

# **PROTOCOL**

## **Transfusion triggers for guiding blood transfusion in septic shock patients – *A systematic review of randomised trials with meta-analysis and trial sequential analysis***

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## Introduction and Background

The main function of the red blood cell (RBC) is the transportation of oxygen from the pulmonary alveoli to the peripheral capillaries. Thus RBC is administered to increase haemoglobin (Hb) and blood oxygen-carrying capacity in patients with signs of impaired tissue oxygenation.

Acute normovolaemic haemorrhage (ANH) in healthy individuals result in unchanged oxygen delivery ( $DO_2$ ) at the cellular level until Hb falls  $< 6.4$  g/dl (4.0 mM). Continued decrease in Hb leads to tissue hypoxia [1].

Sepsis is characterised by inflammation-induced endothelial dysfunction in response to infection, leading to vascular leakage and vasodilatation [2]. Ultimately sepsis results in relative and absolute hypovolaemia, organ hypoperfusion and shock. If shock persists, the result is progressive multiple organ failure and mortality rates close to 50% [3].

Sepsis is one of the leading causes of death worldwide and may account for 9% of all deaths in developed countries [4] thus representing a major global health problem.

The primary treatment of patients with septic shock is to resuscitate with fluids and inotrope/vasopressor drugs to optimise organ perfusion. These interventions may be supplemented with red blood cells (RBCs) in case of persistent hypoperfusion in order to prevent global hypoxaemia and multiple organ failure [5].

However in different groups of critically ill patients, including patients with septic shock,  $DO_2$  increases after RBC transfusion without a corresponding increase in oxygen consumption ( $VO_2$ ) [6]. One possible interpretation of these data is that transfused RBCs do not deliver oxygen as well as genuine cells because of the fundamental heterogeneous tissue perfusion in the septic patient and the biochemical and rheological changes of RBCs *ex vivo*, a phenomenon called "storage lesion". Another is that the cells in the periphery are unable to exploit the increase in available oxygen [7]. The desired effect of RBC transfusion on local tissue ischaemia is still in question. The two trials constituting the evidence behind current guidelines trials and randomising septic patients to different RBC transfusion strategies have showed divergent results. Rivers and colleagues found increased survival with a complex early goal-directed protocol including RBC transfusion if hypoperfusion persisted [8]. On the other hand, the TRICC trial found a tendency towards increased mortality with liberal RBC transfusion in the subgroup of septic patients [9], but the patients were only randomised as normovolaemic patients after initial resuscitation.

The criteria for transfusion remain controversial because the efficacy and safety of RBCs in septic shock is unknown and the intervention may be harmful to some patients.

In general, current recommendations support a restrictive transfusion strategy for the critical ill patient without septic shock or myocardial ischemia, using single unit RBC when haemoglobin is close to 7g/dl [10].

A Cochrane review published in 2009 [11] found 17 randomised clinical trials (RCTs) examining the effects of different transfusion thresholds on a variety of clinical outcome measures, including a

total of 3746 patients. Only three trials included intensive care patients and one of these were in paediatric patients. Most of the data (80%) came from the TRICC trial [9], where 838 resuscitated and normovolaemic intensive care patients were randomised to transfusion trigger of either 7 g/dl (4.4 mM) (restrictive) or 10 g/dl (6.2 mM) (liberal). There was no difference in the primary outcome - 30-day mortality - between the two groups, but in-hospital mortality was higher in the liberally transfused group. Predefined subgroup analyses showed lower mortality in the restrictive group in younger (age < 55 years) and less critically ill patients (Acute Physiology and Chronic Health Evaluation (APACHE) 2-score < 20). Finally, the liberal transfused group of patients had significantly more cardiopulmonary complications during ICU admission than those in the restrictive group. The results of this trial should be interpreted with caution, since the planned inclusion of 1,600 patients was not achieved due to failed inclusion and possible selection bias. The patient population may not be representative for ICU patients in general since cardiovascular disease (CVD) was more common in excluded patients than in the included. Thus, a potential negative effect of a restrictive transfusion regimen in CVD patients, might not have been discovered. Furthermore the patients were transfused with non-leukodepleted RBCs stored in citrate suspension, making it difficult to adapt the results to clinical practice today, where leukodepleted RBCs are used. Finally the patients were all well-resuscitated when randomised and therefore less likely to have tissue hypoperfusion, which may be aimable for increased DO<sub>2</sub> by RBC transfusion. The restrictive transfusion strategy did not appear to impact on the rate of adverse events (i.e. mortality, cardiac events, myocardial ischemia, stroke, pneumonia and thromboembolism) compared to liberal transfusion strategies. Furthermore restrictive transfusion strategies were associated with a statistically significant reduction in rate of infections, but did not reduce hospital or intensive care length of stay. The authors of the Cochrane review concluded that more research is needed and for most patients RBC transfusion is probably not essential until haemoglobin levels drop below 7.0 g/dl (4.4 mM). Nearly two years have elapsed since the Cochrane review was published and we are convinced that an up-to-date systematic review including trial sequential analysis (TSA), comparing different transfusion strategies on patient important clinical outcomes in different patient groups, including critical ill patients, is needed.

## **Objective**

The objective is to perform an up-to-date systematic review of the Cochrane review[11] focusing on supplementing latest evidence and TSA of high quality RCTs comparing the benefits and harms of varying thresholds for transfusion with RBC (liberal vs. restrictive transfusion strategies). In scope of restrictive transfusion strategy it is especially interesting to examine whether the evidence can support this strategy without harming the patients. This protocol will be online available at

<http://www.ctu.dk> and registered in the PROSPERO register (<http://www.crd.york.ac.uk/Prospero/>) before literature search is performed.

## **Methods**

### ***Criteria for considering trials for this review.***

#### **Type of Studies**

Randomised trials will be included if the comparison groups were assigned on the basis of a clear transfusion “trigger” or “threshold”, described as haemoglobin (Hb) or haematocrit (HCT) level(s) that had to be reached before RBC transfusion were administered. Control group patients will be required to be either transfused at Hb/HCT concentrations at higher levels than intervention group or transfused in accordance with current transfusion practices.

We will consider all randomised clinical trials irrespective of language, blinding, publication status, or sample size for inclusion. Quasi-randomised trials (where the method of allocating participants to a treatment are not strictly random, for example, date of birth, hospital record number, alternation) will not be included regarding assessment of benefit, but are to be considered for inclusion regarding assessment of harms.

#### **Patients**

Trials of surgical or medical patients, involving adults and/or children will be included. Neonatal and preterm infants will not be included

#### **Interventions**

Transfusion thresholds (“triggers”) as a means of guiding red blood cell transfusion.

#### **Outcomes**

##### *Primary outcomes*

- Mortality
- Morbidity (non-fatal myocardial infarction, cardiac events, pulmonary oedema, stroke, thromboembolism, renal failure, infection, haemorrhage, mental confusion)

##### *Secondary outcomes*

- The proportion of patients “at risk” who were transfused with allogeneic and/or autologous red blood cells, and the amounts of allogeneic and autologous blood transfused.

- Haemoglobin- /Haematocrit levels (post-operative/discharge)
- Length of hospital stay (LOS)

## ***Search methods for identification of studies***

### **Electronic searches**

We will search the Cochrane Central Register of Controlled Trials (CENTRAL); SilverPlatter MEDLINE (WebSPIRS) (1950 to date); SilverPlatter EMBASE (WebSPIRS) (1980 to date); Science Citation Index Expanded (SCI-EXPANDED) (1900 to present).

We will perform a systematic and sensitive search strategy to identify relevant randomized clinical trials with no language or date restrictions. The search will be conducted within six months of the date the draft is submitted for review. For specific information regarding our search strategies please see Appendix 1.

### **Searching other resources**

We will contact the main authors of studies and experts in this field to ask for any missed, unreported, or ongoing trials. We also search the references of the identified trials to identify further relevant trials.

We also search the references of the identified trials to identify further relevant trials. Moreover, we will search for ongoing clinical trials and unpublished studies on the following Internet sites:

1. [Current Controlled Trials](#)
2. [ClinicalTrials.gov](#)
3. [www.centerwatch.com](#)

### **Selection of studies**

Two authors will independently screen the titles and abstracts identified by the literature search and exclude trials which are obviously not relevant in relation to above mentioned criteria. A detailed description of our search results will be provided.

The remaining trials will be evaluated in full text for eligibility, and the authors will provide detailed description of the included and excluded articles.

### **Data collection and analysis**

Two authors (LBH and NH) will independently extract study characteristics and outcomes using an article extraction form. There will be no blinding to the author, institution or the publication source of trials.

The extraction form will record information regarding:

- Year and language of publication
- Country in which the trial was conducted
- Year of conduct of trial
- Single-centre or multicenter trial
- Inclusion and exclusion criteria.
- All outcomes (as mentioned above)
- Presence of a transfusion threshold
- Transfusion protocol
- Type of surgery involved
- Clinical setting
- Risk of bias according to the domains of bias in the Cochrane Handbook (Higgins 2008) as described below.
- General comments.

Any unclear or missing information will be sought by contacting the authors of the individual trials. If there was any doubt whether the trial reports shared the same participants - completely or partially (by identifying common authors and centres) - the authors of the trials will be contacted to clarify whether the trial report had been duplicated. Disagreements will be resolved by consensus or arbitration of a third author (JW).

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

The validity and design characteristics of each trial are evaluated. To draw conclusions about the overall risk of bias for an outcome it is necessary to evaluate the trials for major sources of bias also defined as *domains* (random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other sources of bias). The Cochrane Collaboration's recommended tool for assessing risk of bias is neither a scale nor a checklist but rather the *domain-based evaluation*. Any assessment of the overall risk of bias involves consideration of the relative importance of the different domains [12].

Even the most realistic assessment of the validity of a trial may involve subjectivity, since it is impossible to know the extent of bias (or even the true risk of bias) in a given trial. Some domains affect the risk of bias across outcomes in a trial; e.g., sequence generation and allocation sequence concealment, while others, such as blinding and incomplete outcome data, may have

different risks of bias for different outcomes within a trial. Thus, the risk of bias is not the same for all outcomes in a trial. We will perform separate sensitivity analyses for patient-reported outcomes and for mortality[13].

We define the trials as having low risk of bias only if they adequately fulfil the criteria listed in the Cochrane Handbook by performing *summary assessments* of the risk of bias for each important outcome (across domains) within and across studies. We will apply a 'risk of bias graph' and a 'risk of bias summary' figure [14].

We will present results for all outcomes including adverse events in a summary of findings (SOF) table [15].

As there is no sufficiently well designed formal statistical method to combine the results of trials with high and low risk of bias, the major approach to incorporating risk of bias assessments in Cochrane reviews is to *restrict* meta-analyses to studies at low- (or lower) risk of bias. We will use the risk of bias (ROB) table described in the Cochrane Handbook section 8.5 [16] as a tool for assessing risk of bias in included studies. We will assess the risk of bias in the different domains as described below.

### **Random sequence generation**

Low risk of bias: the method used generates random sequences, e.g., random number generation, toss of coin.

Unclear: no information on random sequence generation available.

High risk of bias: alternate medical record numbers or other non-random sequence generation.

### **Allocation concealment**

Low risk of bias: allocation method prevents investigators or participants from knowing the next allocation, e.g., central allocation; sealed opaque envelopes; serially-numbered, sequentially-numbered but otherwise identical vehicles, including their contents; or other descriptions of convincing concealment of allocation.

High risk of bias: no information on allocation method available or the description did not allow a clear distinction.

Inadequate: allocation method allowed the investigators or participants to know the next allocation, e.g., alternate medical record numbers; reference to case record numbers or date of birth; an open allocation sequence, unsealed envelopes.

## **Blinding**

Low risk of bias: we consider blinding as adequate if patients and personnel were kept unaware of intervention allocations after inclusion of participants into the study and the method of blinding involved placebo.

Unclear: blinding not described.

High risk of bias: not double blinded; categorized as an open-label study; or without use of placebo.

## **Incomplete outcome data**

Low risk of bias: if the numbers and reasons for dropouts and withdrawals in the intervention groups were described or if it was specified that there were no dropouts or withdrawals.

Unclear: if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated.

High risk of bias: if the number or reasons for dropouts and withdrawals were not described.

## **Selective outcome reporting**

Low risk of bias: if predefined or clinically relevant and reasonably expected outcomes are reported on.

Unclear: not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not.

High risk of bias: one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded.

## **Baseline imbalance**

Adequate: if there was no baseline imbalance in important characteristics.

Unclear: if the baseline characteristics were not reported.

Inadequate: if there was a baseline imbalance due to chance or due to imbalanced exclusion after randomisation.

## **Early stopping**

Low risk of bias: if sample size calculation was reported and the trial was not stopped, or the trial was stopped early by a formal stopping rules at a point where the likelihood of observing an extreme intervention effect due to chance was low.

Unclear: if sample size calculation was not reported and it is not clear whether the trial was stopped early or not.

High risk of bias: if the trial was stopped early due to informal stopping rules or the trial was stopped early by a formal stopping rule at a point where the likelihood of observing an extreme intervention effect due to chance was high.

## **Other bias**

To report on other bias in addition to the above mentioned (e.g., industry bias, academic bias, etc) one should continue using the following pattern:

Low risk of bias: the trial appears to be free of other components that could put it at risk of bias.

Unclear: the trial may or may not be free of other components that could put it at risk of bias.

High risk of bias: there are other factors in the trial that could put it at risk of bias, e.g., 'for-profit' involvement, authors have conducted trials on the same topic, etc.

We will also consider the administration of inappropriate treatment being given to the controls, such as sub optimal dosage of medication or a supra optimal dosage of medication.

## **Statistical methods**

We will perform the meta-analyses according to the *Cochrane Handbook for Systematic Reviews of Interventions*. We use the software package Review Manager 5.

For dichotomous variables, we calculate the risk ratio (RR) with 95% confidence interval (CI) if there are two or more trials for an outcome. For rare events we will calculate odds ratios (OR or Peto's OR) with 95% CI. We report the proportion of patients with the outcome in each group and the *p*-value for the comparison between the groups. For continuous variables, we calculate the mean difference (MD) or the standardized mean difference (SMD) with 95% confidence interval. For both dichotomous and continuous outcomes a *p*-value of less than 0.05 will be considered statistically significant.

We use a random-effects model [17] and a fixed-effect model [18] for meta-analysis in the presence of two or more trials included under the outcomes. In case of discrepancy between the

two models, we will report both the results of the random-effects model and the fixed effect model. Considering the anticipated abundant clinical heterogeneity we will emphasize the random effects model except if one or two trials dominate the available evidence in which case it may be more appropriate to emphasise the results from a fixed-effect model.

Heterogeneity will be explored by chi-squared test with significance set at  $p$ -value 0.10, and the quantity of heterogeneity will be measured by  $I^2$  and  $D^2$  [19]. We will, if possible, explore reasons for heterogeneity by applying metaregression for the covariates: mean age, sex, disease severity, RBC transfusion, units of RBC, duration of the shock. A  $p$ -value of 0.10 will be taken as statistically significant in the univariate metaregression analyses.

The analysis will be performed on an intention-to-treat basis whenever possible using the good outcome and poor outcome scenarios. Otherwise, we adopt the “available-case analysis”. We do not impute any data for the post-randomisation drop-outs for any of the continuous outcomes. We also report the results of risk difference if they are different from the results of risk ratio.

### **Sensitivity analyses**

In sensitivity analyses we impute the standard deviation from  $p$ -values according to the instructions given in the *Cochrane Handbook for Systematic Reviews of Intervention* and use the median for the meta-analysis when mean was not available. If it is not possible to calculate the standard deviation from the  $p$ -value or confidence intervals, we impute the standard deviation as the highest standard deviation noted for that group under that outcome.

### **Subgroup analysis**

We intend to perform the following subgroup analyses comparing estimates of the pooled intervention effect in (primary outcome):

- trials with low risk of bias (adequate generation of allocation sequence, allocation concealment, blinding, incomplete data outcomes, and selective reporting) compared to trials with high risk of bias (one or more of the five components inadequate or unclear)[7]
- trials of septic patients (sepsis as inclusion criteria OR  $\geq 50\%$  of patients having sepsis) to estimates from trials of non-septic patients
- trials of adult patients ( $>18$  years old) to estimates from trials of children ( $<18$  years old)
- trials of surgical patients to estimates from trials of medical patients
- trials stratified according to length of follow up
- trials transfusing leukodepleted RBC suspensions from trials using non-leukodepleted RBC suspensions

Only subgroup analyses showing statistical significant test of interaction ( $p < 0.05$ ) will provide evidence of an intervention effect pending the subgroup.

Causes of moderate to high heterogeneity will be explored using meta-regression including the following covariates if possible: mean age of trial population at baseline, fraction of male patients.

### **Bias exploration**

We plan to use a funnel plot to explore small trial bias [20][21] and to use asymmetry in funnel plot of trial size against treatment effect to assess this bias.

### **Trial sequential analysis**

Meta analyses may result in type-I errors due to an increased risk of random error when few data are collected and due to repeated significance testing when a cumulative meta-analysis is updated with new trials. To assess the risk of type-I errors, we will use TSA.

TSA combines information size estimation for meta analysis (cumulated sample size of included trials) with an adjusted threshold for statistical significance in the cumulative meta analysis [22][23]. The latter, called trial sequential monitoring boundaries, reduce type-I errors. In TSA the addition of each trial in a cumulative meta analysis is regarded as an interim meta analysis and helps to clarify whether additional trials are needed or not. The idea in TSA is that the cumulative Z-curve crosses the trial sequential monitoring boundary, a sufficient level of evidence has been reached and no further trials are needed. If the Z-curve doesn't cross the boundary and the required information size has not been reached, there is insufficient evidence to reach a conclusion.[24][25]. We will apply TSA since it reduces the risk of type-I error in a cumulative meta analysis and may provide important information on how many more patients need to be included in further trials. Information size will be calculated as diversity adjusted information size (DIS)[26], suggested by the relative risk reduction (RRR) of the intervention in the included trials. We will perform trial sequential analysis (TSA) on all primary outcomes and on all secondary outcomes showing statistically significant differences between the two interventions. The required information size will be calculated based on a relative risk reduction of 10-20% and appropriately adjusted for heterogeneity (diversity adjustment) according to an overall type-I error of 5% and a power of 80% considering early and repetitive testing.

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## Appendix 1:

### Searches performed April 2013

#### Search strategy

##### **Cochrane Injuries Group's Specialised Register (searched 1 February 2011)**

(Blood or "Red blood cell" or "Red blood cells" or RBC) and (therap\* or transfus\*) and (polic\* or practice or protocol\* or trigger\* or threshold\* or indicator\* or strateg\* or criteri\* or standard\* or restrict\* or liberal\* or management or program\*)

##### **Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 1)**

#1 MeSH descriptor Blood Transfusion, this term only with qualifiers: MT,ST

#2 transfus\* near5 (polic\*or practic\* or protocol\* or trigger\* or threshold\*or indicator\* or strateg\* or criteri\* or standard\*or require\*)

#3 (Red blood cell\* or RBC) near5 (polic\*or practic\* or protocol\* or trigger\* or threshold\*or indicator\* or strateg\* or criteri\* or standard\*) and (therap\* or transfus\*)

#4 (H?emoglobin or h?emocrit or HB or HCT) near5 (polic\*or practic\* or protocol\* or trigger\* or threshold\*or indicator\* or strateg\* or criteri\* or standard\*)

#5 transfus\* near5 (restrict\* or liberal\*)

#6 (blood transfus\*) near3 (management or program\*)

#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)

##### **MEDLINE (Ovid) 1948 to JanuaryWeek 3 2011**

1. \*Blood Transfusion/

2. ((Red blood cell\* or RBC) adj3 (therap\* or transfus\*)).mp.

3. 1 or 2

4. exp Reference Standards/

5. standards.fs.

6. methods.fs.

7. 4 or 5 or 6

8. 3 and 7

9. (transfus\* adj5 (polic\*or practic\* or protocol\* or trigger\* or threshold\*or indicator\* or strateg\* or criteri\* or standard\* or requir\*)).mp.

10. ((Red blood cell\* or RBC) adj5 (polic\*or practic\* or protocol\* or trigger\* or threshold\*or indicator\* or strateg\* or criteri\* or standard\*)).mp.

11. ((H?emoglobin or h?emocrit or HB or HCT) adj5 (polic\*or practic\* or protocol\* or trigger\* or threshold\*or indicator\* or strateg\* or criteri\* or standard\*)).mp.

12. (transfus\* adj5 (restrict\* or liberal\*)).mp.

13. ((blood or transfus\*) adj3 (management or program\*)).mp.

14. 8 or 9 or 10 or 11 or 12 or 13

15. randomi?ed.ab,ti.

16. randomized controlled trial.pt.

17. controlled clinical trial.pt.

18. placebo.ab.

19. clinical trials as topic.sh.

20. randomly.ab.

21. trial.ti.

22.15 or 16 or 17 or 18 or 19 or 20 or 21

23. (animals not (humans and animals)).sh.

24. 22 not 23

25. 24 and 14

##### **EMBASE (Ovid) 1980 to 2011Week 04**

1. \*Blood Transfusion/

2. ((Red blood cell\* or RBC) adj3 (therap\* or transfus\*)).mp.

3. 1 or 2

4. exp standard/

5. 3 and 4

6. (transfus\* adj5 (polic\*or practic\* or protocol\* or trigger\* or threshold\*or indicator\* or strateg\* or criteri\* or standard\* or requir\*)).mp.

7. ((Red blood cell\* or RBC) adj5 (polic\*or practic\* or protocol\* or trigger\* or threshold\*or indicator\* or strateg\* or criteri\* or standard\*)).mp.

8. ((H?emoglobin or h?emocrit or HB or HCT) adj5 (polic\*or practic\* or protocol\* or trigger\* or threshold\*or indicator\* or strateg\* or criteri\* or standard\*)).mp.

- or criteri\* or standard\*).mp.
- 9. (transfus\* adj5 (restrict\* or liberal\*)).mp.
- 10. ((blood or transfus\*) adj3 (management or program\*)).mp.
- 11. 5 or 6 or 7 or 8 or 9 or 10
- 12. exp Randomized Controlled Trial/
- 13. exp controlled clinical trial/
- 14. randomi?ed.ab,ti.
- 15. placebo.ab.
- 16. \*Clinical Trial/
- 17. randomly.ab.
- 18. trial.ti.
- 19. 12 or 13 or 14 or 15 or 16 or 17 or 18
- 20. exp animal/ not (exp human/ and exp animal/)
- 21. 19 not 20
- 22. 11 and 21

**ISIWeb of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to February 2011) and ISIWeb of Science: Conference Proceedings Citation Index - Science (CPCI-S) (1990 to February 2011)**

- #1 TS=((Blood or "Red blood cell" or "Red blood cells" or RBC or Hemoglobin\* or haemoglobin\* or haemocrit or hemocrit or HB or HCT) SAME transfus\*)
- #2 TS=(polic\* or practice or protocol\* or trigger\* or threshold\* or indicator\* or strateg\* or criteri\* or standard\* or restrict\* or liberal\* or management or program\* or require\*)
- #3 #1 and #2
- #4 TS=(randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random OR randomized controlled trial) OR Topic=(controlled clinical trial OR controlled trial OR clinical trial OR placebo)
- #5 TS=((singl\* OR doubl\* OR trebl\* OR tripl\*) SAME (blind\* OR mask\*))
- #6 #2 or #3
- #7 #3 and #6
- #8 Topic=(human\*)
- #9 #7 and #8

**Appendix 2:**

***Study Selection, Quality Assessment & Data Extraction Form***

First author/language	Journal/Conference Proceedings etc	Year

***Study eligibility***

RCT	Relevant participants	Relevant interventions	Relevant outcomes
Yes / No / Unclear	Yes / No / Unclear	Yes / No / Unclear	Yes / No* / Unclear

Do not proceed if any of the above answers are 'No'. If study to be included in 'Excluded studies' section of the review, record below the information to be inserted into 'Table of excluded studies'.

--

**Freehand space for comments on study design and treatment:**

--

### **Participants and trial characteristics**

<b>Participant characteristics</b>	
<b>Covariate</b>	<b>Further details</b>
<b>Age</b> (mean, median, range, etc)	
<b>Sex of participants</b> (numbers / %, etc)	
<b>Disease status / type, etc</b> (if applicable)	
<b>Baseline SAPS 2 / APACHE</b> (mean, median, range, etc)	
<b>Baseline SOFA</b> (mean, median, range, etc)	
<b>Other Baseline score</b>	

### **Methodological quality**

<b>Random sequence generation</b>	
<b>State here method used to generate allocation and reasons for grading</b> →	<b>Grade</b> (circle)
<ul style="list-style-type: none"> <li>• Low risk of bias: the method used generates random sequences, e.g., random number generation, toss of coin.</li> <li>• High risk of bias: alternate medical record numbers or other non-random sequence generation.</li> <li>• Unclear: no information on random sequence generation available</li> </ul>	Low risk of bias (Random)
	High risk of bias (e.g. alternate)
	Unclear

<b>Concealment of allocation</b>	
<b>Process used to prevent foreknowledge of group assignment in a RCT, which should be seen as distinct from blinding</b>	
<b>State here method used to conceal allocation and reasons for grading</b> →	<b>Grade</b> (circle)
<ul style="list-style-type: none"> <li>• Low risk of bias: allocation method prevents investigators or participants from knowing the next allocation, e.g., central allocation;</li> </ul>	Low risk of bias
	High risk of bias

<p>sealed opaque envelopes; serially-numbered, sequentially-numbered but otherwise identical vehicles, including their contents; or other descriptions of convincing concealment of allocation.</p> <ul style="list-style-type: none"> <li>• High risk of bias: no information on allocation method available or the description did not allow a clear distinction.</li> <li>• Inadequate: allocation method allowed the investigators or participants to know the next allocation, e.g., alternate medical record numbers; reference to case record numbers or date of birth; an open allocation sequence, unsealed envelopes.</li> </ul>	<b>Inadequate</b>
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<b>Blinding</b>	
<b>State here method used to generate allocation and reasons for grading</b> →	<b>Grade (circle)</b>
<ul style="list-style-type: none"> <li>• Low risk of bias: we consider blinding as adequate if patients and personnel were kept unaware of intervention allocations after inclusion of participants into the study and the method of blinding involved placebo.</li> <li>• High risk of bias: not double blinded; categorized as an open-label study; or without use of placebo.</li> <li>• Unclear: blinding not described.</li> </ul>	Low risk of bias (Random)
	High risk of bias (e.g. alternate)
	Unclear

<b>Incomplete outcome data</b>	
Low risk of bias, if the numbers and reasons for dropouts and withdrawals in the intervention groups were described or if it was specified that there were no dropouts or withdrawals	Yes / No
High risk of bias, if the number or reasons for dropouts and withdrawals were not described	Yes / No
Unclear, if the report gave the impression that there had been no dropouts or withdrawals, but this was not specifically stated	Yes / No
<b>Selective outcome reporting</b>	
Low risk of bias, if predefined or clinically relevant and reasonably expected outcomes are reported on	Yes / No
High risk of bias, one or more clinically relevant and reasonably expected outcomes were not reported on; data on these outcomes were likely to have been recorded	Yes / No
Unclear, not all pre-defined, or clinically relevant and reasonably expected outcomes are reported on or are not reported fully, or it is unclear whether data on these outcomes were recorded or not	Yes / No

<b>Baseline imbalance</b>	
Low risk of bias, if there was no baseline imbalance in important characteristics	Yes / No
High risk of bias, if there was a baseline imbalance due to chance or due to imbalanced exclusion after randomisation	Yes / No
Unclear, if the baseline characteristics were not reported	Yes / No
<b>Early stopping</b>	
Low risk of bias, if sample size calculation was reported and the trial was not stopped, or the trial was stopped early by formal stopping rules at a point where the likelihood of observing an extreme intervention effect due to chance was low	Yes / No
High risk of bias, if the trial was stopped early due to informal stopping rules or the trial was stopped early by a formal stopping rule at a point where the likelihood of observing an extreme intervention effect due to chance was high	Yes / No
Unclear, if sample size calculation was not reported and it is not clear whether the trial was stopped early or not	Yes / No
<b>Sponsor bias</b>	
Low risk of bias, if the trial is without specific funding, or is not funded by an instrument, equipment or drug manufacturer	Yes / No
High risk of bias, if the trial funded by an instrument, equipment or drug manufacturer	Yes / No
Unclear, if the source of funding is unclear	Yes / No
<b>Academic bias</b>	
Low risk of bias, if the author of the trial has not conducted previous trials addressing the same interventions	Yes / No
High risk of bias, if the has conducted previous trials addressing the same interventions	Yes / No
Unclear, if it is not clear if the author has conducted previous trials addressing the same interventions	Yes / No

<b>Modified intention-to-treat</b>	
A intention-to-treat analysis is one in which all the participants in a trial being randomized are analysed according to the intervention to which they were allocated, whether they received it or not. A modified intention-to-treat analysis, however, is one in which the patients that did not fulfil the inclusion or had one or more exclusion criteria fulfilled and did not receive intervention is excluded from the analysis.	
Analysed as modified 'intention-to-treat'	Yes / No
Unclear	

Were withdrawals described? Yes  No  not clear

Discuss if appropriate.....  
 .....

<b>Trial characteristics</b>	
	Further details
Single centre / multicentre	
Country / Countries	
How many participants were randomised?	
Number of participants in each intervention group	
Number of participants who received intended intervention (per protocol population)	
Number of participants who were analysed	
Value of "restrictive" intervention trigger	
Value of "liberal" intervention trigger	
Clinical setting (place of intervention)	
Type of patients included	
Number of patients with sepsis	
Number of patients with septic shock	
Median (range) length of follow-up reported in this paper (state weeks, months or years or if not stated)	
Trial design (e.g. parallel / cross-over*)	
Type of RBC suspension being used (ex. SAGM)	

Use of prestorage leukodepletion	
Other	

### **Data extraction**

<b>Outcomes</b>	<b>Available for the trial</b>
<b>1.1 All cause mortality</b>	Yes/No
<b>1.2 Morbidity</b> (non-fatal myocardial infarction, cardiac events, pulmonary oedema, stroke, thromboembolism, renal failure, infection, haemorrhage, mental confusion)	Yes/No
<b>2.1 The proportion of patients “at risk” who were transfused with allogeneic and/or autologous red blood cells</b>	Yes/No
<b>2.2 The amounts of allogeneic and autologous blood transfused.</b>	Yes/No
<b>2.3 haemoglobin- / Haematocrit levels</b> (post-operative/discharge)	Yes/No
<b>2.4 Length of Hospital stay (LOS)</b>	Yes/No

**For Continuous data**

Code of paper	Outcomes (rename)	Unit of measurement	Intervention group		Control group		Details if outcome only described in text
			n	Mean (SD)	n	Mean (SD)	
A etc.	<b>2.2 The amounts of allogeneic and autologous blood transfused</b>	<b>ml/units</b>					
	<b>2.3 haemoglobin- / Haematocrit levels</b> (post-operative/discharge)	<b>%, mM, g/dl, g/l</b>					
	<b>2.4 Length of Hospital stays (LOS)</b>	<b>Days</b>					

<b>For Dichotomous data</b>			
<b>Code of paper</b>	<b>Outcomes</b>	<b>Intervention group E/N</b> E= number of events N = number of participants	<b>Control group E/N</b> E=number of events n = number of participants
	<b>1.1 All cause mortality</b>		
	<b>1.2 Morbidity</b> <ul style="list-style-type: none"> <li>• Myocardial infarction</li> <li>• Cardiac events</li> <li>• Pulmonary oedema</li> <li>• Stroke</li> <li>• Thromboembolism</li> <li>• Renal failure</li> <li>• Infection</li> <li>• Haemorrhage</li> <li>• Mental confusion</li> </ul>		
	<b>2.1 The proportion of patients “at risk” who were transfused with allogeneic and/or autologous red blood cells</b>		

<b>Other information which you feel is relevant to the results</b>		
<p>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.</p>		

**Freehand space for writing actions such as contact with study authors and changes**

*References to other trials*

<b>Did this report include any references to published reports of potentially eligible trials not already identified for this review?</b>		
<b>First author</b>	<b>Journal / Conference</b>	<b>Year of publication</b>
<b>Did this report include any references to unpublished data from potentially eligible trials not already identified for this review? If yes, give list contact name and details</b>		