering the sedation protocol, but any protocol that requires physician approval for changes in amounts of sedation will be excluded. The essential element of protocol directed sedation is that other members of the health care team can alter the level of sedation being administered without consulting with a medical officer.

Usual care is defined as physician led sedation management of mechanically ventilated patients according to the practice where no specific strategies are implemented to change the level of sedation

that is administered to reduce the duration of mechanical ventilation. Sedative agents may or may not be different to those used in the intervention; importantly the intervention is not about the agents that are used but how they are used.

### Types of outcome measures

#### 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

2. Length of ICU stay
3. Hospital length of stay
4. Total dose of sedation
5. Adverse events, e.g. non-planned extubation
6. Incidence of delirium
7. Memory function
8. Psychological recovery
9. Cognitive recovery
10. Quality of life
11. Incidence of tracheostomy

### Search methods for identification of studies

#### Electronic searches

We will search the current issue of the Cochrane Central Register of Controlled trials (CENTRAL) (*The Cochrane Library*); MEDLINE (OvidSP) (from 1990 to date); EMBASE (OvidSP) (from 1990 to date); CINAHL (BIREME host) (from 1990 to date); Database of Abstracts of Reviews of Effects (DARE) (from 1990 to date), LILACS (1990 to date), Current Controlled Trials and the Clinical Center Clinical research studies (US National Institutes of Health) (from 1990 to date). We will use free text and associated exploded subject heading terms (see [Appendix 1](#)) for designing our search strategy. We have chosen the inception date of 1990 because no sedation protocols existed before this time.

We will combine the MEDLINE search strategy with the Cochrane highly sensitive search strategy, as contained in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)). We will adapt our MEDLINE search strategy (see [Appendix 1](#)) for searching all other databases.

We will handsearch relevant journals (including online journals) including *American Journal of Respiratory Critical Care, Critical Care Medicine, Intensive Care Medicine, Critical Care, and American Journal of Critical Care* (1990 to date).

We will handsearch reference lists of identified published trials, abstracts of relevant conference proceedings, and the reference lists of relevant articles to identify any further clinical trials. We will also search conference proceedings citation INdex (CPCI-S), Science Direct (including articles in press), Scopus, Google / Google Scholar. We will undertake citation searches of relevant articles through Web of Science and Scopus. We will contact relevant trial authors to identify any additional studies. We will not impose a language restriction.

### Searching other resources

We will search specific websites for relevant ongoing trials:

- International Clinical trials registry ([www.who.int/trialsearch](http://www.who.int/trialsearch));
- International Standard Randomised Controlled Trials ([www.controlled-trials.com/isrctn](http://www.controlled-trials.com/isrctn));
- Country specific trial websites for the United Kingdom, South Africa, India, Hong Kong, China and Australia and New Zealand.

### Data collection and analysis

#### Selection of studies

Four authors (Leanne Aitken, Tracey Bucknall, Elizabeth Burmeister and Samantha Keogh) will search the databases. Two authors (Leanne Aitken and Tracey Bucknall) will independently decide on the inclusion of studies, having read the methods section of each study and applied the stated criteria in the eligibility form developed for use in this review (see [Appendix 2](#)). We will resolve differences by consulting a third author (Marion Mitchell). Where potential conflicts of interest exist, for example authorship of a potentially included study, the relevant author will be excluded from the process and a fourth author (Samantha Keogh) will be involved.

#### Data extraction and management

We will extract standardized data from each study using the data extraction form (see [Appendix 3](#)). We (Leanne Aitken and Marion Mitchell) will independently extract data for each study. We will resolve any disagreements by discussions or by asking a third author (Tracey Bucknall, Elizabeth Burmeister or Samantha Keogh) to assess the data; a majority decision will then be made. If a study has insufficient data to complete data extraction or data clarification is required we will attempt to contact the authors of the study. Studies will be considered to have sufficient data if at least one of the listed outcomes (either primary or secondary) is reported. Where potential conflicts of interest exist, for example authorship

of an included study, the relevant author will be excluded from the process and an alternate author will be involved.

#### Assessment of risk of bias in included studies

Two authors (Leanne Aitken and Marion Mitchell) will independently assess the methodological quality of the eligible trials. We will resolve disagreements by discussion with a third author (Tracey Bucknall or Samantha Keogh). Where potential conflicts of interest exist, for example authorship of an included study, the relevant author will be excluded from the process and an alternate author will be involved. We will perform the assessment as suggested in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using the Quality Assessment Form (see [Appendix 4](#)).

We will assess the following domains:

- random sequence generation,
- allocation concealment,
- blinding of participants and personnel,
- blinding of outcome assessment,
- incomplete outcome data,
- selective outcome reporting, and
- other potential sources of bias.

We will consider a trial as having a high risk of bias if one or more of the assessment domains (listed above) are rated as high risk or unclear.

We will note judgements based on the risk of selective reporting in the 'Risk of bias' tables that follow each study in the table 'Characteristics of included studies'. We will generate a risk of bias graph and a risk of bias summary. We will also report the risk of selective outcome reporting in the results under assessment of risk of bias in included studies.

#### Measures of treatment effect

Subject to the absence of clinical heterogeneity, we will undertake an analysis using [RevMan 5.1](#) software. Where possible, for continuous data the weighted mean difference (WMD), or standardized mean difference (SMD), and 95% confidence interval (CI) will be used for summary statistics (for example duration of mechanical ventilation, ICU stay and hospital stay). We will use relative risk (RR) to measure treatment effect for proportions (adverse events). We will assess the potential skewness of the data, which is highly likely to be skewed, and then decide on appropriate analysis methods based on the results of the assessment of distributions and the amount of data that is available. Attempts will be made to collect appropriate data summaries or to acquire individual patient data from study authors.

As an estimate of the clinical relevance of any difference between the experimental and control interventions we will calculate the number needed to treat (NNT) with 95% CI, as appropriate.

### Unit of analysis issues

We will use the results of intention-to-treat analyses for all analyses so all data extracted will reflect the original allocation group. In addition we will ensure that the number of observations in the analysis matches the number of units randomized, plus ensure that different groups were not randomized to different interventions or whether groups were randomized to the same intervention. We will check that there were not multiple observations for the same outcome measurement and will ensure that the outcome measurements are all taken from the same time-points. We will ensure that duration of mechanical ventilation is measured on the same group having the same intervention at the same time of their ICU journey.

### Dealing with missing data

We will identify how many drop-outs there are in each study, where this information is given or by liaising with the authors, and will make explicit what methods are used to cope with missing data.

### Assessment of heterogeneity

We will assess clinical heterogeneity for key participant and sedation protocol characteristics. Where heterogeneity is present, we will consider the appropriateness of pooling the data. We will assess statistical heterogeneity using the  $I^2$  statistic. We will only complete a meta-analysis if the studies are sufficiently homogenous in terms of participants, interventions and outcomes. In the absence of sufficient homogeneity between the studies a descriptive presentation of the results will be provided. Subject to identification of sufficient numbers of studies and appropriate homogeneity, meta-regression may be undertaken.

### Assessment of reporting biases

If sufficient studies (that is at least 10) meet the criteria to be included in the analysis, we will construct a funnel plot to explore the symmetry of the intervention effects reported by the studies to assess for publication bias.

### Data synthesis

If the studies are sufficiently homogenous a meta-analysis will be conducted using a fixed-effect model. Where there is a significant level of heterogeneity we will use a random-effects model. We will conduct both fixed-effect and random-effects model analyses to check the results before a decision is made as to the most suitable. Analyses will be considered significant at the  $\alpha = 0.05$  level. Estimates of precision will be assessed by interpretation of confidence intervals, such as widths, overlapping and inclusion of the null hypothesis.

### Subgroup analysis and investigation of heterogeneity

If we are able to determine details from the studies then subgroup analyses will include the following.

- Medical, surgical and trauma intensive care patients, as medical patients often have more comorbidities than surgical and trauma patients while trauma patients might have greater need for analgesia, therefore altering the combined sedative effect of the analgesic and sedative agents they are receiving.
- Nurse led protocols versus protocols led by other members of the health care team (e.g. respiratory therapists) as nurses tend to spend a greater period of time at the bedside and therefore might manage sedation needs differently.
- Units with 1:1 nurse:patient ratio during usual care versus units with  $\geq 1:2$  nurse:patient ratio during usual care, as the level of nursing assessment and intervention that is routinely available may influence effect.
- Patients ventilated via an endotracheal tube versus a tracheostomy tube, as insertion of a tracheostomy tube usually indicates longer term ventilation plans than management with an endotracheal tube.
- Age group, as the impact of protocol directed sedation may vary between different age groups of patients, particularly children compared to adults.

### Sensitivity analysis

We will perform sensitivity analyses to test how sensitive the data are to reasonable changes in the assumptions that are made and in the methods for combining the data. We will test the robustness of the evidence by sensitivity analysis according to randomization (randomized or quasi-randomized) and risk of bias (high, low or unclear). If necessary, we will undertake sensitivity analysis to examine the robustness of effects by excluding specific studies.

### Summary of findings tables

We will use the principles of the GRADE system (Guyatt 2008) to assess the quality of the body of evidence associated with specific outcomes listed below.

- Duration of mechanical ventilation.
- Length of ICU stay.
- Adverse events.

We will construct a 'Summary of findings' (SoF) table using the GRADE software. The GRADE approach appraises the quality of a body 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 (methodologic quality), the directness of the evidence, heterogeneity of the data, precision of effect estimates and risk of publication bias.

## ACKNOWLEDGEMENTS

We would like to thank Harald Herkner (content and statistical editor), John P Kress, Bronagh Blackwood, Jeffrey Man (peer reviewers) and Janet Wale (representative of the CARG consumer panel).

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\* Indicates the major publication for the study

## APPENDICES

### Appendix 1. Search strategy for MEDLINE (Ovid SP)

1. (protocol\* or non?protocol\* or directed or guide\* or algorithm\* or manage\* or ((standar\* or regular\*) adj3 assess\*)).mp. or algorithms/ or exp Guideline/ or exp Clinical Protocols/ or exp Medication Therapy Management/
2. exp Conscious Sedation/ or exp Analgesia, Patient-Controlled/ or exp Analgesics/ or exp “Hypnotics and Sedatives”/ or sedat\*.af. or analge\*.ti,ab.
3. 1 and 2
4. (((mechanical\* or artificial) adj4 (ventil\* or wean\* or respirat\*)) or ((critcal\* or intens\* or emergency) adj5 (care or ill\* or patient\* or unit\* or ward\*)) or (length adj3 stay) or ICU).mp. or exp Intensive Care/ or exp Intensive Care Units/ or exp Critical Care/ or exp Critical Illness/ or exp Respiration, Artificial/ or exp Ventilator Weaning/ or “Length of Stay”/
5. 3 and 4
6. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
7. 5 and 6

### Appendix 2. Study Selection Form

<i>Study Details</i>		Comments
First Author		
Journal / Place of publication		
Year		
<i>Study Eligibility</i>		
Randomized Controlled Trial (RCT)	Yes / No / Unclear	
Relevant participants - Mechanically ventilated - Age ≥ 18 years	Yes / No / Unclear	
Relevant interventions - Protocol directed sedation management	Yes / No / Unclear	
Relevant outcomes - Length of mechanical ventilation (hours) - Length of ICU stay - Length of hospital stay - Total dose of sedation - Adverse events (unplanned extubation)	Yes / No / Unclear	

### Appendix 3. Data Extraction Form

	Response	Comments
Study ID		
Study authors		
Year of study		
<i>Method</i>		
Country of study		

(Continued)

Level of hospital	Tertiary / Metropolitan / Regional / Rural	
Type of hospital	Public / Private	
Number of beds in hospital		
Type of ICU	Open / Closed / Other	
Number of ICU beds	Medical, n = Surgical, n = Cardiothoracic, n = Cardiology, n = Neurological, n = Trauma, n = Mixed med & surg, n = Other, specify____, n =	
Usual nurse:patient ratio	1:1 / 1:2 / $\geq$ 1:3 or greater	
Study design	RCT / Pre-post	
Inclusion criteria applied		
Exclusion criteria applied		
Description of sedation protocol		
Description of 'usual care'		
Usual nurse:patient ratio		
Sedatives used in protocol		
Analgesics used in protocol		
Description of comparator		
Sedatives used in control group		
Analgesics used in control group		
Sedation scale used		
<b>Results</b>	<b>Intervention Group</b>	<b>Control Group</b>

(Continued)

Numbers of participants enrolled			
Duration of MV	N = Duration: mean/median = SD/IQR =	N = Duration: mean/median = SD/IQR =	
Length of ICU stay	N = Length: mean/median = SD/IQR =	N = Length: mean/median = SD/IQR =	
Length of hospital stay	N = Length: mean/median = SD/IQR =	N = Length: mean/median = SD/IQR =	
Adverse Events	Specify event: _____ n = Specify event: _____ n = Specify event: _____ n = Specify event: _____ n =	Specify event: _____ n = Specify event: _____ n = Specify event: _____ n = Specify event: _____ n =	
Incidence of delirium	N =	N =	
Memory function - how measured & results?*			
Psychological status - how measured & results?*			
Cognitive status - how measured & results?*			
Quality of life - how measured & results?*			
ICU mortality	N =	N =	
Hospital mortality	N =	N =	
Incidence of tracheostomy	N =	N =	

\*frequency or mean/median score based on measurement type

## Appendix 4. Quality Assessment Form

<i>Sequence Generation</i>		Comments
Method used to generate sequence/group allocation		
Quality of sequence/group allocation	Low risk / High risk / Unclear	
<i>Allocation Concealment</i>		
Method used to conceal allocation		
Quality of allocation concealment	Low risk / High risk / Unclear	
<i>Blinding</i>		
Participant	Yes / No / Unsure	
Outcome assessor	Yes / No / Unsure	
Other Specify:	Yes / No / Unsure	
<i>Intention-to-treat</i>		
	Intention-to-treat analysis was applied to all participants entering study	
	15% or fewer excluded	
	More than 15% excluded	
	Not analysed as intention-to-treat	
	Unclear	
<i>Outcome Data</i>		
Was outcome data complete?		
Primary Outcome	Yes / No / Unsure	
Secondary Outcome 1	Yes / No / Unsure	

(Continued)

Secondary Outcome 2 (add more rows if necessary)	Yes / No / Unsure
--	-------------------

## HISTORY

Protocol first published: Issue 4, 2012

## CONTRIBUTIONS OF AUTHORS

Conceiving the review: Leanne Aitken (LA), Tracey Bucknall (TB)

Designing the review: LA, TB, Elizabeth Burmeister (EB)

Co-ordinating the review: LA

Undertaking manual searches: LA, TB, EB, Samantha Keogh (SK)

Screening search results: LA, TB, SK

Organizing retrieval of papers: EB

Screening retrieved papers against inclusion criteria: LA, TB, Marion Mitchell (MM), SK

Appraising quality of papers: LA, TB, MM, SK

Abstracting data from papers: LA, MM, TB, EB, SK

Writing to authors of papers for additional information: EB

Providing additional data about papers: LA, MM, EB, SK

Obtaining and screening data on unpublished studies: LA, MM, EB, SK

Data management for the review: EB

Entering data into Review Manager ([RevMan 5.1](#)): EB

RevMan statistical data: EB, Bridie Kent (BK)

Other statistical analysis not using RevMan: EB

Double entry of data: (data entered by person one: EB; data entered by person two:MM)

Interpretation of data: LA, MM, TB, EB, BK, SK

Statistical inferences: LA, MM, TB, EB, BK, SK

Writing the review: LA

Providing guidance on the review: BK

Securing funding for the review: LA, BK

Performing previous work that was the foundation of the present study: LA, TBI, MM

Guarantor for the review (one author): LA

Person responsible for reading and checking review before submission:TB

## **DECLARATIONS OF INTEREST**

Leanne Aitken is an author on one of the studies that may be eligible for inclusion in this review.

Tracey Bucknall is an author on one of the studies that may be eligible for inclusion in this review.

Bridie Kent, Marion Mitchell, Elizabeth Burmeister and Samantha Keogh: none known.

## **SOURCES OF SUPPORT**

### **Internal sources**

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Salary of Leanne Aitken, Marion Mitchell & Elizabeth Burmeister
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Salary of Tracey Bucknall & Bridie Kent
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Salary of Tracey Bucknall
- NHMRC Centre of Research Excellence in Nursing, Australia.  
Salary of Samantha Keogh

### **External sources**

- No sources of support supplied