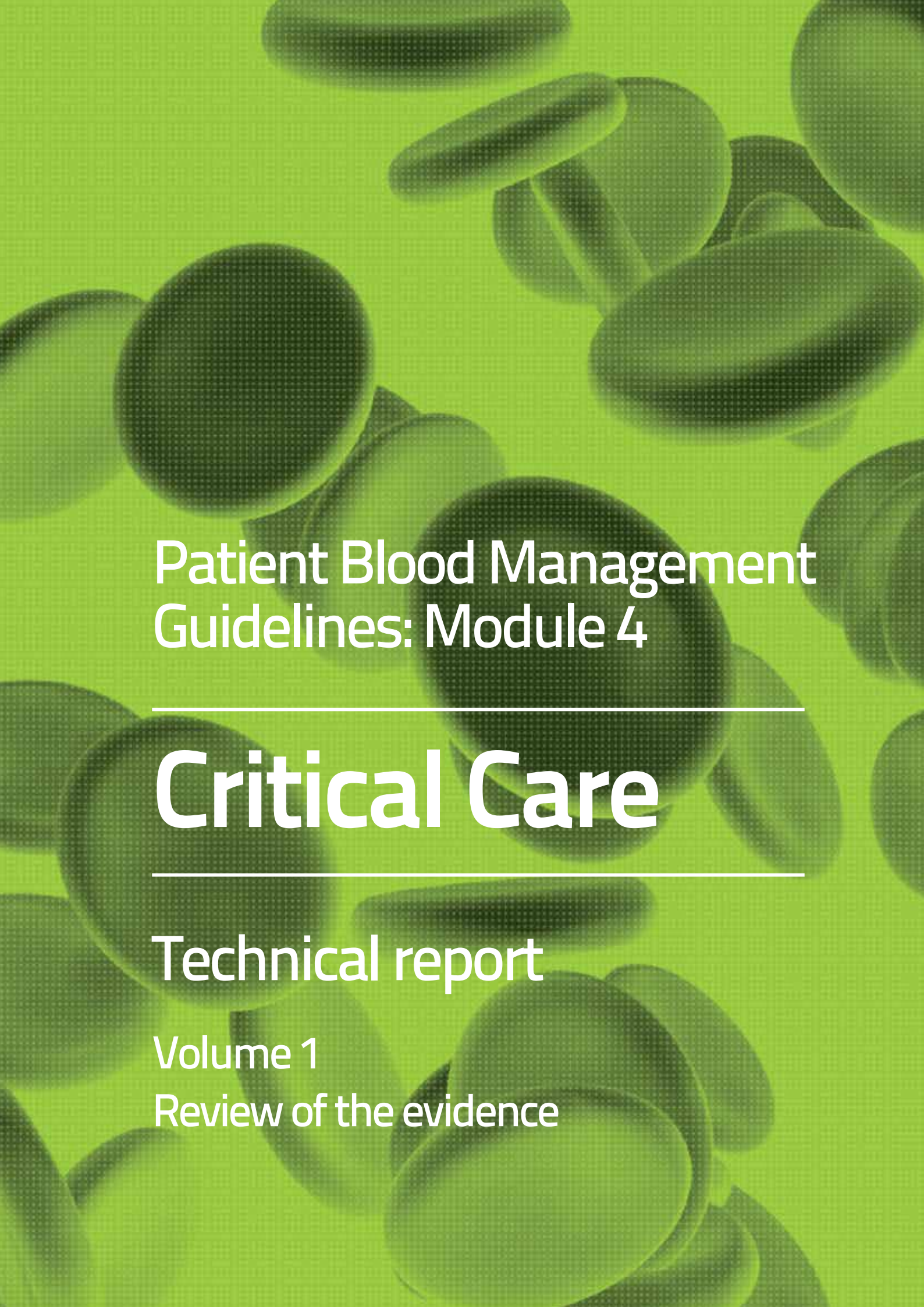

Patient Blood Management Guidelines: Module 4

Critical Care

Technical report

Volume 1
Review of the evidence

Note

This volume presents the main body of evidence found by a systematic literature review on medical patient blood management. Volume 2 presents the related appendixes (Appendix A to Appendix F). These two volumes cover all research questions developed for this topic.

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Abbreviations and acronyms

AHMAC	Australian Health Ministers' Advisory Council
AHMC	Australian Health Ministers' Conference
ALI	acute lung injury
ANZSBT	Australian & New Zealand Society of Blood Transfusion
APACHE	acute physiology and chronic health evaluation
ARCBS	Australian Red Cross Blood Service
ARDS	acute respiratory distress syndrome
ASBT	Australasian Society of Blood Transfusion
CI	confidence interval
CRG	Clinical/Consumer Reference Group
CTEPC	Clinical, Technical and Ethical Principal Committee
ESA	erythropoiesis-stimulating agent
EWG	Expert Working Group
FFP	fresh frozen plasma
GI	gastrointestinal
Hb	haemoglobin
ICU	Intensive care unit
INR	international normalised ratio
JBC	Jurisdictional Blood Committee
MI	myocardial infarction
NBA	National Blood Authority
NHMRC	National Health and Medical Research Council
NZBS	New Zealand Blood Service
PICO	population, intervention, comparator and outcome
PP	practice point
PPO	population, predictor and outcome
PRO	population, risk factor and outcome
PT	prothrombin time
R	recommendation
RBC	red blood cell
RCT	randomised controlled trial
RD	risk difference
RR	relative risk
TGA	Therapeutic Goods Administration
TRICC	transfusion requirements in critical care
TXA	tranexamic acid

1 Introduction

This document presents the methods and results relating to the findings from a systematic literature review on medical patient blood management. It is the first volume of a technical report produced as part of the development process for the *Patient Blood Management Guidelines: Module 4 – Critical Care* – the fourth in a series of six modules that focus on evidence-based patient blood management and will replace the 2001 National Health and Medical Research Council/Australasian Society of Blood Transfusion (NHMRC/ASBT) *Clinical practice guidelines on the use of blood components*.[1] The six modules of the guidelines are being developed in three phases, as shown in Table 1.1.

Table 1.1 Phases of development of guideline modules

Phase	Modules
I	Module 1 – Critical bleeding/massive transfusion
	Module 2 – Perioperative
II	Module 3 – Medical
	Module 4 – Critical care
III	Module 5 – Obstetrics
	Module 6 – Paediatrics/neonates

This volume covers all the research questions. Volume 2 of the technical report presents the related appendixes.

The document *Patient Blood Management Guidelines: Module 4 – Critical Care* gives information on:

- governance arrangements for the guidelines
- committee memberships and affiliations
- the background research team.

2 Methods

2.1 Research question development

An Expert Working Group (EWG) met for the first time in July 2008. At this meeting, members were provided with a comprehensive analysis of existing guidelines relevant to the clinical areas of focus. An independent systematic review expert provided a detailed presentation on framing clinical questions for systematic review. EWG members self-nominated to participate in relevant areas of clinical focus for each module. This action formed the basis for the establishment of a Consumer/Clinical Reference Group (CRG) for each module.

Following the July 2008 meeting, members of each CRG generated questions to be considered for inclusion in their respective guidelines. Before the next meeting, CRG members discussed first-draft questions, and acknowledged that question content would influence consideration of expanding CRG memberships to ensure relevant clinical and consumer representation. CRG members agreed that it would be appropriate to circulate draft questions to relevant clinical colleges and societies for input and feedback at an early stage and before inclusion in a statement of requirement for a systematic reviewer.

Between July 2010 and March 2011, the relevant clinical research questions for this module were developed, prioritised, combined and refined by the EWG, the independent systematic review expert and the CRG (Appendix A). The process resulted in two different types of questions – those that are specific to this module, and those that are generic (i.e. relevant to all six modules that make up the guidelines).

Questions 1–3 are relevant to all six modules of these guidelines; question 4 is specific to transfusion in a critical care setting (i.e. to this module).

- *Question 1* – In critically ill patients, what is the effect of RBC transfusion on patient outcomes? (Interventional question, referred to as Q1)
- *Question 2* – In critically ill patients, what is the effect of non-transfusion interventions to increase haemoglobin concentration on morbidity, mortality and need for RBC blood transfusion? (Interventional question, referred to as Q2)
- *Question 3* – In critically ill patients, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes? (Interventional question, referred to as Q3)
- *Question 4* – In critically ill patients, what is the effect of strategies that minimise blood loss on morbidity, mortality and blood transfusion? (Interventional question, referred to as Q4)

FFP, fresh frozen plasma; RBC, red blood cell

A further question – What is the effect of recombinant factor VIIA (prophylaxis or treatment) on morbidity, mortality and transfusion rate? – was not covered in this review.

Intervention questions were intended to determine the effects of various strategies that can be used in patient blood management on patient outcomes.

2.1.1 Aboriginal and Torres Strait Islander Populations

Prevalence of anaemia in Aboriginal and Torres Strait Islander populations is known to be higher than in the general Australian population.[2] The electronic search terms did not specifically search for or limit retrieval of articles to studies that addressed socioeconomic, Aboriginal or Torres Strait Islander subgroups. However, in accordance with NHMRC guideline development requirements, the reviewers were required to isolate any papers addressing these populations for specific consideration by the CRG. No papers were identified that addressed these populations specifically.

2.2 Literature searches

NHMRC standards and procedures require that clinical practice guidelines be based on systematic identification and synthesis of the best available scientific evidence.[3] Three main strategies were used to identify potentially relevant literature: electronic database searching, manual searching, and literature recommended by expert members of the CRG.

2.2.1 Electronic databases

The systematic review/technical writing group carried out searches using the following primary databases:

- EMBASE and Medline via the EMBASE.com interface
- Cochrane Library Database: a database of systematic reviews, other reviews, clinical trials, methods studies, technology assessments, economic evaluations and Cochrane Groups
- PreMedline: Medline in process, accessed via the PubMed interface.
- Additional secondary databases searched, where indicated, included:
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- AMI (Australasian Medical Index).

Dates of searching the primary and secondary databases are presented in **Appendix A** (Volume 2).

Search strategies for primary and secondary databases were developed in consultation with a specialist search strategist. All strategies were based on the population, intervention, comparator, outcome (PICO), population, predictor, outcome (PPO) or population, risk, outcome (PRO) criteria developed for the research questions (**Appendix 1** in this volume). Full details of all search strategies for these primary and secondary databases are presented in **Appendix A** (Volume 2).

The search also included websites of health technology assessment (HTA) agencies, including the UK National Institute for Health and Clinical Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH), and relevant guidelines websites.

2.2.2 Manual searching of reference lists

Members of the systematic review/technical writing group manually searched reference lists included in relevant articles identified by the systematic literature search. This strategy identified some additional articles that were not found in electronic database searches. Additional articles found by manual searching are indicated in the literature search results presented in **Appendix C** (Volume 2).

2.2.3 Expert sources

Articles recommended by CRG members were considered for inclusion wherever inclusion and exclusion criteria were met.

2.2.4 Background question research

No background questions were identified for this module, and therefore no research was conducted.

2.2.5 Issues relevant to Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse communities

The focus of the systematic review was on physiological parameters surrounding the decision to transfuse. As such, there were no distinct physiological issues relevant to Aboriginal and Torres Strait Islander peoples and culturally and linguistically diverse communities.

The greater prevalence of certain conditions (e.g. anaemia, chronic kidney disease) in some Indigenous Australian communities has a socioeconomic, not physiological, basis. No socioeconomic literature pertaining to Australia's Indigenous population was identified in the literature searches for any research question

2.2.6 Cost effectiveness

While no published cost-effectiveness analyses on the use of a multidisciplinary, multimodal perioperative patient blood management program was identified in the literature searches, a number of studies published information about costs or savings.

When no cost-effectiveness studies relevant to a research question were identified, this is noted for that question in the technical report. Cost or savings analyses, when found, are discussed for each question in the technical report

2.3 Inclusion and exclusion criteria

Inclusion criteria were determined from the PICO, PPO or PRO criteria that formed the basis of the systematically reviewed research questions (**Appendix 1** in this volume). Studies that did not meet one or more of these criteria were excluded.

Additional reasons for excluding studies were:

- non-human studies
- non-English language studies
- non-systematic reviews, editorials, opinion pieces and letters
- research or systematic review protocols not defined.

Titles and abstracts of every record retrieved by searching the primary and secondary databases were reviewed, and full articles were retrieved for further assessment where considered to meet the inclusion criteria. Articles that could not be included or excluded on the basis of information in the title or abstract were retrieved as full text before a final decision was made on inclusion or exclusion.

Articles reporting on the basis of the following study designs were considered for inclusion when PICO, PPO or PRO criteria were met:

systematic reviews of randomised controlled trials (RCTs) and/or cohort studies

- RCTs or pseudo randomised controlled trials
- cohort studies
- case–control studies
- case series, pre–post or post studies
- socioeconomic studies, economic evaluations, cost-effectiveness analysis and so forth.

Studies that initially met inclusion criteria but were later excluded are documented, with reasons for their exclusion, in **Appendix B** (Volume 2). Examples of reasons for exclusion in this circumstance include different systematic reviews reporting the same primary studies, and inadequate data reporting.

2.4 Classification and assessment of evidence

Studies identified for inclusion from the literature search were classified according to the NHMRC levels of evidence hierarchy (Table 2.1). To ensure that modules were based on the best available evidence, studies of higher levels of evidence (Levels I or II) were included in preference to those presenting lower levels of evidence (Levels III or IV). This was to minimise the potential for bias in the evidence base for each systematically reviewed question. However, lower level studies were reviewed where evidence was not available in higher level studies for any of the primary outcomes.

Studies identified from the systematic literature review were assessed according to NHMRC dimensions of evidence (Table 2.2).[4] There are three main domains: strength of the evidence, size of the effect, and relevance of the evidence. The first domain was derived directly from the literature identified for a particular intervention, aetiology or prognostic study. The other two domains were determined in consultation with the CRG as part of the study assessment process during the review of the evidence considered for module development. An aspect of the strength of the evidence domain is the level of evidence of the study, which was determined as described above using the NHMRC levels of evidence hierarchy outlined in Table 2.1.

Table 2.1 NHMRC evidence hierarchy: designations of levels of evidence according to type of research question

Level	Intervention[a]	Prognosis	Aetiology[b]
I[c]	A systematic review of Level II studies	A systematic review of Level II studies	A systematic review of Level II studies
II	A randomised controlled trial	A prospective cohort study[d]	A prospective cohort study
III-1	A pseudo randomised controlled trial (i.e. alternate allocation or some other method)	All or none[e]	All or none[e]
III-2	A comparative study with concurrent controls: • non-randomised, experimental trial[f] • cohort study • case–control study • interrupted time series with a control group	Analysis of prognostic factors amongst persons in a single arm of a randomised controlled trial	A retrospective cohort study
III-3	A comparative study without concurrent controls: • historical control study • two or more single arm study[g] • interrupted time series without a parallel control group	A retrospective cohort study	A case–control study
IV	Case series with either post-test or pre-test/post-test outcomes	Case series, or cohort study of persons at different stages of disease	A cross-sectional study or case series

Source: NHMRC (2009)[4]

[a] Definitions of these study designs are provided on pages 7–8, *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000)[5]

[b] If it is possible and ethical to determine a causal relationship using experimental evidence, then the 'intervention' hierarchy of evidence should be used. If it is only possible or ethical to determine a causal relationship using observational evidence (e.g. groups cannot be allocated to a potential harmful exposure, such as nuclear radiation), then the 'aetiology' hierarchy of evidence should be utilised.

[c] A systematic review will only be assigned a level of evidence as high as the studies it contains, except where those studies contain Level II evidence. Systematic reviews of Level II evidence provide more data than the individual studies, and any meta-analyses will increase the precision of the overall results, reducing the likelihood that the results are affected by chance. Systematic reviews of lower level evidence present results of likely poor internal validity and thus are rated on the likelihood that the results have been affected by bias, rather than whether the systematic review itself is of good quality. Systematic review quality should be assessed separately. A systematic review should consist of at least two studies. In systematic reviews that include different study designs, the overall level of evidence should relate to each individual outcome or result, as different studies (and study designs) might contribute to each different outcome.

[d] At study inception, the cohort is either non-diseased or all at the same stage of the disease. A randomised controlled trial with persons either non-diseased or at the same stage of the disease in both arms of the trial would also meet the criterion for this level of evidence.

[e] All or none of the people with the risk factor(s) experience the outcome; and the data arises from an unselected or representative case series which provides an unbiased representation of the prognostic effect. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of smallpox after large-scale vaccination.

[f] This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e. utilise A vs. B and B vs. C to determine A vs. C).

[g] Comparing single arm studies i.e. case series from two studies. This would also include unadjusted indirect comparisons (ie. utilise A vs. B and B vs. C to determine A vs. C, without statistical adjustment for B).

Table 2.2 NHMRC dimensions of evidence

Dimension	Definition
Strength of evidence	
Level	Each included study is assessed according to its place in the research hierarchy. This illustrates the potential of each included study to adequately answer a particular research question and indicates the degree to which design has minimised the impact of bias on the results
Quality	Included studies are critically appraised for methodological quality. Each study is assessed according to the potential that bias, confounding and/or chance has influenced the results
Statistical precision	Primary outcomes of included studies are assessed to establish whether the effect is real, rather than due to chance. Using a level of significance such as a *p*-value and/or confidence interval, the precision of the estimate of the effect is evaluated. This considers the degree of certainty regarding the existence of a true effect
Size of effect	The clinical importance of the findings of each study is assessed. This concept refers to the measure of effect or point estimate reported in the results of each study (e.g. mean difference, relative risk). For meta-analysis pooled measures of effect are assessed. Size of effect refers to the distance of the point estimate from its null value and also the values included in the corresponding 95% confidence interval. Size of effect indicates the clinical impact a particular factor or intervention will have on a patient and is considered in the context of patient relevant clinical differences
Relevance of evidence	The translation of research evidence to clinical practice is addressed by this dimension. It is regarded as potentially the most subjective of the evidence assessments. There are two questions concerning the appropriateness of outcomes and relevance of study questions: Are the outcomes measured in the study relevant to patients? How closely do the elements of the study research question match with those of the clinical question being considered?

Source: NHMRC (2009)[4]

2.4.1 Quality appraisal

The methodological quality of the included studies was assessed using the criteria presented in **Appendix 3** of this volume.[5] Quality assessment criteria varied according to whether included studies were systematic reviews, RCTs, cohort studies or case–control studies. No weighting of quality criteria was applied, but studies that met all criteria, or all but one, were considered good quality with a low risk of bias. Quality assessments of included studies for all systematically reviewed research questions are presented in **Appendix E** (Volume 2).

2.4.2 Data extraction

Data and information were extracted into evidence summary tables according to the inclusion criteria (PICO, PRO or PPO). Evidence summary tables were based on NHMRC requirements for externally developed guidelines.[6] Extracted data and information included general study details (citation, study design, evidence level, country and setting), characteristics of study participants, details of interventions and comparators, details of internal (e.g. allocation and blinding) and external (applicability and generalisability) study validity; and results for outcomes specified in the inclusion criteria. Where relevant studies were identified, extracted data and information were used to construct study characteristics and results tables of included evidence for each systematically reviewed research question. Evidence summary tables for all included studies are presented in **Appendix F** (Volume 2).

2.5 Assessment of the body of evidence and formulation of recommendations

The body of evidence for each module recommendation was graded in accordance with the NHMRC framework for developing evidence-based recommendations.[4] Assessment of the body of evidence considers the dimensions of evidence of studies relevant to that recommendation (Table 2.2). The NHMRC developed an evidence statement form to be used with each clinical research question considered in guidelines development (**Appendix 3** of this volume). Before the evidence statement form was completed, included studies were critically appraised and relevant data were summarised, as described. This information was required to formulate each recommendation and determine the overall grade of the body of evidence supporting each recommendation.

The key findings from included studies were summarised as evidence statements for each systematically reviewed research question. Where required, separate evidence statements were developed for different patient populations and outcomes. CRG input helped ensure that the size of effects and relevance of evidence were considered when developing evidence statements. Where no evidence or insufficient relevant evidence was identified, this was explained in the evidence statement.

Completed evidence statement forms for each research question are presented in **Appendix D** (Volume 2).

2.5.1 Use of the NHMRC evidence statement form

The NHMRC evidence statement form was applied in five steps.

Step 1 Rating each of the five components

To inform grading of recommendations, the body of evidence underpinning each evidence statement was assessed. Five key components were rated (Table 2.3). The first two components—evidence base and consistency—were derived directly from the literature identified for each research question. During review of identified evidence, CRG guidance was also required to assess the clinical impact, generalisability and applicability of included studies.

For each evidence statement, the five components presented in Table 2.3 were rated according to the matrix shown in Table 2.4. This grading system was designed to accommodate variation in the body of evidence. For example, a large number of studies with minimal bias may be included, but have limited applicability to the Australian healthcare context. Alternatively, a body of evidence may consist of a small number of trials with a moderate risk of bias, but have a very significant clinical impact and high applicability to the Australian healthcare context. Body of evidence rating results were entered into the NHMRC evidence statement form, together with any additional explanatory information relevant to each component. The results section for each research question includes the body of evidence matrix rating assessment for each evidence statement.

Table 2.3 Components of the evidence statement

Component	Definition
Evidence base	
Quantity	Reflects the number of studies included as the evidence base. Also takes into account the number of patients in relation to frequency of the outcomes measured (i.e. study statistical power). Meta-analysis can be used to combine results of studies to increase the power and statistical precision of effect estimates
Level	Reflects the best study type for the specific type of research question (intervention, prognosis). Level I evidence would be the best evidence to answer each question
Quality	Reflects how well studies were designed and conducted in order to eliminate bias
Consistency	Assesses whether findings are consistent across included studies, including a range of study populations and study designs. Meta-analysis of randomised studies should present statistical analysis of heterogeneity that demonstrates little statistical difference between studies. Presentation of an I^2 statistic illustrates the extent of heterogeneity between studies. Clinical heterogeneity between studies should also be explored
Clinical impact	Measures the potential benefit from application of the guidelines to a population. Several factors need to be considered when estimating clinical impact, including relevance of the evidence to the clinical question; statistical precision and size of the effect; relevance of the effect to patients compared with other management options or none. Other relevant factors are the duration of therapy required to achieve the effect, and the balance of risks and benefits (taking into account the size of the patient population)
Generalisability	Addresses how well the subjects and settings of included studies match those of the recommendation. Population issues that could affect recommendations include sex, age, ethnicity, and baseline risk or level of care (e.g. community or hospital setting). This is an important consideration when evidence comes from randomised controlled trials, where setting and entry requirements are generally narrow and therefore may not be representative of all patients to whom the recommendation may be applied in practice. In this circumstance broader-based population studies may be useful for confirming evidence from randomised controlled trials
Applicability	Addresses whether the evidence base is relevant to the Australian healthcare setting in general or to more local settings for specific recommendations (e.g. rural areas or cities). Factors that will affect the applicability of study findings include organisational factors (e.g. availability of trained staff, specialised equipment and resources) and cultural factors (e.g. attitudes to health issues, including those that may affect compliance with guidelines recommendations)

Source: NHMRC (2009)[4]

Table 2.4 Body of evidence matrix

Component	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence base	Several Level I or II studies with low risk of bias	One or two Level II studies with low risk of bias or a systematic review/multiple Level III studies with low risk of bias	Level III studies with low risk of bias, or Level I or II studies with moderate risk of bias	Level IV studies, or Level I to III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency can be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for the guidelines	Population/s studied in the body of evidence are similar to the target population for the guidelines	Population/s studied in the body of evidence are different to the target population but it is clinically sensible to apply this evidence to the target population for the guidelines	Population/s studied in the body of evidence are different to the target population, and hard to judge whether it is sensible to generalise to the target population for the guidelines
Applicability	Directly applicable to the Australian healthcare context	Applicable to Australian healthcare context with a few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

Source: NHMRC (2009)[4]

A rating of N/A was attributed for consistency when only one study was included.

Step 2 Preparation of an evidence statement matrix

An evidence statement matrix was completed to summarise the synthesis of the evidence relating to the evidence statement(s) for each research question. This summary presented ratings for the five components of the body of evidence matrix assessed for each evidence statement. Other relevant issues and dissenting opinions could be recorded if required.

In practice, Steps 1 and 2 to complete the NHMRC evidence statement forms were conducted concurrently for each evidence statement.

Step 3 Formulation of a recommendation based on the body of evidence

Step 3 involved formulating the wording of the recommendation. This wording was intended to reflect the strength of the body evidence; that is, where the evidence base was regarded as poor or unreliable, words such as 'must' or 'should' were not used. The wording of recommendations was developed in conjunction with the CRG during meetings to review the evidence base for research questions.

Step 4 Determination of the grade for the recommendation

The overall grade for each recommendation was determined from a summary of the rating for each component of the body of evidence. Definitions of the NHMRC grades of recommendations are presented in Table 2.5. In accordance with the NHMRC framework, recommendations were not graded A or B unless the evidence base and consistency of evidence were both rated A or B unless only one study was included and consistency was rated 'N/A'. In this situation the quality, size and strength of the evidence base was relied upon to grade the recommendation. The grading of recommendations was determined in conjunction with the CRG.

Developed recommendations were entered into the NHMRC evidence statement forms to accompany the corresponding evidence statement matrix, along with the overall grade determined in this step (**Appendix D**, Volume 2).

Table 2.5 Definitions of NHMRC grades for recommendations

Grade	Definition
A	Body of evidence can be trusted to guide practice
B	Body of evidence can be trusted to guide practice in most situations
C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
D	Body of evidence is weak and recommendations must be applied with caution

Source: NHMRC (2009)[4]

Step 5 Implementation of guidelines recommendations

The NHMRC framework directs that guidelines implementation should be considered at the same time that recommendations are formulated. The NHMRC evidence statement form contains questions related to the implementation of each module (Appendix 3 in this volume). These are:

Will this recommendation result in changes in usual care?

Are there any resource implications associated with implementing this recommendation?

Will the implementation of this recommendation require changes in the way care is currently organised?

- Is the guidelines development group aware of any barriers to the implementation of this recommendation?

This section of the NHMRC evidence statement form was completed in consultation with the CRG when each recommendation was formulated and graded. Implementation issues are recorded in the NHMRC evidence statement forms presented in **Appendix D** (Volume 2).

2.5.2 Practice points

Practice points were developed by the CRG through a facilitated group discussion (**Appendix 4** in this volume) in the following circumstances:

- where the underpinning evidence would have led to a grade D evidence-based recommendation
- where the CRG developed evidence-based recommendations graded C and above, but considered that additional information was required to guide clinical practice. Wherever possible, this guidance was sourced from other evidence-based guidelines assessed to be of high quality
- where insufficient evidence was identified to support the development of an evidence-based recommendation.

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3 Findings of systematic review

This chapter provides the findings of the systematic review, based on the four questions summarised in Box 2.1 (Chapter 2).

3.1 Question 1

Question 1 (Interventional question) In critically ill patients, what is the effect of RBC transfusion on patient outcomes? RBC, red blood cell

The following review will be separated into two sections based on the following comparisons of RBC interventions:

- The first section presents a comparison between (i) RBC transfusion and no transfusion (or transfusion at different doses). This includes data from Level III evidence (observational studies) and provides us with information on whether RBC transfusion is effective.

- The second section presents a comparison between restrictive RBC transfusion and liberal RBC transfusion. This includes data from Level I and II evidence (meta-analysed and single RCTs) and provides us with information on whether reduced RBC transfusion (based on a more restrictive transfusion trigger or Hb/Hct threshold) is as effective as greater RBC transfusion (based on a more liberal transfusion trigger or Hb/Hct threshold).

3.1.1 RBC transfusion

Evidence statements
In critically ill patients, the effect of RBC transfusion on mortality is uncertain (C, C, D, A, B). (See evidence matrix EM1.A in Volume 2 of the technical report)
In critically ill patients, RBC transfusion may be independently associated with an increased risk of ventilator-associated pneumonia (C, NA, B, A, C). (See evidence matrix EM1.B in Volume 2 of the technical report)
In critically ill patients, RBC transfusion may be independently associated with an increased risk of infection (C, A, B, A, C). (See evidence matrix EM1.B in Volume 2 of the technical report)
In critically ill patients, RBC transfusion may be independently associated with an increased risk of ARDS or ALI (C, B, B, A, B). (See evidence matrix EM1.C in Volume 2 of the technical report)
In critically ill patients, the effect of RBC transfusion on organ failure is uncertain (D, NA, C, A, B).

(See evidence matrix EM1.D in Volume 2 of the technical report)	
In critically ill patients, liberal and restrictive RBC transfusion strategies have similar effects on mortality (B, A, NA, A, B). (See evidence matrix EM1.E in Volume 2 of the technical report)	
In critically ill patients, liberal and restrictive RBC transfusion strategies have similar effects on organ failure and dysfunction (B, A, NA, A, B). (See evidence matrix EM1.F in Volume 2 of the technical report)	
In critically ill patients, liberal and restrictive RBC transfusion strategies have similar effects on pneumonia and ARDS (B, NA, NA, A, B). (See evidence matrix EM1.G in Volume 2 of the technical report)	
In critically ill patients, liberal and restrictive RBC transfusion strategies have similar effects on a broad range of infection outcomes (B, NA, NA, A, B). (See evidence matrix EM1.H in Volume 2 of the technical report)	
Recommendations	
R1	In critically ill patients, a restrictive transfusion strategy should be employed (Grade B).
Practice points	
PP1	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.
PP2	Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.
PP3	CRG consensus suggests that, with a: • **Hb concentration <70 g/L**, RBC transfusion is likely to be appropriate; however, transfusion may not be required in well-compensated patients or where other specific therapy is available. • **Hb concentration of 70–90 g/L**, RBC transfusion is not associated with reduced mortality. The decision to transfuse patients (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia. • **Hb concentration >90 g/L**, RBC transfusion is generally unnecessary. For patients undergoing cardiac surgery, refer to *Patient Blood Management Guidelines: Module 2 – Perioperative*;[7] for patients with active bleeding, refer to *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion*.[8]

PP4	For patients with ACS, the following recommendations are taken from *Patient Blood Management Guidelines: Module 3 – Medical*:[9] In ACS patients with a: • **Hb concentration >100 g/L**, RBC transfusion is not advisable is not recommended because of an association with increased mortality (see R1 of Module 3). • **Hb concentration <80 g/L**, RBC transfusion may be associated with reduced mortality and is likely to be appropriate (see PP4 of Module 3). • **Hb concentration of 80–100 g/L**, the effect of RBC transfusion on mortality is uncertain and may be associated with an increased risk of recurrence of MI. Any decision to transfuse should be made with caution and based on careful consideration of the risks and benefits (see PP5 of Module 3).
	ACS, acute coronary syndrome; CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; MI, myocardial infarction; PP, practice point; R, recommendation; RBC, red blood cell

3.1.2 Summary of evidence

The literature review for this question is presented as two separate comparisons: (i) RBC transfusion versus no RBC transfusion (or different transfusion dose) and (ii) restrictive versus liberal RBC transfusion strategies.

As this is an intervention question, the levels of evidence are as follows:

- Level I – a systematic review of two or more Level II studies
- Level II – a randomised controlled trial
- Level III-1 – a pseudorandomised trial
- Level III-2 – a comparative study with concurrent controls (including non-randomised, experimental trials, cohort studies, case-control studies and interrupted time series with a control group)
- Level III-3 – a comparative study without concurrent controls (including historical control studies, two or more single arm studies, interrupted time series without a parallel control group); and Level IV – case series with either post-test or pre-test/post-test outcomes.

For the purposes of this review, a systematic review of Level III-1 to Level III-3 evidence has been classified as Level III evidence.

For this review, only evidence down to Level III-2 was considered. In addition, for Level III evidence, only studies which included ≥ 500 subjects and adjusted for potential confounding variables using multivariate analysis were included; studies in which only univariate analyses were undertaken were excluded. The studies included for this question identified potential confounding variables in various ways. In some cases, variables have been identified which have been shown to be associated with blood transfusion or the specified outcome in previous studies, while in other cases a wide range of variables have been examined using univariate analysis and those shown to be associated with blood transfusion or the outcome have been included in the analysis. In some studies, all potential confounding variables have been included in the multivariate analysis, while in other studies different methods have

been used (e.g. backwards or forwards stepwise regression) to include only those variables which are shown to be significantly associated in the analysis.

There were two different comparisons made in this review: (1) transfusion versus no transfusion (or different transfusion dose); and (2) restrictive transfusion versus liberal transfusion. As it is not considered ethical to withhold blood transfusion, RCTs were not available for the transfusion versus no transfusion comparison; the evidence for this comparison came from observational studies (Level III) only. Proof of causation can only be determined using a randomised, controlled trial. While the results of these adjusted Level III study analyses indicate whether or not blood transfusion is associated with specific outcomes, they do not prove that blood transfusion *causes* these outcomes. However, a number of studies were identified that showed increasing transfusion dose was associated with increased risk of adverse outcomes, which provides some support for a possible causative effect.

3.1.3 RBC transfusion vs. no transfusion (or different transfusion dose)

Methods

Twenty six studies were identified for this population from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search did not identify any Level I studies relevant to this population, intervention and comparator.

Level II evidence

The literature search did not identify any Level II studies relevant to this population, intervention and comparator.

Level III evidence

Twenty six studies were identified for this population, intervention and comparator. Two were systematic reviews and the remaining studies were individual prospective and retrospective cohort studies.[10-35]

The systematic review by Marik and associates included 45 cohort studies examining the association between RBC transfusion and mortality, infectious complications and ARDS.[10] Of the 20 individual studies (from 22 publications) included in the Marik review that were potentially relevant to this question (i.e. were classified as being in critical care or trauma patients), 11 were included in this current review.[12,14-16,18,20,22,24,30,32,34] Reasons for excluding the other studies included in the Marik review were: (i) the studies assessed < 500 subjects;[36-41] (ii) wrong intervention/comparator (age of blood cells);[42-44] and (iv) the analysis was not adjusted for potential confounders.[45] In addition, one study was excluded because there appeared to be errors in the results reported in the publication.[46] Three additional studies included in the Marik study that were conducted in patients with acute coronary syndrome have not been included in this module, but have been included in the medical module.[47-49]

The systematic review by Hill et al (2003) assessed the association between blood transfusion versus no blood transfusion and the risk of postoperative bacterial infection.[11] While 20 studies were included in total, the majority of these studies related to the surgical setting. However, a subgroup analysis of studies in trauma patients was presented that is relevant to this review.

It is difficult to verify the results reported in the Hill review as the ORs reported in their meta-analysis do not appear in the publications they have cited. While it is possible that Hill may have received these estimates directly via the authors of the individual studies, this has not been stated in their publication. *Due to the uncertainty surrounding the results presented in the Hill review, it will not be formally included here.* However, the individual included study which meets the inclusion criteria for this current review has been included.[12]

A total of 21 studies were excluded for assessing < 500 subjects.[36-41,50-64]

The main characteristics of all included studies are summarised in Table 3.3.1.

Table 3.3.1 Question 1 (critical care/trauma): Characteristics and quality of Level III evidence

Author	Study type *Study quality*	Population	Outcomes
Level III evidence			
Marik et al (2008)[10]	Systematic review 45 of cohort studies *Fair*	Critically ill patients (includes patients in trauma, general surgery, cardiac surgery, neurosurgery, cardiac and general ICU patients) N=272,596	Mortality Transfusion-related adverse events
Level III-2 evidence			
Agarwal et al (1993)[12]	Retrospective cohort study *Fair*	Patients with trauma admitted to one of eight hospitals in New York and Connecticut N=5366	Transfusion-related adverse events
Bochicchio et al (2008) [13]	Prospective cohort study *Fair*	Patients admitted for > 48 hours to a trauma centre from 2002-2004. N=1172	Mortality Transfusion-related adverse events
Ciesla et al (2005)[14]	Prospective cohort study *Fair*	Trauma patients admitted to a single surgical ICU between May 1992 and Dec 2003. Had to have an ISS > 15, survive for at least 48 hours after injury, be admitted to the ICU within 24 hours of injury and be aged ≥ 15 years. N=1344	Multiple organ failure
Claridge et al (2002)[15]	Prospective cohort study *Poor*	Patients admitted to a trauma centre from Nov 1996 to Dec 1999 N=1593	Transfusion-related adverse events
Corwin et al (2004)[16]	Prospective cohort study (CRIT) *Fair*	Patients admitted to ICU with an anticipated stay of 48 hours from Aug 2000 to Apr 2001 N=4892	Mortality
Duane et al (2008)[17]	Retrospective cohort study *Poor*	Patients aged ≥ 16 years admitted between Jan 2001 and Dec 2006 with primarily isolated blunt head trauma as defined by having a head abbreviated injury severity score (AIS) of ≥ 2 and all other AIS scores ≤ 1.	Transfusion-related adverse events
Dunne et al (2004)[18]	Prospective cohort study *Fair*	Patients admitted to trauma centre from Jan 1997 to Jul 1999 N=9539	Mortality
Engoren et al (2009)[19]	Retrospective cohort study *Fair*	Patients admitted to the cardiac, burns, neurological and neurosurgical and combined medical-surgical ICUs between Jan 2001 and Apr 2002 N=2123	Mortality
Gong et al (2005)[20]	Prospective cohort study *Fair*	Patients admitted to ICU between Sep 1999 and Aug 2002 with at least one risk factor for ARDS N=688	Transfusion-related adverse events
Hébert et al (1997)[21]	Retrospective/prospective cohort study *Fair*	Patients admitted to six ICUs during 1993 N=3838	Mortality
Khan et al (2007)[22]	Retrospective cohort study *Fair*	Critically ill patients admitted to a medical ICU between Mar 2004 and Mar 2005 N=805	Transfusion-related adverse events

Author	Study type *Study quality*	Population	Outcomes
Leal-Noval et al (2001)[23]	Prospective cohort study *Fair*	Patients admitted to a single surgical ICU from Jun 1994 to Jun 1998 N=738	Transfusion-related adverse events
Malone et al (2003)[24]	Prospective cohort study *Good*	Patients admitted to a trauma centre between Jan 1998 and Dec 2000 N=15,534	Mortality
Müller et al (2008)[25]	Retrospective cohort study *Fair*	Cases admitted to a single ICU immediately after surgery from Mar 1993 to Feb 2005 N=4214	Mortality
Palmieri et al (2006)[26]	Retrospective cohort study *Poor*	Patients with acute burn injury ≥ 20% of TBSA admitted to a participating burn centre within 72 hours of injury from Jan 2002 to Dec 2002. N=620	Infection
Rachoin et al (2009)[27]	Retrospective cohort study *Fair*	Patients surviving more than 24 hours in the ICU between Jul 2003 and Sep 2006 N=2432	Mortality Transfusion-related adverse events
Rüttinger et al (2007)[28]	Retrospective cohort study *Good*	Surgical cases requiring intensive care for > 1 day between Mar 1993 and Feb 2005 N=3037	Mortality
Salim et al (2008)[29]	Retrospective cohort study *Fair*	Patients with traumatic brain injury admitted to ICU between Jul 1998 and Dec 2005 N=1361	Mortality Transfusion-related adverse events
Shorr et al (2004)[30]	Prospective cohort study (CRIT study subgroup) *Fair*	Patients without pneumonia at ICU admission who then required at least 48 hours mechanical ventilation N=1563	Transfusion-related adverse events
Spinella et al (2008)[31]	Retrospective cohort study *Fair*	Trauma patients admitted to a combat support hospital in Iraq between Nov 2003 and Dec 2004 who received blood transfusion (RBC, FFP or fresh whole blood). Subgroup analysis presented here includes only patients who did not receive massive transfusion. N=567	Mortality (survival)
Vincent et al (2002)[32]	Prospective cohort study *Fair*	Patients admitted to ICU during a 2-week period in Nov 1999 N=3534	Mortality
Vincent et al (2008)[33]	Prospective cohort study *Good*	Patients admitted to ICU during a 2-week period in May 2002 N=3534	Mortality
Zilberberg et al (2007)[34]	Prospective cohort study (CRIT reanalysis) *Fair*	Patients admitted to ICU with an anticipated stay of 48 hours from Aug 2000 to Apr 2001 without a diagnosis of ARDS on admission N=4730	Transfusion-related adverse events
Zilberberg et al (2008)[35]	Retrospective cohort study *Fair*	Hospital admissions from Jan 2000 to Dec 2005 who had charges associated with at least one procedure code for insertion of an endotracheal tube and at least one code for 96 continuous hours	Mortality

Author	Study type *Study quality*	Population	Outcomes
		of ventilation N=4334	

ARDS, acute respiratory distress syndrome; ICU, intensive care unit.

The results of previous studies suggest that adjusting the analysis for nadir Hb/Hct has a substantial impact on the association between RBC transfusion and mortality compared with adjusting for baseline Hb/Hct. In addition, a study included in this review provides evidence that adjusting for organ dysfunction during hospitalisation may also modify the association between RBC transfusion and mortality. As such, a special note on the Hb/Hct and anaemia variables adjusted for in the analyses has been provided for each study and adjustment for this and organ dysfunction will be discussed.

Results

The effect of RBC transfusion on mortality

Twelve studies assessed the association between RBC transfusion versus no transfusion and mortality in critical care patients, as shown in Table 3.3.2. Of these, one was a systematic review of Level III-2 studies (Marik et al 2008),[10] and 11 were prospective or retrospective cohort studies. [16,18,19,21,24,27-29,32,33,35]

The study by Marik et al (2008) aimed to examine the association between RBC transfusion and mortality and morbidity in critically ill, hospitalised patients by performing a systematic review and meta-analysis of cohort studies. [10]While the authors did not formally assess the quality of the included studies, they did note that 'in general, multivariate analysis was performed correctly for age and illness severity' and included adjustment for factors such as age, APACHE II score, ISS, SOFA and others.

Twenty of the 45 studies included in the Marik review assessed the association between RBC transfusion and mortality, while 13 of these contributed to the pooled analysis. Ten of the studies included in the pooled analysis showed a significant association between RBC transfusion and increased mortality risk and two showed no significant association. The remaining study conducted in patients aged > 65 years with myocardial infarction showed that for patients with a baseline Hct > 36%, RBC transfusion was significantly associated with an increased risk of mortality (OR 1.38; 95% CI 1.05, 1.80), while for patients with a baseline Hct < 33%, RBC transfusion was significantly associated with a decreased risk of mortality (OR 0.6 (0.47, 0.76).[47] The pooled OR for 12 studies (excluding the Wu study) was 1.69 (95% CI 1.46, 1.92). The authors note there was moderate heterogeneity between studies.

The literature search conducted for this review identified 11 cohort studies which assessed the relationship between RBC transfusion and mortality, as shown in Table 3.3.2. Of these, four were included in the Marik review, one was within the timeframe of the Marik review but not included, and six were published after the Marik review.

Four studies identified for this review were included in the Marik review.[16,18,24,32] Corwin et al (2004) carried out a prospective cohort study in up to 4892 patients from 284 ICUs in 213 hospitals in the USA. [16] Using logistic regression analysis, they found that RBC transfusion of 1-2 units, 3-4 units and > 4 units was significantly associated with increased 30-day mortality compared with no RBC transfusion, with the risk increasing with increasing transfusion dose (ORs 1.48, 2.62 and 4.01, respectively). These analyses were adjusted for baseline and nadir

Hb. Corwin also performed a propensity-matched analysis in 2118 patients which showed a significantly increased risk of 30-day mortality associated with RBC transfusion (MR 1.65; 1.35, 2.03; P<0.001).

The study by Dunne et al (2004) examined the association between blood transfusion in the first 24 hours following admission and mortality in 9539 patients admitted to a trauma centre. [18] They found that blood transfusion was significantly associated with hospital mortality (OR 4.23; 95% CI 3.07, 5.84; P<0.001). It should be noted that this analysis did not adjust for baseline or nadir Hct or Hb.

The study by Malone et al (2003) was a prospective cohort study which examined the association between blood transfusion in the first 24 hours and mortality in 15,534 patients admitted to a trauma centre. [24]They found that blood transfusion in the first 24 hours was significantly associated with increased mortality compared with no blood transfusion in the first 24 hours (OR 2.83; 95% CI 1.82, 4.40; P<0.001). The analysis was not adjusted for baseline or nadir Hct or Hb, although anaemia was considered during the backward stepwise elimination procedure and not included in the final model.

The study by Vincent et al (2002) used two analysis methods to assess the association between RBC transfusion and mortality in up to 3534 patients admitted to 146 ICUs during a 2-week period in 1999. [32] Using logistic regression analysis, RBC transfusion was shown to be associated with 28-day mortality (OR 1.37; 95% CI 1.02, 1.84; P=0.04). This analysis included admitting (baseline) Hb in the model. A propensity-matched analysis was also carried out in 516 transfused patients and 516 non-transfused patients matched on a number of variables including admitting Hb. This also showed that transfusion was significantly associated with increased mortality (P=0.02).

One study published within the timeframe of the Marik review, but not included in it, was identified by the literature search. Hébert et al (1997; *fair quality*) collected data on 4470 patients admitted to six ICUs and assessed the relationship between RBC transfusion (by dose) and ICU mortality. [21] They found in the overall ICU population that RBC transfusions of 1-3 units and 4-6 units were significantly associated with a decreased risk of mortality compared with no RBC transfusion (OR 0.74 and 0.71, respectively), while transfusions of 7-10 units and > 10 units were not associated with ICU mortality. In a subgroup of patients with a cardiovascular diagnosis (N=1302) similar results were seen, with transfusion of 1-3 units and 4-6 units significantly associated with decreased ICU mortality compared with no transfusion (OR 0.61 and 0.49, respectively), and transfusions of 7-10 and > 10 units not significantly associated with ICU mortality. They conclude that 'anemia increases the risk of death in critically ill patients with cardiac disease' and that 'blood transfusions appear to decrease this risk'. These analyses were adjusted for pre-transfusion/minimum Hb.

Six studies were identified by the literature search which were published after the Marik review. Rüttinger et al (2007) examined the relationship between RBC transfusion and mortality in 3037 patients admitted to a surgical ICU. [28] They note that in contrast to RCTs, previous cohort studies have generally shown a significant relationship between RBC transfusion and mortality, and hypothesise that this may be due to a lack of adjustment for disease severity in the analysis.

In order to test their hypothesis, Rüttinger et al performed two different types of adjustment: (i) adjusting for admission variables only and (ii) adjusting for admission variables and variables reflecting the number and extent of organ dysfunction. They also

performed analyses on three sets of RBC transfusion data: (i) based on RBC transfusion vs no RBC transfusion during ICU stay; (ii) based on total RBC transfusion dose vs no RBC transfusion during ICU stay; and (iii) based on the maximum units of RBC transfusion given in a single ICU day vs no RBC transfusion.

The results of their analyses showed that for all three RBC transfusion comparisons noted above, there was a significant association between RBC transfusion and ICU mortality when the analysis was adjusted for admission variables only, while this association was lost when the additional organ dysfunction variables were included in the analysis. The authors conclude that 'red cell transfusion during ICU stay may be only a surrogate marker for disease severity and is not causally related to ICU mortality'.

Salim et al (2008) assessed the relationship between blood transfusion and mortality in 1123 patients with traumatic brain injury admitted to a surgical ICU. [29] Blood transfusion was significantly associated with an increased risk of hospital mortality (OR 2.19; 95% CI 1.27, 3.75). The analysis included adjustment for anaemia.

Vincent et al (2008) performed similar analyses to their 2002 study (Vincent et al 2002) in a cohort of 3147 patients admitted to 198 ICUs during a 2-week period in 2002, but found different results. [32,33] They showed that there was a trend towards decreased mortality in RBC transfused patients when a Cox proportional hazards model analysis was carried out, and significantly decreased mortality in RBC transfused patients when a propensity-matched analysis was carried out. The authors suggest that the reasons for the differences in the results of their two almost identical studies may be the inclusion of East German hospitals in the latter study, but that it is more likely to be due to the improvements in transfusion practices that have been implemented since the initial study was conducted. They conclude that their study 'does not support the view that blood transfusions are associated with increased mortality rates in acutely ill patients'.

Zilberberg et al (2008) performed a retrospective cohort study on 4334 patients admitted to hospital who required mechanical ventilation for at least 96 continuous hours. [35] After adjusting for a number of factors, which included baseline and nadir Hb, they found that RBC transfusion may be associated with increased risk of hospital mortality (OR 1.21; 95% CI 1.00, 1.48).

Zilberberg et al (2008) also assessed the hospital length of stay and costs attributable to transfusion exposure in this patient group and found that hospital length of stay increased by 6.33 days (95% CI: 5.12, 7.62) and cost increased by US$48,973 (95% CI: US45,582, US$52,478).

Engoren et al (2009) performed two separate analyses to examine the association between RBC transfusion and mortality in 2123 patients admitted to the cardiac, burns, neurological and neurosurgical and the combined medical-surgical ICUs at a single medical centre. [19] Using an adjusted Cox proportional hazards model they found that RBC transfusion was not significantly associated with 30-day mortality (HR 1.11; 95% CI 0.86, 1.42). This analysis was not adjusted for baseline or nadir Hct or Hb. A matched-propensity analysis which included 556 patients also found no significant association between RBC transfusion and 30-day mortality. This analysis did include matching on Hb level.

Engoren 2009 also examined the associations between RBC transfusion and 30-180 mortality and 180+ day mortality using both a Cox proportional hazards model and a matched-propensity analysis and found that RBC transfusion was associated with a significantly decreased risk of 180+ day mortality.

Rachoin et al (2009) performed a retrospective cohort study to assess the association between RBC transfusion and mortality in 2432 patients who survived > 24 hours in an ICU. [27] They found that RBC transfusion was significantly associated with increased hospital mortality compared with no RBC transfusion (OR 1.3; 95% 1.02, 1.5). The analysis did not take baseline or nadir Hct or Hb into account.

Three studies assessed the association between RBC transfusion as a continuous variable and mortality/survival.[13,25,31] Bochicchio et al (2008b) assessed RBC transfusion risk by dose in 1172 patients admitted to ICU for > 48 hours at a single centre in the US. [13] They found that each unit of RBC transfused was associated with a significantly increased risk of mortality of 5% (P<0.001). They also noted that FFP was associated with increased risk of mortality.

Müller et al (2008) measured the effect of RBC transfusion by unit (and other variables) on 4-day mortality in 4214 subjects admitted to ICU immediately following surgery. The most common types of surgery were abdominal and vascular surgery. The mean units of RBC transfused on admission day were 0.6 in those who survived 4 days and 3.1 in those who died within 4 days. A multivariable adjusted analysis (which included adjustment for admission APACHE II score and the interaction between number of units transfused and APACHE II score) showed that RBC transfusion was significantly associated with an increased risk of 4-day mortality (OR 1.10; 95% CI 1.02, 1.17).

The study by Spinella et al (2008) examined plasma and red blood cell transfusion in 708 of 3287 patients admitted to a combat-support hospital in Iraq for combat-related trauma injuries who received blood products. When all patients were considered (i.e. including those who had massive transfusion), every 1-unit of RBC transfusion was significantly associated with a reduction in in-hospital survival of 16%. When the analysis was confined to patients who did not have a massive transfusion (N=567) every 1-unit of RBC transfusion was associated with a reduction in in-hospital survival of 23% (OR 0.77; 95% CI 0.64, 0.92; p=0.004).

The authors also note that the use of FFP was associated with increased survival. The authors note that the differential results for FFP and RBC suggest that it is possible to adequately adjust for severity of injury in these adjusted cohort study analyses. They also note that the association between RBC and decreased survival 'may be related to the increased storage age of RBCs transfused to all patients in our study (33 days)'.

Table 3.3.2 Question 1 (critical care/trauma): Results for RBC transfusion vs. no transfusion – Mortality

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Transfusion versus no transfusion									
LEVEL III EVIDENCE									
Marik 2008 Level III Fair	Systematic review of 13 cohort studies N=293,341	Critically ill (includes trauma, general surgery, cardiac surgery, orthopaedic surgery, ACS, ICU)	Hospital/ICU Various	Blood transfusion vs no blood transfusion	Mortality	NR	NR	OR 1.69 (1.46, 1.92)	Blood transfusion is significantly associated with <u>increased</u> mortality P=NR
						Author notes that in general, multivariate analysis was performed correcting for age and illness severity (APACHE score, ISS, SOFA score etc).			
LEVEL III-2 EVIDENCE									
Studies included in the Marik 2008 review									
Corwin 2004 Level III-2 Fair	1 prospective cohort study (CRIT) N=NR[d]	Critically ill patients admitted to ICU and with an anticipated stay of 48 hours	ICU US	RBC transfusion <u>1-2 units</u> vs no RBC transfusion	30-day mortality	NR	NR	OR 1.48 (1.07, 2.05)	*Transfusion of 1-2 units of RBCs is significantly associated with an <u>increased</u> risk of mortality compared with no transfusion* P=0.018
						<u>Logistic regression analysis</u> adjusted for: duration on study, baseline Hb, nadir Hb and mean age of blood.			
Corwin 2004 Level III-2 Fair	1 prospective cohort study (CRIT) N=NR[d]	Critically ill patients admitted to ICU and with an anticipated stay of 48 hours	ICU US	RBC transfusion <u>3-4units</u> vs no RBC transfusion	30-day mortality	NR	NR	OR 2.62 (1.80, 3.81)	*Transfusion of 3-4 units of RBCs is significantly associated with an <u>increased</u> risk of mortality compared with no transfusion* P<0.0001
						<u>Logistic regression analysis</u> adjusted for: duration on study, baseline Hb, nadir Hb and mean age of blood.			
Corwin 2004 Level III-2 Fair	1 prospective cohort study (CRIT) N=NR[d]	Critically ill patients admitted to ICU and with an anticipated stay of 48 hours	ICU US	RBC transfusion <u>>4units</u> vs no RBC transfusion	30-day mortality	NR	NR	OR 4.01 (2.74, 5.87)	*Transfusion of >4 units of RBCs is significantly associated with an <u>increased</u> risk of mortality compared with no transfusion* P<0.0001
						<u>Logistic regression analysis</u> adjusted for: duration on study, baseline Hb, nadir Hb and mean age of blood.			

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Corwin 2004 Level III-2 Fair	1 prospective cohort study (CRIT) N=2118	Critically ill patients admitted to ICU and with an anticipated stay of 48 hours	ICU US	RBC transfusion vs no RBC transfusion	30-day mortality	NR	NR	MR 1.65 (1.35, 2.03)	*RBC transfusion is significantly associated with an increased risk of 30-day mortality* P<0.001
						Propensity analysis adjusted for: propensity for transfusion (patients demographics, baseline APACHE II and SOFA scores, origin of admission, admitting diagnoses, medical history and hospital LOS)			
Dunne 2004 Level III-2 Fair	1 prospective cohort study N=9539	Patients admitted to a trauma centre from Jan 1997 to June 1999	Hospital US	Blood transfusion in first 24 hours vs no blood transfusion in first 24 hours	Hospital mortality	212/954 (22.2)	120/8585 (1.4)	OR 4.23 (3.07, 5.84)	*RBC transfusion in the first 24 hours is significantly associated with an increased risk of mortality* P<0.0001
						Adjusted for: age, ISS, GCS, race, and gender.			
Malone 2003 Level III-2 Good	1 prospective cohort study N=15,534	Patients aged ≥ 18 years admitted to a trauma centre between Jan 1998 and Dec 2000	Trauma centre US	Blood transfusion in first 24 hours vs no blood transfusion in first 24 hours	Hospital mortality	377/1703 (22.1)	313/13,831 (2.3)	OR 2.83 (1.82, 4.40)	*RBC transfusion in the first 24 hours is significantly associated with increased mortality* P<0.001
						Adjusted for: anaemia at admission, admission base deficit, serum lactate, and shock index, age, gender, race, Glasgow coma scale score and injury severity score.			
Vincent 2002 Level III-2 Fair	1 prospective cohort study (ABC) N=3534	Patients admitted to 146 general medical and/or surgical ICUs during a 2-week period in Nov 1999	ICU Western Europe	RBC transfusion vs no RBC transfusion	28-day mortality	331/1140 (29.0)	283/1896 (14.9)	OR 1.37 (1.02, 1.84)	*Transfusion is significantly associated with increased mortality* P=0.04
						Logistic regression analysis adjusted for: admitting SOFA score, admitting APACHE II score, age and admitting Hb level.			
Vincent 2002 Level III-2 Fair	1 prospective cohort study (ABC) N=1032	Patients admitted to 146 general medical and/or surgical ICUs during a 2-week period in Nov 1999	ICU Western Europe	RBC transfusion vs no RBC transfusion	28-day mortality	117/516 (22.7)	88/516 (17.1)	NR	*Transfusion is significantly associated with increased mortality* P=0.02
						Matched propensity analysis matched for: age, sex, admission type, diagnosis on admission, admitting SOFA score, admitting APACHE II score, day 1 haemoglobin, recent history of anaemia, recent acute blood loss, whether the patients was in shock on admission, and hospital length of stay.			
Studies not included in the Marik 2008 review									
Hébert 1997 Level III-2 Fair	Retrospective/prospective cohort study N=3838	Patients admitted to six ICUs during 1993 who were ≥ 16 years and did not meet brain death criteria within 24 hours of admission	ICU Canada	RBC transfusion 1-3 units vs no RBC transfusion	ICU mortality	191/754 (25.3)	585/3084 (19.0)	OR 0.74 (0.57, 0.96)	*RBC transfusion of 1-3 units is significantly associated with decreased mortality compared with no transfusion* P=0.01
						Adjusted for significant variables: Sex, institution, pre-transfusion/minimum Hb, APACHE II score, transfusion status			

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Hébert 1997 Level III-2 Fair	Retrospective/prospective cohort study N=1236	Patients admitted to six ICUs during 1993 who were ≥ 16 years and did not meet brain death criteria within 24 hours of admission with a cardiovascular diagnosis	ICU Canada	RBC transfusion 1-3 units vs no RBC transfusion	ICU mortality	49/201 (24.4)	181/1035 (17.5)	OR 0.61 (0.37, 1.00) Adjusted for significant variables: Sex, institution, pre-transfusion/minimum Hb, APACHE II score, transfusion status	*RBC transfusion of 1-3 units is significantly associated with decreased mortality compared with no transfusion* P=0.0256
Hébert 1997 Level III-2 Fair	Retrospective/prospective cohort study N=3406	Patients admitted to six ICUs during 1993 who were ≥ 16 years and did not meet brain death criteria within 24 hours of admission	ICU Canada	RBC transfusion 4-6 units vs no RBC transfusion	ICU mortality	98/322 (30.4)	585/3084 (19.0)	OR 0.71 (0.50, 0.99) Adjusted for significant variables: Sex, institution, pre-transfusion/minimum Hb, APACHE II score, transfusion status	*RBC transfusion of 4-6 units is significantly associated with decreased mortality compared with no transfusion* P=0.02
Hébert 1997 Level III-2 Fair	Retrospective/prospective cohort study N=1103	Patients admitted to six ICUs during 1993 who were ≥ 16 years and did not meet brain death criteria within 24 hours of admission with a cardiovascular diagnosis	ICU Canada	RBC transfusion 4-6 units vs no RBC transfusion	ICU mortality	16/68 (23.5)	181/1035 (17.5)	OR 0.49 (0.23, 1.03) Adjusted for significant variables: Sex, institution, pre-transfusion/minimum Hb, APACHE II score, transfusion status	*RBC transfusion of 4-6 units is significantly associated with decreased mortality compared with no transfusion* P=0.0304
Hébert 1997 Level III-2 Fair	Retrospective/prospective cohort study N=3229	Patients admitted to six ICUs during 1993 who were ≥ 16 years and did not meet brain death criteria within 24 hours of admission	ICU Canada	RBC transfusion 7-10 units vs no RBC transfusion	ICU mortality	56/145 (38.6)	585/3084 (19.0)	OR 0.93 (0.59, 1.46) Adjusted for significant variables: Sex, institution, pre-transfusion/minimum Hb, APACHE II score, transfusion status	*RBC transfusion of 7-10 units is not significantly associated with mortality compared with no transfusion* P=0.37

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Hébert 1997 Level III-2 Fair	Retrospective/prospective cohort study N=1069	Patients admitted to six ICUs during 1993 who were ≥ 16 years and did not meet brain death criteria within 24 hours of admission with a cardiovascular diagnosis	ICU Canada	RBC transfusion 7-10 units vs no RBC transfusion	ICU mortality	16/34 (47.1)	181/1035 (17.5)	OR 0.96 (0.39, 2.41)	*RBC transfusion of 7-10 units is not significantly associated with mortality compared with no transfusion* P=0.47
						Adjusted for significant variables: Sex, institution, pre-transfusion/minimum Hb, APACHE II score, transfusion status			
Hébert 1997 Level III-2 Fair	Retrospective/prospective cohort study N=3249	Patients admitted to six ICUs during 1993 who were ≥ 16 years and did not meet brain death criteria within 24 hours of admission	ICU Canada	RBC transfusion >10 units vs no RBC transfusion	ICU mortality	71/165 (43.0)	585/3084 (19.0)	OR 0.90 (0.59, 1.38)	*RBC transfusion of >10 units is not significantly associated with mortality compared with no transfusion* P=0.32
						Adjusted for significant variables: Sex, institution, pre-transfusion/minimum Hb, APACHE II score, transfusion status			
Hébert 1997 Level III-2 Fair	Retrospective/prospective cohort study N=3249	Patients admitted to six ICUs during 1993 who were ≥ 16 years and did not meet brain death criteria within 24 hours of admission	ICU Canada	RBC transfusion >10 units vs no RBC transfusion	ICU mortality	14/27 (51.9)	181/1035 (17.5)	OR 0.64 (0.24, 1.69)	*RBC transfusion of >10 units is not significantly associated with mortality compared with no transfusion* P=0.184
						Adjusted for significant variables: Sex, institution, pre-transfusion/minimum Hb, APACHE II score, transfusion status			
Studies published since the Marik 2008 review									
Rüttinger 2007 Level III-2 Good	1 retrospective cohort study N=3037	Patients spending at least 1 day in a surgical ICU from Mar 1993 to Feb 2005	Surgical ICU Germany	RBC transfusion vs no RBC transfusion (during ICU stay)	ICU mortality	NR	NR	OR 1.847 (1.263, 2.701)	RBC transfusion is significantly associated with an increased risk of ICU mortality P=0.002
						Adjusted for: admission variables only.			
Rüttinger 2007 Level III-2 Good	1 retrospective cohort study N=3037	Patients spending at least 1 day in a surgical ICU from Mar 1993 to Feb 2005	Surgical ICU Germany	RBC transfusion vs no RBC transfusion (during ICU stay)	ICU mortality	NR	NR	OR 0.898 (0.532, 1.516)	RBC transfusion is not associated with ICU mortality P=0.688
						Adjusted for: admission variables and variables representing global organ dysfunction during ICU stay (maximum APACHE II score, maximum number of failing organs, duration of invasive ventilation, duration of catecholamine therapy, duration of renal replacement therapy).			

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Rüttinger 2007 Level III-2 Good	1 retrospective cohort study N=NR	Patients spending at least 1 day in a surgical ICU from Mar 1993 to Feb 2005	Surgical ICU Germany	RBC transfusion 1-2 units vs no RBC transfusion (during ICU stay)	ICU mortality	NR	NR	OR 0.840 (0.494, 1.426) Adjusted for: admission variables only.	RBC transfusion of 1-2 units is not associated with ICU mortality P=0.518
Rüttinger 2007 Level III-2 Good	1 retrospective cohort study N=NR	Patients spending at least 1 day in a surgical ICU from Mar 1993 to Feb 2005	Surgical ICU Germany	RBC transfusion 1-2 units vs no RBC transfusion (during ICU stay)	ICU mortality	NR	NR	OR 0.683 (0.351, 1.283) Adjusted for: admission variables and variables representing global organ dysfunction during ICU stay (maximum APACHE II score, maximum number of failing organs, duration of invasive ventilation, duration of catecholamine therapy, duration of renal replacement therapy).	RBC transfusion of 1-units is not associated with ICU mortality P=0.261
Rüttinger 2007 Level III-2 Good	1 retrospective cohort study N=NR	Patients spending at least 1 day in a surgical ICU from Mar 1993 to Feb 2005	Surgical ICU Germany	RBC transfusion 3-4 units vs no RBC transfusion (during ICU stay)	ICU mortality	NR	NR	OR 1.572 (0.902, 2.738) Adjusted for: admission variables only.	RBC transfusion of 3-4 units is not associated with ICU mortality P=0.110
Rüttinger 2007 Level III-2 Good	1 retrospective cohort study N=NR	Patients spending at least 1 day in a surgical ICU from Mar 1993 to Feb 2005	Surgical ICU Germany	RBC transfusion 3-4 units vs no RBC transfusion (during ICU stay)	ICU mortality	NR	NR	OR 1.108 (0.515, 2.386) Adjusted for: admission variables and variables representing global organ dysfunction during ICU stay (maximum APACHE II score, maximum number of failing organs, duration of invasive ventilation, duration of catecholamine therapy, duration of renal replacement therapy).	RBC transfusion of 3-4 units is not associated with ICU mortality P=0.793
Rüttinger 2007 Level III-2 Good	1 retrospective cohort study N=NR	Patients spending at least 1 day in a surgical ICU from Mar 1993 to Feb 2005	Surgical ICU Germany	RBC transfusion 5-8 units vs no RBC transfusion (during ICU stay)	ICU mortality	NR	NR	OR 3.863 (2.383, 6.254) Adjusted for: admission variables only.	RBC transfusion of 5-8 units is significantly associated with increased ICU mortality P<0.001
Rüttinger 2007 Level III-2 Good	1 retrospective cohort study N=NR	Patients spending at least 1 day in a surgical ICU from Mar 1993 to Feb 2005	Surgical ICU Germany	RBC transfusion 5-8 units vs no RBC transfusion (during ICU stay)	ICU mortality	NR	NR	OR 1.161(0.598, 2.255) Adjusted for: admission variables and variables representing global organ dysfunction during ICU stay (maximum APACHE II score, maximum number of failing organs, duration of invasive ventilation, duration of catecholamine therapy, duration of renal replacement therapy).	RBC transfusion of 5-8 units is not associated with ICU mortality P=0.660

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Rüttinger 2007 Level III-2 Good	1 retrospective cohort study N=NR	Patients spending at least 1 day in a surgical ICU from Mar 1993 to Feb 2005	Surgical ICU Germany	RBC transfusion >8 units vs no RBC transfusion (during ICU stay)	ICU mortality	NR	NR	OR 5.372 (3.219, 8.965) Adjusted for: admission variables only.	RBC transfusion of >8 units is significantly associated with increased ICU mortality P<0.001
Rüttinger 2007 Level III-2 Good	1 retrospective cohort study N=NR	Patients spending at least 1 day in a surgical ICU from Mar 1993 to Feb 2005	Surgical ICU Germany	RBC transfusion >8 units vs no RBC transfusion (during ICU stay)	ICU mortality	NR	NR	OR 0.737 (0.358, 1.514) Adjusted for: admission variables and variables representing global organ dysfunction during ICU stay (maximum APACHE II score, maximum number of failing organs, duration of invasive ventilation, duration of catecholamine therapy, duration of renal replacement therapy).	RBC transfusion of 5-8 units is not associated with ICU mortality P=0.406
Rüttinger 2007 Level III-2 Good	1 retrospective cohort study N=NR	Patients spending at least 1 day in a surgical ICU from Mar 1993 to Feb 2005	Surgical ICU Germany	RBC transfusion 1-2 units vs no RBC transfusion (maximum on a single day)	ICU mortality	NR	NR	OR 1.281 (0.858, 1.913) Adjusted for: admission variables only.	RBC transfusion of 1-2 units is not associated with ICU mortality P=0.225
Rüttinger 2007 Level III-2 Good	1 retrospective cohort study N=NR	Patients spending at least 1 day in a surgical ICU from Mar 1993 to Feb 2005	Surgical ICU Germany	RBC transfusion 1-2 units vs no RBC transfusion (maximum on a single day)	ICU mortality	NR	NR	OR 0.780 (0.455, 1.337) Adjusted for: admission variables and variables representing global organ dysfunction during ICU stay (maximum APACHE II score, maximum number of failing organs, duration of invasive ventilation, duration of catecholamine therapy, duration of renal replacement therapy).	RBC transfusion of 1- units is not associated with ICU mortality P=0.366
Rüttinger 2007 Level III-2 Good	1 retrospective cohort study N=NR	Patients spending at least 1 day in a surgical ICU from Mar 1993 to Feb 2005	Surgical ICU Germany	RBC transfusion 3-4 units vs no RBC transfusion (maximum on a single day)	ICU mortality	NR	NR	OR 3.620 (2.191, 5.982) Adjusted for: admission variables only.	RBC transfusion of 3-4 units is significantly associated with increased ICU mortality P<0.001
Rüttinger 2007 Level III-2 Good	1 retrospective cohort study N=NR	Patients spending at least 1 day in a surgical ICU from Mar 1993 to Feb 2005	Surgical ICU Germany	RBC transfusion 3-4 units vs no RBC transfusion (maximum on a single day)	ICU mortality	NR	NR	OR 0.812 (0.358, 1.844) Adjusted for: admission variables and variables representing global organ dysfunction during ICU stay (maximum APACHE II score, maximum number of failing organs, duration of invasive ventilation, duration of catecholamine therapy, duration of renal replacement therapy).	RBC transfusion of 3-4 units is not associated with ICU mortality P=0.619

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Rüttinger 2007 Level III-2 Good	1 retrospective cohort study N=NR	Patients spending at least 1 day in a surgical ICU from Mar 1993 to Feb 2005	Surgical ICU Germany	RBC transfusion >4 units vs no RBC transfusion (maximum on a single day)	ICU mortality	NR	NR	OR 6.203 (3.511, 10.959)	RBC transfusion of >4 units is significantly associated with increased ICU mortality P<0.001
						Adjusted for: admission variables only.			
Rüttinger 2007 Level III-2 Good	1 retrospective cohort study N=NR	Patients spending at least 1 day in a surgical ICU from Mar 1993 to Feb 2005	Surgical ICU Germany	RBC transfusion >4 units vs no RBC transfusion (maximum on a single day)	ICU mortality	NR	NR	OR 0.812 (0.354, 1.863)	RBC transfusion of >4 units is not associated with ICU mortality P=0.623
						Adjusted for: admission variables and variables representing global organ dysfunction during ICU stay (maximum APACHE II score, maximum number of failing organs, duration of invasive ventilation, duration of catecholamine therapy, duration of renal replacement therapy).			
Salim 2008 Level III-2 Fair	1 retrospective cohort study N=1123	Patients with traumatic brain injury admitted to a surgical ICU between Jul 1998 and Dec 2005	ICU US	Blood transfusion vs no blood transfusion	Hospital mortality	NR	NR	OR 2.19 (1.27, 3.75)	*RBC transfusion is significantly associated with increased mortality* P=0.0044
						Adjusted for: anaemia, head AIS, age, gender, ISS, head injury, spinal column injury, systolic blood pressure on admission, and heart rate on admission.			
Vincent 2008 Level III-2 Good	1 prospective cohort study (SOAP) N=3147	Patients admitted to 198 general medical and/or surgical ICUs during a 2-week period in May 2002	ICU Western Europe	RBC transfusion vs no RBC transfusion	30-day mortality	NR	NR	OR 0.89 (0.76, 1.05)	*RBC transfusion is not associated with 30-day mortality* P=0.159
						Cox proportional hazards analysis adjusted for: age, gender, medical admission, cancer, haematologic cancer, COPD, HIV infection, cirrhosis, heart failure, diabetes, SAPS II, sepsis on admission, SOFA score on admission, country.			
Vincent 2008 Level III-2 Good	1 prospective cohort study (SOAP) N=1642	Patients admitted to 198 general medical and/or surgical ICUs during a 2-week period in May 2002	ICU Western Europe	RBC transfusion vs no RBC transfusion	30-day mortality	NR	NR	HR 0.73 (0.59, 0.90)	*RBC transfusion is significantly associated with decreased mortality* P=0.004
						Matched propensity analysis matched for: age, gender, medical admission, trauma, solid cancer, haematologic cancer, CPOD, cirrhosis, heart failure, diabetes, SAPS II, sepsis on admission, SOFA (respiratory, hepatic, haematologic, renal, CNS, cardiovascular):, mechanical ventilation, haemofiltration, haemodialysis.			
Vincent 2008 Level III-2 Good	1 prospective cohort study (SOAP) N=3147	Patients admitted to 198 general medical and/or surgical ICUs during a 2-week period in May 2002	ICU Western Europe	RBC transfusion vs no RBC transfusion (time-dependent variable)	30-day mortality	NR	NR	OR 0.69 (0.48, 1.01)	*RBC transfusion may be associated with decreased 30-day mortality* P=0.055
						Cox proportional hazards analysis adjusted for: age, gender, medical admission, cancer, haematologic cancer, COPD, HIV infection, cirrhosis, heart failure, diabetes, SAPS II, sepsis on admission, SOFA score on admission, country			

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Vincent 2008 Level III-2 Good	1 prospective cohort study (SOAP) N=1642	Patients admitted to 198 general medical and/or surgical ICUs during a 2-week period in May 2002	ICU Western Europe	RBC transfusion vs no RBC transfusion (time-dependent variable)	30-day mortality	NR	NR	HR 0.57 (0.36, 0.90)	*RBC transfusion is significantly associated with decreased mortality* P=0.016
						Matched propensity analysis matched for: age, gender, medical admission, trauma, solid cancer, haematologic cancer, CPOD, cirrhosis, heart failure, diabetes, SAPS II, sepsis on admission, SOFA (respiratory, hepatic, haematologic, renal, CNS, cardiovascular):, mechanical ventilation, haemofiltration, haemodialysis.			
Zilberberg 2008 Level III-2 Fair	1 retrospective cohort study N=4334	Critically ill patients admitted to hospital between Jan 2000 and Dec 2005 requiring prolonged acute mechanical ventilation	Hospital US	RBC transfusion vs no RBC transfusion	Hospital mortality	938/2912 (32.2)	342/1432 (23.9)	OR 1.21 (1.00, 1.48)	*Transfusion may be significantly associated with increased hospital mortality.* P=NR
						Adjusted for: age, sex, race, Charlson Comorbidity Index, baseline and nadir hemoglobin, hospital-acquired pneumonia, blood stream infection, gastrointestinal endoscopy, abdominal surgery, cardiac surgery (on and off bypass), orthopaedic surgery, hospital length of stay.			
Engoren 2009 Level III-2 Fair	1 retrospective cohort study N=2213	Patients admitted to the cardiac, burns, neurological and neurosurgical and the combined medical-surgical ICUs at a single medical centre between January 2001 and April 2002	ICU US	RBC transfusion vs no RBC transfusion	30-day mortality	101/404 (25)	265/1809 (15)	HR 1.11 (0.86, 1.42)	*RBC transfusion is not associated with 30-day mortality* P=0.42
						Cox proportional hazard model adjusted for: cardiac arrest in ICU, mechanical ventilation, pulmonary artery catheter, continuous venovenous haemofiltration, risk of death, endotracheal tube on arrival in ICU, age, score on Glasgow Coma Scale.			
Engoren 2009 Level III-2 Fair	1 retrospective cohort study N=556	Patients admitted to the cardiac, burns, neurological and neurosurgical and the combined medical-surgical ICUs at a single medical centre between January 2001 and April 2002	ICU US	RBC transfusion vs no RBC transfusion	30-day mortality	52/278 (19)	67/278 (24)	NR	*RBC transfusion is not associated with 30-day mortality* P=NR
						Matched analysis (binary logistic regression model) matched for: APACHE II score and propensity for transfusion (includes sex, type of ICU, intubation and reintubation, cardiac arrest, surgery, mechanical ventilation, tracheostomy, central venous catheter, pulmonary artery catheter, haemodialysis, continuous venovenous haemofiltration, readmission to ICU, admitting service, Glasgow Coma Score, age, urea nitrogen, creatinine, Hb, height, weight, days in ICU)			

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Engoren 2009 Level III-2 Fair	1 retrospective cohort study N=1847	Patients admitted to the cardiac, burns, neurological and neurosurgical and the combined medical-surgical ICUs at a single medical centre between January 2001 and April 2002	ICU US	RBC transfusion vs no RBC transfusion	30-180-day mortality	49/303	149/1544	HR 1.14 (0.83, 1.58) Cox proportional hazard model adjusted for: reintubation, tracheostomy, haemodialysis, APACHE score, and age.	*RBC transfusion is not associated with 30-180-day mortality* P=0.41
Engoren 2009 Level III-2 Fair	1 retrospective cohort study N=437	Patients admitted to the cardiac, burns, neurological and neurosurgical and the combined medical-surgical ICUs at a single medical centre between January 2001 and April 2002	ICU US	RBC transfusion vs no RBC transfusion	30-180-day mortality	31/226	36/211	NR Matched analysis (binary logistic regression model) matched for: APACHE II score and propensity for transfusion (includes sex, type of ICU, intubation and reintubation, cardiac arrest, surgery, mechanical ventilation, tracheostomy, central venous catheter, pulmonary artery catheter, haemodialysis, continuous venovenous haemofiltration, readmission to ICU, admitting service, Glasgow Coma Score, age, urea nitrogen, creatinine, Hb, height, weight, days in ICU)	*RBC transfusion may be associated with 30-180-day mortality* P=NR
Engoren 2009 Level III-2 Fair	1 retrospective cohort study N=1649	Patients admitted to the cardiac, burns, neurological and neurosurgical and the combined medical-surgical ICUs at a single medical centre between January 2001 and April 2002	ICU US	RBC transfusion vs no RBC transfusion	180+-day mortality	126/254	352/1395	HR 0.75 (0.57, 0.99) Cox proportional hazard model adjusted for: tracheostomy, central venous catheter, haemodialysis, height, age.	*RBC transfusion is significantly associated with decreased 180+ day mortality* P=0.04
Engoren 2009 Level III-2 Fair	1 retrospective cohort study N=370	Patients admitted to the cardiac, burns, neurological and neurosurgical and the combined medical-surgical ICUs at a single medical centre between January 2001 and April 2002	ICU US	RBC transfusion vs no RBC transfusion	180+-day mortality	63/195	74/175	HR 0.71 (0.50, 0.99) Matched analysis (binary logistic regression model) matched for: APACHE II score and propensity for transfusion (includes sex, type of ICU, intubation and reintubation, cardiac arrest, surgery, mechanical ventilation, tracheostomy, central venous catheter, pulmonary artery catheter, haemodialysis, continuous venovenous haemofiltration, readmission to ICU, admitting service, Glasgow Coma Score, age, urea nitrogen, creatinine, Hb, height, weight, days in ICU)	*RBC transfusion is significantly associated with decreased 180+ day mortality* P=0.046

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Rachoin 2009 Level III-2 Fair	1 retrospective cohort study N=2432	Patients aged ≥ 18 years surviving more than 24 hours in the ICU between Jul 2003 and Sep 2006	ICU US	RBC transfusion vs no RBC transfusion	Hospital mortality	81/609 (13.3)	158/1823 (8.7)	OR 1.3 (1.02, 1.5)	*RBC transfusion is significantly associated with <u>increased</u> mortality* P=0.03
						Adjusted for: nosocomial infections, prolonged ICU length of stay, prolonged hospital length of stay, number of transfusions, APACHE II score, age, gender, use of pressors, need for mechanical ventilation and race.			
Transfusion dose									
LEVEL III EVIDENCE									
Bochicchio 2008 Level III-2 Fair	1 prospective cohort study N=1172	Trauma patients admitted to a single centre for > 48 hours from 2002-2004	Hospital US	Per unit RBC transfused	Hospital mortality	NA		OR 1.05 (1.03, 1.07)	*RBC transfusion is significantly associated with a 5% <u>increased risk of mortality</u> in trauma patients per unit transfused* P<0.001
						Adjusted for age, sex, race, Injury Severity Score, admission Glasgow Coma Scale, units of FFP and units of platelets.			
Müller 2008 Level III-2 Fair	1 retrospective cohort study N=4214	Patients admitted to ICU immediately following surgery From Mar 1993 to Feb 2005	ICU Germany	Per unit RBC transfused	4-day mortality	NA		OR 1.10 (1.02, 1.17)	*RBC transfusion is significantly associated with a 10% <u>increased risk of mortality</u> per unit transfused* P=NR
						A backward selection algorithm was used to construct the final model. The final model was adjusted for: age, admission APACHE II score, admission day need for ventilation, admission SBP, admission PTT, body temperature at admission, vascular operation, interaction between RBC units transfused and APACHE II score.			
Spinella 2008 Level III-2 Fair	1 retrospective cohort study N=567	Trauma patients admitted to a combat support hospital in Iraq between Nov 2003 and Dec 2004 who received blood transfusion (RBC, FFP or fresh whole blood). Subgroup analysis presented here includes patients who did not receive massive transfusion.	Hospital Iraq	Per unit RBC transfused	In-hospital <u>survival</u>	NA		OR 0.77 (0.64, 0.92)	*RBC transfusion is significantly associated with a 23% <u>decreased risk of survival</u> per unit transfused* P=0.004
						Adjusted for confounding variables associated with survival on univariate analysis. Variables with P<0.02 on univariate analysis included in the model unless colinearity existed between variables. Adjusted for: FFP, ISS, GCS score ≤ 8, base deficit ≥ 4, admission temperature, SBP and Hct.			

ACS, acute coronary syndrome; AIS, abbreviated injury score; APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; GCS, Glasgow Coma Scale; Hb, haemoglobin; HIV, human immunodeficiency virus; HR, hazard ratio; ICU, intensive care unit; ISS, injury severity score; LOS, length of stay; MR, mortality ratio; NR, not reported; OR, odds ratio; RBC, red blood cell; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment; US, United States of America.

In summary, the four studies included in the Marik review all showed that RBC transfusion was associated with increased mortality, [16,18,24,32] while the study by Hébert et al (1997) which was not included in the Marik review showed that RBC transfusion of < 7 units was associated with decreased mortality compared with no RBC transfusion. [21]

The results of the six studies published since the Marik review which assessed transfusion versus no transfusion were mixed. Rüttinger et al (2007) note that when they performed the analysis adjusting only for admission characteristics, there was an increased risk of mortality associated with RBC transfusion. [28] However, when they added variables reflecting the number and extent of organ dysfunction into the analysis (i.e. maximum APACHE II score, maximum number of failing organs, duration of invasive ventilation, duration of catecholamine therapy, duration of renal replacement therapy), this association was lost. Of the three studies which showed a significant association between RBC transfusion and increased risk of mortality, two did not adjust for these variables,[29,35] while one adjusted for admission APACHE score.[27] The remaining two studies by Vincent et al (2008) and Engoren et al (2009) showed that RBC transfusion was associated with decreased mortality[33],and included adjustment for organ failure (via SOFA score) and APACHE II score plus various other organ dysfunction variables.[19] Thus, as suggested by Rüttinger, transfusion may be a surrogate marker for disease severity and not significantly associated with mortality. A summary of the study results by adjustment for Hb and organ failure is shown in Table 3.3.3.

Table 3.3.3 Transfusion vs no transfusion: summary of results by adjustment for Hb/organ failure

Study	Baseline variables		Hospitalisation variables		RBC transfusion vs no transfusion
	Hb	Organ dysfunction	Hb	Organ dysfunction	
No admission Hb/organ failure					
Dunne 2005[18]					↑ mortality
Admission Hb only					
Malone 2003[24]	Anaemia				↑ mortality
Salim 2008[29]	Anaemia				↑ mortality
Admission + hospitalisation Hb only					
Corwin 2004[16]	Hb		Nadir Hb		↑ mortality
Zilberberg 2008[35]	Hb		Nadir Hb		↑ mortality
Admission Hb/organ failure					
Vincent 2002[32]	Hb	SOFA/APACHE II			↑ mortality
Rüttinger 2007[28]	Hb	APACHE II			↑ mortality/no difference
Engoren 2009[19]	Hb	APACHE II			No difference
Rachoin 2009[27]		APACHE II[a]			↑ mortality
Admission organ failure only					
Vincent 2008[33]		SOFA			↓ mortality/no difference
Admission + hospitalisation Hb/organ failure					
Hébert 1997[21]		APACHE II	Pre-transfusion/minimum Hb		↓ mortality/no difference
Rüttinger 2007[28]	Hb	APACHE II		Global organ dysfunction	No difference

APACHE II, Acute Physiology and Chronic Health Evaluation II; Hb, haemoglobin; RBC, red blood cell; SOFA, Sequential Organ Failure Assessment

[a] Studies that included only baseline APACHE II adjustment are included under 'Admission Hb/organ failure' as the APACHE II score includes hematocrit measurement.

The effect of RBC transfusion on organ failure/dysfunction

One Level III-2 study provided data on the association between RBC transfusion as a continuous outcome and organ failure/dysfunction. Ciesla et al (2005) assessed the association between 12-hr RBC transfusion and multiple organ failure in 1344 trauma patients aged ≥ 15 years who were admitted to ICU within 24 hours of injury and who survived for at least 48 hours. [14] Two separate analyses were conducted: one in which RBC transfusion was dichotomised into two categories (> 6 units and ≤ 6 units) and one in which RBC transfusion units were considered as a continuous variable. Both analyses showed that a greater dose of RBC transfused was associated with an increased risk of multiple organ failure, with an OR of 3.40 for the dichotomous analysis and 1.07 for the continuous analysis.

Table 3.3.4 Question 1 (critical care/trauma): Results for RBC transfusion (dose) – multiple organ failure

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion > 6 units n/N (%)	**Transfusion ≤ 6** units n/N (%)	Risk estimate (95% CI)	*Significance* P-value
LEVEL III EVIDENCE									
Transfusion dose (dichotomous)									
Ciesla 2005 Level III-2 Fair	1 prospective cohort study N=1344	Patients admitted to the Rocky Mountain regional Trauma Center's surgical ICU between May 1992 and Dec 2003.	ICU US	12-hour RBC transfusion > 6 units vs ≤ 6 units	Multiple organ failure (defined as a total score of ≥ 4 on the Denver MOF scoring system occurring 48 hours after injury)	NR	NR	OR 3.40 (2.53, 4.58) Adjusted for: year, age, Injury Severity Score.	*12-hr transfusion of > 6 units is significantly associated with an increased risk of multiple organ failure* *P<0.001*
Transfusion dose (continuous)									
Ciesla 2005 Level III-2 Fair	1 prospective cohort study N=1344	Patients admitted to the Rocky Mountain regional Trauma Center's surgical ICU between May 1992 and Dec 2003.	ICU US	12-hour per unit RBC transfusion	Multiple organ failure (defined as a total score of ≥ 4 on the Denver MOF scoring system occurring 48 hours after injury)	NA Adjusted for: year, age, Injury Severity Score.		OR 1.07 (1.05, 1.09)	*12-hr RBC transfusion is significantly associated with a 7% increased risk of multiple organ failure per unit transfused* P<0.001

AIS, abbreviated injury score; ARDS, acute respiratory distress syndrome; CI, confidence interval; ICU, intensive care unit; ISS, injury severity score; MOF, multiple organ failure; PE, pulmonary embolism; RBC, red blood cell; SBP, systolic blood pressure; US, United States of America.

The effect of RBC transfusion on transfusion-related adverse events

Complications

One study assessed the association between blood transfusion versus no transfusion and transfusion-related adverse events as a group (complications; including ARDS, acute renal failure, acute respiratory failure, bacteraemia/fungaemia, multiple organ failure, pulmonary embolism, pneumonia and sepsis) in 1123 patients with traumatic brain injury admitted to a surgical ICU. As shown in Table 3.3.5. Salim et al (2008*)* found that blood transfusion was significantly associated with an increased risk of complications (OR 3.67; 95% CI 2.18, 6.17; P<0.001). [29] *While this outcome has been presented here, it will not be considered further as it relates to a very broad outcome that was assessed at only a single centre.*

Table 3.3.5 Question 1 (critical care/trauma): Results for RBC transfusion vs. no transfusion– transfusion-related adverse events (complications)

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
COMPLICATIONS									
LEVEL III EVIDENCE									
Salim 2008 Level III-2 Fair	1 retrospective cohort study N=1123	Patients with traumatic brain injury admitted to a surgical ICU between Jul 1998 and Dec 2005	ICU US	Blood transfusion vs no blood transfusion	Complications (ARDS, acute renal failure, acute respiratory failure, bacteraemia/fungaemia, MOF, PE, pneumonia and sepsis)	NR	NR	OR 3.67 (2.18, 6.17) Adjusted for: anaemia, anaemia and transfusion interaction, head AIS, age, gender, ISS, head injury, spinal column injury, SBP, heart rate.	*RBC transfusion is significantly associated with an increased risk of complications* P<0.0001

AIS, abbreviated injury score; ARDS, acute respiratory distress syndrome; CI, confidence interval; ICU, intensive care unit; ISS, injury severity score; MOF, multiple organ failure; PE, pulmonary embolism; RBC, red blood cell; SBP, systolic blood pressure; US, United States of America.

Pneumonia

One study, by Leal-Noval et al (2001) assessed the relationship between RBC transfusion dose (i.e. ≥ 4 units vs < 4 units) and pneumonia in 738 patients admitted to ICU following cardiac/vascular surgery. [23] After multivariate analysis they found that transfusion of ≥ 4 units of RBCs was significantly associated with an increased risk of pneumonia (OR 2.6; 95% CI 1.1, 5.8; p=0.016). *The results of this analysis will not be considered further as the comparison does not assess transfusion versus no transfusion.*

One study, by Shorr et al (2004), examined the association between RBC transfusion versus no transfusion and ventilator-associated pneumonia in up to 1518 critically ill patients without pneumonia at baseline admitted to one of 248 ICUs. [30] They found that RBC transfusion was significantly associated with an increased risk of ventilator-associated pneumonia and late-onset ventilator-associated pneumonia regardless of transfusion dose.

Table 3.3.6 Question 1 (critical care/trauma): Results for RBC transfusion vs. no transfusion – transfusion-related adverse events (pneumonia)

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
PNEUMONIA									
LEVEL III-2 EVIDENCE									
Leal-Noval 2001 Level III-2 *Fair*	1 prospective cohort study N=738	Patients admitted to ICU following cardiac/vascular surgery.	ICU Spain	RBC transfusion ≥ 4 units vs RBC transfusion < 4 units	Pneumonia	NR	NR	OR 2.6 (1.1, 5.8)	*RBC transfusion ≥ 4 units is significantly associated with an <u>increased</u> risk of pneumonia compared with RBC transfusion < 4 units* P=0.016
						Univariate analysis showed the following potential confounders: mechanical ventilation ≥ 48 hours, transfusion ≥ 4 U blood components, transfusion ≥ 4 U RBC, arterial hypotension, reintervention, transfusion ≥ 2 U plasma, reintubation and neurologic dysfunction. Final multivariate analysis adjusted for: Reintubation, mechanical ventilation ≥ 48 hours, neurologic dysfunction, arterial hypotension.			
Shorr 2004 Level III-2 *Fair*	1 prospective cohort study (subgroup of CRIT) N=1518	Critically ill patients admitted to one of 248 ICUs and with an anticipated stay of 48 hours without pneumonia at baseline	ICU US	RBC transfusion vs no RBC transfusion	Ventilator-associated pneumonia	181/801 (22.6)	130/717 (18.1)	OR 1.89 (1.33, 2.68)	*Transfusion is significantly associated with <u>increased</u> risk of VAP* P=0.0004
						Adjusted for: age; sex; major admitting diagnosis of trauma, respiratory failure, or neurologic; ICU type; APACHE II score at baseline; use of continuous sedation; H2 blockade at baseline; antibiotics at baseline; nutritional status; APACHE hemoglobin; transfusion; period of observation; and duration of mechanical ventilation.			
Shorr 2004 Level III-2 *Fair*	1 prospective cohort study (subgroup of CRIT) N=NR	Critically ill patients admitted to one of 248 ICUs and with an anticipated stay of 48 hours without pneumonia at baseline	ICU US	RBC transfusion <u>1-2 units</u> vs no RBC transfusion	Ventilator-associated pneumonia	NR	NR	OR 1.90 (1.28, 2.82)	*Transfusion of 1-2 units is significantly associated with <u>increased</u> risk of VAP compared with no transfusion.* P=0.0027
						Adjusted for: age; sex; major admitting diagnosis of trauma, respiratory failure, or neurologic; ICU type; APACHE II score at baseline; use of continuous sedation; H2 blockade at baseline; antibiotics at baseline; nutritional status; APACHE hemoglobin; transfusion; period of observation; and duration of mechanical ventilation.			
Shorr 2004 Level III-2 *Fair*	1 prospective cohort study (subgroup of CRIT) N=NR	Critically ill patients admitted to one of 248 ICUs and with an anticipated stay of 48 hours without pneumonia at baseline	ICU US	RBC transfusion <u>>2 units</u> vs no RBC transfusion	Ventilator-associated pneumonia	NR	NR	OR 1.87 (1.24, 2.82)	*Transfusion of > 2 units is significantly associated with <u>increased</u> risk of VAP compared with no transfusion* P=0.0014
						Adjusted for: age; sex; major admitting diagnosis of trauma, respiratory failure, or neurologic; ICU type; APACHE II score at baseline; use of continuous sedation; H2 blockade at baseline; antibiotics at baseline; nutritional status; APACHE hemoglobin; transfusion; period of observation; and duration of mechanical ventilation.			
Shorr 2004 Level III-2 *Fair*	1 prospective cohort study (subgroup of CRIT) N=1518	Critically ill patients admitted to one of 248 ICUs and with an anticipated stay of 48 hours without pneumonia at baseline	ICU US	RBC transfusion vs no RBC transfusion	<u>Late-onset</u> ventilator-associated pneumonia	NR	NR	OR 2.16 (1.27, 3.66)	*Transfusion is significantly associated with <u>increased</u> risk of late-onset VAP* P=0.0043
						Adjusted for: age; sex; major admitting diagnosis of trauma, respiratory failure, or neurologic; ICU type; APACHE II score at baseline; use of continuous sedation; H2 blockade at baseline; antibiotics at baseline; nutritional status; APACHE hemoglobin; transfusion; period of observation; and duration of mechanical ventilation.			

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Shorr 2004 Level III-2 *Fair*	1 prospective cohort study (subgroup of CRIT) N=NR	Critically ill patients admitted to one of 248 ICUs and with an anticipated stay of 48 hours without pneumonia at baseline	ICU US	RBC transfusion 1-2 units vs no RBC transfusion	Late-onset ventilator-associated pneumonia	NR	NR	OR 1.96 (1.07, 3.58)	*Transfusion of 1-2 units is significantly associated with increased risk of VAP compared with no transfusion* P=0.0295
						Adjusted for: age; sex; major admitting diagnosis of trauma, respiratory failure, or neurologic; ICU type; APACHE II score at baseline; use of continuous sedation; H2 blockade at baseline; antibiotics at baseline; nutritional status; APACHE hemoglobin; transfusion; period of observation; and duration of mechanical ventilation.			
Shorr 2004 Level III-2 *Fair*	1 prospective cohort study (subgroup of CRIT) N=NR	Critically ill patients admitted to one of 248 ICUs and with an anticipated stay of 48 hours without pneumonia at baseline	ICU US	RBC transfusion >2 units vs no RBC transfusion	Late-onset ventilator-associated pneumonia	NR	NR	OR 2.37 (1.31, 4.28)	*Transfusion of >2 units is significantly associated with increased risk of VAP compared with no transfusion* P=0.0041
						Adjusted for: age; sex; major admitting diagnosis of trauma, respiratory failure, or neurologic; ICU type; APACHE II score at baseline; use of continuous sedation; H2 blockade at baseline; antibiotics at baseline; nutritional status; APACHE hemoglobin; transfusion; period of observation; and duration of mechanical ventilation.			

APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; ICU, intensive care unit; NR, not reported; OR, odds ratio; RBC, red blood cell; U, units; US, United States of America; VAP, ventilator-associated pneumonia.

Infection

Seven studies examined the relationship between blood transfusion and infection as shown in Table 3.3.7. One was a systematic review,[10] and six were individual cohort studies.[12,13,15,17,26,27]

The study by Marik et al (2008) aimed to examine the association between RBC transfusion and mortality and morbidity in critically ill, hospitalised patients by performing a systematic review and meta-analysis of cohort studies. [10]While the authors did not formally assess the quality of the included studies, they did note that 'in general, multivariate analysis was performed correctly for age and illness severity' and included adjustment for factors such as age, APACHE II score, ISS, SOFA and others.

Nine of the 45 studies included in the Marik review assessed the association between RBC transfusion and infectious complications. While the authors note there was moderate heterogeneity in the analysis, seven of the nine studies showed a significant association between blood transfusion and infectious complications, while the remaining two showed no significant difference. The pooled OR for nine studies was 1.88 (95% CI 1.52, 2.24).

Of the nine studies included in the Marik review assessment of infectious complication, only three were considered relevant to the critical care/trauma population.[37,40,46] These were excluded for the following reasons: (i) < 500 subjects,[37,40] and (ii) errors in the results reported in the publication.[46]

Five studies included in the infectious complications analysis in the Marik review were from a surgical population, which was not initially considered for this review. However, one of these was conducted in a surgical ICU and so was included in the section on pneumonia.[23]

The remaining study listed in the Marik review analysis was by Taylor 2004. This appears to be an error as the two studies by Taylor in the Marik review were published in 2002 and 2006. The data provided for the Taylor 2004 study does not match any found in either of these two publications, so will not be considered further.

One study that was identified in the Marik review but was not included in the pooled analysis of infectious complications is included in this review. Claridge et al (2002) assessed the association between RBC transfusion within 48 hours and no RBC transfusion within 48 hours in patients admitted to a single trauma centre. [15] The results of their adjusted analysis showed that RBC transfusion was significantly associated with an increased risk of infection (OR 1.084; 95% CI 1.028, 1.142).

A single additional study published after the Marik review that compared RBC transfusion and no transfusion was included in this review. Rachoin et al (2009) assessed 2432 patients surviving > 24 hours in ICU to determine the relationship between RBC transfusion and nosocomial infection. [27] They found that RBC transfusion significantly increased the risk of nosocomial infection (OR 1.6; 95% CI 1.4, 1.8; P<0.001).

Four studies assessed the relationship between transfusion as a continuous outcome and infection.[12,13,17,26] Agarwal et al (1993) examined the relationship between total RBC units transfused and infection in up to 5366 patients with trauma. In the overall trauma population, total RBC units transfused overall and total RBC units transfused in the first 24 hours were significantly associated with infections (major and minor) and major infections. Similar results were seen in subgroups of patients with penetrating trauma and blunt

trauma. In the subgroup of patients with trauma resulting from a low fall, total RBC units transfused was significantly associated with any and major infection, while total RBC units transfused in the first 24 hours was not significantly associated with major infection. All significant p values were < 0.001.

Bochicchio et al (2008) analysed the association between units of RBC transfused and infection in 1172 trauma patients admitted to a single centre between 2002 and 2004. They found that RBC transfusion was significantly associated with a large increase in risk of infection (OR 2.8; 95% CI 1.96, 3.94; p<0.001).

The study by Duane et al (2008) assessed the relationship between dose of RBC transfusion and infection in 788 patients aged ≥ 16 years with isolated blunt head trauma.[17] RBC transfusion was significantly associated with a 26% increased risk of infection per unit transfused.

Palmieri et al (2006) examined the association between dose of RBC transfusion and infection in 620 patients admitted to a burns unit with acute burn injury covering ≥ 20% of the total body surface area. [26] The definition of infection included UTI. Pneumonia, blood stream infection, wound infection and venous central catheter infection as defined by the Centers for Disease Control. They found that blood transfusion was significantly associated with a 13% increased risk of infection per unit transfused.

Table 3.3.7 Question 1 (critical care/trauma): Results for RBC transfusion vs. no transfusion (or by dose) – transfusion-related adverse events (infection)

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance P-value
Transfusion versus no transfusion									
Level III evidence									
Marik 2008 Level III Fair	Systematic review of 9 cohort studies N~26,500	Critically ill (includes trauma, general surgery, cardiac surgery, orthopaedic surgery, ACS, ICU)	Hospital/ICU Various	Blood transfusion vs no blood transfusion	Infectious complications	NR	NR	OR 1.88 (1.52, 2.24)	Blood transfusion is significantly associated with <u>increased</u> risk of infectious complications P=NR
						Author notes that in general, multivariate analysis was performed correcting for age and illness severity (APACHE score, ISS, SOFA score etc).			
Level III-2 evidence									
Claridge 2002 Level III-2 Poor	1 prospective cohort study N=1593	Trauma patients admitted to trauma centre from Nov 1996 to Dec 1999	Hospital US	RBC transfusion within 48 hours vs no RBC transfusion within 48 hours	Infection	102/309 (33)	98/1284 (7.6)	OR 1.084 (1.028, 1.142)	RBC transfusion is significantly associated with <u>increased</u> risk of infection P=0.0028
						Adjusted for: sex, ICU admissions, GCS, APACHE II score, Ps, ISS, age, units of RBC transfused within 48 hours.			
Rachoin 2009 Level III-2 Fair	1 retrospective cohort study N=2432	Patients aged ≥ 18 years surviving more than 24 hours in the ICU between Jul 2003 and Sep 2006	ICU US	RBC transfusion vs no RBC transfusion	Nosocomial infection	64/609 (10.5)	90/1823 (4.9)	OR 1.6 (1.4, 1.8)	RBC transfusion is significantly associated with <u>increased</u> risk of nosocomial infection P<0.001
						Adjusted for: nosocomial infections, prolonged ICU length of stay, prolonged hospital length of stay, in-hospital mortality, number of transfusions, APACHE II score, age, gender, use of pressors, need for mechanical ventilation and race.			

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance P-value
Transfusion dose									
Level III-2 evidence									
Agarwal 1993 Level III-2 Fair	1 retrospective cohort study N=5366	Trauma patients admitted to one of eight hospitals (all trauma)	Hospital US	Total units transfused	Infection (major and minor)	NA		NR	Total RBC transfusion is a significant predictor of infection in all trauma patients P<0.001
						The following considered in the stepwise logistic regression analysis: age, Glasgow Coma Scale, respiration rate, shock, log of total amount of blood, sex and injury severity score Individual analyses included different final variables.			
Agarwal 1993 Level III-2 Fair	1 retrospective cohort study N=NR	Trauma patients admitted to one of eight hospitals (penetrating trauma)	Hospital US	Total units transfused	Infection (major and minor)	NA		NR	Total RBC transfusion is a significant predictor of infection in penetrating trauma patients P<0.001
						The following considered in the stepwise logistic regression analysis: age, Glasgow Coma Scale, respiration rate, shock, log of total amount of blood, sex and injury severity score Individual analyses included different final variables.			
Agarwal 1993 Level III-2 Fair	1 retrospective cohort study N=NR	Trauma patients admitted to one of eight hospitals (blunt trauma)	Hospital US	Total units transfused	Infection (major and minor)	NA		NR	Total RBC transfusion is a significant predictor of infection in blunt trauma patients P<0.001
						The following considered in the stepwise logistic regression analysis: age, Glasgow Coma Scale, respiration rate, shock, log of total amount of blood, sex and injury severity score Individual analyses included different final variables.			
Agarwal 1993 Level III-2 Fair	1 retrospective cohort study N=NR	Trauma patients admitted to one of eight hospitals (low fall trauma)	Hospital US	Total units transfused	Infection (major and minor)	NA		NR	*Total RBC transfusion is a significant predictor of infection in low fall trauma patients* P<0.001
						The following considered in the stepwise logistic regression analysis: age, Glasgow Coma Scale, respiration rate, shock, log of total amount of blood, sex and injury severity score Individual analyses included different final variables.			
Agarwal 1993 Level III-2 Fair	1 retrospective cohort study N=NR	Trauma patients admitted to one of eight hospitals (all trauma)	Hospital US	Total units transfused	Major infection	NA		NR	*Total RBC transfusion is a significant predictor of major infection in all trauma patients* P<0.001
						The following considered in the stepwise logistic regression analysis: age, Glasgow Coma Scale, respiration rate, shock, log of total amount of blood, sex and injury severity score Individual analyses included different final variables.			

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance P-value
Agarwal 1993 Level III-2 Fair	1 retrospective cohort study N=NR	Trauma patients admitted to one of eight hospitals (penetrating trauma)	Hospital US	Total units transfused	Major infection	NA		NR	*Total RBC transfusion is a significant predictor of major infection in penetrating trauma patients* P<0.001
						The following considered in the stepwise logistic regression analysis: age, Glasgow Coma Scale, respiration rate, shock, log of total amount of blood, sex and injury severity score Individual analyses included different final variables.			
Agarwal 1993 Level III-2 Fair	1 retrospective cohort study N=NR	Trauma patients admitted to one of eight hospitals (blunt trauma)	Hospital US	Total units transfused	Major infection	NA		NR	*Total RBC transfusion is a significant predictor of major infection in blunt trauma patients* P<0.001
						The following considered in the stepwise logistic regression analysis: age, Glasgow Coma Scale, respiration rate, shock, log of total amount of blood, sex and injury severity score Individual analyses included different final variables.			
Agarwal 1993 Level III-2 Fair	1 retrospective cohort study N=NR	Trauma patients admitted to one of eight hospitals (low fall trauma)	Hospital US	Total units transfused	Major infection	NA		NR	*Total RBC transfusion is a significant predictor of major infection in low fall trauma patients* P<0.001
						The following considered in the stepwise logistic regression analysis: age, Glasgow Coma Scale, respiration rate, shock, log of total amount of blood, sex and injury severity score Individual analyses included different final variables.			
Agarwal 1993 Level III-2 Fair	1 retrospective cohort study N=NR	Trauma patients admitted to one of eight hospitals (all trauma)	Hospital US	Total units transfused in first 24 hours	Major infection	NA		NR	*Total RBC transfusion in the first 24 transfusion is a significant predictor of major infection in all trauma patients* P<0.001
						The following considered in the stepwise logistic regression analysis: age, Glasgow Coma Scale, respiration rate, shock, log of total amount of blood, sex and injury severity score Individual analyses included different final variables.			
Agarwal 1993 Level III-2 Fair	1 retrospective cohort study N=NR	Trauma patients admitted to one of eight hospitals (penetrating trauma)	Hospital US	Total units transfused in first 24 hours	Major infection	NA		NR	*Total RBC transfusion in the first 24 hours transfusion is a significant predictor of major infection in penetrating trauma patients* P<0.001
						The following considered in the stepwise logistic regression analysis: age, Glasgow Coma Scale, respiration rate, shock, log of total amount of blood, sex and injury severity score Individual analyses included different final variables.			

Study Level of evidence Quality	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	Significance P-value
Agarwal 1993 Level III-2 Fair	1 retrospective cohort study N=NR	Trauma patients admitted to one of eight hospitals (blunt trauma)	Hospital US	Total units transfused in first 24 hours	Major infection	NA		NR	*Total RBC transfusion in the first 24 hours transfusion is a significant predictor of major infection in blunt trauma patients* P<0.001
						The following considered in the stepwise logistic regression analysis: age, Glasgow Coma Scale, respiration rate, shock, log of total amount of blood, sex and injury severity score Individual analyses included different final variables.			
Agarwal 1993 Level III-2 Fair	1 retrospective cohort study N=NR	Trauma patients admitted to one of eight hospitals (low fall trauma)	Hospital US	Total units transfused in first 24 hours	Major infection	NA		NR	*Total RBC transfusion in the first 24 hours transfusion is not a significant predictor of major infection in low fall trauma patients* P≥0.05
						The following considered in the stepwise logistic regression analysis: age, Glasgow Coma Scale, respiration rate, shock, log of total amount of blood, sex and injury severity score Individual analyses included different final variables.			
Bochicchio 2008 Level III-2 Fair	1 prospective cohort study N=1172	Trauma patients admitted to a single centre for > 48 hours from 2002-2004	Hospital US	Per unit RBC transfused	Infection	NA		OR 2.8 (1.96, 3.94)	*RBC transfusion is a significantly associated with a 280% increased risk of infection in trauma patients per unit transfused* P<0.001
						Adjusted for age, sex, race, Injury Severity Score, admission Glasgow Coma Scale, units of FFP and units of platelets.			
Duane 2008 Level III-2 Poor	1 retrospective cohort study N=788	Blunt head trauma patients aged ≥ 16 years with primarily isolated head trauma as defined by having a head abbreviated injury severity score (AIS) of ≥ 2 and all other AIS scores ≤ 1	Trauma centre US	Per unit RBC transfusion	Infection	NA		OR 1.26 (1.06, 1.50)	*RBC transfusion is significantly associated with a 26% increased risk of infection per unit transfused* *P=0.009*
						Adjusted for: age, neurosurgical procedure and minimum Hct.			
Palmieri 2006 Level III-2 Poor	1 retrospective cohort study N=620	Patients with acute burn injury ≥ 20% of TBSA admitted to a burn centre within 72 hours of injury from Jan 2002 to Dec 2002	Burn centre US	Per unit transfused	Infection (included UTI, pneumonia, BSI, wound infection and central venous catheter infection as defined by the CDC)	NA		OR 1.13	*Blood transfusion is significantly associated with increased risk of infection of 13% per unit transfused* P<0.001
						Infection analysis assumed to be adjusted for the same variables as survival analysis: age, sex, total body surface area, inhalation injury, number of infections, number of operations, admission to first operation, admission to first transfusion, admission to last transfusion, escharotomies, cardiac disease, ARDS, blood stream infection.			

ACS, acute coronary syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; GCS, Glasgow Coma Scale; ICU, intensive care unit; ISS, injury severity score; NR, not reported; OR, odds ratio; RBC, red blood cell; SOFA, Sequential Organ Failure Assessment; US, United States of America

ARDS and ALI

Four studies investigated the relationship between RBC transfusion versus no transfusion and ARDS. The review by Marik et al (2008) performed a pooled analysis of six Level III studies, five of which showed a significant association between RBC transfusion and ARDS. [10] The pooled analysis found that RBC transfusion was associated with a significant increase in the risk of ARDS (OR 2.5; 95% CI 1.66, 3.34).

Three studies that were included in the pooled analysis in the Marik review were excluded from this review. The reasons for exclusion were: (i) the study assessed < 500 subjects; [36,39] and (ii) there appeared to be errors in the results reported in the publication.[46] Three studies identified for this review were included in the Marik review. [20,22,34]

The study by Gong et al (2005) included 688 adult ICU patients with at least one risk factor for ARDS. [20] They found that RBC transfusion was associated with a significant increase in the risk of ARDS (OR 2.19; 95% CI 1.42, 3.36). The study by Khan et al (2007; *fair quality*) investigated the association between RBC transfusion and ARDS/ALI. [22] The study included 805 critically ill medical ICU patients and found that RBC transfusion was not significantly associated with an increased risk of ARDS/ALI, with an odds ratio of 1.39 (95% CI 0.79, 2.43).

The study by Zilberberg et al (2007) was a prospective cohort study of 4730 critically ill patients admitted to 248 ICUs in the United States. [34] Patients were required to have an expected ICU stay of at least 48 hours and no ARDS at baseline. The study compared patients who did or did not receive RBC transfusion and found that RBC transfusion was significantly associated with an increased risk of ARDS (OR 2.797; 95% CI 1.899, 4.120). The study also examined the effect of RBC dosage and found a significantly increased risk of ARDS with transfusion of either 1-2 RBC units ($p=0.0005$) and >2 RBC units ($p<0.0001$) compared to no transfusion.

Table 3.3.8 Question 1 (critical care/trauma): Results for RBC transfusion vs. no transfusion – transfusion-related adverse events (ARDS/ALI)

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
ARDS									
LEVEL III EVIDENCE									
Marik 2008 Level III Fair	Systematic review of 6 cohort studies N~11,000	Critically ill (includes trauma, general surgery, cardiac surgery, orthopaedic surgery, ACS, ICU)	Hospital/ICU Various	Blood transfusion vs no blood transfusion	ARDS	NR	NR	OR 2.5 (1.66, 3.34)	Blood transfusion is significantly associated with increased ARDS P=NR
						Author notes that in general, multivariate analysis was performed correcting for age and illness severity (APACHE score, ISS, SOFA score etc).			
LEVEL III-2 EVIDENCE									
Gong 2005 Level III-2 Fair	1 prospective cohort study N=688	Patients aged ≥ 18 years admitted to ICU between Sep 1999 and Aug 2002 with at least one risk factor for ARDS	ICU US	RBC transfusion vs no RBC transfusion	ARDS	134/362 (37.0)	87/326 (26.7)	OR 2.19 (1.42, 3.36)	*RBC transfusion is significantly associated with an increased risk of ARDS* P<0.001
						Adjusted for: age, APACHE III score, trauma, diabetes, direct pulmonary injury, transfer from another hospital, haematologic failure, heart rate >99 beats per minute, respiratory rate >33 breaths per minute, haematocrit >37.5%, arterial pH <7.33, albumin ≤2.3 g/dL.			
Khan 2007 Level III-2 Fair	1 retrospective cohort study N=805	Critically ill patients who had been admitted to the medical ICU between March 2004 and March 2005; without pulmonary oedema and in ICU ≥ 24 hours	ICU US	Transfusion (including RBC, FFP and platelet) vs no transfusion	ALI/ARDS	NR	97/543	OR 1.39 (0.79, 2.43)	*Transfusion of RBCs is not associated with an increased risk of ALI/ARDS* P=NR
						Adjusted for: haematocrit, APACHE III score, age, INR, sepsis, aspiration, pancreatitis, and pneumonia, and the propensity for transfusion with particular blood products.			
Zilberberg 2007 Level III-2 Fair	1 prospective cohort study (CRIT) N=4730	Critically ill patients admitted to one of 248 ICUs and with an anticipated stay of 48 hours without ARDS at baseline	ICU US	RBC transfusion vs no RBC transfusion	ARDS	164/2056 (8.0)	82/2674 (3.1)	OR 2.797 (1.899, 4.120)	*RBC transfusion is significantly associated with an increased risk of ARDS* P<0.0001
						Adjusted for: gender; admitting diagnoses of neurological disorder, gastrointestinal disease, and chronic obstructive pulmonary disease; medical history of diabetes and malignancy; baseline APACHE II score; antibiotics use at baseline; total serum bilirubin of more than 2.0 mg/dl; serum creatinine of more than 2.0 mg/dl; admitting diagnosis; age; ICU type; SOFA score; H2 antagonists at baseline; continuous sedation; nutritional status; Hb level; Albumin ≤2.3 g/dL.			

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Transfusion n/N (%)	No transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Zilberberg 2007 Level III-2 Fair	1 prospective cohort study (CRIT) N=4730	Critically ill patients admitted to one of 248 ICUs and with an anticipated stay of 48 hours without ARDS at baseline	ICU US	RBC transfusion 1-2 units vs no RBC transfusion	ARDS	NR	NR	OR 2.191 (1.409, 3.407)	*RBC transfusion of 1-2 units is significantly associated with an increased risk of ARDS compared with no transfusion* P=0.0005
						Adjusted for: gender; admitting diagnoses of neurological disorder, gastrointestinal disease, and chronic obstructive pulmonary disease; medical history of diabetes and malignancy; baseline APACHE II score; antibiotics use at baseline; total serum bilirubin of more than 2.0 mg/dl; serum creatinine of more than 2.0 mg/dl; admitting diagnosis; age; ICU type; SOFA score; H2 antagonists at baseline; continuous sedation; nutritional status; Hb level; Albumin ≤2.3 g/dL.			
Zilberberg 2007 Level III-2 Fair	1 prospective cohort study (CRIT) N=4730	Critically ill patients admitted to one of 248 ICUs and with an anticipated stay of 48 hours without ARDS at baseline	ICU US	RBC transfusion >2 units vs no RBC transfusion	ARDS	NR	NR	OR 3.784 (2.417, 5.924)	*RBC transfusion of >2 units is significantly associated with an increased risk of ARDS compared with no transfusion* P<0.0001
						Adjusted for: gender; admitting diagnoses of neurological disorder, gastrointestinal disease, and chronic obstructive pulmonary disease; medical history of diabetes and malignancy; baseline APACHE II score; antibiotics use at baseline; total serum bilirubin of more than 2.0 mg/dl; serum creatinine of more than 2.0 mg/dl; admitting diagnosis; age; ICU type; SOFA score; H2 antagonists at baseline; continuous sedation; nutritional status; Hb level; Albumin ≤2.3 g/dL.			

ACS, acute coronary syndrome; ALI, acute lung injury; APACHE II, Acute Physiology and Chronic Health Evaluation II; ARDS, acute respiratory distress syndrome; CI, confidence interval; dL, decilitre; FFP, fresh frozen plasma; g, grams; Hb, haemoglobin; ICU, intensive care unit; INR, international normalised ratio; ISS, injury severity score; mg, milligrams; NR, not reported; OR, odds ratio; RBC, red blood cell; SOFA, Sequential Organ Failure Assessment; US, United States of America.

3.1.4 Restrictive vs. liberal RBC transfusion

CRITICAL CARE/TRAUMA

Of the adverse outcomes specified for this question, all three are covered: mortality, organ failure/dysfunction and transfusion-related reactions.

Methods

There were seven studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified two Level I studies examining the effect of RBC transfusion in critical care/trauma patients.

Level II evidence

The literature search identified five Level II studies examining the effect of RBC transfusion in critical care/trauma patients.

Level III evidence

The literature search did not identify any Level III studies relevant to this population, intervention or comparator.

Level IV evidence

Level IV evidence was not searched for this question.

Results

Level I evidence

Two Level I studies were identified for this population. The review by Carless et al (2010) included a mixed population (including critical care, surgical and medical settings) and is discussed in the following section (mixed/general population). [65] In addition, the Carless review includes data from only two of the five Level II publications considered relevant to this review and identified for this section.

The second Level I study was by Kramer et al (2009) and examined the effect of anaemia and red blood cell transfusion in neurocritical care. [66] The characteristics of this study are summarised in Table 3.3.9.

Table 3.3.9 Question 1 (critical care/trauma): Characteristics and quality of Level I evidence

Author	Study type *Study quality*	Population	Outcomes
Level I evidence			
Kramer et al (2009)[66]	Systematic review of Level II and Level III studies *Poor*	Patients with traumatic brain injury or aneurysmal subarachnoid haemorrhage N=NR	Mortality Transfusion-related adverse events

NR, not reported

Kramer et al (2009) performed a systematic review to identify studies assessing the association between RBC transfusion (and anaemia) on mortality. [66] *As this study included both Level II and Level III studies, and it did not assess the quality of the included studies, or synthesise the results of these studies, it was not be formally included in this review. It was, however, used to help identify studies to be included in this review.*

Based on their review, Kramer et al (2009) note that 'there have been no randomized controlled trials that have adequately assessed optimal transfusion thresholds specifically among brain-injured patients' and that 'lower hemoglobin concentrations are consistently associated with worse physiologic parameters and clinical outcomes; however, this relationship may not be altered by more aggressive use of red blood cell transfusions'.

Level II evidence

Five publications reporting on two Level II studies were identified for this population. The two main publications were those by Hébert et al (1995) and Hébert et al (1999); the Hébert 1995 study reports the results of a pilot study in critical care patients while the Hébert 1999 study reports the results of a multicentre RCT. [67,68] The three remaining publications report on subgroup analyses of data from the Hébert 1999 study, with the subgroups being (i) patients with cardiovascular disease (Hébert et al 2001), (ii) trauma patients (McIntyre et al 2004) and patients with head injury (McIntyre et al 2006) [69-71] The main characteristics of these studies are summarised in Table 3.3.10.

Table 3.3.10 Question 1 (critical care/trauma): Characteristics and quality of Level II evidence

Author	Study type *Study quality*	Population	Outcomes
Level II evidence			
Hébert et al (1995)[67]	RCT Fair	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission N=69	Mortality
Hébert et al (1999)[68]	RCT Fair	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission N=838	Mortality Transfusion-related adverse events
Hébert et al (2001)[69]	RCT Fair	Normovolaemic critically ill patients with cardiovascular disease admitted to ICU with Hb < 9 g/dL within 72 hours of admission N=357	Mortality
McIntyre et al (2004)[70]	RCT Fair	Normovolaemic critically ill trauma patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission N=203	Mortality Transfusion-related adverse events
McIntyre et al (2006)[71]	RCT Fair	Normovolaemic critically ill patients with moderate to severe head injury admitted to ICU with Hb < 9 g/dL within 72 hours of admission N=67	Mortality

dL, decilitre; g, grams; Hb, haemoglobin; ICU, intensive care unit; RCT, randomised controlled trial.

The effect of restrictive vs. liberal RBC transfusion strategies on mortality

All five publications from the two included studies provide data on the effect of restrictive versus liberal RBC transfusion on mortality. In the small pilot study by Hébert et al (1995),

there was no significant difference in mortality between restrictive and liberal transfusion at three different follow-up periods: in-ICU, 30 days and 120 days. [67]

In the larger study by Hébert et al (1999), there was no statistically significant difference in mortality between restrictive and liberal transfusion at any of the follow-up time periods. [68] However, there was a trend in favour of restrictive transfusion for in-hospital mortality (RD -5.8%; 95% CI-11.7%, 0.3%; p=0.05) and the primary efficacy outcome, 30-day mortality (adjusted OR 0.72; 95% CI 0.50, 1.07; p=0.07). According to the sample size calculations reported in this publication, a sample size of 1620 patients would allow the authors to 'rule out an absolute difference in the 30-day mortality rate of 5.5 percent between groups'. The final sample size in this study was nearly half that, at 838, thus it is possible that the study was underpowered to detect a difference between treatment arms.

A number of subgroup analyses were carried out in the Hébert et al (1999) study (age, APACHE II score, cardiac disease, trauma, severe infections and septic shock) and in subsequent publications (cardiovascular disease, trauma and head injury).[69-71] The results in these subgroups were generally similar to those seen in the overall group with the following exceptions:

- Significantly lower mortality in the restrictive transfusion group (5.7%) compared with the liberal transfusion group (13.0%) in the subgroup aged < 55 years.[68]

- Significantly lower mortality in the restrictive transfusion group (8.7%) compared with the liberal transfusion group (16.1%) in the subgroup with an APACHE II score ≤20.[68]

The subgroup with ischaemic heart disease examined in the Hébert et al (2001) publication is the only one which consistently had a numerical (although not statistically significant) increased risk of mortality, ranging from 2.1% to 6.3% in the restrictive transfusion group.[69]

Table 3.3.11 Question 1 (critical care/trauma): Results for restrictive vs. liberal RBC transfusion – Mortality

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%)	Liberal transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
LEVEL II EVIDENCE									
Overall critical care population									
Hébert 1995 Level II Fair	1 RCT N=69	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	ICU mortality	5/33 (15)	7/36 (19)	RD -0.04 (-0.22, 0.14)[a]	*No difference* P=0.64
Hébert 1999 Level II Fair	1 RCT N=838	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	ICU mortality	56/418 (13.4)	68/420 (16.2)	RD -0.023 (-0.076, 0.020)[c]	*No difference* *P=0.29*
Hébert 1999 Level II Fair	1 RCT N=838	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	Hospital mortality	93/418 (22.2)	118/420 (28.1)	RD -0.058 (-0.117, 0.003)[c]	*No <u>significant</u> difference* *P=0.05*
Hébert 1995 Level II Fair	1 RCT N=69	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	30-day mortality	8/33 (24)	9/36 (25)	RD -0.01 (-19, 21) [a]	*No difference* *P=0.94*
Hébert 1999 Level II Fair	1 RCT N=838	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	30-day mortality	78/418 (18.7)	98/420 (23.3)	OR 0.72 (0.50, 1.07) (adjusted) RD -0.047 (-0.102, 0.0084)[a]	*No <u>significant</u> difference* *P=0.07* *No difference* *P=0.10*
Hébert 1999 Level II Fair	1 RCT N=838	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	60-day mortality	95/418 (22.7)	111/420 (26.5)	RD -0.037 (-0.095, 0.021)[c]	*No difference* *P=0.23*

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%)	Liberal transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Hébert 1995 Level II Fair	1 RCT N=46[e]	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	120-day mortality	13/24 (54)	11/22 (50)	RD 0.04 (-0.25, 0.33)[a]	*No difference* *P=0.78*
Hébert 1995 Level II Fair	1 RCT N=69[f]	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	120-day mortality	21/33 (64)	25/36 (69)	RD -0.06 (-0.28, 0.16)[a]	*No difference* *P=0.61*
Critical care population by age									
Hébert 1999 Level II Fair	1 RCT N=504	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup aged ≥ 55 years	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	30-day mortality	NR	NR	NR	*No difference* *P>0.36*
Hébert 1999 Level II Fair	1 RCT N=334	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup aged < 55 years	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	30-day mortality	5.7%	13.0%	RD -0.073 (-0.135, -0.011)[a]	*Favours restrictive transfusion* *P=0.03*
Critical care population by APACHE II score									
Hébert 1999 Level II Fair	1 RCT N=414	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with APACHE II score > 20	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	30-day mortality	NR	NR	NR	*No difference* *P>0.36*
Hébert 1999 Level II Fair	1 RCT N=424	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with APACHE II score ≤ 20	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	30-day mortality	8.7%	16.1%	RD -0.074 (-0.136, -0.01)[a]	*Favours restrictive transfusion* *P=0.02*

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%)	Liberal transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Critical care population with cardiovascular disease									
Hébert 2001 Level II Fair	1 RCT N=357	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with cardiovascular disease	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	ICU mortality	31/160 (19)	32/197 (16)	RD 0.031 (-0.048, 0.111)	*No difference* *P=0.49*
Hébert 2001 Level II Fair	1 RCT N=257	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with ischaemic heart disease	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	ICU mortality	26/111 (23)	25/147 (17)	RD 0.063 (-0.035, 0.162)	*No difference* *P=0.27*
Hébert 2001 Level II Fair	1 RCT N=357	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with cardiovascular disease	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	Hospital mortality	43/160 (27)	56/197 (28)	RD -0.019 (-0.109, 0.069)	*No difference* *P=0.81*
Hébert 2001 Level II Fair	1 RCT N=257	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with ischaemic heart disease	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	Hospital mortality	32/111 (29)	39/147 (27)	RD 0.021 (-0.089, 0.132)	*No difference* *P=0.78*
Hébert 2001 Level II Fair	1 RCT N=357	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with cardiovascular disease	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	30-day mortality	36/160 (23)	45/197 (23)	RD -0.003 (-0.091, 0.084)	*No difference* *P=1.0*
Hébert 2001 Level II Fair	1 RCT N=257	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with ischaemic heart disease	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	30-day mortality	29/111 (26)	31/147 (21)	RD 0.049 (-0.056, 0.153)	*No difference* *P=0.38*

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%)	Liberal transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Hébert 2001 Level II Fair	1 RCT N=357	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with cardiovascular disease	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	60-day mortality	42/160 (26)	53/197 (27)	RD -0.008 (-0.10, 0.084)	*No difference* *P=0.9*
Hébert 2001 Level II Fair	1 RCT N=257	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with ischaemic heart disease	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	60-day mortality	32/111 (29)	36/147 (25)	RD 0.04 (-0.069, 0.149)	*No difference* *P=0.48*
Critical care population with trauma									
McIntyre 2004 Level II Fair	1 RCT N=203	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; trauma subgroup	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	ICU mortality	8/100 (8)	6/103 (6)	RD 0.02 (-0.05, 0.09)[c]	*No difference* *P=0.59*
McIntyre 2004 Level II Fair	1 RCT N=203	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; trauma subgroup	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	Hospital mortality	10/100 (10)	10/103 (10)	RD 0.00 (-0.08, 0.08)[c]	*No difference* *P=1.00*
McIntyre 2004 Level II Fair	1 RCT N=203	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; trauma subgroup	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	30-day mortality Adjustment for age, admission APACHE II score and pulmonary artery catheter use	10/100 (10)	9/103 (9)	RD 0.013 (-0.068, 0.093) Adjusted OR 0.72 (0.24, 2.19)	*No difference* *P=0.81*
McIntyre 2004 Level II Fair	1 RCT N=203	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; trauma subgroup	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	60-day mortality	10/100 (10)	10/103 (10)	RD 0.00 (-0.08, 0.08)	*No difference* *P=1.00*

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%)	Liberal transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Critical care population with closed head injury									
McIntyre 2006 Level II Fair	1 RCT N=67	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; closed head injury	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	ICU mortality	3/29 (10)	3/38 (8)	RD 0.02 (-0.12, 0.16)[c]	*No difference* *P=0.73*
McIntyre 2006 Level II Fair	1 RCT N=67	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; closed head injury	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	Hospital mortality	5/29 (17)	5/38 (13)	RD 0.04 (-0.13, 0.22)[a]	*No difference* *P=0.64*
McIntyre 2006 Level II Fair	1 RCT N=67	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; closed head injury	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	30-day mortality Adjustment for age, admission APACHE II score and pulmonary artery catheter use	5/29 (17)	5/38 (13)	RD 0.041 (-0.134, 0.215) Adjusted OR 0.76 (0.12, 4.93)	*No difference* *P=0.64*
McIntyre 2006 Level II Fair	1 RCT N=67	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; closed head injury	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	60-day mortality	5/29 (17)	5/38 (13)	RD 0.04 (-0.13, 0.22)[c]	*No difference* *P=0.64*
Critical care population with severe infection or septic shock									
Hébert 1999 Level II Fair	1 RCT N=218	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with severe infection or septic shock	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	30-day mortality	26/114 (22.8)	31/104 (29.7)	NR	*No difference* *P=0.36*

APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; ICU, intensive care unit; NR, not reported; OR, odds ratio; RCT, randomised controlled trial; RD, risk difference.

[a] Analyses in publication show liberal vs restrictive rather than restrictive vs liberal. Recalculated post hoc to show restrictive vs liberal.

[b] Calculated post-hoc assuming all missing patients died.

[c] Post-hoc analysis for this review.

[d] Incorrect number included in publication. Correct number taken from McIntyre 2004

[e] Due to unavailability for follow up, included only 46 of the original 69 patients.

[f] Post-hoc analysis assuming missing patients died.

The effect of restrictive vs. liberal RBC transfusion strategies on organ failure/dysfunction

All five publications from the two included studies provide data on the effect of restrictive versus liberal RBC transfusion on organ failure/dysfunction. In the small pilot study by Hébert et al (1995), there was no significant difference in the number of ICU patients with ≥ 3 organ failures or the mean MOD score between treatment groups (P=0.38 and 0.44, respectively).[67]

In the Hebert et al (1995) study, a numerically greater proportion of patients in the restrictive transfusion group (27%) had ≥ 3 organs fail compared with the liberal group (17%); and it is possible that with a bigger sample, this may have reached statistical significance. This contrasts with the similar but larger Hebert et al (1999) study in which similar proportions of patients in each arm had ≥ 3 organ failures (17.5% and 19.3%, respectively).[68]

In the Hebert 1999 study, there was a significantly lower endpoint and mean change from baseline in MOD score in the restrictive transfusion group compared with the liberal transfusion group (P=0.03 and 0.04, respectively).[68]Subgroup analyses generally showed no difference between treatment groups with regards to endpoint MOD score or change from baseline in MOD score with the exception of the following subgroups: those aged < 55 years (P=0.03), those with an APACHE II score ≤ 20 (P=0.01) and those with cardiovascular disease (P=0.08).

Table 3.3.12 Question 1 (critical care/trauma): Results for restrictive vs. liberal RBC transfusion – organ failure/dysfunction

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%) or Mean ± SD	Liberal transfusion n/N (%) or Mean ± SD	Risk estimate (95% CI)	*Significance* P-value
LEVEL II EVIDENCE									
Overall critical care population									
Hébert 1995 Level II Fair	1 RCT N=69	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	≥ 3 organ failures	9/33 (27.3)	6/36 (16.7)	RD 0.106 (-0.09, 0.29)	*No difference* *P=0.38*
Hébert 1995 Level II Fair	1 RCT N=69	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	MOD score	9.3±3.6 (N=33)	10.0±3.8 (N=36)	MD -0.70 (- 2.4, 1.0) [a]	*No difference* *P=0.44*
Hébert 1999 Level II Fair	1 RCT N=838	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	≥ 3 organ failures	73/418 (17.5)	81/420 (19.3)	RD -0.02 (-0.07, 0.03)[a]	*No difference* *P=0.53*
Hébert 1999 Level II Fair	1 RCT N=838	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	MOD score	10.7±7.5 (N=418)	11.8±7.7 (N=420)	MD -1.1 (- 2.2, -0.8) [a]	*Favours restrictive transfusion* *P=0.03*
Hébert 1999 Level II Fair	1 RCT N=838	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	Change from baseline in MOD score	3.2±7.0 (N=418)	4.2±7.4 (N=420)	MD -1.0 (-2.0, -0.1) [a]	*Favours restrictive transfusion* *P=0.04*
Critical care population by age									
Hébert 1999 Level II Fair	1 RCT N=504	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup aged ≥ 55 years	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	MOD score (adjusted for those who died)	NR	NR	NR	*No difference* *P>0.30*

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%) or Mean ± SD	Liberal transfusion n/N (%) or Mean ± SD	Risk estimate (95% CI)	*Significance* P-value
Hébert 1999 Level II Fair	1 RCT N=334	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup aged < 55 years	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	MOD score (adjusted for those who died)	8.8 ± 5.7	10.3 ± 6.6	NR	*Favours restrictive transfusion* *P=0.03*
Critical care population by APACHE II score									
Hébert 1999 Level II Fair	1 RCT N=414	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with APACHE II score > 20	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	MOD score (adjusted for those who died)	NR	NR	NR	*No difference* *P>0.30*
Hébert 1999 Level II Fair	1 RCT N=424	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with APACHE II score ≤ 20	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	MOD score (adjusted for those who died)	8.3 ± 6.2	10.0 ± 7.2	NR	*Favours restrictive transfusion* *P=0.01*
Critical care population with cardiovascular disease									
Hébert 1999 Level II Fair	1 RCT N=326	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with primary or secondary diagnosis of cardiac disease	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	MOD score (adjusted for those who died)	NR	NR	NR	*No difference* *P>0.30*
Hébert 2001 Level II Fair	1 RCT N=357	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with cardiovascular disease	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	MOD score	11.1±7.6 (N=160)[b]	11.9±7.9 (N=197)[b]	MD -0.7 (-2.4, 0.8) [a, b]	*No difference* *P=0.39*
Hébert 2001 Level II Fair	1 RCT N=357	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with cardiovascular disease	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	Change from baseline in MOD score	2.7±6.9 (N=160)[b]	4.0±7.3 (N=197)[b]	MD -1.3 (-2.8, 0.2) [a, b]	*No significant difference* *P=0.081*

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%) or Mean ± SD	Liberal transfusion n/N (%) or Mean ± SD	Risk estimate (95% CI)	*Significance* P-value
Hébert 2001 Level II Fair	1 RCT N=258	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with ischaemic heart disease	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	MOD score	11.8±8.2 (N=111)[b]	11.6±7.5 (N=147)[b]	MD 0.3 (-1.7, 2.2) [a, b]	*No difference* *P=0.8*
Hébert 2001 Level II Fair	1 RCT N=258	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with ischaemic heart disease	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	Change from baseline in MOD score	3.0±7.1 (N=111)[b]	3.4±6.7 (N=147)[b]	MD -0.4 (-2.2, 1.3)[a, b]	*No difference* *P=0.61*
Critical care population with trauma									
Hébert 1999 Level II Fair	1 RCT N=200	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with trauma	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	MOD score (adjusted for those who died)	NR	NR	NR	*No difference* *P>0.30*
McIntyre 2004 Level II Fair	1 RCT N=203	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; trauma subgroup	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	MOD score	9.2±6.3 (N=100)[b]	9.0±6.0 (N=103)[b]	NR	*No difference* *P=0.81*
McIntyre 2004 Level II Fair	1 RCT N=203	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; trauma subgroup	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	Change from baseline in MOD score	1.2±6.1 (N=100)[b]	1.9±5.7 (N=103)[b]	NR	*No difference* *P=0.44*
Critical care population with closed head injury									
McIntyre 2006 Level II Fair	1 RCT N=67	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; closed head injury	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	MOD score	12.1 ± 6.4 (N=29)[b]	10.6 ± 6.3 (N=38)[b]	NR	*No difference* *P=0.35*
McIntyre 2006 Level II Fair	1 RCT N=67	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; closed head injury	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	Change from baseline in MOD score	4.5 ± 6.2 (N=29)[b]	3.4 ± 6.2 (N=38)[b]	NR	*No difference* *P=0.49*

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%) or Mean ± SD	Liberal transfusion n/N (%) or Mean ± SD	Risk estimate (95% CI)	*Significance* P-value
Critical care population with severe infection or septic shock									
Hébert 1999 Level II Fair	1 RCT N=218	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; subgroup with severe infection or septic shock	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	MOD score (adjusted for those who died)	NR	NR	NR	*No difference* *P>0.30*

APACHE II, Acute Physiology and Chronic Health Evaluation II; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; ICU, intensive care unit; MD, mean difference; MOD, multiple organ dysfunction; NR, not reported; RCT, randomised controlled trial; RD, risk difference; SD, standard deviation.

[a] Analyses in publication show liberal vs restrictive rather than restrictive vs liberal. Reversed post hoc to show restrictive vs liberal.

[b] Analysis assumes all non-survivors had all organs fail at death.

The effect of restrictive vs. liberal RBC transfusion strategies on transfusion-related adverse events

Three publications from one trial provided information on the rate of transfusion-related adverse events.[68,70,71] Complications that were considered for inclusion in this section were any pulmonary or infectious adverse events.

Hebert et al (1999)assessed the effect of restrictive versus liberal transfusion strategies on complications that occurred during the ICU stay.[68]The study found no statistically significant difference in most pulmonary or infectious adverse events between the two transfusion strategies, with the exception of ARDS, which showed a trend towards a lesser rate in those in the restrictive transfusion strategy group (RD -3.8%; 95% CI -7.8%, 0.2%; P=0.06). There was also a numerically greater rate of septic shock in the restrictive transfusion group compared with the liberal transfusion group (RD2.9%; 95% CI -0.8%, 6.7%), although this was not statistically significant. This study did not recruit enough subjects to meet the threshold determined in its power calculation. As such, it is possible that this study is underpowered to detect differences in AEs.

The McIntyre et al (2004) and McIntyre et al (2006) studies assessed the risk of infection in trauma and closed head injury subgroups, respectively, from the Hebert 1999 study. [70,71] Both studies showed no significant difference in the proportion of patients who developed an infection (p=0.28 and p=0.78, respectively), which was similar to the result seen in the overall critical care population examined in the Hebert 1999 study (RD -1.9%; 95% CI-6.1%, 2.4%).

Table 3.3.13 Question 1 (critical care/trauma) Results for restrictive vs. liberal RBC transfusion – transfusion-related adverse events

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%)	Liberal transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
LEVEL II EVIDENCE									
Pulmonary adverse events									
Hébert 1999 Level II Fair	1 RCT N=838	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	All pulmonary adverse events (includes pneumonia and ARDS)	106/418 (25.4)	122/420 (29.0)	RD -0.037 (-0.097, 0.023)[a]	*No difference* *P=0.22*
Hébert 1999 Level II Fair	1 RCT N=838	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	ARDS	32/418 (7.7)	48/420 (11.4)	RD -0.038 (-0.078, 0.002)[a]	*No significant difference* *P=0.06*
Infectious adverse events									
Hébert 1999 Level II Fair	1 RCT N=838	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	All infectious adverse events	42/418 (10.0)	50/420 (11.9)	RD -0.019 (-0.061, 0.024)[a]	*No difference* *P=0.38*
McIntyre 2004 Level II Fair	1 RCT N=203	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; trauma	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	Infection	8/100 (8.0)	13/103 (12.6)	NR	*No difference* *0.28*
McIntyre 2006 Level II Fair	1 RCT N=67	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission; closed head injury	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	Infection	2/29 (6.9)	2/38 (5.3)	NR	*No difference* *P=0.78*
Hébert 1999 Level II Fair	1 RCT N=838	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	Pneumonia	87/418 (20.8)	86/420 (20.5)	RD 0.003 (-0.051, 0.058)[a]	*No difference* *P=0.92*

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%)	Liberal transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Hébert 1999 Level II Fair	1 RCT N=838	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	Bacteraemia	30/418 (7.2)	40/420 (9.5)	RD -0.023 (-0.061, 0.014)[a]	*No difference* *P=0.22*
Hébert 1999 Level II Fair	1 RCT N=838	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	Catheter-related sepsis	21/418 (5.0)	17/420 (4.0)	RD 0.01 (-0.018, 0.038)[a]	*No difference* *P=0.50*
Hébert 1999 Level II Fair	1 RCT N=838	Normovolaemic critically ill patients admitted to ICU with Hb < 9 g/dL within 72 hours of admission	ICU Canada	Restrictive transfusion (Hb maintained between 7-9 g/dL) vs liberal (Hb maintained between 10-12 g/dL)	Septic shock	41/418 (9.8)	29/420 (6.9)	RD 0.029 (-0.008, 0.067)[a]	*No difference* *P=0.13*

ARDS, acute respiratory distress syndrome; CI, confidence interval; dL, decilitre; g, grams; Hb, haemoglobin; ICU, intensive care unit; NR, not reported; RCT, randomised controlled trial; RD, risk difference.

[a] Analyses in publication show liberal vs restrictive rather than restrictive vs liberal. Recalculated post hoc to show restrictive vs liberal.

MIXED/GENERAL POPULATION

While the aim of this review is to assess the effect of allogeneic RBC transfusion on adverse outcomes specifically in *critical care* patients, there is a large amount of evidence available in other populations, in particular in the surgical setting. Thus, studies which assessed the effect of allogeneic RBC transfusion across a wide population (including critical care) were considered eligible for assessment. Of the adverse outcomes specified for this question, three are covered for this wide population: mortality, organ failure/dysfunction and transfusion-related adverse events.

Methods

There was one study identified for this population from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified one systematic review of Level II evidence (RCT) examining the effect of RBC transfusion in a mixed population from critical care, trauma, surgical and medical settings.

Level II evidence

The literature search did not identify any Level II studies relevant to this population, intervention and comparator.

Level III evidence

The literature search did not identify any Level III studies relevant to this population, intervention and comparator.

Level IV evidence

Level IV evidence was not searched for this question.

Results

Level I evidence

One Level I study was identified which assessed the efficacy and safety of restrictive versus liberal RBC transfusion in a mixed population which included medical, critical care and surgical patients. This study by Carless et al (2010)was a Cochrane review with the literature updated to August 2009.[65] The review assessed data from 17 RCTs including a total of 3746 patients. Six of the included studies were in a critical care/trauma setting, one of which was in the paediatric critical care setting; the remaining studies were in surgical patients (eight studies) and in the medical setting (3 studies). Of the six critical care/trauma studies included in Carless et al (2010), only two were considered eligible for inclusion in this review.[67,68] The remaining four studies were excluded for including the wrong outcomes (Fortune et al 1987), for being in the wrong population (paediatric; Lacroix et al 2007),for being published prior to 1985 (Topley 1956),and for including < 100 subjects (Zygun et al 2009).[72-75] *Thus, while the Carless review provides a comprehensive assessment of the efficacy and safety of restrictive versus liberal RBC transfusion in a broad population, its generalisability to the critical care/trauma population needs to be considered. Therefore, this data is provided for interest and will not be considered further.*

Table 3.3.14 Question 1 (Mixed): Characteristics and quality of Level I evidence

Level I evidence			
Author	Study type *Study quality*	Population	Outcomes
Carless et al (2010)[65]	Systematic review of 17 RCTs *Good*	Any (2 GI haemorrhage, 1 leukaemia, 8 surgery, 5 critical care/trauma and 1 paediatric critical care)	Mortality Organ failure/dysfunction Transfusion-related adverse events

GI, gastrointestinal; RCT, randomised controlled trial.

The effect of restrictive vs. liberal RBC transfusion strategies on mortality

One Level I study assessed the effect of a restrictive versus liberal RBC transfusion strategy on mortality in a mixed population, as shown in Table 3.3.15. *Post-hoc analyses conducted for this review including only the critical care/trauma studies are presented also.* The authors note that there was a variation in the thresholds used in the individual studies for the restrictive and liberal transfusion strategies. For restrictive transfusion, the majority of trials used an Hb threshold of between 7.0 g/dL and 9.0 g/dL, while two studies specified Hct levels of 25% or 30%. The definition of liberal transfusion varied to a greater degree and included transfusion in all in some trials, transfusion sufficient to maintain a Hb of ≥ 9, 10 or 12 g/dL in most studies, and Hct 32% in two trials.

The study by Carless et al (2010) showed no difference between the two strategies for all mortality outcomes with the exception of in-hospital mortality, where restrictive transfusion resulted in 22% less mortality than liberal transfusion (RR 0.78; 95% CI 0.62, 0.98). The results for 30-day mortality also suggested a possible reduction in mortality for restrictive transfusion, although this failed to reach statistical significance. Based on their review, which includes an assessment of harms as well, the authors' conclude that 'the existing evidence supports the use of restrictive transfusion triggers in patients who are free of serious cardiac disease'.

When the analysis was restricted only to critical care/trauma studies, the results were similar, although the analysis of hospital mortality was not statistically significant, possibly due to a lack of statistical power (RR 0.79; 95% CI 0.63, 1.00).

Table 3.3.15 Question 1 (general): Results for restrictive vs. liberal RBC transfusion – Mortality

Study Level of evidence *Quality*[a]	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%)	Liberal transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value Heterogeneity[b] P value
LEVEL I EVIDENCE									
Any population (includes critical care, trauma, surgical, GI haemorrhage and leukaemia)									
Carless 2010 Level I *Good*	2 RCTs N=821	Any (critical care, trauma, surgical, GI haemorrhage and leukaemia)	*Hospital* Various	Restrictive transfusion trigger vs liberal transfusion trigger	< 14-day mortality	1/408 (0.2)	3/413 (0.7)	RR 0.44 (0.006, 2.96)	No difference P=0.40 *No heterogeneity* *(Phet=0.84; I^2=0%)*
Carless 2010 Level I *Good*	9 RCTs N=2461	Any (critical care, trauma, surgical, GI haemorrhage and leukaemia)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	30-day mortality	113/1226 (9.2)	134/1235 (10.9)	RR 0.83 (0.66, 1.05)	No difference P=0.12 *No heterogeneity* *(Phet=0.65; I^2=0%)*
Carless 2010 Level I *Good*	2 RCTs N=922	Any (critical care, trauma, surgical, GI haemorrhage and leukaemia)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	60-day mortality	100/460 (21.7)	113/462 (24.5)	RR 1.09 (0.46, 2.60)	No difference P=0.85 *Moderate heterogeneity* *(Phet=0.19; I^2=42%)*
Carless 2010 Level I/II *Poor*	1 RCT N=69	Any (critical care, trauma, surgical, GI haemorrhage and leukaemia)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	120-day mortality	13/33 (39.4)	11/36 (30.6)	RR 1.29 (0.67, 2.47)	No difference P=NR (Phet=NA)
Carless 2010 Level I *Good*	4 RCTs N=1409	Any (critical care, trauma, surgical, GI haemorrhage and leukaemia)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	Hospital mortality	96/701 (13.7)	126/708 (17.8)	RR 0.78 (0.62, 0.98)	Favours restrictive transfusion *No heterogeneity* *P=0.031 (Phet=0.53; I^2=0%)*
Carless 2010 Level I *Good*	3 RCTs N=736	Any (critical care, trauma, surgical, GI haemorrhage and leukaemia)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	ICU mortality	19/373 (5.1)	15/363 (4.1)	RR 1.15 (0.59, 2.23)	No difference P=0.68 *No heterogeneity* *(Phet=0.52; I^2=0%)*

Study Level of evidence *Quality*[a]	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%)	Liberal transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value Heterogeneity[b] P value
Carless 2010 Level I/II *Poor*	1 RCT N=214	Any (critical care, trauma, surgical, GI haemorrhage and leukaemia)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	Mortality (unspecified follow-up)	12/109 (11.0)	17/105 (16.2)	RR 0.68 (0.34, 1.35)	No difference P=NR (Phet=NA)
Critical care/trauma (post-hoc analysis)									
Carless 2010 Level I *Good*	3 RCTs N=1544	Critical care/trauma (including paediatric study)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	30-day mortality	100/771 (13.0)	121/773 (15.7)	RR 0.83 (0.66, 1.06) [c]	No difference P=0.13 *No heterogeneity* *(Phet=0.80; I^2=0%)*
Carless 2010 Level I *Good*	2 RCTs N=907	Critical care/trauma (excluding paediatric study)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	30-day mortality	86/451 (19.1)	107456 (23.2)	RR 0.81 (0.63, 1.05) [c]	No difference *No heterogeneity* *P=0.11 (Phet=0.66; I^2=0%)*
Carless 2010 Level I/II *Poor*	1 RCT N=838	Critical care/trauma	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	60-day mortality	95/418 (22.7)	111/420 (26.4)	RR 0.86 (0.68, 1.09)	No difference P=0.21 (Phet=NA)
Carless 2010 Level I/II *Poor*	1 RCT N=69	Critical care/trauma	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	120-day mortality	13/33 (39.4)	11/36 (30.6)	RR 1.29 (0.67, 2.47)	No difference P=0.44 (Phet=NA)
Carless 2010 Level I/II *Poor*	1 RCT N=838	Critical care/trauma	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	Hospital mortality	93/418 (22.2)	118/420 (28.1)	RR 0.79 (0.63, 1.00)	No significant difference P=0.05 (Phet=NA)
Carless 2010 Level I *Good*	3 RCTs N=736	Critical care/trauma (including paediatric study)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	ICU mortality	19/373 (5.1)	15/363 (4.1)	RR 1.15 (0.59, 2.23) [c]	No difference P=0.68 *No heterogeneity* *(Phet=0.52; I^2=0%)*

Study Level of evidence *Quality*[a]	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%)	Liberal transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value Heterogeneity[b] P value
Carless 2010 Level I *Good*	2 RCTs N=736	Critical care/trauma (excluding paediatric study)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	ICU mortality	8/53 (15.1)	7/46 (15.2)	RR 0.95 (0.34, 2.68) [c]	No difference P=0.92 *No heterogeneity* *(Phet=0.31; I^2=3%)*

CI, confidence interval; GI, gastrointestinal; ICU, intensive care unit; NA, not applicable; NR, not reported; RCT, randomised controlled trial; RR, risk ratio

Notes: Mortality denotes all-cause mortality unless specifically stated otherwise. Statistically significant results shown in shading.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2 <25%; moderate heterogeneity if I2 between 25-50%; substantial heterogeneity I2 >50%.

[c] Risk estimate calculated post hoc from individual study data.

The effect of restrictive vs. liberal RBC transfusion strategies on organ failure/dysfunction

One Level I study assessed the effect of RBC transfusion on organ failure/dysfunction. The study by Carless et al (2010) showed no significant difference in renal failure between the restrictive and liberal transfusion groups in the overall analysis (which includes two studies; one in surgical patients and one in paediatric critical care patients) or the post-hoc analysis including only paediatric critical care patients. However, given the magnitude of the risk estimate in the larger surgical study (RR 1.86) it is possible that there is an effect and that this analysis is underpowered.

Table 3.3.16 Question 1 (Mixed): Results for restrictive vs. liberal RBC transfusion – organ failure/dysfunction

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%)	Liberal transfusion n/N (%)	Risk estimate (95% CI)	*Significance* P-value Heterogeneity P value
LEVEL I EVIDENCE									
General/mixed (includes surgery and critical care only)									
Carless 2010 Level I *Good*	2 RCTs N=1065	Any (critical care and surgical only)	*Hospital* Various	Restrictive transfusion trigger vs liberal transfusion trigger	Renal failure	10/532 (1.9)	5/533 (0.9)	RR 1.86 (0.66, 5.22)	No difference P=0.24 *No heterogeneity* *(Phet=0.50; I^2=0%)*
Critical care (post-hoc analysis)									
Carless 2010 Level I/II *Poor*	1 RCT N=637	Paediatric critical care	*Hospital* Unknown	Restrictive transfusion trigger vs liberal transfusion trigger	Renal failure	2/320 (0.6)	0/317 (0)	RR 4.95 (0.24, 102.77)	No difference P=0.30 (Phet=NA)

CI, confidence interval; NA, not applicable; RCT, randomised controlled trial; RR, risk ratio.

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Only applicable to Level I studies with formal meta-analysis. Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

The effect of restrictive vs. liberal RBC transfusion strategies on transfusion-related adverse events

One Level I study assessed the effect of a restrictive RBC transfusion threshold on transfusion-related adverse events including pulmonary oedema, pneumonia and infection. The study by Carless et al (2010) showed that a restrictive strategy significantly reduced the risk of infection (RR 0.76; 95% CI 0.60, 0.97).[65] There was no significant difference for pneumonia or pulmonary oedema. However, the risk estimate for pulmonary oedema was low (RR 0.49) and the event rate was small (2.9% for restrictive versus 6.3% for liberal) suggesting that this analysis may have been underpowered.

The pulmonary oedema outcome did not include any data from critical care studies. However, both the pneumonia and infection outcomes included data from studies in critical care populations. When the analyses were restricted only to critical care/trauma studies, the results for both outcomes were similar to those observed for the general population analyses.

Table 3.3.17 Question 1 (Mixed): Results for restrictive vs. liberal RBC transfusion – Transfusion-related adverse events

Study Level of evidence[a] Quality	No. of trials / sample size included in analysis	Patient population	Setting Location	Intervention vs comparator	Outcome	Results			
						Restrictive transfusion n/N (%)	Liberal transfusion n/N (%)	Risk estimate (95% CI)	Significance P-value Heterogeneity[b]
LEVEL I EVIDENCE									
Any population (includes critical care and surgical)									
Carless 2010 Level I Good	4 RCTs N=1633	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	Pulmonary oedema	24/818 (2.9)	51/815 (6.3)	RR 0.49 (0.18, 1.31)	No difference P=0.16 Mild heterogeneity (Phet=0.30; I^2=19%)
Carless 2010 Level I Good	4 RCTs N=1679	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	Pneumonia	99/840 (11.8)	100/839 (11.9)	RR 1.00 (0.78, 1.29)	No difference P=0.98 No heterogeneity (Phet=0.68; I^2=0%)
Carless 2010 Level I Good	4 RCTs N=1788	Any (includes critical care and surgical)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	Infection	94/891 (10.5)	124/897 (13.8)	RR 0.76 (0.60, 0.97)	Favours restrictive transfusion P=0.029 No heterogeneity (Phet=0.43; I^2=0%)
Critical care (post-hoc analysis)									
Carless 2010 Level I Good	2 RCTs N=1475	Critical care/trauma (including paediatric study)	Hospital Various	Restrictive transfusion trigger vs liberal transfusion trigger	Pneumonia	98/738 (13.3)	96/737 (13.0)	RR 1.02 (0.79, 1.32) [c]	No difference P=0.86 No heterogeneity (Phet=0.88; I^2=0%)
Carless 2010 Level I/II *Poor*	1 RCT N=637	Paediatric critical care	*Hospital* Unknown	Restrictive transfusion trigger vs liberal transfusion trigger	Infection	65/320 (20.3)	79/317 (24.9)	RR 0.82 (0.61, 1.09)	Favours restrictive transfusion P=NR

CI, confidence interval; RCT, randomised controlled trial; RR, risk ratio

[a] Where only one study is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

[c] Risk estimate calculated post hoc from individual study data.

3.2 Question 2

Question 2 (Interventional question)

In critically ill patients, what is the effect of non-transfusion interventions to increase haemoglobin concentration on morbidity, mortality and need for RBC blood transfusion?

RBC, red blood cell

3.2.1 Non-transfusion interventions

***Evidence statements* – erythropoiesis-stimulating agents**
In a heterogeneous population of critically ill patients, ESAs have no effect on mortality. (A, A, NA, A, B) (See evidence matrix EM2.A in Volume 2 of the technical report)
In critically ill trauma patients, ESAs may be associated with decreased mortality. (A, A, B, B, B) (See evidence matrix EM2.A in Volume 2 of the technical report)
In a heterogeneous population of critically ill patients, ESAs do not appear to reduce the incidence of RBC transfusion, when a restrictive transfusion strategy is employed. (B, C, NA, A, B) (See evidence matrix EM2.B in Volume 2 of the technical report)
In critically ill non-trauma patients, the effect of ESAs on the incidence of RBC transfusion is uncertain. (A, C, NA, A, B) (See evidence matrix EM2.B in Volume 2 of the technical report)
In critically ill trauma patients, ESAs appear to have no effect on the incidence of RBC transfusion. (A, C, C, A, B) (See evidence matrix EM2.B in Volume 2 of the technical report)
In a heterogeneous population of critically ill patients, ESAs may increase the risk of thromboembolic events. (B, C, C, A, B) (See evidence matrix EM2.C in Volume 2 of the technical report)
***Evidence statements* – iron therapy**
In critically ill patients, the effect of iron therapy on mortality is uncertain. (D, A, NA, A, B) (See evidence matrix EM2.D in Volume 2 of the technical report)
In critically ill patients, the effect of oral iron therapy on RBC transfusion is uncertain. (D, D, NA, A, B) (See evidence matrix EM2.E in Volume 2 of the technical report)
In critically ill patients, the effect of iron therapy on thromboembolic events is unknown. (No evidence)

Recommendation	
R2	ESAs should not be routinely used in critically ill anaemic patients (Grade B).*
ESA, erythropoiesis-stimulating agent; R, recommendation	

3.2.2 ESAs vs no ESAs for critically ill patients

Methods

There were two Level I studies,[76,77] and two subsequently published Level II studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

There were two systematic reviews of randomised controlled trials (RCTs) that evaluated the use of erythropoiesis stimulating agents (ESAs) in critically ill patients. [76,77] The main characteristics of these reviews are summarised in **Table 3.3.18**.

Both systematic reviews compare the use of erythropoietin (EPO) with treatment without EPO. Zarychanski et al (2007)[76] included one RCT (N=40) in a burns unit population, (Still et al [1995][78]) one RCT (N=86) in long-term acute care patients, (Silver et al [2006][79]) and seven RCTs (N=3188) in mixed (medical and surgical) intensive care unit (ICU) populations. [80-86] Turaga et al (2007)[77] included one RCT (N=40) in a burns unit population,[78] and four RCTs (N=1646) in mixed ICU populations.[80,81,84,85] Zarychanski et al (2007) is used as the basis for this review as it is more comprehensive than Turaga et al (2007) and of higher quality.

Napolitano et al (2008)[87] separated out and conducted subgroup analyses on the trauma patients from the two largest studies analysed by Zarychanski et al (2007). (Corwin et al [2002][81]; Corwin et al [2007][82])

Table 3.3.18 Question 2 (ESAs): Characteristics and quality of Level I evidence

Level I evidence				
Study	Study type *Study quality*	Population N	Comparison	Outcomes
Zarychanski et al (2007)[76]	Systematic review *Good*	Critically ill patients N=3314	EPO vs no EPO	Mortality RBC transfusion Thromboembolic events
Turaga et al (2007)[77]	Systematic review *Poor*	Critically ill patients N=1686	EPO vs no EPO	RBC transfusion volume

* This recommendation is based on the lack of effect of ESAs on mortality in a heterogeneous population of critically ill patients.

Level I evidence				
Study	Study type *Study quality*	Population N	Comparison	Outcomes
Subgroup analysis				
Napolitano et al (2008)[87]	*Fair* Subgroup analysis of the results from Corwin et al (2002) and Corwin et al (2007)	Trauma patients admitted to an ICU for at least 2 days with Hb < 120 g/L	IV EPO (40,000 U/week) for a total of four doses (Corwin et al [2002]) or three doses (Corwin et al [2007]) vs placebo	Mortality RBC transfusion Thromboembolic events

EPO, erythropoietin; Hb, haemoglobin; ICU, intensive care unit; RBC, red blood cell

Level II evidence

A literature search was conducted to identify Level II evidence published after the literature search conducted in the Zarychanski et al (2007) systematic review. [76 †] Two studies were identified and the main characteristics of these studies are summarised in **Table 3.3.19**. Both studies compared EPO with placebo. Endre et al (2010) assessed general ICU and cardiothoracic patients, [88] and Nirula et al (2010) assessed patients with traumatic brain injury. [89]

Table 3.3.19 Question 2 (ESAs): Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Endre et al (2010)[88]	RCT *Fair*	General ICU patients or high-risk cardiothoracic surgery patients (pCr >1.7 mg/dL or GFR 25 to 50 mL/min, and scheduled to undergo CPB for valvular heart disease or CABG plus risk factor[a] N=162	Daily IV EPO (500 U/kg to a maximum of 50,000 U for 2 days)	Matching placebo	Mortality Thromboembolic events
Nirula et al (2010)[89]	RCT *Poor*	Blunt trauma patients with an admission GCS < 13 and evidence of traumatic brain injury on CT. N=16	IV EPO (40,000 units) within 6 hours of the time of injury	Matching placebo	Mortality Thromboembolic events

CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; CT, x-ray computed tomography; EPO, erythropoietin; GCS, Glasgow Coma Scale; GFR, glomerular filtration rate; ICU, intensive care unit; IV, intravenous; pCr, plasma creatinine concentration; RCT, randomised controlled trial

[a] Extra-cardiac vascular disease, diabetes mellitus, ejection fraction <25%, use of a preoperative intra-arterial balloon pump, emergency surgery, or other surgery.

† The literature search in Zarychanski et al (2007) included papers published from 1950 to February 2007.

Results

Mortality

As shown in **Table 3.3.20**, the meta-analysis conducted by Zarychanski et al (2007) found no significant difference between EPO and control when all critical care studies were pooled (9 trials; OR 0.86; 95% CI 0.71, 1.05), but the authors reported a borderline significant reduction in mortality in patients treated with EPO compared with control within studies which reported the use of a restrictive (Hb ≤ 80 g/L) transfusion practice (3 trials; 14% vs 16%; OR 0.73; 95% CI 0.53, 1.00). [76]There were no significant differences between treatment arms among:

- patients admitted to mixed medical and surgical units[‡];
- patients who received 40,000 U/week EPO;
- patients who received more than 40,000 U/week EPO;
- studies that adopted a liberal transfusion practice;
- high quality studies[§];
- unblinded studies; or
- studies that reported adequate allocation concealment.

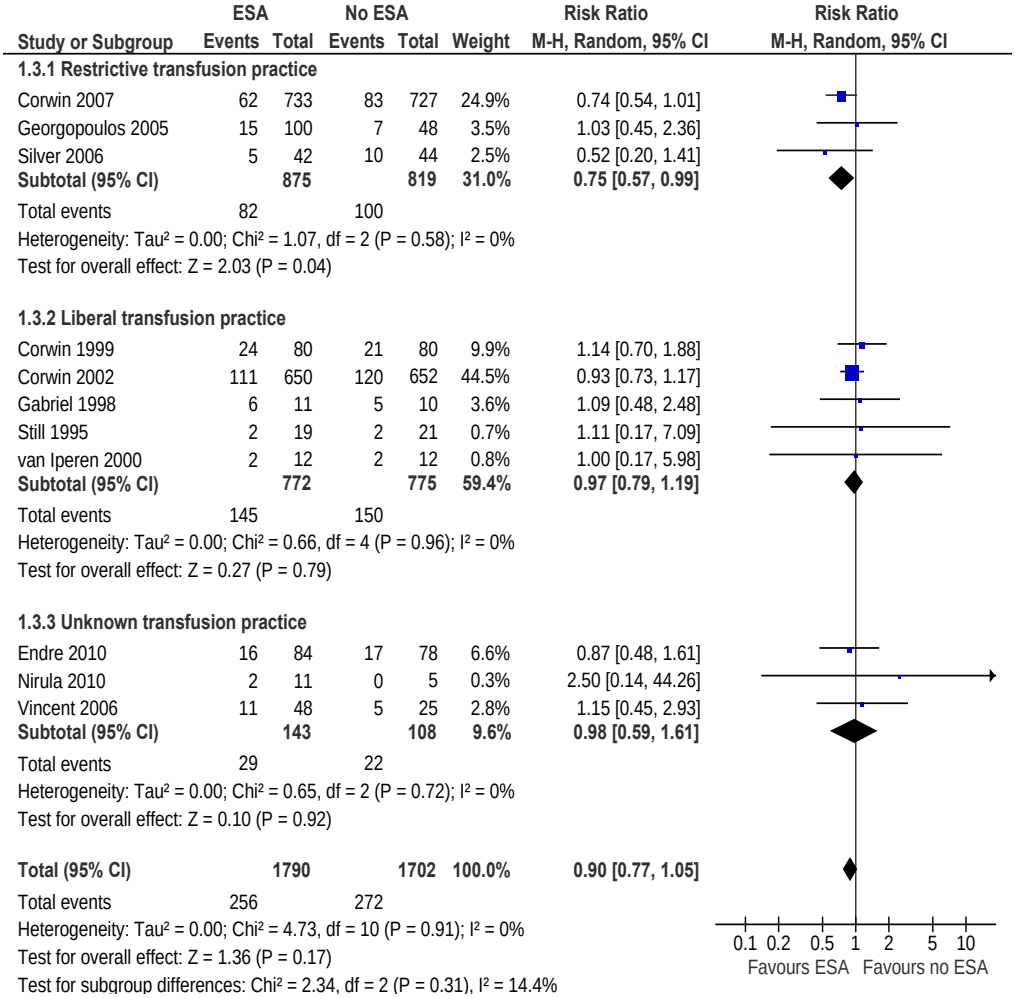
Neither of the RCTs published after the Zarychanski et al (2007) review found a significant difference between EPO and control in the incidence of mortality. (Endre et al [2010][88]; Nirula et al [2010][89]) A meta-analysis was conducted in order to update Zarychanski et al (2007) with the results from the subsequently published RCTs (see **Figure 3.1**). After the addition of the two RCTs, there was still no significant difference in the mortality rates of critically ill patients treated with and without EPO (11 trials; 14% vs 16%; RR 0.90; 95% CI 0.77, 1.05). The results by liberal and restrictive practice subgroups remain unchanged.

Figure 3.2 presents a meta-analysis by clinical setting using the results from Napolitano et al (2008)[87] to separate Corwin et al (2002)[81] and Corwin et al (2007)[82] into trauma and other medical and surgical ICU subgroups. These subgroups were meta-analysed with the results from Zarychanski et al (2007) and the subsequently published RCTs. EPO, compared with placebo, significantly reduced mortality in critically ill trauma patients (3 trials; 4% vs 8%; RR 0.51; 95% CI 0.33, 0.80), but there was no significant difference in burns unit patients (1 trial; 11% vs 10%; RR 1.11; 95% CI 0.17, 7.09), long-term acute care patients (1 trial; 12% vs 23%; RR 0.52; 95% CI 0.20, 1.41), or other medical and surgical ICU patients (8 trials; 22% vs 22%; RR 1.01; 95% CI 0.85, 1.19).

[‡] The two trials that enrolled patients with burns or patients admitted to a long-term acute care hospital were excluded.

[§] As appraised by Zarychanski et al (2007).

Figure 3.1 Meta-analysis of EPO vs no EPO in critically ill patients (mortality by transfusion practice)



Restrictive was defined as ≤80 g/L Hb. Liberal was defined as >80 g/L Hb.

Figure 3.2 Meta-analysis of EPO vs no EPO in critically ill patients (mortality by setting)

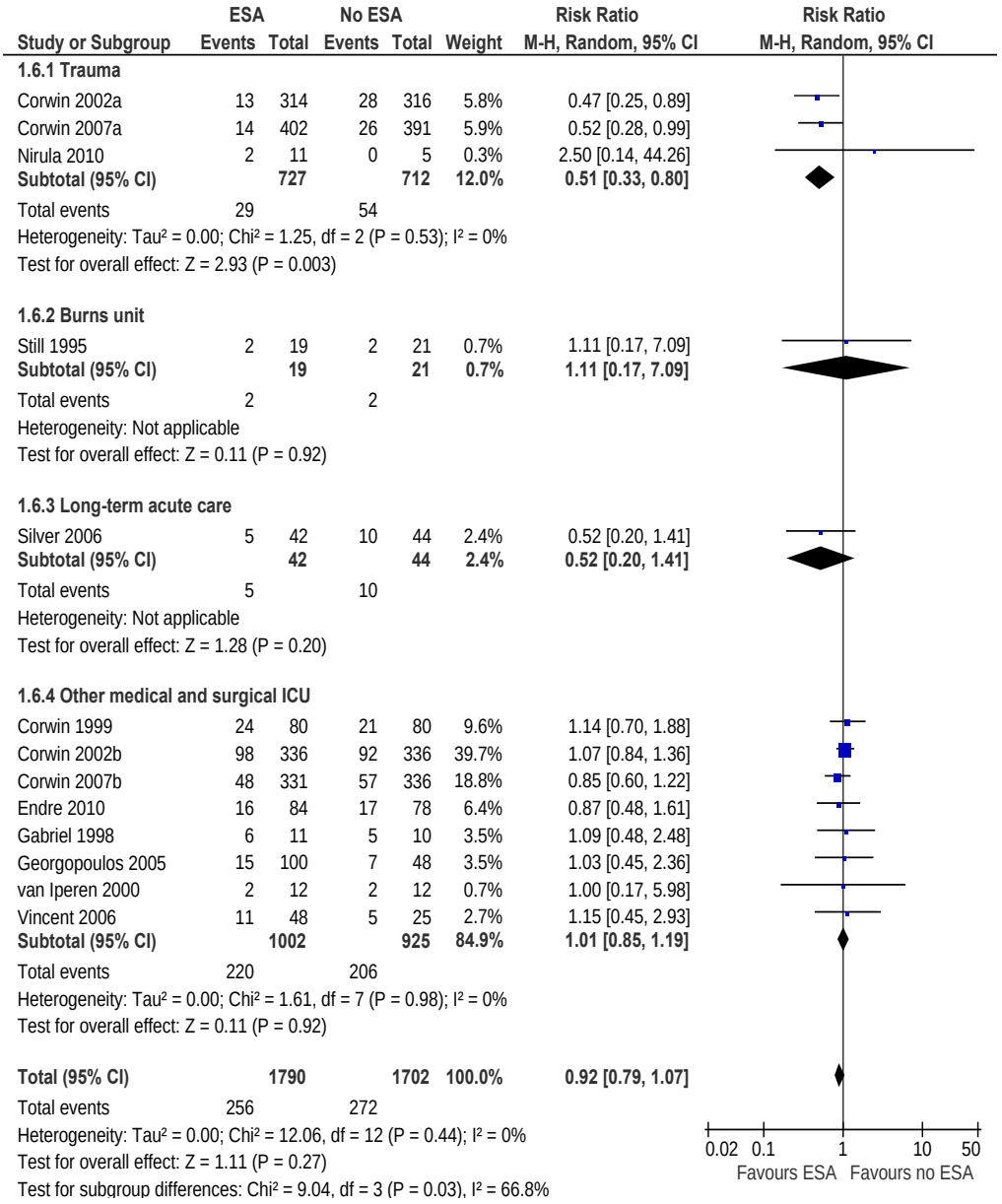


Table 3.3.20 Question 2: Results for ESAs vs no ESAs in critically ill patients (mortality)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
Level I studies								
Zarychanski et al (2007)[76] *Good*	Critically ill patients	EPO vs no EPO	21 to 140 days	Mortality, n/N (%) 9 trials (N=3314)	238/1695 (14.0)	255/1619 (15.8)	OR 0.86 (0.71, 1.05)	*No significant difference* P=0.14 *No significant heterogeneity*[a] P*het*=NR (I^2=0)
				Mortality (patients admitted to mixed medical and surgical units[b]) 7 trials (N=3188)	NR	NR	OR 0.88 (0.72, 1.07)	*No significant difference* P>0.05 *No significant heterogeneity*[a] P*het*=NR (I^2=0)
				Mortality (40 000 U/wk EPO), n/N (%) 5 trials (N=3020)	NR	NR	OR 0.82 (0.66, 1.02)	*No significant difference* P>0.05 *No significant heterogeneity*[a] P*het*=NR (I^2=0)
				Mortality (>40 000 U/wk EPO), n/N (%) 4 trials (N=302)	NR	NR	OR 1.26 (0.74, 2.15)	*No significant difference* P>0.05 *No significant heterogeneity*[a] P*het*=NR (I^2=0)
				Mortality (restrictive transfusion[c]), n/N (%) 3 trials (N=1694)	82/875 (9.4)	100/819 (12.2)	OR 0.73 (0.53, 1.00)	*Favours EPO* P=0.05 *No significant heterogeneity*[a] P*het*=NR (I^2=0)
				Mortality (liberal transfusion[d]), n/N (%) 4 trials (N=245)	NR	NR	OR 1.18 (0.66, 2.11)	*No significant difference* P>0.05 *No significant heterogeneity*[a] P*het*=NR (I^2=0)
				Mortality (high quality[e] RCTs), n/N (%) 3 trials (N=2848)	NR	NR	OR 0.81 (0.65, 1.01)	*No significant difference* P>0.05 *No significant heterogeneity*[a] P*het*=NR (I^2=2.8)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
				Mortality (unblinded studies), n/N (%) 2 trials (N=172)	NR	NR	OR 1.03 (0.42, 2.53)	*No significant difference* P>0.05 *No significant heterogeneity*[a] P*het*=NR (I^2=0)
				Mortality (studies with adequate allocation concealment), n/N (%) 2 trials (N=1450)	NR	NR	OR 0.84 (0.68, 1.04)	*No significant difference* P>0.05 *No significant heterogeneity*[a] P*het*=NR (I^2=0)
Level II studies								
Endre et al (2010)[88] *Fair*	General ICU and cardiothoracic patients	EPO vs placebo	30 days	Survival (N=162)	NR	NR	HR 0.95 (0.52, 1.7)	*Favours EPO* P>0.05
				Mortality (within 7 days), n/N (%) (N=162)	9/84 (10.7)	13/78 (16.7)	NR	*No significant difference* P=0.36
				Mortality (within 30 days), n/N (%) (N=162)	16/84 (19.0)	17/78 (21.8)	NR	*No significant difference* P=0.70
Nirula et al (2010)[89] *Poor*	Traumatic brain injury patients	EPO vs placebo	NR	In hospital mortality, n/N (%) (N=16)	2/11 (18.2)	0/5 (0)	RR 2.50 (0.14, 44.26)[g]	*No significant difference* P=0.53[g]
Subgroup analysis								
Napolitano et al (2008)[87] *Fair* *Analysis of two good quality RCTS*[h]	Trauma patients	EPO vs placebo	29 days	Mortality (Corwin et al [2002]; prospective dataset), n/N (%) (N=630)	13/314 (4.1)	28/316 (8.9)	Unadjusted HR 0.46 (0.24, 0.89) Fully adjusted HR 0.55 (0.28, 1.08) Final best fit HR[i] 0.50 (0.26, 0.97)[i]	*Favours EPO* P<0.05

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
				Mortality (Corwin et al [2002]; retrospective dataset[i]), n/N (%) (N=559)	11/289 (3.8)	18/270 (6.7)	Unadjusted HR 0.57 (0.27, 1.20) Fully adjusted HR 0.64 (0.28, 1.47) Final best fit HR[k] 0.65 (0.29, 1.44)	*No significant difference* P>0.05
				Mortality (Corwin et al [2007]), n/N (%) (N=793)	14/402 (3.5)	26/391 (6.6)	Unadjusted HR 0.51 (0.27, 0.98) Fully adjusted HR 0.36 (0.18, 0.74) Final best fit HR[l] 0.38 (0.19, 0.74)	*Favours EPO* P<0.05
				Mortality (ISS < 15), n/N (N=199)	4/103 (3.9)	4/96 (4.2)	RR 0.86 (0.10, 7.23)[g]	*No significant difference* P=0.92[g] *Moderate heterogeneity*[a] *P*het=0.20 (I^2=40)
				Mortality (ISS 15-24), n/N (N=391)	6/200 (3.0)	8/191 (4.2)	RR 0.71 (0.25, 2.04)[g]	*No significant difference* P=0.53[g] *No significant heterogeneity*[a] P*het*=0.71 (I^2=0)
				Mortality (ISS ≥ 25), n/N (N=753)	17/386 (4.4)	37/367 (10.1)	RR 0.45 (0.25, 0.79)[g]	*Favours ESA* P=0.005[g] *No significant heterogeneity*[a] P*het*=0.39 (I^2=0)
				Mean (SD) time of death, days (N=1423)	NR	NR	MD -0.36 (-1.14, 0.42)[g]	*No significant difference* P=0.37[g] *No significant heterogeneity*[a] P*het*=0.46 (I^2=0)

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis-stimulating agents; ICU, intensive care unit; ISS, Injury Severity Score; HR, hazard ratio; NA, not applicable; NR, not reported; OR, odds ratio; RCT, randomised controlled trial; RR, relative risk

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if *Phet*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

[b] The two trials that enrolled patients with burns (Still et al [1995]) or patients admitted to long-term acute care hospital (Silver et al [2006]) were excluded.

[c] Haemoglobin≤80 g/L.

[d] Haemoglobin≥90 g/L.

[e] As appraised by Zarychanski et al.

[f] Sudden death; patient did not have occlusion in the left-anterior descending artery; baseline left-ventricular ejection fraction (LVEF) 49%.

[g] Calculated for the purpose of this systematic review using Review Manager.

[h] Subgroup analysis of the trauma patients from Corwin et al (2002) and Corwin et al (2007).

[i] Best fit model included the factors treatment group, age (<55 and ≥55), race, baseline creatinine, ferritin, and serum erythropoietin concentration.

[j] This retrospective population does not include 12 of the 47 deaths reported on or before day 28 in EPO 2 (Corwin et al [2002]), and the distribution of these missing deaths was uneven (10 placebo and 2 EPO).

[k] Retrospective best fit model included the factors treatment group, age (<55 and ≥55), race, baseline creatinine, ferritin, and serum erythropoietin concentration.

[l] Best fit model included the factors treatment group, age (<55 and ≥55), race, baseline creatinine, ferritin, and serum erythropoietin concentration.

Blood transfusion

Zarychanski et al (2007) found that critically ill patients treated with EPO had a significantly lower incidence of red blood cell (RBC) transfusion (7 trials; 46% vs 54%; OR 0.73; 95% CI 0.64, 0.84) and a significantly lower mean volume of RBCs transfused (weighted mean difference [WMD] -0.41[**]; -0.74, -0.10) compared with control (**Table 3.3.21**). [76] Neither of the studies published after Zarychanski et al (2007) reported RBC transfusion as an outcome.

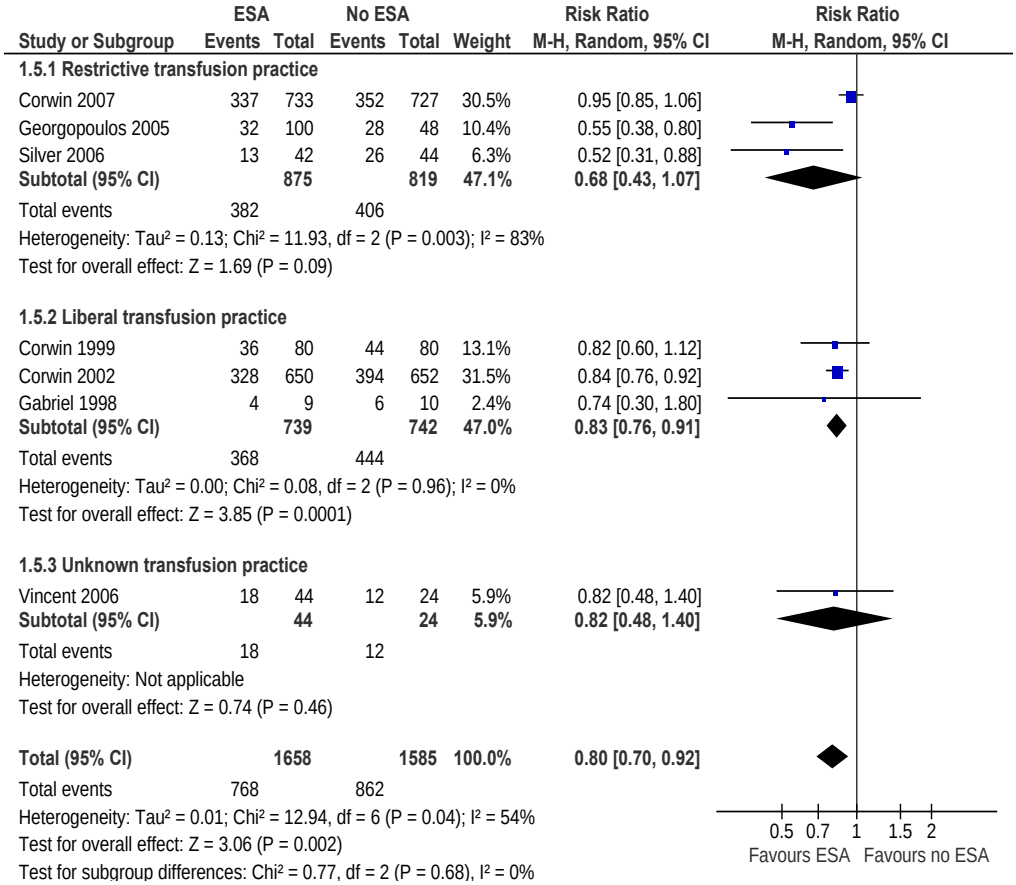
Figure 3.3 presents a subgroup analysis of the results from Zarychanski et al (2007) by transfusion practice. There was no significant difference in RBC transfusion incidence between EPO and no EPO when a restrictive (Hb ≤ 80 g/L) transfusion practice was used (3 trials; 43.7%; RR 0.68; 95% CI 0.43, 1.07); although there was significant heterogeneity due to differences in setting and treatment. Silver et al (2006) was in a long-term acute care setting,[79] and half of the patients in the intervention arm of Georgopoulos et al (2006) received 40,000 U, three times a week, rather than 40,000/wk).[84] This finding is driven by the results from Corwin et al (2007),[82] where the mean pre-transfusion haemoglobin concentration was 80 g/L.

EPO significantly reduced RBC transfusion incidence, compared with control, in studies with less restrictive (Hb > 80 g/L) transfusion practices (3 trials; 50% vs 60%; RR 0.83; 95% CI 0.76, 0.91). This finding is driven by the results from Corwin et al (2002),[81] where the mean pre-transfusion haemoglobin concentration was 85 g/L.

Figure 3.4 presents a meta-analysis by clinical setting using the results from Napolitano et al (2008)[87] to separate Corwin et al (2002)[81] and Corwin et al (2007)[82] into trauma and other medical and surgical ICU subgroups. These subgroups were meta-analysed with the results from Zarychanski et al (2007). EPO, compared with placebo, significantly reduced the incidence of RBC transfusion in both trauma and critically ill non-trauma patients within Corwin et al (2002), but there was no significant difference between treatment arms for either subgroup in Corwin et al (2007). Overall, the relationship between EPO and decreased RBC transfusion incidence was not-significant for trauma patients (2 trials; 53% vs 58%; RR 0.92; 95% CI 0.82, 1.02), but was significant for long-term acute care patients (1 trial; 31% vs 59%; RR 0.52; 95% CI 0.31, 0.88) and other medical and surgical ICU patients (6 trials; 41% vs 51%; RR 0.81; 95% CI 0.72, 0.91).

[**] This point estimate decrease represents a transfusion savings of less than 0.5 units per patient.

Figure 3.3 Meta-analysis of EPO vs no EPO in critically ill patients (blood transfusion by transfusion practice)



Restrictive was defined as ≤80 g/L Hb. Liberal was defined as >80 g/L Hb.

Figure 3.4 Meta-analysis of EPO vs no EPO in critically ill patients (blood transfusion by setting)

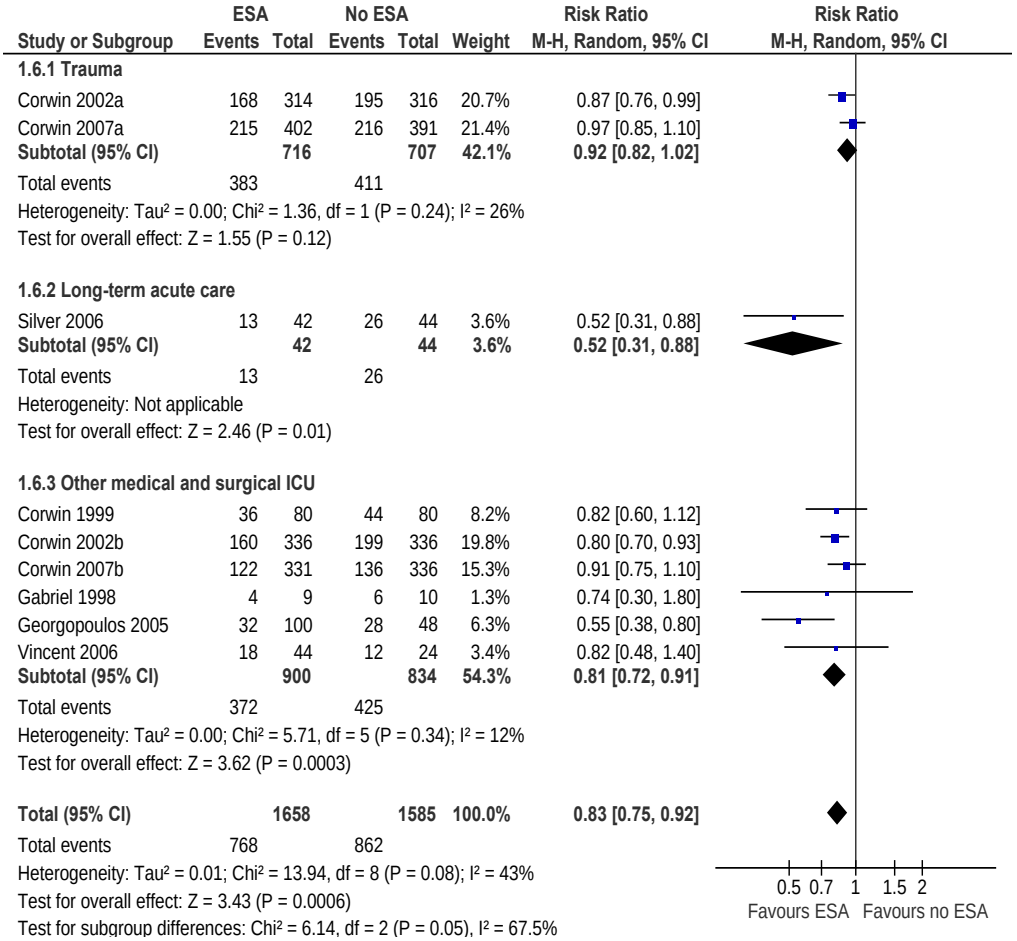


Table 3.3.21 Question 2: Results for ESAs vs no ESAs in critically ill patients (blood transfusion)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
Level I studies								
Zarychanski et al (2007)[76] *Good*	Critically ill patients	EPO vs no EPO	21 to 140 days	Incidence of RBC transfusion, n/N (%) 7 trials (N=3243)	768/1658 (46.3)	862/1585 (54.4)	OR 0.73 (0.64, 0.84)	*Favours EPO* P<0.001 *Substantial heterogeneity*[a] P*het*=NR (I^2=54.7)
				Mean volume of RBCs transfused, units 5 trials (N=3020)	NR	NR	WMD -0.41[b] (-0.74, -0.10)	*Favours EPO* P<0.05 *Substantial heterogeneity*[a] P*het*=NR (I^2=79.2)
Subgroup analysis								
Napolitano et al (2008)[87] *Fair* *Analysis of two good quality RCTS*[c]	Trauma patients	EPO vs placebo	29 days	Incidence of RBC transfusion (Corwin et al [2002]), n/N (%) (N=630)	168/314 (53.5)	195/316 (61.7)	RR 0.87 (0.76, 0.99)	*Favours EPO* P<0.05
				Incidence of RBC transfusion (Corwin et al [2007]), n/N (%) (N=793)	215/402 (53.5)	216/391 (55.2)	RR 0.97 (0.85, 1.10)	*No significant difference* P>0.05
				Mean (SD) volume of RBCs transfused (Corwin et al [2002]), units (N=363)	2.6 (4.9)	3.1 (5.3)	MD -0.5 (-1.30, 0.30)[d]	*No significant difference* P=0.22[d]
				Mean (SD) volume of RBCs transfused (Corwin et al [2007]), units	4.3 (3.8)	4.3 (5.1)	MD 0.0 (-0.63, 0.63)[d]	*No significant difference* P=1.00
				Mean (SD) volume of RBCs transfused (overall), units	NR	NR	MD -0.19 (-0.68, 0.30)	*No significant difference* P=0.45 *No significant heterogeneity* P*het*=0.33 (I^2=0)

CI, confidence interval; EPO, erythropoietin; ESA, erythropoiesis stimulating agent; NR, not reported; OR, odds ratio; RBC, red blood cell; RR, relative risk; WMD, weighted mean difference

[a] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

[b] This point estimate decrease represents a transfusion savings of less than 0.5 units per patient.

[c] Subgroup analysis of the trauma patients from Corwin et al (2002) and Corwin et al (2007).

[d] Calculated for the purpose of this systematic review using Review Manager.

Thromboembolic events

Both studies[88,89] published after Zarychanski et al (2007) reported the incidence of thromboembolic events (**Table 3.3.22**). [76] The results of these trials were meta-analysed with the results from Zarychanski et al (2007). The updated meta-analyses found no significant difference between ESAs and no ESAs in deep vein thrombosis (DVT; 7 trials; 5% vs 4%; RR 1.06; 95% CI 0.69, 1.64; **Figure 3.5**), stroke (3 trials; 2% vs 3%; RR 0.76; 95% CI 0.41, 1.41; **Figure 3.6**), or myocardial infarction (2 trials; 2% vs 1%; RR 0.80; 95% CI 0.05, 13.82; **Figure 3.7**).

Figure 3.5 Meta-analysis of ESAs vs no ESAs in critically ill patients (deep vein thrombosis)

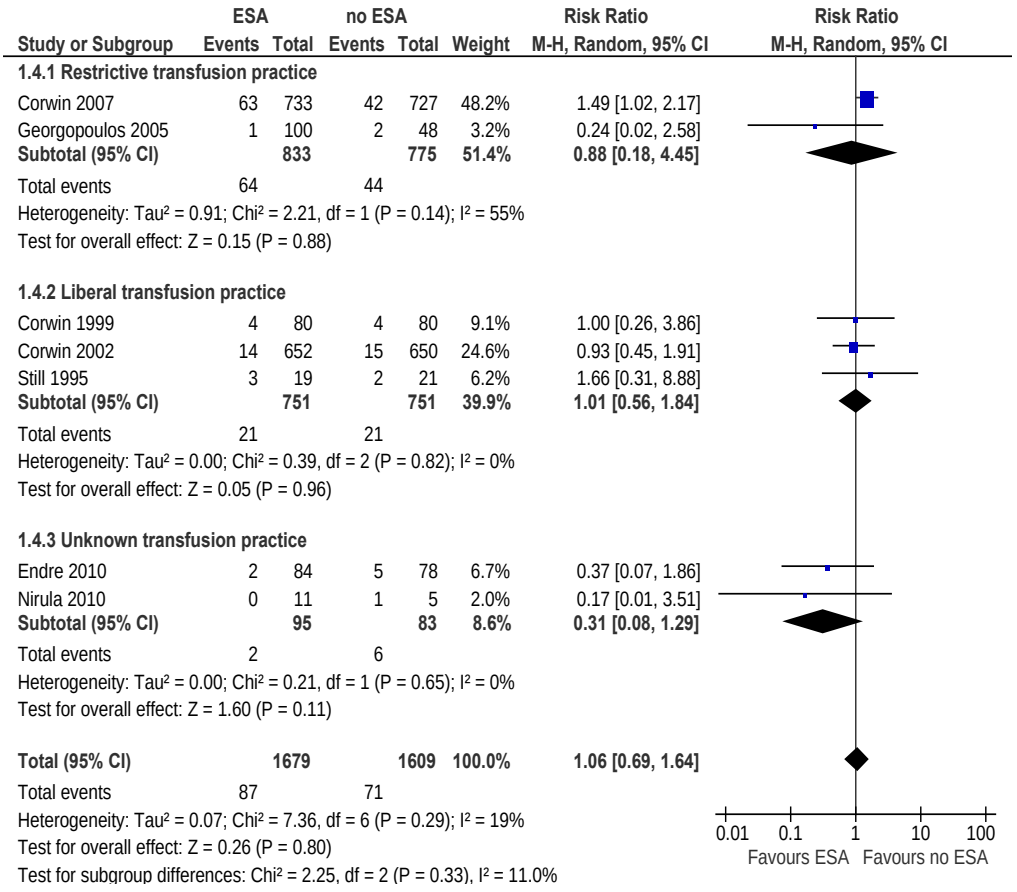


Figure 3.6 Meta-analysis of ESAs vs no ESAs in critically ill patients (stroke)

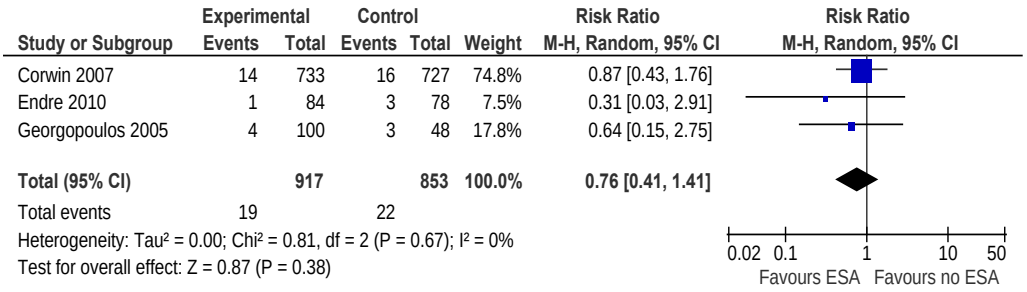


Figure 3.7 Meta-analysis of ESAs vs no ESAs in critically ill patients (myocardial infarction)

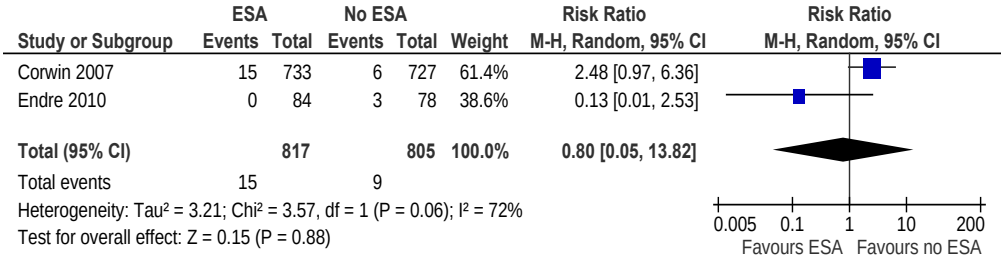


Table 3.3.22 Question 2: Results for ESAs vs no ESAs in critically ill patients (thromboembolic events)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
Level I studies								
Zarychanski et al (2007)[76] *Good*	Critically ill patients	EPO vs no EPO	140 days	MI, n/N (%) 1 trial (N=1460)	15/733 (2.1)	6/727 (0.8)	RR 2.48 (0.97, 6.36)[a]	*No significant difference* P=0.06[a]
			42 to 140 days	Stroke, n/N (%) 2 trials (N=1608)	18/833 (2.2)	19/775 (2.5)	RR 0.82 (0.43, 1.55)[a]	*No significant difference* P=0.54[a] *No significant heterogeneity*[b] P*het*=0.71 (I^2=0)
			28 to 140 days	DVT, n/N (%) 5 trials (N=3110)	85/1582 (5.4)	65/1528 (4.3)	RR 1.29 (0.94, 1.78)[a]	*No significant difference* P=0.11[a] *No significant heterogeneity*[b] P*het*=0.48 (I^2=0)
Level II studies								
Endre et al (2010)[88] *Fair*	General ICU and cardiothoracic patients	EPO vs placebo	30 days	DVT, n/N (%) (N=162)	2/84 (2.4)	5/78 (6.4)	RR 0.37 (0.07, 1.86)[a]	*No significant difference* P=0.23[a]
				Pulmonary embolism, n/N (%) (N=162)	1/84 (1.2)	1/78 (1.3)	RR 0.93 (0.06, 14.59)[a]	*No significant difference* P=0.96[a]
				Stroke, n/N (%) (N=162)	1/84 (1.2)	3/78 (3.8)	RR 0.31 (0.03, 2.91)[a]	*No significant difference* P=0.31[a]
				MI, n/N (%) (N=162)	0/84 (0.0)	3/78 (3.8)	RR 0.13 (0.01, 2.53)[a]	*No significant difference* P=0.18[a]
				Other thromboembolism, n/N (%) (N=162)	1/84 (1.2)	0/78 (0)	RR 2.79 (0.12, 67.45)[a]	*No significant difference* P=0.53[a]
Nirula et al (2010)[89] *Poor*	Traumatic brain injury patients	EPO vs placebo	NR	DVT, n/N (%) (N=16)	0/11 (0.0)	1/5 (20.0)	RR 0.17 (0.01, 3.51)	*No significant difference* P=0.25

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
Subgroup analyses								
Napolitano et al (2008)[87] *Fair* *Analysis of two good quality RCTS*[c]	Trauma patients	EPO vs placebo	29 days	Thromboembolic events (Corwin et al [2002]), n/N (%) (N=630)	35/314 (11.1)	42/316 (13.3)	RR 0.84 (0.56, 1.28)	*No significant difference* P>0.05
				Thromboembolic events (Corwin et al [2007]), n/N (%) (N=793)	66/402 (16.4)	49/391 (12.5)	RR 1.31 (0.93, 1.85)	*No significant difference* P>0.05
				Thromboembolic events (pooled), n/N (%) (N=1423)	101/716 (14.1)	91/707 (12.9)	RR 1.07 (0.69, 1.65)[a]	*No significant difference* P=0.77[a] *Substantial heterogeneity*[b] P*het*=0.11 (I^2=62)
				Venous thromboembolic events (Corwin et al [2002]), n/N (%) (N=630)	30/314 (9.6)	28/316 (8.9)	RR 1.08 (0.66, 1.76)	*No significant difference* P>0.05
				Venous thromboembolic events (Corwin et al [2007]), n/N (%) (N=793)	50/402 (12.4)	37/391 (9.5)	RR 1.31 (0.88, 1.96)	*No significant difference* P>0.05
				Venous thromboembolic events (pooled), n/N (%) (N=793)	80/716 (11.2)	65/707 (9.2)	RR 1.21 (0.89, 1.66)[a]	*No significant difference* P=0.22[a] *No significant heterogeneity*[b] P*het*=0.54 (I^2=0)
				Thromboembolic events (Corwin et al [2007]; subjects receiving heparin on study day 1), n/N (%) (N=300)	18/150 (12.0)	16/150 (10.7)	RR 1.13 (0.60, 2.12)	*No significant difference* P>0.05

CI, confidence interval; DVT, deep vein thrombosis; EPO, erythropoietin; ESA; erythropoiesis stimulating agent; MI, myocardial infarction; NR, not reported; RR, relative risk

[a] Calculated for the purpose of this systematic review using Review Manager.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if P*het*>0.1 and I^2<25%; (ii) mild heterogeneity if I^2<25%; moderate heterogeneity if I^2 between 25%-50%; substantial heterogeneity if I^2>50%.

3.2.3 Iron therapy vs no iron therapy for critically ill patients

Methods

There were two Level II studies identified from the systematic review and hand searching process (see Appendix C, Volume 2). [85,90]

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

No Level I evidence evaluating the use of iron therapy in critically ill patients with was identified.

Level II evidence

Two RCTs evaluating the use of iron therapy in critically ill patients were identified (**Table 3.3.23**). Pieracci et al (2009) compared oral iron with placebo in critically ill patients who had undergone surgery.[90] Van Iperen et al (2000) compared IV iron and folic acid with folic acid alone in patients admitted into an ICU in the Netherlands.[85] Van Iperen et al (2000) included a third treatment arm where patients received EPO, IV iron and folic acid. The comparison between the EPO and iron alone treatment arms was included in the meta-analysis conducted by Zarychanski et al (2007).[76]

Table 3.3.23 Question 2 (iron therapy): Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type *Study quality*	Population N	Intervention	Control	Outcomes
Pieracci et al (2009)[90]	RCT *Poor*	Critically ill patients with anaemia (<13 g/dL) and an expected ICU length of stay of at least 5 days. Patients received ESA treatment at the discretion of the attending physician[a] N=200	325 mg oral iron three times a day until hospital discharge or for 42 days. + 500 mg oral ascorbic acid three times a day + 1 mg oral cyanocobalamin daily + 1 mg folic acid daily	Placebo + 500 mg oral ascorbic acid three times a day until hospital discharge or for 42 days. + 1 mg oral cyanocobalamin daily + 1 mg folic acid daily	Mortality RBC transfusion
van Iperen et al (2000)[85]	RCT *Poor*	ICU patients with anaemia (Hb < 11.2 g/dL or, in the case of cardiac disease, Hb < 12.1 g/dL) N=24	1 mg/day IV folic acid for 21 days and 20 mg/day IV iron saccharate from Days 1 to 14	1 mg/day IV folic acid for 21 days	Mortality RBC transfusion

Hb, haemoglobin; ICU, intensive care unit; IV, intravenous; RBC, red blood cell; RCT, randomised controlled trial

[a] 6% of patients who received iron therapy required EPO compared with 9.5% of patients in the placebo arm (P=0.35).

Results

Mortality

Both Pieracci et al (2009) and van Iperen et al (2000) reported mortality (**Table 3.3.24**).[85,90] Neither study found a significant difference in mortality between patients who did and did not receive iron therapy. A meta-analysis of these studies was conducted (**Figure 3.8**), which found no significant difference in mortality between iron therapy and no iron therapy (10% vs 12%; RR 0.81; 95% CI 0.39, 1.71). The studies were not, however, powered to detect a mortality difference and the lengths of follow-up were only 21 days and 42 days for van Iperen et al (2000) and Pieracci et al (2009) respectively.

Figure 3.8 Meta-analysis of iron therapy vs no iron therapy in critically ill patients (mortality)

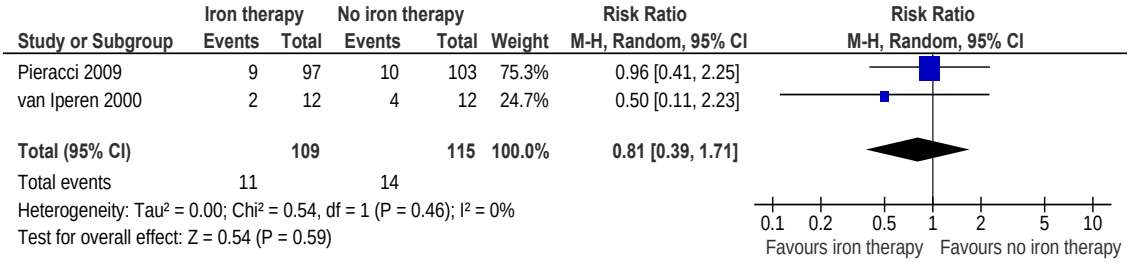


Table 3.3.24 Question 2: Results for iron therapy in critically ill patients (mortality)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
Level II studies								
Pieracci et al (2009)[90] *Poor*	Critically ill surgical patients	Oral iron vs placebo	42 days or hospital discharge	Mortality, n/N (%) (N=200)	9/97 (9.4)	10/103 (9.9)	NR	*No significant difference* P=0.90
van Iperen et al (2000)[85] *Poor*	ICU patients	IV iron vs no iron therapy	21 days	Mortality, n/N (%) (N=24)	2/12 (16.7)	4/12 (33.3)	RR 0.50 (0.11, 2.23)[a]	*No significant difference* P=0.36[a]

CI, confidence interval; ICU, intensive care unit; IV, intravenous; NR, not reported; RR, relative risk

[a] Calculated for the purpose of this systematic review using Review Manager.

Blood transfusion

Pieracci et al (2009) found that, in patients who were critically ill following surgery, treatment with oral iron significantly reduced the incidence of RBC transfusion compared with placebo (29.9% vs 44.7%; P=0.03; **Table 3.3.25**).[90] This treatment effect was consistent for:

- Patients who had iron-deficient erythropoiesis;
- Patients who had received a blood transfusion prior to study enrolment; and
- Patients with an APACHE II score greater than 12.

But there was no significant difference in RBC transfusion incidence between treatment arms for:

- Patients without iron-deficient erythropoiesis;
- Patients who did not receive a blood transfusion prior to study enrolment; and
- Patients with an APACHE II score lower than 12.

Patients in Pieracci et al (2009) received ESAs at the discretion of the attending physician. 6% of patients who received iron therapy required EPO compared with 9.5% of patients in the placebo arm (P=0.35).[90]

Van Iperen et al (2000) found no significant difference between IV iron with folic acid and folic acid alone in the mean volume of blood transfused alone (MD -7; 95% CI -15.86, 1.86). [85]

Table 3.3.25 Question 2: Results for iron therapy in critically ill patients (blood transfusion)

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
Level II studies								
Pieracci et al (2009)[90] *Poor*	Critically ill surgical patients	Oral iron vs placebo	42 days or hospital discharge	Incidence of RBC transfusion, n/N (%) (N=200)	29/97 (29.9)	46/103 (44.7)	NR	*Favours iron therapy* P=0.03
				Incidence of RBC transfusion (patients with iron-deficient erythropoiesis), n/N (%) (N=200)	NR/NR (30.7)	NR/NR (68.4)	NR	*Favours iron therapy* P<0.01
				Incidence of RBC transfusion (patients without iron-deficient erythropoiesis), n/N (%) (N=200)	NR	NR	NR	*No significant difference* P>0.05
				Incidence of RBC transfusion (patients who had received a blood transfusion prior to study enrolment), n/N (%) (N=200)	NR	NR	NR	*Favours iron therapy* P<0.01
				Incidence of RBC transfusion (patients who had not received a blood transfusion prior to study enrolment), n/N (%) (N=200)	NR/NR (29.6)	NR/NR (35.7)	NR	*No significant difference* P=0.39
				Incidence of RBC transfusion (patients with an APACHE II score greater than 12), n/N (%) (N=200)	NR/NR (37.3)	NR/NR (59.6)	NR	*Favours iron therapy* P=0.02
				Incidence of RBC transfusion (patients with an APACHE II score lower than 12), n/N (%) (N=200)	NR	NR	NR	*No significant difference* P=0.24

Study *Quality*	Patient population	Intervention vs comparator	Length of follow-up	Outcome No. trials (no. patients)	Results			
					Intervention	Comparator	Risk estimate (95% CI)	Significance P-value Heterogeneity P-value (I^2)
van Iperen et al (2000)[85] *Poor*	ICU patients	IV iron vs no iron therapy	21 days	Total volume of blood transfused, units (N=24)	63	140	NR	NR
				Mean (SD) volume of blood transfused, units (N=24)	5 (7)	12 (14)	MD -7 (-15.86, 1.86)	*No significant difference* P>0.05

APACHE, Acute Physiological and Chronic Health Evaluation; CI, confidence interval; EPO, erythropoietin; ICU, intensive care unit; IV, intravenous; MD, mean difference; NR, not reported; RBC, red blood cell; SD, standard deviation

Thromboembolic events

Neither of the included studies reported the incidence of thromboembolic events as an outcome.

3.3 Question 3

Question 3 (Interventional question)

In critically ill patients, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes?

FFP, fresh frozen plasma

3.3.1 Fresh Frozen Plasma

Evidence statements
In patients with trauma, the effect of FFP on mortality is uncertain. (D, C, D, B, B) (See evidence matrix EM3.A in Volume 2 of the technical report)
In patients with trauma, FFP may be associated with transfusion-related serious adverse events. (D, B, C, B, B) (See evidence matrix EM3.B in Volume 2 of the technical report)
In non-trauma patients, FFP may be associated with transfusion-related serious adverse events. (D, NA, D, B, B) (See evidence matrix EM3.C in Volume 2 of the technical report)
In critically ill elderly patients, the effect of FFP on mortality is uncertain. (D, NA, NA, B, B) (See evidence matrix EM3.D in Volume 2 of the technical report)
In critically ill elderly patients, transfusion of FFP may be independently associated with the development of ARDS or ALI. (D, NA, B,A, B) (See evidence matrix EM3.E in Volume 2 of the technical report)

Practice points	
PP5	The routine use of FFP in critically ill patients with coagulopathy is not advised. The underlying causes of coagulopathy should be identified.
PP6	The administration of FFP may be independently associated with adverse events, including ARDS and ALI. The decision to transfuse these products to an individual patient should take into account the relative risks and benefits.
PP7	Assessment of bleeding risk is complex and requires careful consideration of patients' clinical status and laboratory parameters. Specialist haematology advice may also be required. However, patients with an INR ≤2 may not benefit from the administration of FFP and can generally undergo invasive procedures within the ICU without any serious bleeding; higher INRs may be tolerated in certain clinical situations.
ALI, acute lung injury; ARDS, acute respiratory distress syndrome; FFP, fresh frozen plasma; ICU, intensive care unit; INR, international normalised ratio; PP, practice point	

Summary of the evidence

Transfusion of fresh frozen plasma (FFP) is a therapeutic intervention used in a range of clinical scenarios, including critical bleeding and massive transfusion, surgery, warfarin reversal in patients with and without severe bleeding, liver disease, coagulation factor deficiencies, and thrombotic thrombocytopenic purpura (TTP). In critically ill patients, FFP is often used in patients with abnormal coagulation test results under the assumptions that these tests accurately predict bleeding, and that transfusion will reduce that risk. The use of plasma is associated with a range of side effects including infection, allergic reactions, hemolysis, transfusion related circulatory volume overload (TACO) and transfusion related acute lung injury (TRALI). Therefore, the risks and benefits of FFP transfusion in critically ill patients need to be carefully considered prior to use.

The current systematic review presents the efficacy and safety results of studies comparing FFP transfusion with either (i) no FFP or (ii) FFP using a different transfusion protocol (e.g. restrictive vs liberal transfusion). Studies in a perioperative setting or critical bleeding/massive transfusion setting were also excluded, as these have been covered in other modules of the PBM guidelines.

As this is an intervention question, the levels of evidence are as follows: Level I – a systematic review of two or more Level II studies; Level II – an RCT; Level III – (I) a pseudo-randomised RCT, (II) a comparative study with concurrent controls and (III) a comparative study without concurrent controls; and Level IV – case series with either post-test or pre-test/post-test outcomes. For this question, the search was limited to studies that could be categorised as Level III or above.

The literature search identified no systematic reviews that specifically addressed the PICO criteria specified in the Researchl Protocol. The search identified two RCTs and seven Level III-2 cohort studies. To minimise bias, the eligible cohort studies were limited to those that adjusted for confounding variables using multivariate logistic regression.

The included studies assessed the use of FFP in the following populations: trauma, critically ill elderly patients, and patients with severe closed head injury.

FFP TRANSFUSION STRATEGIES FOR PATIENTS WITH TRAUMA

Methods

There were five studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no systematic reviews comparing FFP transfusion strategies in patients with trauma.

Level II evidence

The literature search identified no RCTs comparing FFP transfusion strategies in patients with trauma.

Level III evidence

There were five studies identified from the systematic review and hand searching process (see Appendix C, Volume 2). The main characteristics of these studies are summarised in **Table 3.3.19**.

The objective of the retrospective study by Inaba et al (2010) was to determine the outcomes (in-hospital mortality and complications) of plasma administration in trauma patients who required blood but did not undergo a massive transfusion. [91] The study used propensity scoring to match patients in two cohorts: those who received plasma in the first 12 hours of admission and those who did not. It should be noted that patients who received plasma more than 12 hours after admission were included in the non-plasma group.

The study by Bochicchio et al (2008a) was a prospective observational cohort study of 766 trauma patients admitted to the ICU, who received MV for ≥ 48 h, and who did not have pneumonia on admission. [92] The study was designed to assess the relationship between transfusions of RBC concentrate, FFP, or platelets and the incidence of ventilator associated pneumonia (VAP).

The study by Bochicchio et al (2008b) was designed to examine risk-adjusted outcome in trauma with stratification by blood product type. [13] Prospective data were collected daily for 1,172 consecutive trauma patients admitted to the ICU during a 2-year period, including transfusion rates of blood products (PRBCs, FFP, platelets). Outcome assessment included infection rate, ventilator days, ICU and hospital length of stay, and mortality.

The study by Spinella et al (2008) was a retrospective review of 708 patients transfused at least one unit of a blood product at one combat support hospital between November 2003 and December 2004. [31] The study population included combat victims who received one or more units of any blood product, including RBCs, FFP, and fresh whole blood. A subgroup analysis that included only those who did not receive a massive transfusion was also performed to provide another method to determine whether the effects measured in the primary analysis were predominantly influenced by patients who received massive transfusions. It should be noted that a proportion of the patients underwent surgical procedures.

The study by Watson et al (2009) was a prospective cohort study evaluating clinical outcomes in bluntly injured adults with haemorrhagic shock. [93] All patients required blood transfusion for enrolment. Patients with isolated traumatic brain injury and those not surviving beyond 48 hours were excluded. It should be noted that Factor VIIa use was not able to be controlled for as it was not originally a data point recorded in the overall cohort analysis. Its use has only been prospectively collected since December of 2006, and consequently differences in factor VIIa use may represent a significant confounder for the results of this study.

All studies used multivariate logistic regression analyses to control for variables that could influence outcomes and create bias. It should also be noted that in all the studies, the majority of patients received RBC transfusions in addition to FFP transfusion; however, the impact of other transfusion interventions on outcomes was adjusted for in the analysis.

Table 3.3.26 Question 3 (FFP): Characteristics and quality of Level III evidence

Level III evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Inaba et al (2010)[91]	Retrospective observational cohort study *Good*	Trauma patients requiring nonmassive transfusion (<10 U packed RBC within 12 hours of admission) N=1685	FFP during the first 12 hours after admission	No FFP during the first 12 hours after admission	In-hospital mortality In-hospital complications Ventilation days ICU LOS Hospital LOS
Bochicchio et al (2008a)[92]	Prospective observational cohort study *Fair*	Trauma patients who received MV N=766	FFP	No FFP	VAP
Bochicchio et al (2008b)[13]	Prospective observational cohort study *Fair*	Trauma patients N=1172	FFP	No FFP	Infection Hospital LOS ICU LOS Mortality
Spinella et al (2008)[31]	Retrospective cohort study Poor	Combat victims who received one or more units of any blood product, who did not receive massive transfusion N=567	FFP transfusion (units)	N/A	In-hospital mortality (survival)
Watson et al (2009)[93]	Prospective observational cohort study *Poor*	Severely injured blunt trauma patients with haemorrhagic shock, where the majority of patients did not require massive transfusion N= 1175	FFP transfusion (1 unit)	N/A	Mortality Multiple organ failure Nosocomial infection Acute Respiratory Distress Syndrome

FFP, fresh frozen plasma; ICU, Intensive Care Unit; LOS, Length of Stay; MV mechanical ventilation; RBC, red blood cell; VAP, ventilator associated pneumonia

Results

Mortality

Mortality was reported in four of the included studies. [13,31,91,93] **Table 3.3.27** provides a summary of these results.

Bochicchio et al (2008b) found that FFP transfusion was significantly and independently associated with mortality: OR 1.03 (95% CI 1.02, 1.05; P<0.001).[13] In contrast, Spinella et al (2008) found that FFP transfusion was significantly and independently associated with improved survival: OR 1.22 (95% CI 1.0, 1.48; P=0.05).[31] Both Inaba et al (2010) and Watson et al (2009) reported no significant association between FFP transfusion and mortality, although Inaba et al (2010) reported a trend for greater mortality in patients treated with FFP.[91,93]

Table 3.3.27 Question 3: Results for different FFP transfusion strategies (mortality)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	*Significance* [a] P-value
LEVEL III-2 STUDIES										
Inaba et al (2010)	Level III-2 *Good*	N=1685 (including 516 patients who received FFP in the first 12 hours). After propensity score matching, 284 matched pairs were available for analysis.	Trauma patients requiring nonmassive transfusion (<10 U packed RBC within 12 hours of admission)	A single site in the USA	FFP during the first 12 hours after admission	In-hospital mortality	49/284 (17.3%)	40/284 (14.1%)	OR: 1.3 (0.8–2.0)	*No significant effect* P=0.30
							Included in the propensity score model were all variables that differed significantly (at the p<0.05 level) between the plasma and no plasma cohorts (injury mechanism, ventilator requirements, systolic blood pressure and GCS on admission, ISS, Abbreviated Injury Scale, total volumes of PRBC, platelets, and cryoprecipitate received at 12 and 24 hours and during the total hospital stay).			
Bochicchio et al (2008b)	Level III-2 *Fair*	N=1172 (including 56 patients who received FFP *only*)	Trauma patients	Trauma centre in the USA	FFP vs no FFP	Mortality	NR	NR	OR: 1.03 (1.02–1.05)	*FFP transfusion is significantly and independently associated with mortality* P<0.001
							Multiple logistic regression analyses were used for binary outcomes, using the covariates age, sex, race, and ISS as adjusters.			
Spinella et al (2008)	Level III-2 *Poor*	N= 567 (including 215 who received FFP transfusion)	Combat victims who received one or more units of any blood product, who did not receive massive transfusion	A combat support hospital in Iraq	Different amounts of FFP (units)	In-hospital survival	NR	NR	OR: 1.22 (1.0, 1.48)	*An increase in FFP transfusion units is significantly and independently associated with improved survival* P=0.05
							Multivariate logistic regression was used to adjust for confounding variables that were associated with survival on univariate analysis. Potential confounding variables included Glasgow Coma Scale score, age, heart rate (bpm), systolic blood pressure (mm Hg), temperature, haematocrit, pH, base deficit, INR, red blood cell (units), massive transfusion, rFVIII% use, Injury Severity Score (ISS).			

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	*Significance* [a] P-value
Watson et al (2009)	Level III-2 *Poor*	N= 1,175 (including 764 patients who were given FFP)	Severely injured blunt trauma patients with haemorrhagic shock, where the majority of patients did not require massive transfusion	Seven institutions in USA	Different amounts of FFP (units)	Mortality	NR	NR	HR: 0.996 (0.96–1.03)	*No significant effect* P=0.821
							Confounders for the final regression model included patient age, gender, abbreviated injury scores (head, neck, chest, abdomen, extremities, and spine), acute physiology and chronic health evaluation II score, presenting Glasgow Coma Score, 24-hour blood, and crystalloid requirements, worst base deficit in the first 12 hours, lowest core body temperature in the first 24 hours, initial emergency department international normalized ratio, the requirement of early operative intervention (exploratory laparotomy or thoracotomy/sternotomy), comorbidities (hypertension, diabetes, prior myocardial infarction, chronic obstructive pulmonary disease, renal disease, and liver disease), and relevant prehospital medications (aspirin, coumadin, and other platelet inhibitors).			

CI, confidence interval; FFP, fresh frozen plasma; HR, hazard ratio; INR, international normalisation ratio; ISS, injury severity score; NR, not reported; OR, odds ratio; USA, United States

Bleeding events

There were no studies reporting the incidence of bleeding events in patients with trauma receiving different FFP transfusion strategies.

Transfusion related serious adverse events

Transfusion related serious adverse events were reported in four of the included studies.[13,91-93] **Table 3.3.28** provides a summary of these results.

All four studies reported that FFP transfusion was significantly and independently associated with a range transfusion related serious adverse events; however, the individual studies reported different specific types of events.

For most adverse outcomes, Inaba et al (2010) reported a trend suggesting greater harm in patients treated with FFP. [91] For overall complications [OR 1.7 (95% CI 1.1, 2.4; P=0.016)] and ARDS [OR 3.0 (95% CI 1.4, 6.2; P=0.004)], this effect was statistically significant.

Bochicchio et al (2008a) found that FFP transfusion was significantly and independently associated with VAP: OR 3.34 (95% CI 1.18, 9.43; P=0.23).[92] Bochicchio et al (2008b) found that FFP transfusion was significantly and independently associated with infection: OR 1.02 (95% CI 1.01, 1.04; P<0.001).[13] Watson et al (2009) found that FFP transfusion was significantly and independently associated with ARDS [HR 1.021 (95% CI 1.001, 1.049; P=0.38)] and MOF [OR 1.021 (95% CI 1.002, 1.04; P=0.029), but not with nosocomial infection. [93]

Table 3.3.28 Question 3: Results for different FFP transfusion strategies (transfusion related serious adverse events)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	*Significance* [a] P-value
LEVEL III-2 STUDIES										
Inaba et al (2010)	Level III-2 *Good*	N=1685 (including 516 patients who received FFP in the first 12 hours). After propensity score matching, 284 matched pairs were available for analysis.	Trauma patients requiring nonmassive transfusion (<10 U packed RBC within 12 hours of admission).	A single site in the USA	FFP during the first 12 hours after admission	Overall complications	76/284 (26.8%)	52/284 (18.3%)	1.7 (1.1–2.4)	*FFP transfusion is significantly and independently associated with overall complications* P=0.016
						ARDS	28/284 (9.9%)	10/284 (3.5%)	3.0 (1.4–6.2)	*FFP transfusion is significantly and independently associated with* ARDS P=0.004
						MODS	24/284 (8.5%)	14/284 (4.9%)	1.8 (0.9–3.5)	*No significant effect* P=0.13
						Pneumonia	32/284 (11.3%)	20/284 (7.0%)	1.7 (0.9–3.0)	*No significant effect* P=0.11
						Sepsis	27/284 (9.5%)	15/284 (5.3%)	1.9 (1.0–3.6)	*No significant effect* P=0.08
						Line sepsis	6/284 (2.1%)	4/284 (1.4%)	1.5 (0.4–5.4)	*No significant effect* P=0.75
						Bacteraemia and fungemia	10/284 (3.5%)	9/284 (3.2%)	1.1 (0.5–2.8)	*No significant effect* P>0.99
						ARF	9/284 (3.2%)	4/284 (1.4%)	2.3 (0.7–7.5)	*No significant effect* P=0.27
						Included in the propensity score model were all variables that differed significantly (at the p<0.05 level) between the plasma and no plasma cohorts (injury mechanism, ventilator requirements, systolic blood pressure and GCS on admission, ISS, Abbreviated Injury Scale, total volumes of PRBC, platelets, and cryoprecipitate received at 12 and 24 hours and during the total hospital stay).			
Bochicchio et al (2008a)	Level III-2 *Fair*	N=766 (including 386 patients who received FFP)	Trauma patients who received MV	Single site in the USA	FFP vs no FFP	VAP	NR	NR	OR: 3.34 (1.18, 9.43)	*FFP transfusion is significantly and independently associated with VAP* *P=0.023*
						All data were subjected to univariate analysis with respect to VAP, and all variables found to be associated with VAP (p < 0.20) (sex, ISS, ventilator days, ICU length of stay prior to VAP) were entered in a stepwise logistic regression model with blood transfusion as the dependent variable.				

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	*Significance* [a] P-value
Bochicchio et al (2008b)	Level III-2 *Fair*	N=1172 (including 56 patients who received FFP)	Trauma patients	Trauma centre in the USA	FFP vs no FFP	Infection	NR	NR	1.02 (1.01–1.04)	*FFP transfusion is significantly and independently associated with infection* *P<0.001*
							Multivariate logistic regression was used to adjust for confounding variables that were associated with survival on univariate analysis. Potential confounding variables included Glasgow Coma Scale score, age, heart rate (bpm), systolic blood pressure (mm Hg), temperature, haematocrit, pH, base deficit, INR, red blood cell (units), massive transfusion, rFVIII% use, Injury Severity Score (ISS).			
Watson et al (2009)	Level III-2 *Poor*	N= 1,175 (including 764 patients who were given FFP)	Severely injured blunt trauma patients with haemorrhagic shock, where the majority of patients did not require massive transfusion	Seven institutions in USA	Different amounts of FFP (units)	Nosocomial infection	NR	NR	HR: 1.013 (0.993–1.033)	*No significant effect* *P=0.198*
						ARDS	NR	NR	HR: 1.025 (1.001–1.049)	*An increase in FFP transfusion units is significantly and independently associated with ARDS* P=0.038
						MOF	NR	NR	HR: 1.021 (1.002–1.04)	An increase in FFP transfusion units is significantly and independently associated with MOF P=0.029
							Confounders for the final regression model included patient age, gender, abbreviated injury scores (head, neck, chest, abdomen, extremities, and spine), acute physiology and chronic health evaluation II score, presenting Glasgow Coma Score, 24-hour blood, and crystalloid requirements, worst base deficit in the first 12 hours, lowest core body temperature in the first 24 hours, initial emergency department international normalized ratio, the requirement of early operative intervention (exploratory laparotomy or thoracotomy/sternotomy), comorbidities (hypertension, diabetes, prior myocardial infarction, chronic obstructive pulmonary disease, renal disease, and liver disease), and relevant prehospital medications (aspirin, coumadin, and other platelet inhibitors).			

ARDS, acute respiratory distress syndrome; ARF, acute renal failure; CI, confidence interval; FFP, fresh frozen plasma; HR, hazard ratio; ICU, intensive care unit; INR, international normalisation ratio; ISS, injury severity score; MODS, multiple organ dysfunction syndrome' MOF; multiple organ failure; MV, mechanical ventilation; NR, not reported; OR, odds ratio; PRBC, packed red blood cells; RBC, red blood cell; USA, United States; VAP, ventilator associated pneumonia

FFP TRANSFUSION STRATEGIES FOR NON-TRAUMA PATIENTS

Methods

There was one study identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no systematic reviews comparing FFP transfusion strategies in patients with trauma.

Level II evidence

The literature search identified no RCTs comparing FFP transfusion strategies in patients with trauma.

Level III evidence

There was one study identified from the systematic review and hand searching process (see Appendix C, Volume 2). The main characteristics of these studies are summarised in **Table 3.3.29**.

In the study by Sarani et al (2008), 380 non-trauma patients who received fresh frozen plasma from 2004 to 2005 were compared with 2,058 non-trauma patients who did not receive fresh frozen plasma. [94] The primary outcome was the incidence of infectious complications, including ventilator associated pneumonia (VAP) and bloodstream infection (BSI). It should be noted that the multivariate analysis only adjusted for three variables: PRBC transfusion, APACHE score and age.

Table 3.3.29 Question 3 (FFP, non-trauma): Characteristics and quality of Level III evidence

Level III evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Sarani et al (2008)[94]	Retrospective observational cohort study *Poor*	Patients admitted to the surgical intensive care unit excluding trauma patients N=2438	FFP transfusion (increasing units)	N/A	Infectious complications, including VAP and BSI

BSI, bloodstream infection; FFP, fresh frozen plasma; ICU; VAP, ventilator associated pneumonia

Results

Mortality

There were no studies comparing mortality in critically ill non-trauma patients receiving different FFP transfusion strategies.

Bleeding events

There were no studies reporting the incidence of bleeding events in patients with trauma receiving different FFP transfusion strategies.

Transfusion related serious adverse events

Sarani et al (2008) found that FFP transfusion was significantly and independently associated with the incidence of infectious complications [OR 1.039 (95% CI 1.013, 1.067; P<0.01)]. [94]
Table 3.3.30 provides a summary of these results.

Table 3.3.30 Question 3: Results for different FFP transfusion strategies (transfusion related serious adverse events)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	*Significance* [a] P-value
LEVEL III-2 STUDIES										
Sarani et al (2008)	Level III-2 *Poor*	N=2438 (including 380 patients who received FFP and 2,058 patients who did not).	Patients admitted to the surgical intensive care unit, excluding patients with trauma.	A single site in the USA	Different amounts of FFP (units)	Infectious complications	NR	NR	OR: 1.039 (1.013, 1.067)	*FFP transfusion is significantly and independently associated with infectious complications* *P<0.01*
							Multivariate logistic regression analyses with FFP, PRBCs, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and age were used to evaluate the association between FFP and infectious complication.			

CI, confidence interval; FFP, fresh frozen plasma; NR, not reported; OR, odds ratio; USA, United States

FFP TRANSFUSION STRATEGIES FOR CRITICALLY ILL ELDERLY PATIENTS

Methods

There were two studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no systematic reviews comparing FFP transfusion strategies in critically ill elderly patients.

Level II evidence

The literature search identified no RCTs comparing FFP transfusion strategies in critically ill elderly patients.

Level III evidence

There were two studies identified from the systematic review and hand searching process (see Appendix C, Volume 2). The main characteristics of these studies are summarised in **Table 3.3.31**.

The study by Dara et al (2005) collected data on all patients admitted to a medical ICU during a 5-month period who had abnormal coagulation, defined as an INR ≥ 1.5 times normal. [95] The average age of patients was 70 years, and it should be noted that 51% of patients were undergoing invasive procedures. Outcomes measured in this study included new bleeding episodes, FFP complications, ALI, circulatory overload, allergic reactions, hospital mortality ICU length of stay among survivors; however, only hospital mortality was measured in the multivariate logistic regression analysis.

The study by Khan et al (2007) was a single-centre retrospective cohort study in consecutive patients admitted to a medical ICU. [22] The reasons for FFP transfusion were active bleeding in 52% of patients, prior to invasive procedure in 31% of patients, and other conditions in 17% of patients. The incidence of ALI/ARDS was compared in patients who received blood product transfusions and those who did not, using univariate and multivariate propensity analyses.

In both studies, a proportion of patients also received RBC transfusions. In the study by Dara et al (2005), some patients also received Vitamin K. [95]

Table 3.3.31 Question 3 (FFP, elderly): Characteristics and quality of Level III evidence

Level III evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Dara et al (2005)[95]	Retrospective cohort study *Fair*	Critically ill elderly patients with abnormal coagulation (INR ≥ 1.5 times normal) N=115 (including 44 patients who received FFP transfusion)	FFP transfusion (median dose was 17 mL/kg)	No FFP	New bleeding episodes FFP complications Acute lung injury Circulatory overload Allergic reactions Hospital mortality ICU length of stay among survivors *Note: only hospital mortality was measured in the multivariate logistic regression analysis.*
Khan et al (2007)[22]	Retrospective cohort study *Good*	Critically ill elderly patients admitted to a medical ICU N= 841 (including 298 patients who were transfused with blood products and 122 were transfused with FFP)	FFP	No FFP	ALI/ARDS

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; FFP, fresh frozen plasma; ICU, Intensive Care Unit;

Results

Mortality

Mortality was only reported in the study by Dara et al (2005). The study found that FFP transfusion was not independently associated with mortality: OR 0.94 (95% CI 0.36, 2.39).[95] **Table 3.3.32** provides a summary of these results.

Table 3.3.32 Question 3: Results for different FFP transfusion strategies (mortality)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	*Significance* [a] P-value
LEVEL III-2 STUDIES										
Dara et al (2005)	Level III-2 *Fair*	N=115 (including 44 patients who received FFP transfusion)	Critically ill elderly patients with abnormal coagulation (INR ≥ 1.5 times normal)	24-bed medical ICU in the USA	FFP vs no FFP	Hospital mortality	NR	NR	OR: 0.94 (0.36-2.39) Potential confounding variables included age, sex, Acute Physiology and Chronic Health Evaluation (APACHE) III Score, INR level, indication	*No significant effect* P-value not reported

CI, confidence interval; FFP, fresh frozen plasma; ICU, intensive care unit; INR, international normalisation ratio; NR, not reported; OR, odds ratio; USA, United States

Bleeding events

There were no studies reporting the incidence of bleeding events in patients with trauma receiving different FFP transfusion strategies.

Transfusion related serious adverse events

Transfusion related serious adverse events were reported in the study by Khan et al (2007). [22] **Table 3.3.33** provides a summary of these results. The study found that FFP transfusion was significantly and independently associated with ARDS/ALI: OR 2.48 (95% CI: 1.29, 4.74).

Table 3.3.33 Question 3: Results for different FFP transfusion strategies (transfusion related serious adverse events)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	*Significance* [a] P-value
LEVEL III-2 STUDIES										
Khan et al (2007)	Level III-2 *Good*	N= 841 (including 298 patients who were transfused with blood products and 122 were transfused with FFP)	Critically ill elderly patients admitted to a medical ICU	A 24-bed general medical non-cardiac medical ICU (MICU) in the USA	FFP vs no FFP	ALI/ARDS	NR	NR	OR: 2.48 (1.29–4.74)	*FFP transfusion is significantly and independently associated with ARDS/ALI* P-value not reported
							All data were subjected to univariate analysis with respect to VAP, and all variables found to be associated with VAP ($p < 0.20$) (sex, ISS, ventilator days, ICU length of stay prior to VAP) were entered in a stepwise logistic regression model with blood transfusion as the dependent variable.			

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CI, confidence interval; FFP, fresh frozen plasma; ICU, intensive care unit; ISS, injury severity score; NR, not reported; OR, odds ratio; VAP ventilator associated pneumonia

DIFFERENT FFP TRANSFUSION STRATEGIES FOR PATIENTS WITH TRAUMATIC BRAIN INJURY

Methods

There was one study identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no systematic reviews examining different transfusion strategies in patients with traumatic brain injury.

Level II evidence

There was one eligible study identified from the systematic review and hand searching process (see Appendix C, Volume 2). The main characteristics of this study are summarised in **Table 3.3.34**.

The study by Etemadrezaie et al (2007) was good quality double-blind RCT in 90 patients with severe closed head injury. [96] Patients were randomised to receive either FFP or normal saline. It should be noted that FFP is not commonly used in Australia for this indication, and patients enrolled in this study were not actively bleeding. *Since the results of this study have limited applicability to the Australian critical care setting, no evidence statements have been made in relation to this subpopulation. Evidence for patients with traumatic brain injury is provided for interest and will not be considered further.*

Table 3.3.34 Question 3 (FFP, traumatic brain injury): Characteristics and quality of Level II evidence

Level II evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Etemadrezaie (2007)[96]	RCT *Good*	Patients with severe closed head injury (Glasgow coma scale ≤ 8), no mass lesion required evacuation and no history of coagulopathy. N=90	FFP 10-15 mL/kg	Normal saline 10-15 mL/kg	Mortality New lesion Intracerebral haemorrhage Subarachnoid haemorrhage Intraventricular haemorrhage Extraaxial haematoma

FFP, fresh frozen plasma; RCT, randomised controlled trial

Results

Mortality

Mortality was reported in the study by Etemadrezaie et al (2007). **Table 3.3.35** provides a summary of these results. The study found a significant increase in the risk of mortality in patients treated with FFP (RR 1.83; 95% CI: 1.16, 2.88; p=0.009).[96] It should be noted that FFP is not commonly used in Australia for this indication, and the results of this study therefore have limited applicability to the Australian critical care setting.

Table 3.3.35 Question 3: Results for different transfusion strategies in patients with traumatic brain injury (mortality)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value *Heterogeneity* [b] P-value (I^2)
LEVEL II STUDIES										
Etemadrezaie (2007)	Level II Good	90	Patients with severe closed head injury (Glasgow coma scale ≤ 8), no mass lesion required evacuation and no history of coagulopathy.	Shahid Kamyab (Emdadi) Hospital, Mashhad, Iran	FFP 10-15 mL/kg vs. Normal saline 10-15 mL/kg	Mortality	28/44 (64)	16/46 (35)	1.83 (1.16-2.88)	*FFP is significantly associated with increased mortality* P=0.009

CI, confidence interval; FFP, fresh frozen plasma

[a] Relative risk and statistical significance were calculated independently in Review Manager 5, using Mantel-Haenszel statistical methods and a random effects analysis model.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2<25%; moderate heterogeneity if I2 between 25%-50%; substantial heterogeneity if I2>50%.

Bleeding events

A number of different types of bleeding event were reported in the study by Etemadrezaie et al (2007). **Table 3.3.36** provides a summary of these results.

There was a significantly increased risk of intracerebral haemorrhage in patients treated with FFP compared to normal saline (RR 17.76; 95% CI: 1.06, 298.69). There was no significant benefit associated with FFP treatment for: the development of new lesions, subarachnoid haemorrhage, intraventricular haemorrhage or extraaxial haematoma.[96] It should be noted that FFP is not commonly used in Australia for this indication, and the results of this study therefore have limited applicability to the Australian critical care setting.

Table 3.3.36 Question 3: Results for different transfusion strategies in patients with traumatic brain injury (bleeding events)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Relative risk (95% CI)	*Significance* [a] P-value *Heterogeneity* [b] P-value (I^2)
LEVEL II STUDIES										
Etemadrezaie (2007)	Level II Good	90	Patients with severe closed head injury (Glasgow coma scale ≤ 8), no mass lesion required evacuation and no history of coagulopathy.	Shahid Kamyab (Emdadi) Hospital, Mashhad, Iran	FFP 10-15 mL/kg vs. Normal saline 10-15 mL/kg	New lesion	9/44 (20)	4/46 (9)	2.35 (0.78-7.09)	*Favours comparator* P=0.13
						Intracerebral haemorrhage	8/44 (18)	0/46 (0)	17.76 (1.06-298.69)	*Favours comparator* P=0.05
						Subarachnoid haemorrhage	2/44 (5)	2/46 (4)	1.05 (0.15-7.10)	*No significant effect* P=0.96
						Intraventricular haemorrhage	1/44 (2)	0/46 (0)	3.13 (0.13-74.93)	*No significant effect* P=0.96
						Extraaxial haematoma	0/44 (0)	1/46 (2)	0.35 (0.01-8.33)	*No significant effect* P=0.51

CI, confidence interval; FFP, fresh frozen plasma

[a] Relative risk and statistical significance were calculated independently in Review Manager 5, using Mantel-Haenszel statistical methods and a random effects analysis model.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I2<25%; (ii) mild heterogeneity if I2<25%; moderate heterogeneity if I2 between 25%-50%; substantial heterogeneity if I2>50%.

Transfusion related serious adverse events

There were no studies reporting the incidence of transfusion related serious adverse events in patients with traumatic brain injury receiving plasma transfusions.

3.3.2 Fibrinogen concentrate and cryoprecipitate

Evidence statements
In patients with trauma, the effect of cryoprecipitate on mortality is uncertain. (D, NA, NA, B, B) (See evidence matrix EM3.H in Volume 2 of the technical report)
In patients with trauma, the effect of cryoprecipitate on transfusion-related serious adverse events is uncertain. (D, NA, D, B, B) (See evidence matrix EM3.I in Volume 2 of the technical report)

Practice points	
PP8	The routine use of cryoprecipitate and fibrinogen concentrate in critically ill patients with coagulopathy is not advised. The underlying causes of coagulopathy should be identified.
PP9	The effect of cryoprecipitate and fibrinogen on transfusion-related serious adverse events is uncertain. The decision to transfuse cryoprecipitate or fibrinogen to an individual patient should take into account the relative risks and benefits.
PP, practice point	

Summary of the evidence

Fibrinogen and cryoprecipitate are therapeutic interventions used in for the correction of low fibrinogen levels. In critically ill patients, fibrinogen and cryoprecipitate transfusions are used in patients with hypofibrinogenaemia under the assumptions that low fibrinogen levels accurately predict bleeding, and that transfusion will reduce that risk.

The current systematic review presents the efficacy and safety results of studies comparing fibrinogen or cryoprecipitate transfusion with either (i) no fibrinogen or cryoprecipitate or (ii) fibrinogen or cryoprecipitate using a different transfusion protocol (e.g. at a different fibrinogen trigger level). Studies in a perioperative setting or critical bleeding/massive transfusion setting were also excluded, as these have been covered in other modules of the PBM guidelines.

As this is an intervention question, the levels of evidence are as follows: Level I – a systematic review of two or more Level II studies; Level II – an RCT; Level III – (I) a pseudo-randomised RCT, (II) a comparative study with concurrent controls and (III) a comparative study without concurrent controls; and Level IV – case series with either post-test or pre-test/post-test outcomes. For this question, the search was limited to studies that could be categorised as Level III or above.

The literature search identified no systematic reviews that specifically addressed the PICO criteria specified in the Research Protocol. The search identified one Level III-2 cohort

studies. To minimise bias, the eligible cohort studies were limited to those that adjusted for confounding variables using multivariate logistic regression.

The included study assessed the use of cryoprecipitate in patients with trauma.

FIBRINOGEN/CRYOPRECIPITATE TRANSFUSION STRATEGIES FOR PATIENTS WITH TRAUMA

Methods

There were four studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no systematic reviews comparing FFP transfusion strategies in patients with trauma.

Level II evidence

The literature search identified no RCTs comparing FFP transfusion strategies in patients with trauma.

Level III evidence

There was one study identified from the systematic review and hand searching process (see Appendix C, Volume 2). The main characteristics of this study are summarised in **Table 3.3.37**.

The study by Watson et al (2009) was a prospective cohort study evaluating clinical outcomes in bluntly injured adults with haemorrhagic shock. [93] All patients required blood transfusion for enrollment. Patients with isolated traumatic brain injury and those not surviving beyond 48 hours were excluded. It should be noted that Factor VIIa use was not able to be controlled for as it was not originally a data point recorded in the overall cohort analysis. Its use has only been prospectively collected since December of 2006, and consequently differences in factor VIIa use may represent a significant confounder for the results of this study. Multivariate logistic regression was used to control for variables that could influence outcomes and create bias. It should also be noted that the majority of patients received RBC transfusions in addition to FFP transfusion.

Table 3.3.37 Question 3 (fibrinogen/cryoprecipitate): Characteristics and quality of Level III evidence

Level III evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Watson et al (2009)[93]	Prospective observational cohort study *Poor*	Severely injured blunt trauma patients with haemorrhagic shock, where the majority of patients did not require massive transfusion N= 1175	Cryoprecipitate (1 unit)	N/A	Mortality Multiple organ failure Nosocomial infection Acute Respiratory Distress Syndrome

Results

Mortality

Mortality was reported in the study by Watson et al 2009, and **Table 3.3.38** provides a summary of these results. The study reported no significant effect on mortality as a result of cryoprecipitate transfusion. [93]

Table 3.3.38 Question 3: Results for different cryoprecipitate transfusion strategies (mortality)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	*Significance* [a] P-value
LEVEL III-2 STUDIES										
Watson et al (2009)	Level III-2 *Poor*	N= 1,175 (including 479 patients who were given cryoprecipitate)	Severely injured blunt trauma patients with haemorrhagic shock, where the majority of patients did not require massive transfusion	Seven institutions in USA	Different amounts of cryoprecipitate (units)	Mortality	NR	NR	HR: 1.006 (0.96–1.06)	*No significant effect* P=0.828
							Confounders for the final regression model included patient age, gender, abbreviated injury scores (head, neck, chest, abdomen, extremities, and spine), acute physiology and chronic health evaluation II score, presenting Glasgow Coma Score, 24-hour blood, and crystalloid requirements, worst base deficit in the first 12 hours, lowest core body temperature in the first 24 hours, initial emergency department international normalized ratio, the requirement of early operative intervention (exploratory laparotomy or thoracotomy/sternotomy), comorbidities (hypertension, diabetes, prior myocardial infarction, chronic obstructive pulmonary disease, renal disease, and liver disease), and relevant prehospital medications (aspirin, coumadin, and other platelet inhibitors).			

CI, confidence interval; HR, hazard ratio; NR, not reported; USA, United States

Bleeding events

There were no studies reporting the incidence of bleeding events in patients with trauma receiving different FFP transfusion strategies.

Transfusion related serious adverse events

Transfusion related serious adverse events were reported in the study by Watson et al (2009) and **Table 3.3.39** provides a summary of these results. The study found that an increase in cryoprecipitate transfusion units was independently and significantly associated with MOF [HR 0.956 (95 % CI 0.923–0.989; P=0.01)], but not ARDS or nosocomial infection.[93]

Table 3.3.39 Question 3: Results for different cryoprecipitate transfusion strategies (transfusion related serious adverse events)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	*Significance* [a] P-value
LEVEL III-2 STUDIES										
Watson et al (2009)	Level III-2 *Poor*	N= 1,175 (including 479 patients who were given cryoprecipitate)	Severely injured blunt trauma patients with haemorrhagic shock, where the majority of patients did not require massive transfusion	Seven institutions in USA	Different amounts of cryoprecipitate (units)	Nosocomial infection	NR	NR	HR: 0.997 (0.968–1.028)	*No significant effect* P=0.858
						ARDS	NR	NR	HR: 1.03 (0.997–1.065)	*No significant effect* P=0.076
						MOF	NR	NR	HR: 0.956 (0.923–0.989)	*An increase in cryoprecipitate transfusion units is significantly and independently associated with MOF* P=0.01
						Confounders for the final regression model included patient age, gender, abbreviated injury scores (head, neck, chest, abdomen, extremities, and spine), acute physiology and chronic health evaluation II score, presenting Glasgow Coma Score, 24-hour blood, and crystalloid requirements, worst base deficit in the first 12 hours, lowest core body temperature in the first 24 hours, initial emergency department international normalized ratio, the requirement of early operative intervention (exploratory laparotomy or thoracotomy/sternotomy), comorbidities (hypertension, diabetes, prior myocardial infarction, chronic obstructive pulmonary disease, renal disease, and liver disease), and relevant prehospital medications (aspirin, coumadin, and other platelet inhibitors).			

ARDS, acute respiratory distress syndrome; CI, confidence interval; HR, hazard ratio; MOF; multiple organ failure; NR, not reported; USA, United States;

3.3.3 Platelet transfusion

Evidence statements
In patients with trauma, the effect of platelet transfusion on mortality is uncertain. (D, A, NA, B, B) (See evidence matrix EM3.J in Volume 2 of the technical report)
In patients with trauma, the effect of platelet transfusion on transfusion-related serious adverse events is uncertain. (D, C, C, B, B) (See evidence matrix EM3.K in Volume 2 of the technical report)
In critically ill elderly patients, the effect of platelet transfusion on transfusion-related serious adverse events is uncertain. (D, NA, C, A, B) (See evidence matrix EM3.L in Volume 2 of the technical report)

Practice points	
PP10	The effect of platelet transfusion on transfusion-related serious adverse events is uncertain. The decision to transfuse platelets to an individual patient should take into account the relative risks and benefits.
PP11	In critically ill patients, in the absence of acute bleeding, the administration of platelets may be considered appropriate at a platelet count of $<20 \times 10^9$.
PP12	Assessment of bleeding risk is complex and requires careful consideration of patients' clinical status and laboratory parameters. Specialist haematology advice may also be required. However, patients with a platelet count $\geq 50 \times 10^9$ can generally undergo invasive procedures within the ICU without any serious bleeding; lower platelet counts may be tolerated in certain clinical situations.

Research recommendations
Further research evaluating the effects of a lower platelet trigger is warranted.
Evaluation of the utility of POC testing in guiding coagulation management is required.

Summary of the evidence

Platelet transfusions are frequently used to correct thrombocytopenia in critically ill patients. The use of platelet transfusion is associated with a range of side effects including bacterial contamination, allergic reactions, febrile reactions, venous thromboembolism, TRALI and TACO. Therefore, the risks and benefits of platelet transfusion in critically ill patients need to be carefully considered prior to use.

The current systematic review presents the efficacy and safety results of studies comparing platelet transfusion with either (i) no platelet transfusion or (ii) platelet transfusion using a different transfusion protocol (e.g. restrictive vs liberal transfusion). Studies in a perioperative setting or critical bleeding/massive transfusion setting were also excluded, as these have been covered in other modules of the PBM guidelines. Evidence relating to non-massively transfused oncology patients is presented in the Medical module of the PBM guidelines.

As this is an intervention question, the levels of evidence are as follows: Level I – a systematic review of two or more Level II studies; Level II – an RCT; Level III – (I) a pseudo-randomised RCT, (II) a comparative study with concurrent controls and (III) a comparative study without concurrent controls; and Level IV – case series with either post-test or pre-test/post-test outcomes. For this question, the search was limited to studies that could be categorised as Level III or above.

The literature search identified no systematic reviews that specifically addressed the PICO criteria specified in the Research Protocol. The search identified four Level III-2 cohort studies. To minimise bias, the eligible cohort studies were limited to those that adjusted for confounding variables using multivariate logistic regression.

The included studies assessed the use of platelet transfusion in the following populations: trauma and critically ill elderly patients.

PLATELET TRANSFUSION STRATEGIES FOR PATIENTS WITH TRAUMA

Methods

There were three studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no systematic reviews comparing platelet transfusion strategies in patients with trauma.

Level II evidence

The literature search identified no RCTs comparing platelet transfusion strategies in patients with trauma.

Level III evidence

There were three studies identified from the systematic review and hand searching process (see Appendix C, Volume 2). The main characteristics of these studies are summarised in **Table 3.3.40**.

The study by Bochicchio et al (2008a) was a prospective observational cohort study of 766 trauma patients admitted to the ICU, who received MV for ≥ 48 h, and who did not have pneumonia on admission. [92] The study was designed to assess the relationship between transfusions of RBC concentrate, FFP, or platelets and the incidence of ventilator associated pneumonia (VAP).

The study by Bochicchio et al (2008b) was designed to examine risk-adjusted outcome in trauma with stratification by blood product type. [13] Prospective data were collected daily for 1,172 consecutive trauma patients admitted to the ICU during a 2-year period, including transfusion rates of blood products (PRBCs, FFP, platelets). Outcome assessment included infection rate, ventilator days, ICU and hospital length of stay, and mortality.

The study by Watson et al (2009) was a prospective cohort study evaluating clinical outcomes in bluntly injured adults with haemorrhagic shock. [93] All patients required blood transfusion for enrollment. Patients with isolated traumatic brain injury and those not surviving beyond 48 hours were excluded. It should be noted that Factor VIIa use was not able to be controlled for as it was not originally a data point recorded in the overall cohort analysis. Its use has only been prospectively collected since December of 2006, and consequently differences in factor VIIa use may represent a significant confounder for the results of this study.

All studies used multivariate logistic regression analyses to control for variables that could influence outcomes and create bias. It should also be noted that in all the studies, the majority of patients received RBC transfusions in addition to platelet transfusion; however, the impact of other transfusion interventions on outcomes was adjusted for in the analysis.

Table 3.3.40 Question 3 (platelets, trauma): Characteristics and quality of Level III evidence

Level III evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Bochicchio et al (2008a)[92]	Prospective observational cohort study *Poor*	Trauma patients who received MV N=766	Platelet transfusion	No platelet transfusion	VAP
Bochicchio et al (2008b)[13]	Prospective observational cohort study *Poor*	Trauma patients N=1172	Platelet transfusion	No platelet transfusion	Infection Hospital LOS ICU LOS Mortality
Watson et al (2009)[93]	Prospective observational cohort study *Poor*	Severely injured blunt trauma patients with haemorrhagic shock, where the majority of patients did not require massive transfusion N= 1175	Platelet transfusion (1 unit)	N/A	Mortality Multiple organ failure Nosocomial infection Acute Respiratory Distress Syndrome

ICU, Intensive Care Unit; LOS, Length of Stay; MV mechanical ventilation; VAP, ventilator associated pneumonia;

Results

Mortality

Mortality was reported in two of the included studies. **Table 3.3.41** provides a summary of these results. Both studies reported no significant association between platelet transfusion and mortality.[13,93]

Table 3.3.41 Question 3: Results for different platelet transfusion strategies (mortality)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	*Significance* [a] P-value
LEVEL III-2 STUDIES										
Bochicchio et al (2008b)	Level III-2 *Poor*	N=1172 (including 4 patients who received platelets *only*)	Trauma patients	Trauma centre in the USA	Platelet transfusion vs no platelet transfusion	Mortality	NR	NR	OR: 1.03 (1.02–1.04) Multivariate logistic regression was used to adjust for confounding variables that were associated with survival on univariate analysis. Potential confounding variables included Glasgow Coma Scale score, age, heart rate (bpm), systolic blood pressure (mm Hg), temperature, haematocrit, pH, base deficit, INR, red blood cell (units), massive transfusion, rFVIII% use, Injury Severity Score (ISS).	*No significant effect* P-value not reported Note: the authors used a P-value of <0.001 to determine significance
Watson et al (2009)	Level III-2 *Poor*	N= 1,175 (including 481 patients who were given platelets)	Severely injured blunt trauma patients with haemorrhagic shock, where the majority of patients did not require massive transfusion	Seven institutions in USA	Different amounts of platelet transfusion (units)	Mortality	NR	NR	HR: 0.948 (0.83–1.08) Confounders for the final regression model included patient age, gender, abbreviated injury scores (head, neck, chest, abdomen, extremities, and spine), acute physiology and chronic health evaluation II score, presenting Glasgow Coma Score, 24-hour blood, and crystalloid requirements, worst base deficit in the first 12 hours, lowest core body temperature in the first 24 hours, initial emergency department international normalized ratio, the requirement of early operative intervention (exploratory laparotomy or thoracotomy/sternotomy), comorbidities (hypertension, diabetes, prior myocardial infarction, chronic obstructive pulmonary disease, renal disease, and liver disease), and relevant prehospital medications (aspirin, coumadin, and other platelet inhibitors).	*No significant effect* P=0.419

CI, confidence interval; HR, hazard ratio; INR, international normalisation ratio; NR, not reported; OR, odds ratio; USA, United States

Bleeding events

There were no studies reporting the incidence of bleeding events in patients with trauma receiving different platelet transfusion strategies.

Transfusion related serious adverse events

Transfusion related serious adverse events were reported in the three included studies.[13,92,93] **Table 3.3.42** provides a summary of these results. Only one study reported that platelet transfusion was significantly and independently associated with a range transfusion related serious adverse events;[92] however it should be noted that the individual studies reported different specific types of events. The other studies reported no significant effect for serious adverse event outcomes.[13,93]

Table 3.3.42 Question 3: Results for different platelet transfusion strategies (transfusion related serious adverse events)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	*Significance* [a] P-value
LEVEL III-2 STUDIES										
Bochicchio et al (2008a)	Level III-2 *Poor*	N=766 (including 45 patients who received platelets)	Trauma patients who received MV	Single site in the USA	Platelet transfusion vs no platelet transfusion	VAP	NR	NR	OR: 4.19 (1.37, 12.83)	*Platelet transfusion is significantly and independently associated with VAP* P=0.012
							All data were subjected to univariate analysis with respect to VAP, and all variables found to be associated with VAP ($p < 0.20$) (sex, ISS, ventilator days, ICU length of stay prior to VAP) were entered in a stepwise logistic regression model with blood transfusion as the dependent variable.			
Bochicchio et al (2008b)	Level III-2 *Poor*	N=1172 (including 4 patients who received platelets *only*)	Trauma patients	Trauma centre in the USA	FFP vs no FFP	Infection	NR	NR	OR: 0.94 (0.96–1)	*No significant effect* *P-value not reported*
							Multivariate logistic regression was used to adjust for confounding variables that were associated with survival on univariate analysis. Potential confounding variables included Glasgow Coma Scale score, age, heart rate (bpm), systolic blood pressure (mm Hg), temperature, haematocrit, pH, base deficit, INR, red blood cell (units), massive transfusion, rFVIII% use, Injury Severity Score (ISS).			
Watson et al (2009)	Level III-2 *Poor*	N= 1,175 (including 481 patients who were given platelets)	Severely injured blunt trauma patients with haemorrhagic shock, where the majority of patients did not require massive transfusion	Seven institutions in USA	Different amounts of platelet transfusion (units)	Nosocomial infection	NR	NR	HR: 1.01 (0.942–1.082)	*No significant effect* P=0.782
						ARDS	NR	NR	HR: 1.073 (0.985–1.168)	*No significant effect* P=0.105
						MOF	NR	NR	HR: 1.045 (0.978–1.117)	*No significant effect* P=0.196
							Confounders for the final regression model included patient age, gender, abbreviated injury scores (head, neck, chest, abdomen, extremities, and spine), acute physiology and chronic health evaluation II score, presenting Glasgow Coma Score, 24-hour blood, and crystalloid requirements, worst base deficit in the first 12 hours, lowest core body temperature in the first 24 hours, initial emergency department international normalized ratio, the requirement of early operative intervention (exploratory laparotomy or thoracotomy/sternotomy), comorbidities (hypertension, diabetes, prior myocardial infarction, chronic obstructive pulmonary disease, renal disease, and liver disease), and relevant prehospital medications (aspirin, coumadin, and other platelet inhibitors).			

ARDS, acute respiratory distress syndrome; CI, confidence interval; FFP, fresh frozen plasma; HR, hazard ratio; ICU, intensive care unit; INR, international normalisation ratio; ISS, injury severity score; MOF; multiple organ failure; NR, not reported; OR, odds ratio; USA, United States of America; VAP, ventilator associated pneumonia

PLATELET TRANSFUSION STRATEGIES FOR CRITICALLY ILL ELDERLY PATIENTS

Methods

There was one study identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no systematic reviews comparing platelet transfusion strategies in critically ill elderly patients.

Level II evidence

The literature search identified no RCTs comparing platelet transfusion strategies in critically ill elderly patients.

Level III evidence

There was one study identified from the systematic review and hand searching process (see Appendix C, Volume 2). The main characteristics of this study are summarised in **Table 3.3.43**.

The study by Khan et al (2007) was a single-centre retrospective cohort study in consecutive patients admitted to a medical ICU. [22] The reasons for platelet transfusion were active bleeding in 35% of patients, prior to invasive procedure in 52% of patients, and other conditions in 13% of patients. The incidence of ALI/ARDS was compared in patients who received blood product transfusions and those who did not, using univariate and multivariate propensity analyses.

Table 3.3.43 Question 3 (platelets, elderly): Characteristics and quality of Level III evidence

Level III evidence					
Study	Study type Study quality	Population N	Intervention	Comparator	Outcomes
Khan et al (2007)[22]	Retrospective cohort study *Good*	Critically ill elderly patients admitted to a medical ICU N= 841 (including 298 patients who were transfused with blood products and 122 were transfused with platelet)	Platelet transfusion	No platelet transfusion	ALI/ARDS

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ICU, Intensive Care Unit;

Results

Mortality

There were no studies reporting the incidence of bleeding events in critically ill elderly patients receiving different platelet transfusion strategies.

Bleeding events

There were no studies reporting the incidence of bleeding events in patients with trauma receiving different platelet transfusion strategies.

Transfusion related serious adverse events

Transfusion related serious adverse events were reported in the study by Khan et al (2007). **Table 3.3.44** provides a summary of these results. The study found that platelet transfusion was significantly and independently associated with ARDS/ALI: OR 3.89 (95% CI 1.36, 11.52).[22]

Table 3.3.44 Question 3: Results for different platelet transfusion strategies (transfusion related serious adverse events)

Study	Level of evidence *Quality*	Sample size	Patient population	Setting	Intervention	Outcome	Results			
							Intervention	Comparator	Risk estimate (95% CI)	*Significance* [a] P-value
LEVEL III-2 STUDIES										
Khan et al (2007)	Level III-2 *Good*	N= 841 (including 298 patients who were transfused with blood products and 122 were transfused with platelet)	Critically ill elderly patients admitted to a medical ICU	A 24-bed general medical non-cardiac medical ICU (MICU) in the USA	platelet vs no platelet	ALI/ARDS	NR	NR	OR: 3.89 (1.36–11.52) All data were subjected to univariate analysis with respect to VAP, and all variables found to be associated with VAP ($p < 0.20$) (sex, ISS, ventilator days, ICU length of stay prior to VAP) were entered in a stepwise logistic regression model with blood transfusion as the dependent variable.	*Platelet transfusion is significantly and independently associated with ARDS/ALI* P-value: NR

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CI, confidence interval; ICU, intensive care unit; ISS, injury severity score; NR, not reported; OR, odds ratio; VAP, ventilator associated pneumonia

3.4 Question 4

Question 4 (Interventional)

In critically ill patients, what is the effect of strategies that minimise blood loss on morbidity, mortality and blood transfusion?

3.4.1 Cell Salvage

Evidence statements – Cell salvage
In trauma patients, use of cell salvage does not appear to have an effect on mortality (B, B, D, A, B). (See evidence matrix EM4.A in Volume 2 of the technical report)
In trauma patients, use of intra-operative cell salvage reduces allogeneic transfusion volume (B, B, A, A, B). (See evidence matrix EM4.B in Volume 2 of the technical report)
In trauma patients the effect of cell salvage on allogeneic transfusion incidence is unknown (No evidence).
In patients undergoing emergency surgery for ruptured abdominal aortic aneurysm, the effect of cell salvage on mortality is uncertain (D, A, D, A, B). (See evidence matrix EM4.C in Volume 2 of the technical report)
In patients undergoing emergency surgery for ruptured abdominal aortic aneurysm, cell salvage may reduce allogeneic transfusion volume (D, B, C, A, C). (See evidence matrix EM4.D in Volume 2 of the technical report)
In patients undergoing emergency surgery for ruptured abdominal aortic aneurysm, the effect of cell salvage on allogeneic RBC transfusion incidence is uncertain (D, C, NA, A, B). (See evidence matrix EM4.E in Volume 2 of the technical report)
In critically ill patients the effect of cell salvage on thromboembolic events is unknown (No evidence).

Practice point	
PP13	In critically ill trauma patients and patients undergoing emergency surgery for ruptured abdominal aortic aneurysm, the use of cell salvage may be considered.

PP, practice point

Research recommendation
In critically ill trauma patients, while intraoperative cell salvage reduces allogeneic blood transfusion, concern remains regarding patient selection and safety, in particular the reinfusion of contaminated blood. Further research into this promising area is indicated. In patients undergoing emergency surgery for ruptured AAA, cell salvage may reduce allogeneic transfusion volume. Further research is indicated.

Intraoperative cell salvage is a medical procedure that involves the collection of blood lost during surgery followed by re-infusing the collected blood into the patient. One of the key aims of cell salvage is the reduction of allogeneic transfusion, and the consequent reduction in transfusion-related adverse events. The systematic review examined evidence for the efficacy of intraoperative cell salvage in critical care patients.

Methods

There were eleven studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

Three of the identified studies included data on hospital costs. The literature search identified no literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified no systematic reviews examining the use of cell salvage in critical care patients.

Level II evidence

The literature search identified one Level II study examining the use of cell salvage in critical care patients. The main characteristics of this study are summarised in Table 3.3.45.

Table 3.3.45 Question 4 (Cell salvage): Characteristics and quality of Level II evidence

Level II evidence			
Author	Study type Study quality	Population	Outcomes
Bowley et al (2006)[97]	RCT *Fair*	Adult patients undergoing surgery for abdominal trauma N=44	Allogeneic transfusion volume, survival, costs.

Level III evidence

The literature search identified ten Level III studies examining the use of cell salvage in critical care patients. The main characteristics of these studies are summarised in Table 3.3.46. The study by Serracino-Inglott (2005) was published as a short report in the technical section of the Annals of the Royal College of Surgeons of England.[98] The study has been included, but was assessed to be of poor quality.

Table 3.3.46 Question 4 (Cell salvage): Characteristics and quality of Level III evidence

Level III evidence			
Author	Study type Study quality	Population	Outcomes
Alonso-Perez et al (1999)[99]	Retrospective cohort study *Poor*	Patients aged 75 or over undergoing emergency operations for ruptured abdominal aortic aneurysm. N=112	Mortality
Alonso-Perez et al (2001)[100]	Retrospective cohort study *Poor*	Patients undergoing emergency operations for ruptured abdominal aortic aneurysm. N=144	Mortality
Brown et al (2010)[101]	Retrospective cohort study *Fair*	Adult trauma patients undergoing urgent surgery N=94	Allogeneic transfusion volume, blood loss, mortality, blood product cost
Jurkovich et al (1984)[102]	Retrospective cohort study *Poor*	Adult acute trauma patients undergoing surgery N = 85	Allogeneic transfusion volume, blood loss, mortality
Markovic et al (2009)[103]	Historically controlled cohort study *Poor*	Patients undergoing surgery for ruptured abdominal aortic aneurysm. Emergency surgery N=60	Blood loss, allogeneic RBC transfusion, allogeneic plasma transfusion, mortality
Ozmen et al (1992)[104]	Retrospective cohort study *Poor*	Patients with penetrating abdominal trauma, gastrointestinal tract injuries and a Penetrating Abdominal Trauma Index score ≥20. N = 70	Allogeneic transfusion volume, mortality
Posacioglu et al (2002)[105]	Retrospective cohort study *Poor*	Patients undergoing surgery for ruptured abdominal aortic aneurysm. N=56	Mortality, allogeneic transfusion volume
Serracino-Inglott et al (2005)[98]	Cohort study *Poor*	Patients undergoing surgery for ruptured abdominal aortic aneurysm. N=154	Survival
Shuhaiber et al (2003)[106]	Retrospective cohort study *Poor*	Patients undergoing emergency abdominal aortic aneurysm repairs. N=25	Blood loss, allogeneic transfusion volume and incidence
Tawfick et al (2008)[107]	Retrospective cohort study *Poor*	Patients undergoing open abdominal aortic aneurysm repairs. N=187	Blood loss, allogeneic transfusion volume and incidence, mortality, cost

Level IV evidence

The literature search identified no Level IV studies examining the use of cell salvage in critical care patients that addressed the evidence gap in the identified in the Level III studies.

Results

Mortality

Four studies were identified that examined the effect of intraoperative cell salvage on mortality in trauma patients (Table 3.3.47).

The study by Bowley (2006) is a randomised controlled trial of cell salvage in 44 patients with abdominal trauma. The authors reported no significant difference in mortality between subjects who received cell salvage and subjects who did not (p=1.0). There was also no significant difference when the analysis was restricted to patients with enteric injury (p=0.47).[97]

Brown (2010) is a matched cohort study of trauma patients undergoing urgent surgery whose treatment included or did not include cell salvage. No significant difference in mortality was found between the two treatment groups (p=0.56). [101]

Jurkovich (1984) reported similar mortality rates in trauma patients whose treatment include cell salvage (27%) and those treated without cell salvage (25%).[102] Ozmen (1992) examined mortality within 72 hours of surgery in trauma patients. None of the 50 patients who did not have cell salvage died within 72 hours of surgery, while 2 of the 20 patients who did have cell salvage died within 72 hours of surgery.[104] The Jurkovich (1984) and Ozmen (1992) studies did not match the subjects in the two treatment groups.

Table 3.3.47 Question 4: Results for cell salvage in trauma patients - Mortality/Survival

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome	Results			
						Cell salvage n/N (%)	No cell salvage n/N (%)	Risk estimate (95% CI)	*Significance* P-value
MORTALITY – TRAUMA PATIENTS									
Level II studies									
Bowley (2006) Level II *Fair*	RCT N=44	Adult patients undergoing surgery for abdominal trauma	Hospital South Africa	Intraoperative cell salvage vs. no cell salvage	Survival (all subjects)	7/21 (33%)	8/23 (55%)	NR	*Use of cell salvage is not associated with improved survival.* P=1.0
					Survival (subjects with enteric injury)	7/18 (38.8%)	4/17 (23.5%)	NR	*Use of cell salvage is not associated with improved survival.* P=0.47
Level III studies									
Brown (2010) *Fair*	Retrospective matched cohort study N=94	Adult trauma patients undergoing urgent surgery.	Hospital US	Intraoperative cell salvage vs. no cell salvage	Mortality	6/47 (13)	10/47 (21)	NR	*Use of cell salvage is not associated with increased mortality.* P=0.56
Jurkovich (1984) *Poor*	Retrospective cohort study N=85	Adult acute trauma patients undergoing surgery.	Hospital US	Intraoperative cell salvage vs. no cell salvage	Mortality	6/22 (27)	16/63 (25)	NR	*Patients treated with and without cell salvage had similar mortality rates.* P=NR
Ozmen (1992) *Poor*	Retrospective cohort study N=70	Adult patients with abdominal trauma and a Penetrating Abdominal Trauma Index score ≥20.	Hospital US	Intraoperative cell salvage vs. no cell salvage	Mortality (within 72 hours of surgery)	2/20 (10)	0/50 (0)	NR	*Patients treated with cell salvage had a higher mortality rate*. P=NR

CI, confidence interval; NR, not reported; RCT, randomised controlled trial; United States of America.

Allogeneic transfusion volume

Four studies were identified that examined the effect of intraoperative cell salvage on mortality in trauma patients (Table 3.3.48).

Bowley (2006) reported that subjects who received cell salvage required significantly lower mean volumes of allogeneic blood (6.47 units) compared to subjects who did not receive cell salvage(11.17 units; p=0.008).[97]

Brown (2010) found that the use of intraoperative cell salvage was associated with significant reduction in allogeneic blood requirement both during the operation (p=0.002) and overall (p<0.001). [101]

In contrast, the studies by Jurkovich (1984) and Ozmen (1992) both reported that subjects who received cell salvage required greater volumes of allogeneic blood than subjects who did not (6800 mL vs. 3300 mL in Jurkovich and 6.95 units vs. 3.58 units in Ozmen, respectively).[102,104] It should be noted that both of these studies did not match the patients in the two treatment groups, potentially confounding the results.

Table 3.3.48 Question 4: Results for cell salvage in trauma patients - Allogeneic transfusion volume

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome		Results			
							Cell salvage Mean±SD (n)	No cell salvage Mean±SD (n)	Risk estimate (95% CI)	*Significance* P-value
ALLOGENEIC TRANSFUSION VOLUME – TRAUMA PATIENTS										
Level II studies										
Bowley (2006) Level II *Fair*	RCT N=44	Adult patients undergoing surgery for abdominal trauma	Hospital South Africa	Intraoperative cell salvage vs. no cell salvage	Allogeneic transfusion volume (units) First 24 hours post-injury		6.47 ±5.14 (21)	11.17±6.06 (23)	NR	*Use of cell salvage is associated with significantly reduced allogeneic transfusion volume.* P=0.008
Level III studies										
Brown (2010) *Fair*	Retrospective matched cohort study N=94	Adult trauma patients undergoing urgent surgery.	Hospital US	Intraoperative cell salvage vs. no cell salvage	Allogeneic transfusion volume (Units)	Preoperative	2±2 (47)	3±1 (47)	NR	*Use of intraoperative cell salvage is not associated with preoperative allogeneic transfusion volume.* P=0.16
						Intraoperative	2±1 (47)	4±2 (47)	NR	*Use of intraoperative cell salvage is associated with significantly lower intraoperative allogeneic transfusion volume.* P=0.002
						Total	4±2 (47)	8±3 (47)	NR	*Use of intraoperative cell salvage is associated with significantly lower total allogeneic transfusion volume.* P<0.001
Jurkovich (1984) *Poor*	Retrospective cohort study N=85	Adult acute trauma patients undergoing surgery.	Hospital US	Intraoperative cell salvage vs. no cell salvage	Allogeneic transfusion volume (mL)		6800±900 (22)	3300±580 (63)	NR	*Patients treated with cell salvage had a greater mean allogeneic transfusion volume.* P=NR
Ozmen (1992) *Poor*	Retrospective cohort study N=70	Adult patients with abdominal trauma and a Penetrating Abdominal Trauma Index score ≥20.	Hospital US	Intraoperative cell salvage vs. no cell salvage	Allogeneic transfusion volume (units)		6.95[a] (20)	3.58[a] (50)	NR	*Patients treated with cell salvage had a greater mean allogeneic transfusion volume.* P=NR

CI, confidence interval; mL, millilitres; NR, not reported; RCT, randomised controlled trial; United States of America.
[a] Mean values calculated *post hoc* from total values and subject number.

Allogeneic transfusion incidence

No studies were identified that investigated an association between the use of intraoperative cell salvage and transfusion incidence in trauma patients.

Thromboembolic events

No studies were identified that investigated an association between the use of intraoperative cell salvage and thromboembolic events in trauma patients.

Hospital costs

Two studies compared the per-patient costs for trauma patients who underwent surgery with or without cell salvage. Bowley (2006) reported that patients who had cell salvage had lower mean costs (£812.23 per patient) compared to patients who did not have cell salvage (£990.04 per patient), however this difference did not reach significance (p=0.2). These cost measurements did not include the capital, maintenance and operating technician costs for the cell salvage machine. [97] The study by Brown (2010) found that mean per-patient costs (including blood products and cell salvage machine operating costs) were significantly lower in patients who had cell salvage compared to patients who did not (US$1616 vs. US$2584, respectively; p=0.004).[101]

Table 3.3.49 Question 4: Results for cell salvage in trauma patients - Hospital costs

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome	Results			
						Cell salvage Mean±SD (n)	No cell salvage Mean±SD (n)	Risk estimate (95% CI)	*Significance* P-value
HOSPITAL COSTS – TRAUMA PATIENTS									
Level II studies									
Bowley (2006) Level II *Fair*	RCT N=44	Adult patients undergoing surgery for abdominal trauma	Hospital South Africa	Intraoperative cell salvage vs. no cell salvage	Mean per-patient costs, £ Excludes capital and maintenance costs and cell salvage technician costs.	812.23±451.26	990.04±479.48	NR	*Use of cell salvage is not associated with changes in costs.* P=0.2
Level III studies									
Brown (2010) *Fair*	Retrospective matched cohort study N=94	Adult trauma patients undergoing urgent surgery.	Hospital US	Intraoperative cell salvage vs. no cell salvage	Blood product costs per-patient, mean US$ Includes cell salvage machine operating costs.	1616	2584	NR	*Use of intraoperative cell salvage is associated with significantly lower blood product costs.* P=0.004

CI, confidence interval; mL, millilitres; NR, not reported; RCT, randomised controlled trial; United States of America.

USE OF CELL SALVAGE IN NON-TRAUMA CRITICALLY ILL PATIENTS

Results

Mortality

Six studies were identified that examined mortality in non-trauma critical care patients who did or did not have intraoperative cell salvage (see Table 3.3.50). All studies included patients undergoing surgery to repair abdominal aortic aneurysms (AAA).

The study by Alonso-Perez (1999) was a cohort study involving patients from 21 hospitals in Spain. The study examined patients aged 75 years or over undergoing emergency AAA surgery. The study found no significant difference in mortality between patients who had cell salvage and those who did not, with an odds ratio of 1.8 (95% CI 0.3, 9.5; p=0.706).[99] The 2001 study by Alonso-Perez was conducted at 10 hospitals in Europe and North and South America. The study compared patients who received cell salvage with those who did not and found no significant difference in mortality (p=0.45).[100]

The study by Markovic (2009) investigated the use of cell salvage in emergency AAA surgery at a single centre in Serbia. The study found similar mortality rates with no significant difference between the cell salvage patients and the non-salvage patients, with a p-value of 0.62.[103] Posacioglu (2002) also reported no significant difference in mortality between ruptured AAA patients in Turkey who received cell salvage and those who did not (p=0.495).[105]

Serracino-Inglott (2005) reported the results of a study performed at a single centre in the United Kingdom. The authors compared patients who received cell salvage during ruptured AAA repair with those who did not have cell salvage. The authors found no significant difference in overall survival between the two groups (p=0.07). When patients who died in theatre were excluded from the analysis they found a significantly higher survival rate in patients who had cell salvage (79% vs. 56%; p=0.01).[98]

The study by Tawfick (2008) included both elective and emergency surgeries. Only the results for emergency surgeries are included here. The authors report a lower mortality rate in subjects who had cell salvage (22%) compared to subjects who did not have cell salvage (32%).[107]

Table 3.3.50 Question 4: Results for cell salvage in non-trauma patients - Mortality

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome	Results			
						Cell salvage n/N (%)	No cell salvage n/N (%)	Risk estimate (95% CI)	*Significance* P-value
MORTALITY – NON-TRAUMA PATIENTS									
Level III Studies									
Alonso-Perez (1999) Level III-2 *Poor*	Retrospective cohort study N=112	Patients aged ≥75 undergoing surgery for ruptured abdominal aortic aneurysm.	21 hospitals Spain	Intraoperative cell salvage vs. no cell salvage	Mortality	6/8 (75%)	NR	OR 1.8 (0.3, 9.5)	*Use of cell salvage is not significantly associated with mortality.* P=0.706
Alonso-Perez (2001) Level III-2 *Poor*	Retrospective cohort study N=144	Patients undergoing surgery for ruptured abdominal aortic aneurysm.	10 hospitals Spain, France, Portugal, United States, Brazil, Chile	Intraoperative cell salvage vs. no cell salvage	Mortality	NR	NR	NR	*Use of cell salvage is not significantly associated with mortality.* P=0.45
Markovic (2009) Level III-3 *Poor*	Historically controlled cohort study Emergency surgery N=60	Patients undergoing surgery for ruptured abdominal aortic aneurysm.	Single centre Serbia	Intraoperative cell salvage vs. no cell salvage	Intraoperative mortality	7/30	4/30	NR	P=NR
					Postoperative mortality	5/30	10/30	NR	P=NR
					Overall mortality	12/30	14/30	NR	*Use of cell salvage is not significantly associated with mortality.* P=0.62
Posacioglu (2002) Level III-2 *Poor*	Retrospective cohort study N=56	Patients undergoing surgery for ruptured abdominal aortic aneurysm.	Hospital Turkey	Intraoperative cell salvage vs. no cell salvage	Mortality	16/40 (40)	8/16 (50)	NR	*Use of cell salvage is not associated with mortality.* P=0.495
Serracino-Inglott (2005) Level III-2 *Poor*	Cohort study N=154	Patients undergoing surgery for ruptured abdominal aortic aneurysm.	Hospital United Kingdom	Intraoperative cell salvage vs. no cell salvage	Overall survival [a]	27/40 (68)	58/114 (51)	NR	*The use of cell salvage is not significantly associated with mortality.* P=0.07
					Survival, excluding patients who died in theatre	79%	56%	NR	*Favours cell salvage* P=0.01

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome	Results			
						Cell salvage n/N (%)	No cell salvage n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Tawfick (2008) Level III-2 *Poor*	Retrospective cohort study Emergency surgery=55	Patients undergoing open abdominal aortic aneurysm repair.	Hospital Ireland	Intraoperative cell salvage vs. no cell salvage	Mortality (emergency surgery, 30-day)	6/27 (22)	9/28 (32)	NR	*Patients treated with cell salvage had a lower mortality rate.* P=NR

CI, confidence interval; NR, not reported.

[a] Affected subject numbers calculated post hoc from percentages

Allogeneic transfusion volume

Four studies examined allogeneic transfusion in patients undergoing emergency surgery to repair AAAs (Table 3.3.51).

Markovic (2009) reported the use of both RBC and plasma in patients treated with or without cell salvage. [103] The authors found that the use of cell salvage was associated with a significant reduction in intraoperative (p=0.0380), post-operative (p=0.0097) and total allogeneic RBC transfusion (p=0.0089). The study found no significant difference in the requirement for intraoperative plasma (p=0.240), but did find a significant reduction in post-operative plasma (p=0.026) and total plasma requirement (p=0.0062) with the use of cell salvage.

Posacioglu (2002) also investigated the use of RBC and FFP transfusion in patients with ruptured AAAs. In this study the use of cell salvage depended on the surgeon's preference, availability of the device and rarity of patient's blood type. The authors found that the use of cell salvage was associated with a significant increase in the requirement for allogeneic RBC (p=0.026) and FFP (p=0.006).[105]

The study by Shuhaiber (2003) found that patients who had cell salvage had a lower mean allogeneic RBC transfusion volume (2800 mL) than patients who did not have cell salvage (3161mL).[106] The Tawfick (2008) study included both elective and emergency surgeries. Only the results for emergency surgeries are included here. The study found that patients who had cell salvage had a lower mean allogeneic transfusion volume (6 units) compared to subjects whose surgery did not include cell salvage (12 units).[107]

Table 3.3.51 Question 4: Results for cell salvage in non-trauma patients - Allogeneic transfusion volume

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome	Results			
						Cell salvage n/N (%)	No cell salvage n/N (%)	Risk estimate (95% CI)	*Significance* P-value
ALLOGENEIC TRANSFUSION VOLUME – NON-TRAUMA PATIENTS									
Level III studies									
Markovic (2009) Level III-3 *Poor*	Historically controlled cohort study Emergency surgery N=60	Patients undergoing surgery for ruptured abdominal aortic aneurysm.	Single centre Serbia	Intraoperative cell salvage vs. no cell salvage	Intraoperative RBC transfusion (mL, mean ± SD)	913.8±602	1146.3±595	NR	*Favours cell salvage.* P=0.0380
					Postoperative RBC transfusion (mL, mean ± SD)	976.3±927	1609.6±998	NR	*Favours cell salvage.* P=0.0097
					Total allogeneic RBC transfusion (mL, mean ± SD)	1890.1±1186	2755.9±1265	NR	*Favours cell salvage.* P=0.0089
					Intraoperative plasma transfusion (mL, mean ± SD)	627.8±508	817.0±551	NR	*No significant difference* P=0.240
					Postoperative plasma transfusion (mL, mean ± SD)	595.6±1021	828.8±640	NR	*Favours cell salvage.* P=0.0410
					Total allogeneic plasma transfusion (mL, mean ± SD)	1223.4±1223	1645.8±947	NR	*Favours cell salvage.* P=0.0062
Posacioglu (2002) Level III-2 *Poor*	Retrospective cohort study N=56	Patients undergoing surgery for ruptured abdominal aortic aneurysm.	Hospital Turkey	Intraoperative cell salvage vs. no cell salvage	Allogeneic RBC transfusion volume (postoperative) (units, mean±SD)	5.8±3.84	3.63±2.87	NR	*Favours no cell salvage.* P=0.026
					Allogeneic FFP transfusion volume (postoperative) (units, mean±SD)	4.45±4.03	1.5±1.37	NR	*Favours no cell salvage.* P=0.006
Shuhaiber (2003) Level III-2 *Poor*	Retrospective cohort study Emergency surgery=25	Patients undergoing emergency abdominal aortic aneurysm repair.	Single hospital United Kingdom	Intraoperative cell salvage vs. no cell salvage	Allogeneic transfusion volume, mL (mean (SD))	2800 (857)	3161 (2155)	NR	*Patients whose surgery included cell salvage had lower mean allogeneic transfusion volume.* P=NR

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome	Results			
						Cell salvage n/N (%)	No cell salvage n/N (%)	Risk estimate (95% CI)	*Significance* P-value
Tawfick (2008) Level III-2 *Poor*	Retrospective cohort study Emergency surgery=55	Patients undergoing open abdominal aortic aneurysm repair.	Hospital Ireland	Intraoperative cell salvage vs. no cell salvage	Allogeneic RBC transfusion volume (Units, mean (range)) (emergency surgery)	6 (0-34)	12 (3-38)	NR	*Patients treated with cell salvage had a lower mean allogeneic transfusion volume.* P=NR

CI, confidence interval; FFP, fresh frozen plasma; NR, not reported; RBC, red blood cell; SD, standard deviation.

Allogeneic transfusion incidence

Three studies examined allogeneic transfusion incidence in patients undergoing surgery to repair AAAs (Table 3.3.52). All studies investigated the use of cell salvage in emergency AAA repair surgery.

The study by Markovic (2009) reported the proportion of patients who required allogeneic RBC and plasma transfusions. All patients who did not receive cell salvage required both RBC and plasma transfusions. Of the 30 patients whose surgery included cell salvage, one patient did not require an allogeneic RBC transfusion and five patients did not require allogeneic plasma transfusion.[103] The Shuhaiber (2003) study reported that all patients required allogeneic transfusion, regardless of whether they had cell salvage.[106] The study by Tawfick (2008) found a lower incidence of allogeneic transfusion in patients who had cell salvage (20/27) compared to patients treated without cell salvage (28/28).[107]

Table 3.3.52 Question 4: Results for cell salvage in non-trauma patients - Allogeneic transfusion incidence

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome	Results			
						Cell salvage n/N (%)	No cell salvage n/N (%)	Risk estimate (95% CI)	*Significance* P-value
ALLOGENEIC TRANSFUSION INCIDENCE – NON-TRAUMA PATIENTS									
Level III Studies									
Markovic (2009) Level III-3 *Poor*	Historically controlled cohort study Emergency surgery N=60	Patients undergoing surgery for ruptured abdominal aortic aneurysm.	Single centre Serbia	Intraoperative cell salvage vs. no cell salvage	Allogeneic RBC transfusion incidence	29/30	30/30	NR	P=NR
					Allogeneic plasma transfusion incidence	25/30	30/30	NR	*Patients treated with cell salvage had a lower incidence of allogeneic transfusion.* P=NR
Shuhaiber (2003) Level III-2 *Poor*	Retrospective cohort study Emergency surgery=25	Patients undergoing emergency abdominal aortic aneurysm repair.	Single hospital United Kingdom	Intraoperative cell salvage vs. no cell salvage	Allogeneic transfusion incidence	4/4	21/21	NR	*No difference* P=NR
Tawfick (2008) Level III-2 *Poor*	Retrospective cohort study Emergency surgery=55	Patients undergoing open abdominal aortic aneurysm repair.	Hospital Ireland	Intraoperative cell salvage vs. no cell salvage	Allogeneic RBC transfusion incidence	20/27	28/28	NR	*Patients treated with cell salvage had a lower incidence of allogeneic transfusion.* P=NR

CI, confidence interval; NR, not reported.

Thromboembolic events

No studies were identified that investigated an association between the use of intraoperative cell salvage and transfusion incidence in non-trauma critical care patients.

Hospital costs

Tawfick (2008) reported the mean per-patient cost for non-trauma critical care patients treated with and without intraoperative cell salvage (Table 3.3.53). The study found that patients whose surgery included cell salvage had lower mean costs (€13780.27 per patient) compared to patients who did not receive cell salvage (€19016.77 per patient).[107]

Table 3.3.53 Question 4: Results for cell salvage in non-trauma patients - Hospital costs

Study Level of evidence *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome	Results			
						Cell salvage n/N (%)	No cell salvage n/N (%)	Risk estimate (95% CI)	*Significance* P-value
HOSPITAL COSTS – NON-TRAUMA PATIENTS									
Level III studies									
Tawfick (2008) Level III-2 *Poor*	Retrospective cohort study N=187 Emergency surgery=55 Elective surgery=132	Patients undergoing open abdominal aortic aneurysm repair.	Hospital Ireland	Intraoperative cell salvage vs. no cell salvage	Mean per-patient cost, € Emergency and elective surgeries Includes transfusion costs, consumables and hospital bed costs.	13780.27	19016.77	Difference: 5236.50	*Patients treated with cell salvage had a lower mean cost per patient.* P=NR

CI, confidence interval; NR, not reported.

Tranexamic acid (TXA)TXA Evidence statements
In acutely bleeding critically ill trauma patients, treatment with TXA within three hours of injury reduces the risk of mortality (A, B, B, A, A). (See evidence matrix EM4.F in Volume 2 of the technical report)
In acutely bleeding critically ill trauma patients, treatment with TXA does not have an effect on allogeneic transfusion incidence (A, NA, D, A, A). (See evidence matrix EM4.G in Volume 2 of the technical report)
In acutely bleeding critically ill trauma patients, treatment with TXA does not have an effect on allogeneic transfusion volume (A, NA, D, A, A). (See evidence matrix EM4.H in Volume 2 of the technical report)
In acutely bleeding critically ill trauma patients, treatment with TXA does not have an effect on the risk of stroke, pulmonary embolism or deep vein thrombosis, and reduces the incidence of myocardial infarction (A, NA, C, A, A). (See evidence matrix EM4.I in Volume 2 of the technical report)
In critically ill patients with upper gastrointestinal bleeding, treatment with TXA may reduce the risk of mortality (C, B, B, A, B). (See evidence matrix EM4.J in Volume 2 of the technical report)
In critically ill patients with upper gastrointestinal bleeding, treatment with TXA does not appear to affect allogeneic transfusion incidence (C, A, D, A, B). (See evidence matrix EM4.K in Volume 2 of the technical report)
In critically ill patients with upper gastrointestinal bleeding, the effect of TXA on the risk of thromboembolic events is uncertain (C, C, NA, A, B). (See evidence matrix EM4.L in Volume 2 of the technical report)
In critically ill patients the effect of TXA on blood loss is unknown (no evidence).

Recommendations	
R3	In acutely bleeding critically ill trauma patients, TXA should be administered within 3 hours of injury (Grade B).
R4	In critically ill patients with upper GI bleeding, consider the use of TXA (Grade C).
Practice points	
PP14	TXA should be given as early as possible, preferably within 3 hours of injury. The late administration of TXA is less effective and may be harmful.
PP15	The suggested dose of TXA administered is a 1 g bolus followed by a 1 g infusion over 8 hours. This is the dose administered in the large multicentre RCT CRASH-2.

Research gap
The dosing, safety and efficacy of TXA in GI bleeding needs to be established through well designed RCTs.

Tranexamic acid is a synthetic derivative of the amino acid lysine which acts as an antifibrinolytic by competitively inhibiting the activation of plasminogen to plasmin, a molecule responsible for the degradation of fibrin. Tranexamic acid tablets and solution for injection are approved in Australia for a number of indications including cardiac surgery, total knee or hip arthroplasty, traumatic hyphaema and for patients with coagulopathies undergoing minor surgery. The systematic review examined the evidence for the use of tranexamic acid in critical care patients.

Methods

There were two studies identified from the systematic review and hand searching process (see Appendix C, Volume 2).

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

Level I evidence

The literature search identified four systematic reviews examining the use of TXA in critical care patients. The systematic reviews were assessed and for each patient group the most comprehensive and recent good quality review was selected, resulting in the inclusion of two Level I studies. The main characteristics of these studies are summarised in Table 3.3.54.

Table 3.3.54 Question 4 (Tranexamic acid): Characteristics and quality of Level II evidence

Level I evidence			
Author	Study type Study quality	Population	Outcomes
Gluud et al (2008)[108]	SR *Good*	Patients with upper gastrointestinal bleeding 7 RCTs of good to poor quality N=1654	Mortality, allogeneic transfusion incidence
Roberts et al (2011)[109]	SR *Good*	Adult trauma patients 2 RCTs (1 good quality, 1 fair quality) N=20451	Mortality, thromboembolic events, allogeneic transfusion incidence and volume

Level II evidence

An additional literature search was conducted to identify Level II literature for patient groups not included in the Level I studies and to identify any additional RCTs published after the literature searches in the Level I studies. This search did not identify any additional Level II studies. Subarachnoid haemorrhage was considered outside the scope of this review.

Results

Mortality

A single systematic review, Roberts 2011, was identified that examined the effect of TXA on mortality in trauma patients.[109] The review includes 2 RCTs with a total of 20451 patients.

The risk of all-cause mortality in trauma patients was significantly reduced with TXA treatment. A fixed effects analysis of data from both RCTs gave a relative risk of 0.90 (95% CI 0.85, 0.97; p=0.0025). This analysis had no significant heterogeneity (I^2 0%, Phet=0.38).

Roberts 2011 included a number of other mortality-related outcomes for which the data came only from the CRASH-2 RCT (Shakur 2010).[110] The review reported that the CRASH-2 RCT found no significant difference between patients who received TXA and those who did not in mortality due to vascular occlusion (p=0.096), mortality due to stroke (p=0.40), mortality due to pulmonary embolism (p=0.63), mortality due to multi-organ failure (p=0.25) and mortality due to head injury (p=0.60).The review also reported that treatment with TXA significantly reduced the risk of mortality due to myocardial infarction, with a relative risk of 0.32 (95% CI 0.14, 0.75; p=0.0053). The risk of mortality due to bleeding was also significantly reduced with TXA, with a relative risk of 0.85 (95% CI 0.76, 0.96; p=0.0077).

The original publication of the CRASH-2 trial included in Roberts 2011 reported a lower rate of mortality in patients treated with TXA if they were treated within 1 hour of injury (RR 0.87; 95% CI 0.75, 1.00) or between 1 and 3 hours after injury (RR 0.87; 95% CI 0.75, 1.00). The study found no difference in mortality with TXA if treatment was more than 3 hours after injury (RR 1.00; 95% CI 0.86, 1.17).[110]

Table 3.3.55 Question 4: Results for tranexamic acid in trauma patients - Mortality

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome	Results			
						Tranexamic acid n/N (%)	Placebo n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
MORTALITY									
Trauma patients									
Roberts (2011) Level I *Good*	2 RCTs N=20451	Adult trauma patients (>16 years)	Hospital Various countries, including Australia	Tranexamic acid vs. placebo	Mortality due to vascular occlusion (includes MI, stroke and PE) 1 RCT, N=20211	NR	NR	RR 0.69 (0.44, 1.07)	*No difference* P=0.096
					Mortality due to stroke 1 RCT, N=20211	NR	NR	RR 1.60 (0.52, 4.89)	*No difference* P=0.40
					Mortality due to PE 1 RCT, N=20211	NR	NR	RR0.86 (0.46, 1.61)	*No difference* P=0.63
					Mortality due to MI 1 RCT, N=20211	NR	NR	RR 0.32 (0.14, 0.75)	*Favours tranexamic acid* P=0.0053
					Mortality due to bleeding 1 RCT, N=20211	NR	NR	RR 0.85 (0.76, 0.96)	*Favours tranexamic acid* P=0.0077
					Mortality due to multi-organ failure 1 RCT, N=20211	NR	NR	RR 0.90 (0.75, 1.08)	*No difference* P=0.25
					Mortality due to head injury 1 RCT, N=20211	NR	NR	RR 0.97 (0.87, 1.08)	*No difference* P=0.60
					Mortality due to other causes 1 RCT, N=20211	NR	NR	RR 0.94 (0.74, 1.20)	*No difference* P=0.63
					Mortality in patients treated ≤1 hour after injury 1 RCT N=20211	509/3747 (13.6)	581/3704 (15.7)	RR 0.87 (0.75, 1.00)	*Favours tranexamic acid* P=NR

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome	Results			
						Tranexamic acid n/N (%)	Placebo n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
					Mortality in patients treated >1 to ≤3 hours after injury 1 RCT N=20211	463/3037 (15.2)	528/2996 (17.6)	RR 0.87 (0.75, 1.00)	*Favours tranexamic acid* P=NR
					Mortality in patients treated >3 hours after injury 1 RCT N=20211	491/3272 (15.0)	502/3362 (14.9)	RR 1.00 (0.86, 1.17)	*No difference* P=NR
					All-cause mortality 2 RCTs, N=20451	1475/10180 (14.5)	1631/10187 (16.0)	Fixed effects: RR 0.90 (0.85, 0.97)	*Favours tranexamic acid* P=0.0025 No significant heterogeneity[b] P=0.38 (I^2=0%)

CI, confidence interval; MI, myocardial infarction; NR, not reported; PE, pulmonary embolism; RCT, randomised controlled trial; RR, risk ratio.

[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

Allogeneic transfusion incidence

The systematic review by Roberts 2011 investigated the effect of TXA treatment on allogeneic transfusion incidence in trauma patients. The results of the analysis are shown in Table 3.3.56. The review found no significant difference in the incidence of transfusion between patients who received TXA and those who did not, with a relative risk of 0.98 (95% CI 0.96, 1.01; p=0.21).[109]

Table 3.3.56 Question 4: Results for tranexamic acid in trauma patients - Allogeneic transfusion incidence

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome	Results			
						Tranexamic acid n/N (%)	Placebo n/N (%)	Risk estimate (95% CI)	*Significance* P-value
ALLOGENEIC TRANSFUSION INCIDENCE									
Trauma patients									
Roberts (2011) Level I *Good*	1 RCT N=20211	Adult trauma patients (>16 years)	Hospital Various countries, including Australia	Tranexamic acid vs. placebo	Allogeneic transfusion incidence	5067/10060 (50.4)	5160/10067 (51.3)	Fixed effects: RR 0.98 (0.96, 1.01)	*No difference* P=0.21

CI, confidence interval; NR, not reported; RCT, randomised controlled trial; RR, risk ratio.

[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

Allogeneic transfusion volume

The systematic review by Roberts 2011 investigated the effect of TXA treatment on allogeneic transfusion volume in trauma patients. The results of the analysis are shown in Table 3.3.57. The review found no significant difference in the mean transfusion volume between patients treated with TXA and those treated with placebo, with a weighted mean difference of -0.17 units (95% CI -0.39, 0.05).[109]

Table 3.3.57 Question 4: Results for tranexamic acid in trauma patients - Allogeneic transfusion volume

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome	Results			
						Tranexamic acid Mean±SD	Placebo Mean±SD	Risk estimate (95% CI)	*Significance* P-value
ALLOGENEIC TRANSFUSION VOLUME									
Trauma patients									
Roberts (2011) Level I *Good*	1 RCT N=20211	Adult trauma patients (>16 years)	Hospital Various countries, including Australia	Tranexamic acid vs. placebo	Allogeneic transfusion volume, units	3.05±7.7	3.22±8.02	Fixed effects: WMD -0.17 (-0.39, 0.05)	*No difference* P=NS

CI, confidence interval; DVT, deep vein thrombosis; MI, myocardial infarction; NR, not reported; PE, pulmonary embolism; RCT, randomised controlled trial; RR, risk ratio; WMD, weighted mean difference.

[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

Thromboembolic events

The systematic review by Roberts 2011 investigated the effect of TXA treatment on the incidence of thromboembolic events in trauma patients.[109] The results of the analysis are shown in Table 3.3.58. The review found no significant difference in the incidence of stroke (p=0.42), pulmonary embolism (p=0.93) and deep vein thrombosis (p=0.91). There was a significant reduction in the risk of myocardial infarction with TXA treatment, with a relative risk of 0.64 (95% CI 0.42, 0.97; p=0.035). The authors found no significant difference in the total incidence of thromboembolic events between patients treated with TXA and patients treated with placebo (RR 0.84; 95% CI 0.68, 1.02; p=0.084).

Table 3.3.58 Question 4: Results for tranexamic acid in trauma patients - Thromboembolic events

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome	Results			
						Tranexamic acid n/N (%)	Placebo n/N (%)	Risk estimate (95% CI)	*Significance* P-value
THROMBOEMBOLIC EVENTS									
Trauma patients									
Roberts (2011) Level I *Good*	1 RCT N=20211	Adult trauma patients (>16 years)	Hospital Various countries, including Australia	Tranexamic acid vs. placebo	Stroke events	NR	NR	RR 0.86 (0.61, 1.23)	*No difference* P=0.42
					PE events	NR	NR	RR1.01 (0.73, 1.41)	*No difference* P=0.93
					DVT events	NR	NR	RR 0.98 (0.63, 1.51)	*No difference* P=0.91
					MI events	NR	NR	RR 0.64 (0.42, 0.97)	*Favours tranexamic acid* P=0.035
					Vascular occlusive events (MI, stroke, PE, DVT)	NR	NR	RR 0.84 (0.68, 1.02)	*No difference* P=0.084

CI, confidence interval; DVT, deep vein thrombosis; MI, myocardial infarction; NR, not reported; PE, pulmonary embolism; RCT, randomised controlled trial; RR, risk ratio.

[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

Blood loss

No studies were identified that investigated an association between the use of TXA and blood loss in trauma patients.

USE OF TRANEXAMIC ACID IN TRAUMA PATIENTS

Results

Mortality

One systematic review was identified that investigated the effect of TXA treatment on mortality in non-trauma critical care patients.[108] The details of the results are shown in Table 3.3.59.

The review by Gluud 2008 included 7 RCTs of patients with upper gastrointestinal bleeding. The review found no significant effect of TXA on mortality due to bleeding (RR 0.66; 95% CI 0.40, 1.10). There was a significant reduction in all-cause mortality in patients treated with TXA compared to patients treated with placebo, with a relative risk of 0.61 (95% CI 0.42, 0.89). This analysis had no significant heterogeneity (Phet=0.87).

Table 3.3.59 Question 4: Results for tranexamic acid in non-trauma patients - Mortality

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome	Results			
						Tranexamic acid n/N (%)	Placebo n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
MORTALITY									
Gastrointestinal bleeding									
Gluud (2008) Level I *Good*	7 RCTs N=1654	Patients with upper gastrointestinal bleeding	Hospital United Kingdom, Sweden and Australia	Tranexamic acid (4-8g daily IV or oral) vs. placebo	Mortality due to bleeding	3%	5%	RR 0.66 (0.40, 1.10)	No difference P=Not significant Heterogeneity[b] P=NR (I^2=NR)
					All-cause mortality	5%	8%	RR 0.61 (0.42, 0.89)	*Favours tranexamic acid.* P=Significant No significant heterogeneity[b] P=0.87 (I^2=NR)

CI, confidence interval; IV, intravenous; NR, not reported; OR, odds ratio; RCT, randomised controlled trial; RR, risk ratio.

[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

Allogeneic transfusion volume

No studies were identified that investigated an association between the use TXA and allogeneic transfusion volume in non-trauma critical care patients.

Allogeneic transfusion incidence

One systematic review was identified that investigated the effect of TXA on transfusion incidence in non-trauma critical care patients.[108] The results from this review are shown in Table 3.3.60.

The review by Gluud 2008 included seven RCTs of patients with upper gastrointestinal bleeding. Four of the included RCTs reported transfusion incidence. The review found no significant difference in transfusion incidence between TXA and placebo treatments, with a relative risk of 1.0 (95% CI 0.93, 1.11). This analysis contained no significant heterogeneity (Phet=0.59).

Table 3.3.60 Question 4: Results for tranexamic acid in non-trauma patients - Allogeneic transfusion incidence

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome	Results			
						Tranexamic acid n/N (%)	Placebo n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
ALLOGENEIC TRANSFUSION INCIDENCE									
Gastrointestinal bleeding									
Gluud (2008) Level I *Good*	4 RCTs	Patients with upper gastrointestinal bleeding	Hospital United Kingdom, Sweden and Australia	Tranexamic acid (4-8g daily IV or oral) vs. placebo	Allogeneic transfusion incidence 4 RCTs	56%	57%	RR 1.0 (0.93, 1.11)	No difference P=Not significant No significant heterogeneity[b] P=0.59 (I^2=NR)

CI, confidence interval; IV, intravenous; NR, not reported; RCT, randomised controlled trial; RR, risk ratio.

[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.

[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

Blood loss

No studies were identified that investigated an association between the use TXA and blood loss in non-trauma critical care patients.

Thromboembolic events

One systematic review was identified that investigated the effect of TXA treatment on mortality in non-trauma critical care patients.[108] The details of the results are shown in Table 3.3.61.

The review by Gluud 2008 included 7 RCTs of patients with upper gastrointestinal bleeding. Three of the included RCTs reported thromboembolic events. The review found no significant effect of TXA on the combined thromboembolic events of MI, PE and cerebral infarction (RR 1.4; 95% CI 0.36, 5.28). The review also found no significant difference in the incidence of deep vein thrombosis (RR 2.3; 95% CI 0.61, 8.94).

Table 3.3.61 Question 4: Results for tranexamic acid in non-trauma patients - Thromboembolic events

Study Level of evidence[a] *Quality*	No. of trials / sample size included in analysis	Patient population / Surgical procedure	Setting Location	Intervention vs. comparator	Outcome	Results			
						Tranexamic acid n/N (%)	Placebo n/N (%)	Risk estimate (95% CI)	*Significance* P-value *Heterogeneity*[b]
THROMBOEMBOLIC EVENTS									
Gastrointestinal bleeding									
Gluud (2008) Level I *Good*	3 RCTs N=1048	Patients with upper gastrointestinal bleeding	Hospital United Kingdom, Sweden and Australia	Tranexamic acid (4-8g daily IV or oral) vs. placebo	Thromboembolic events: MI, PE, cerebral infarction 3 RCTs	5/522 (1.0)	4/526 (0.8)	RR 1.4 (0.36, 5.28)	No difference P=Not significant Heterogeneity[b] P=0.36 (I^2=NR)
					Thromboembolic events: DVT 3 RCTs	6/522 (1.1)	2/526 (0.4)	RR 2.3 (0.61, 8.94)	No difference P=Not significant No significant heterogeneity[b] P=0.96 (I^2=NR)

CI, confidence interval; DVT, deep vein thrombosis; g, grams; IV, intravenous; MI, myocardial infarction; NR, not reported; OR, odds ratio; PE, pulmonary embolism; RCT, randomised controlled trial; RR, risk ratio; UK, United Kingdom.
[a] Where only one RCT is available in a systematic review, the level of evidence will be downgraded to Level I/II. The quality of the included level II study will be rated based on the quality assessment of the systematic review.
[b] Heterogeneity defined as follows: (i) no significant heterogeneity if Phet>0.1 and I^2<25%; (ii) mild heterogeneity if I^2 <25%; moderate heterogeneity if I^2 between 25-50%; substantial heterogeneity I^2 >50%.

3.4.2 ε-Aminocaproic acid (EACA)

EACA Evidence statements
In critically ill patients, the effect of EACA on mortality is unknown. (No evidence)
In critically ill patients, the effect of EACA on allogeneic transfusion incidence is unknown. (No evidence)
In critically ill patients, the effect of EACA on allogeneic transfusion volume is unknown. (No evidence)
In critically ill patients, the effect of EACA on blood loss is unknown. (No evidence)
In critically ill patients, the effect of EACA on thromboembolic events is unknown. (No evidence)

Epsilon (ε)-aminocaproic acid is a synthetic derivative of the amino acid lysine. It acts as an antifibrinolytic by competitively inhibiting the activation of plasminogen to plasmin, a molecule responsible for the degradation of fibrin. It should be noted that ε-aminocaproic acid injection is not currently registered in Australia.

Methods

There were no studies identified from the systematic review and hand searching process (see Appendix C, Volume 2) that examined the use of EACA in critical care patients. Subarachnoid haemorrhage was considered outside the scope of this review.

The literature search identified no socioeconomic literature or literature pertaining to Australia's Indigenous population relevant to this research question.

4 Appendixes

4.1 Appendix 1. Research question structure

The structure of the foreground research questions for critical care patient blood management is presented in Table 4.1.1 (generic questions relevant to all modules of the patient blood management guidelines) and Table 4.1.2 (questions specific to the critical care patient blood management guidelines). As the generic research questions were designed to identify evidence relevant to all modules, Table 4.1.1 specifies subgroups relevant to the critical care module's population.

Table 4.1.1 Structure of generic research questions

Generic questions			
1. In critically ill patients, what is the effect of RBC (allogeneic) transfusion on patient outcomes? *Intervention vs. Comparator = (1) vs. (1), (2) vs. (2)* (Interventional question, Q1)			
Population	Intervention	Comparison	Outcomes (primary, unless specified)
Critically ill patients[a] Subgroups: • Trauma • Traumatic brain injury • Sepsis/septic shock[b] • ARDS/ALI • Burns • Cardiovascular[c] Stratify by: • Bleeding/non-bleeding • Severity of illness, in particular APACHE/ SOFA/ SAPS score	1. RBC (allogeneic) transfusion (including dose) 2. Restrictive transfusion (e.g. Hb trigger of <70 g/L and maintained between 70 and 90 g/L)	1. No transfusion (or alternative doses) 2. Liberal transfusion (e.g. Hb trigger of <100 g/L and maintain between 100 and 120 g/L	• mortality • organ failure and organ dysfunction (SOFA, MODS, APACHE SAPS) • transfusion-related SAEs (TACO, TRALI, other[d])
2. In critically ill patients, what is the effect of non-transfusion interventions to increase haemoglobin concentration on morbidity, mortality and need for RBC blood transfusion? (Interventional question, Q2)			
Population	Intervention	Comparison	Outcomes (primary, unless specified)
Critically ill patients[a] Subgroups: • Trauma	1. ESA 2. Oral and/or parenteral iron therapy (IV or IM) 3. Combination of these	No intervention or any active head-to-head (e.g., 1 vs. 2, 1 vs. 3,2 vs. 3)	• mortality • transfusion frequency • transfusion volume (in transfused patients only)

• Traumatic brain injury • Sepsis/septic shock • ARDS/ALI • Burns • Cardiovascular[c]	Nb. Look at all dose regimens		• thromboembolic events (stroke, MI, DVT, PE)
3. In critically ill patients, what is the effect of fresh frozen plasma, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcome? *Intervention vs. Comparator = (1) vs. (1), (2) vs. (2), etc* (Interventional question, Q3)			
Population	**Intervention**	**Comparison**	**Outcomes** (primary, unless specified)
Critically ill patients[a] Subgroups: • Trauma • Traumatic brain injury • Sepsis/septic shock • ARDS/ALI • Burns • Cardiovascular[c] • Transplant patients Stratify by: • Bleeding/non-bleeding	1. FFP 2. Cryoprecipitate 3. Platelet transfusion 4. Fibrinogen concentrate	1. No FFP or FFP using a different FFP transfusion protocol 2. No cryoprecipitate or cryoprecipitate using a different cryoprecipitate transfusion protocol 3. No platelet transfusion or platelet transfusion using a different platelet transfusion protocol 4. No fibrinogen concentrate or fibrinogen using a different fibrinogen transfusion protocol	• mortality • bleeding events (major and minor) • transfusion-related SAEs (TACO, TRALI, other[d])

Abbreviations: ALI, acute lung injury; APACHE, Acute Physiology and Chronic Health Evaluation; ARDS, acute respiratory distress syndrome; ESA, erythropoiesis stimulating agent; FFP, fresh frozen plasma; Hb, haemoglobin; IM, intramuscular; IV, intravenous; LOS, length of stay; MI, myocardial infarction; MODS, multiple organ dysfunction score; RBC, red blood cell; RCT, randomised controlled trial; SAE, serious adverse event; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; SR, systematic review; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related immunomodulation

[a] The search will ensure that included studies are generalisable to the critical care population. Where higher level evidence only addresses a specific critical care subgroup (e.g. sepsis), a search of lower level evidence will be conducted. Studies that are exclusively in critical bleeding/massive transfusion populations will be excluded on the basis that they have already been covered in Module 1. Studies in perioperative populations will also be excluded unless they report results for subgroups that are critically ill, as these studies have already been covered in Module 2.

[b] In studies of patients with sepsis or septic shock, look for goal directed therapy.

[c] Including ACS, cardiology, cardiac/vascular surgery and cardiogenic shock.

[d] Other transfusion-related SAEs includes haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions.

Table 4.1.2 Structure of foreground research questions specific to critical care patient blood management

Specific question			
4. In critically ill patients, what is the effect of strategies that minimise blood loss on morbidity, mortality and blood transfusion? *Intervention vs. comparator* = (1) vs. (1), (2) vs. (2), (3) vs. (3), (2) vs. (3) (Interventional question, Q1)			
Population	Intervention	Comparison	Outcomes (primary, unless specified)
Acutely bleeding critically ill patients excluding patients undergoing elective and/or cardiac surgery[a] Subgroups: • Trauma • Non-trauma (including massive transfusion)	1. Cell salvage 2. Tranexamic acid 3. ε-aminocaproic acid	1. No cell salvage 2. No tranexamic acid 3. No ε-aminocaproic acid	• mortality • allogeneic transfusion volume[a] • allogeneic transfusion frequency • blood loss[b] • thromboembolic events (stroke, MI, DVT, PE)[c]

[a] The search will ensure that included studies are generalisable to the critical care population. Where higher level evidence only addresses a specific critical care subgroup (e.g. sepsis), a search of lower level evidence will be conducted. Studies that are exclusively in critical bleeding/massive transfusion populations will be excluded on the basis that they have already been covered in Module 1. Studies in perioperative populations will also be excluded unless they report results for subgroups that are critically ill, as these studies have already been covered in Module 2.

[b] These outcomes are only relevant to interventions (2) and (3)

[c] Trial-based definitions of thromboembolic events will be recorded in the Technical Report.

4.2 Appendix 2. Quality assessment

Each included study was assessed using the quality criteria for the relevant study type, as shown below. Studies were considered:

- good quality, with a low risk of bias, if they met all, or all but one, of the criteria
- fair quality, with a medium risk of bias, if they did not meet two or three criteria
- poor quality, with a high risk of bias, if they did not meet four or more criteria.

4.2.1 Systematic reviews

Study type:				Systematic review	
Citation:					
Y	N	NR	NA	Quality criteria	
				A. Was an adequate search strategy used?	
✓				Was a systematic search strategy reported?	I
				Were the databases searched reported?	III
				Was more than one database searched?	III
				Were search terms reported?	IV
				Did the literature search include hand searching?	IV
				B. Were the inclusion criteria appropriate and applied in an unbiased way?	
				Were inclusion/exclusion criteria reported?	II
				Was the inclusion criteria applied in an unbiased way?	III
				Was only level II evidence included?	I-IV
				C. Was a quality assessment of included studies undertaken?	
				Was the quality of the studies reported?	III
				Was a clear, pre-determined strategy used to assess study quality?	IV
				D. Were the characteristics and results of the individual studies appropriately summarised?	
				Were the characteristics of the individual studies reported?	III
				Were baseline demographic and clinical characteristics reported for patients in the individual studies?	IV
				Were the results of the individual studies reported?	III
				E. Were the methods for pooling the data appropriate?	
				If appropriate, was a meta-analysis conducted?	III-IV
				F. Were the sources of heterogeneity explored?	
				Was a test for heterogeneity applied?	III-IV
				If there was heterogeneity, was this discussed or the reasons explored?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]				Systematic review:	
				Included studies:	

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

[a] Assess criterion using Y (yes), N (no), NR (not reported) or NA (not applicable).

[b] Error categories as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (eg, good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.

[c] Where applicable, provide clarification for any of the criteria, particularly where it may result in downgrading of the study quality. For quality assessment of systematic reviews, this should include a statement regarding the methodological quality of the studies included in the systematic review.

[d]Quality ratings are good, fair or poor.

Source of quality criteria: NHMRC (2000)[5]

4.3 Randomised controlled trials

Study type:				Randomised controlled trial	
Citation:					
Y	N	NR	NA	Quality criteria	
				A. Was assignment of subjects to treatment group randomised?	
✓				Was the use of randomisation reported?	I
				Was the method of randomisation reported?	III
				Was the method of randomisation appropriate?	I-III
				A. Was allocation to treatment groups concealed from those responsible for recruiting subjects?	
				Was a method of allocation concealment reported?	III
				Was the method of allocation concealment adequate?	III
				B. Was the study double-blinded?	
				Were subjects and investigators blinded to treatment arm?	II-IV
				C. Were patient characteristics and demographics similar between treatment arms at baseline?	
				Were baseline patient characteristics and demographics reported?	III
				Were the characteristics similar between treatment arms?	III-IV
				D. Were all randomised participants included in the analysis?	
				Was loss to follow-up reported?	II
				Was loss to follow-up appropriately accounted for in the analysis?	III-IV
				E. Was outcome assessment likely to be subject to bias?	
				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
				Was outcome assessment blinded to treatment allocation?	III
				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				F. Were the statistical methods appropriate?	
				Were the methods used for comparing results between treatment arms appropriate?	III
				If the study was carried out at more than one site, are the results comparable for all sites?	IV
				G. If appropriate, were any subgroup analyses carried out?	
				Were subgroup analyses reported?	III-IV
				Were subgroup analyses appropriate?	III-IV
Comments:					
Quality rating: [Good/Fair/Poor]					

[a] Assess criterion using Y (yes), N (no), NR (not reported) or NA (not applicable).
[b] Error categories as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (eg, good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.
[c] Where applicable, provide clarification for any of the criteria, particularly where it may result in downgrading of the study quality.
[d] Quality ratings are good, fair or poor.
Source of quality criteria: NHMRC (2000)[5]

4.3.1 Cohort studies

Study type:				Cohort study	
Citation:					
Y	N	NR	NA	Quality criteria	
				A. Was the selection of subjects appropriate?	
✓				Were the two groups being studied selected from source populations that are comparable in all respects other than the factor under investigation?	II-IV
				Was the likelihood that some eligible subjects might have the outcome at the time of enrolment adequately accounted for in the analysis?	III
				B. Were all recruited participants included in the analysis?	
				Does the study report whether all people who were asked to take part did so, in each of the groups being studied?	III
				Was loss to follow-up and exclusions from analysis reported?	II
				Was loss to follow-up and exclusions from analysis appropriately accounted for in the analysis?	III-IV
				C. Does the study design/analysis adequately control for potential confounding variables?	
				Does the study adequately control for demographic characteristics, clinical features, and other potential confounding variables in the study design or analysis?	II-IV
				D. Was outcome assessment subject to bias?	
				Were all relevant outcomes measured in a standard, valid, and reliable way?	III-IV
				Was outcome assessment blinded to exposure status?	III
				If outcome assessment was not blinded, were outcomes objective and unlikely to be influenced by blinding of assessment?	III
				E. Was follow-up adequate?	
				Was follow-up long enough for outcomes to occur?	III
Comments:					
Quality rating: [Good/Fair/Poor]					

Note: Quality criteria adapted from NHMRC (2000) How to use the evidence: assessment and application of scientific evidence. NHMRC, Canberra.

[a] Assess criterion using Y (yes), N (no), NR (not reported) or NA (not applicable).

[b] Error categories as follows: (I) leads to exclusion of the study; (II) automatically leads to a poor rating; (III) leads to a one grade reduction in quality rating (eg, good to fair, or fair to poor); and (IV) errors that are may or may not be sufficient to lead to a decrease in rating.

[c] Where applicable, provide clarification for any of the criteria, particularly where it may result in downgrading of the study quality.

[d] Quality ratings are good, fair or poor.

Source of quality criteria: NHMRC (2000)[5]

4.4. NHMRC evidence statement form

Key question(s):		**Evidence table ref:**
1. Evidence base *(number of studies, level of evidence and risk of bias in the included studies)*		
	A	One or more Level I studies with a low risk of bias or several Level II studies with a low risk of bias
	B	One or two Level II studies with a low risk of bias or SR/several Level III studies with a low risk of bias
	C	One or two Level III studies with a low risk of bias or Level I or II studies with a moderate risk of bias
	D	Level IV studies or Level I to III studies/SRs with a high risk of bias
2. Consistency *(if only one study was available, rank this component as 'not applicable')*		
	A	All studies consistent
	B	Most studies consistent and inconsistency can be explained
	C	Some inconsistency, reflecting genuine uncertainty around question
	D	Evidence is inconsistent
	NA	Not applicable (one study only)
3. Clinical impact *(Indicate in the space below if the study results varied according to some **unknown** factor (not simply study quality or sample size) and thus the clinical impact of the intervention could not be determined)*		
	A	Very large
	B	Substantial
	C	Moderate
	D	Slight/Restricted
	NA	Not applicable/no difference/underpowered
4. Generalisability *(How well does the body of evidence match the population and clinical settings being targeted by the Guidelines?)*		
	A	Evidence directly generalisable to target population
	B	Evidence directly generalisable to target population with some caveats
	C	Evidence not directly generalisable to the target population but could be sensibly applied
	D	Evidence not directly generalisable to target population and hard to judge whether it is sensible to apply

5. Applicability *(Is the body of evidence relevant to the Australian healthcare context in terms of health services/delivery of care and cultural factors?)*		
	A	Evidence directly applicable to Australian healthcare context
	B	Evidence applicable to Australian healthcare context with few caveats
	C	Evidence probably applicable to Australian healthcare context with some caveats
	D	Evidence not applicable to Australian healthcare context

Other factors *(Indicate here any other factors that you took into account when assessing the evidence base (for example, issues that might cause the group to downgrade or upgrade the recommendation)*

Evidence statement matrix

Please summarise the development group's synthesis of the evidence relating to the key question, taking all the above factors into account

Component	Rating	Description
Evidence base		
Consistency		
Clinical impact		
Generalisability		
Applicability		

Indicate any dissenting opinions

Recommendation *What recommendation(s) does the guidelines development group draw from this evidence? Use action statements where possible*	**Grade** of recommendation	

IMPLEMENTATION OF RECOMMENDATION

Please indicate yes or no to the following questions. Where the answer is yes please provide explanatory information about this. This information will be used to develop the implementation plan for the guidelines

Will this recommendation result in changes in usual care?	**YES**	**NO**
Are there any resource implications associated with implementing this recommendation?	**YES**	**NO**
Will the implementation of this recommendation require changes in the way care is currently organised?	**YES**	**NO**
Are the guidelines development group aware of any barriers to the implementation of this recommendation?	**YES**	**NO**

4.5. Facilitated group discussion for development of practice points

4.5.1 Background

Often, there are insufficient high-quality data in the contemporary clinical literature to produce clinical guidelines with an evidence-based recommendation. Thus, there remains a role for expert opinion and consensus in guidelines development. The use of expert opinion as a form of 'evidence' requires a formal consensus development process among the guidelines developers, with rigorous rules that will lead to the same attributes of validity, reliability and applicability demanded for more rigorous evidence-based practice methodology.

4.5.2 Role of the clinical/consumer reference group

The CRG provided expert opinion for the development of practice points relevant to the recommendation being considered under the consensus process.

The consensus process was followed only for recommendations where:

- the systematic review found no Level I to IV evidence to address the relevant clinical question, or where recommendations developed by the systematic review process were ranked with a Grade D (poor) quality evidence base
- the CRG determined that additional clinical practice guidance is required for recommendations developed by the systematic review process that are graded above D.

Applying the consensus process to recommendations with Grade D (poor) evidence could result in:

- the rejection of the recommendation
- the confirmation of the recommendation
- the development of a "practice point" to supplement the recommendation, or
- rejection of the recommendation and the development of a practice point on its own.

4.5.3 Chair of CRG meetings

The Chair of CRG meetings facilitated and guided the process of reaching a consensus decision on practice points. Specifically, the Chair's role was to:

- assist the CRG in defining decisions that need to be made
- help the CRG through the stages of reaching an agreement
- keep the meeting moving
- focus discussion to the point at hand
- ensure everyone has the opportunity to participate
- test whether consensus has been reached.

The Chair helped to direct the consensus process, not its content, and did not make decisions for the CRG.

4.5.4 Pre-meeting process

Before CRG meetings, the systematic reviewer/technical writer distributed draft versions of the results of the systematic review. Where evidence was not found or the body of evidence was graded D, this was indicated in the draft report to highlight the need for the consensus process to develop practice points. In addition:

- A consensus response template and a list of numbered Grade D evidence statements for clinical questions for which no evidence could be found was developed by the systematic reviewer/technical writer and distributed to the CRG/NBA members and the systematic review expert 2 weeks in advance of the meeting in which a decision was required, using the evidence statement format proposed in the research protocol for Phase I.
- The CRG/NBA members and the systematic review expert were asked to consider and rate proposals taking into account the research literature, clinical opinion and expertise and the realities of the relevant healthcare settings.
- The completed consensus templates were sent to the systematic reviewer/technical writer a few days before the CRG meeting date for consolidation.
- The systematic reviewer/technical writer collated all responses and distributed the results 2 days before the meeting. These were then reviewed and deliberated on at the face-to-face consensus meeting.

4.5.5 Development of practice points: overview of consensus decision-making process

The process outlined below was used to develop practice points through consensus.

Stage 1 – Introduction

- **Describe the process.** The Chair described the consensus process, participants' roles and responsibilities, ground rules and guiding principles.
- **State where there was a need for practice point development.** The Chair described where evidence was not found or was inadequate to develop recommendations above Grade D, or where a practice point might be required to supplement recommendations.

Stage 2 – Open discussion

- **Clarify the practice point.** The Chair opened the floor to a general discussion and suggestions for practice point content. This time was not used for raising objections or concerns but for suggesting content for the practice point. Suggestions were recorded in the relevant section of the draft results report.
- **State concerns.** When the CRG was satisfied that the practice point was complete, the Chair provided an opportunity for concerns or issues to be raised.

Stage 3 – Resolve concerns

- **Review concerns.** The group reviewed any concerns raised. If the concerns were many and the time was short, the discussion on practice point development was carried over to a later meeting.
- **Resolve concerns.** The Chair had the first option to resolve the listed concerns by:
  - clarifying the wording of the practice point
  - changing the wording of the practice point or adding a practice point to supplement the recommendation
  - explaining why the recommendation as stated was not in conflict with the group's values

- see whether those with concerns would stand aside (i.e. “have concerns, but can live with them”).

Stage 4 – First call for consensus

- When all concerns had been resolved, the Chair called for consensus.

Stage 5 – Consideration of group principles and values and second call for consensus

- When concerns had been adequately discussed but remain unresolved, the group assessed how the unresolved concerns related to group principles and values.
- After considering these principles, the Chair made one of the following conclusions:
  - the member withdrew the concern, consensus was reached and a practice point could be made (or a Grade D evidence-based recommendation could be confirmed)
  - the member stood aside so a practice point could be made (or Grade D evidence-based recommendation could be confirmed), and the differing schools of thought were documented
  - the member was not willing to withdraw the concern or stand aside, and the CRG declared itself blocked—the recommendation or practice point was not accepted.

4.5.6 Guiding principles and values

These principles and values were used through the development of consensus-based practice points:

- Consensus is reached when all members of the CRG strongly agree or agree with the practice point. Consensus is not achieved on the basis of a “majority”.
- The opinions of all members of the group are equally valid and important, notwithstanding that some members may have discipline-specific expert opinion.
- Where consensus is not reached (one or more members disagree or strongly disagree with the practice point), the dissenting members are allowed to present their case. This may be done immediately in the current meeting, or be carried over to the subsequent meeting to allow the members to succinctly formulate their concerns or provide other documentation or research.
- Issues of semantics, language or content, while recognised as important, should preferably not absorb discussion time within CRG meetings.
- CRG members are respectfully asked to reflect on their own values and conflicts of interests, and be mindful of the extent to which these may influence their opinions.

4.5.7 Ground rules

- Members agree to take turns speaking and not interrupt each other.
- Members agree to call each other by their first names, not “he” or “she”.
- Members agree not to blame, attack or engage in put-downs, and will ask questions of each other for the purposes of gaining clarity and understanding.
- Members agree to stay away from establishing hard positions and express themselves in terms of personal needs and interests and the outcomes that they wish to realise.
- Members agree to listen respectfully and to try sincerely to understand the other person’s needs and interests.
- Members recognise that, even when they do not agree, each of them is entitled to their own perspective.

- Members will not dwell on things that did not work in the past, but instead will focus on the future they would like to create.
- Members agree to make a conscious, sincere effort to refrain from unproductive argument, venting or narration, and agree to use their time during the meeting to work toward what they perceive to be the fairest and most constructive agreement possible.
- Members will speak up when something is not working for them during the consensus process.
- Members will request a break when they need to.
- Members will point out when they feel the Chair is not being impartial as to person and neutral as to result.
- CRG members not present at the meeting will have the opportunity to provide feedback via email when developed practice points are circulated to the entire CRG after the meeting.

4.5.8 Post-meeting process

After the CRG meeting, the systematic reviewers/technical writers consolidated the outcomes from the meeting and circulated the results of the consensus process (all resultant practice points) to all members of the CRG, the NBA and the systematic review expert (including members who were not present at the meeting), together with a consensus response template.

All CRG/NBA members and the systematic review expert were asked to consider all resultant practice points and to provide any additional concerns or suggestions for amendments to these.

The completed consensus templates and all responses were sent to IMS Health for consolidation.

The systematic reviewers/technical writers collated all responses and distributed the results 2 days before the following CRG–NBA consensus meeting. These were then reviewed and amended as appropriate, and consensus for each of the practice points was ratified at the face-to-face consensus meeting.

References

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