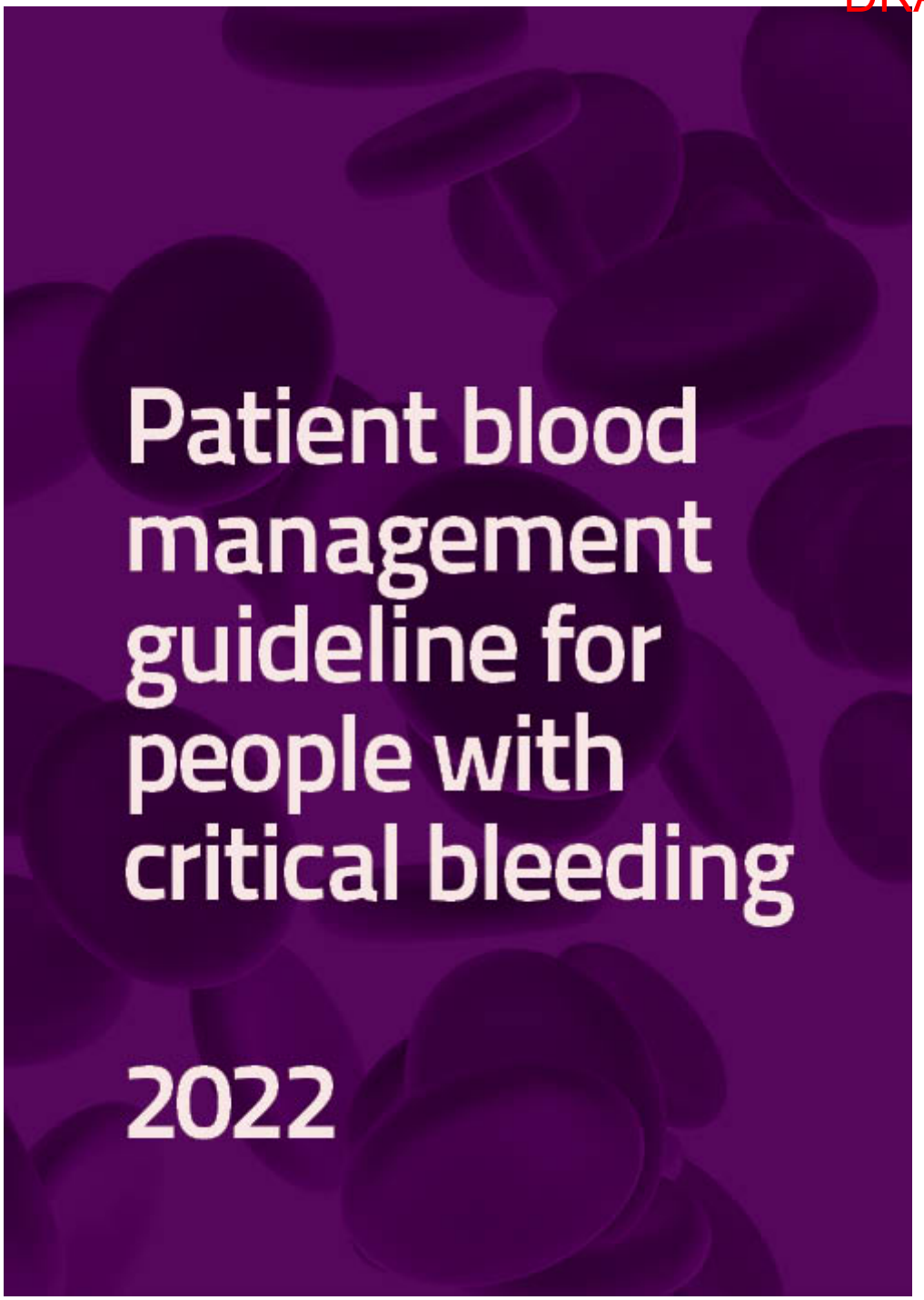
Patient blood management guideline for people with critical bleeding
2022

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Contact

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Sections

1. Summary of recommendations and good practice statements

The Clinical/Consumer Reference Group (reference group) developed:

- recommendations (R) based on a systematic review, graded as either strong or weak and for or against an intervention
- good practice statements (GPS) based on indirect evidence.

A more detailed description is provided in **Box 3** in Methodology.

Table 1.1: Recommendations and good practice statements		Section
Major haemorrhage protocol		
R1	In patients with critical bleeding, it is recommended that institutions use a major haemorrhage protocol that includes a multidisciplinary approach to haemorrhage control, correction of coagulopathy and normalisation of physiological derangement. *(Strong recommendation, very low certainty about the evidence)*	6.1

Table 1.1: Recommendations and good practice statements		Section
R2	In patients with critical bleeding requiring a major haemorrhage protocol, the following parameters should be measured early and frequently*: • temperature • acid–base status • ionised calcium • haemoglobin • platelet count • PT/INR • APTT • fibrinogen level *in addition to standard continuous physiological monitoring. *(Strong recommendation, low or very low certainty about the evidence)*	6.1.1
GPS1	Values indicative of critical physiological derangement include: • temperature < 35°C • pH < 7.2, base excess < −6 mEq/L, lactate > 4 mmol/L • ionised calcium < 1 mmol/L • PT > 1.5 × upper limit of normal • INR > 1.5 • APTT > 1.5 × upper limit of normal • fibrinogen level < 2.0 g/L The reference group agreed that is it good practice to monitor the above parameters and include a full blood count and coagulation profile upon initiation of a major haemorrhage protocol and at least after administration of every 4 units of RBC.	6.1.1
R3	In patients with critical bleeding, the implementation of a major haemorrhage protocol with a high ratio of RBC:FFP:PLT* may be beneficial, although there is insufficient evidence to support a 1:1:1 ratio over a 2:1:1 ratio^. *1 adult unit of pooled or apheresis platelets in Australia is equivalent to platelets derived from 4 single whole blood donor units. ^A ratio of 2:1:1 of RBC:FFP:PLT is lower than a ratio of 1:1:1, as the number of units of RBC increases without a proportionate increase in FFP or PLT. *(Weak recommendation, low or very low certainty about the evidence)*	6.1.2
GPS2	In patients with critical bleeding, the reference group agreed that it is good practice for the ratio of RBC:FFP:PLT be no lower than 2:1:1 for a major haemorrhage protocol. refer to R3	6.1.2
GPS3	The reference group agreed that the ratio of RBC:FFP:PLT of at least 2:1:1 be activated as soon as possible and be maintained throughout resuscitation. Do not use a reactive approach to blood component resuscitation. refer to R1	6.1.2
R4	In patients with critical bleeding, the following initial doses of FFP and PLT are suggested: • FFP: a minimum 1 unit per 2 units of RBC • PLT*: a minimum of 1 adult unit per 8 units of RBC	6.1.3

Table 1.1: Recommendations and good practice statements		Section
	*1 adult unit of pooled or apheresis platelets in Australia is equivalent to platelets derived from 4 single whole blood donor units. *(Weak recommendation, low or very low certainty about the evidence)*	
GPS4	For other blood components and products, the reference group agreed that the following doses are a guide: • Fibrinogen replacement: 8-10 units of whole blood cryoprecipitate, or 4-5 units of apheresis cryoprecipitate, or 3-4 grams fibrinogen concentrate* • Prothrombin complex concentrate for warfarin reversal^: 25 to 50 IU/kg There is insufficient evidence to provide a recommendation about timing and/or dose of these blood components or products. *Fibrinogen concentrate is approved in Australia for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenaemia and hypofibrinogenaemia. Use of fibrinogen concentrate outside these indications (including critical bleeding) is considered 'off-label.' ^refer to An update of consensus guidelines for warfarin reversal	6.1.3
GPS5	The reference group agreed that it is good practice to administer blood components through a blood warming device whenever possible and aim to maintain the patient core temperature ≥ 35°C.	6.1.3
GPS6	The reference group agreed that it is good practice to administer group specific blood components as soon as possible.* *refer to ANZSBT Guidelines for transfusion and immunohaematology laboratory practice	6.1.3
Blood conservation strategies		
R5	The reference group suggest against the use of rFVIIa in patients with critical bleeding*. *rFVIIa is approved in Australia and New Zealand for the control of bleeding and prophylaxis for surgery in patients with specific bleeding disorders. Use of rFVIIa outside these indications (including critical bleeding after trauma) is considered 'off-label' and is associated with harm. Use of rFVIIa should only be considered in exceptional circumstance where all other available measures to control bleeding have been exhausted. *(Weak recommendation against, low or very low certainty about the evidence)*	6.2.1
R6	In trauma patients with critical bleeding, the reference group suggest the early use (within 3 hours of injury) of tranexamic acid as part of a major haemorrhage protocol. *(Weak recommendation, low certainty of evidence about the evidence)*	6.2.1
R7	In obstetric patients with critical bleeding, the early use (within 3 hours of the onset of haemorrhage) of tranexamic acid may be considered as part of a major haemorrhage protocol. *(Weak recommendation, low certainty of evidence about the evidence)*	6.2.1
GPS7	The reference group agreed that the use of viscoelastic haemostatic assays* may be beneficial in patients with critical bleeding. There is insufficient evidence to provide a recommendation.	6.2.3

Table 1.1: Recommendations and good practice statements		Section
	If viscoelastic haemostatic assays are used in the assessment of patients with critical bleeding they must be used in conjunction with a major haemorrhage protocol. *Interpretation of results requires specific expertise and training.	
GPS8	The reference group agreed that the use of cell salvage* in patients with critical bleeding may be considered as part of a major haemorrhage protocol. There is insufficient evidence to provide a recommendation. *The use of cell salvage requires specific expertise and training.	6.2.4
ANZSBT: Australian & New Zealand Society of Blood Transfusion, APTT: activated partial thromboplastin time, FFP: fresh frozen plasma, GPS: good practice statement, INR: international normalised ratio, IU: international units, PLT: platelet, PT: prothrombin time, R: recommendation, RBC: red blood cell, rFVIIa: recombinant activated factor VII		

2. Major haemorrhage protocol (MHP)

The reference group developed an MHP template that is an update of the massive transfusion protocol published in the *Patient Blood Management Guidelines: Module 1 Critical Bleeding/ Massive Transfusion* (2011). The MHP template is designed to be adapted to meet local institutions' patient population and resources.

For public consultation please refer to the major haemorrhage protocol (PDF) under Accompanying materials on the public consultation page on the NBA website.

3. Introduction

Patient blood management improves patient outcomes by ensuring that the focus of the patient's medical and surgical management is on improving and conserving the patient's own blood. When a PBM approach is used, patients usually require fewer transfusions, reducing the risk of transfusion-associated complications. The decision to transfuse should take into account the full range of available treatments and balance the evidence for efficacy and improved clinical outcome against the potential risks.

Critical bleeding with major haemorrhage in a clinical emergency is associated with significant morbidity and mortality. This guideline recommends health service organisations use an MHP to direct the management of people with critical bleeding. More research is needed to clarify the ideal timing and ratio of blood components and products, and the benefits of strategies to conserve a person's own blood.

This guideline provides recommendations and good practice statements for the management of people with critical bleeding and supersedes the *Patient Blood Management Guidelines: Module 1 Critical Bleeding/ Massive Transfusion* (2011). The literature review used to develop this guideline included studies published up to 29 September 2021 for all questions except recombinant activated factor VII which included studies published up to 12 August 2019.

Background

Major haemorrhage can occur in any surgical, medical, obstetric, or trauma patient and often requires the administration of large volumes of blood components. The management of major haemorrhage is clinically and logistically complex and is associated with significant morbidity and mortality *[?]*. Data from the Australian New Zealand Massive Transfusion Registry demonstrated, that between 2011-2015, 19.4% of patients who received a massive transfusion died while in hospital *[238]*. Over the past two decades there has been considerable evidence published evaluating different strategies to improve patient outcomes in major haemorrhage *[236]*. Despite this, substantial evidence gaps remain and applicability of results across trauma and non-trauma settings is unclear *[236]*. In the context of PBM, an MHP supports the appropriate and timely use of blood components and blood conservation strategies to prevent and treat coagulopathy and maintain vital organ perfusion.

Clinical need for this guideline

This guideline is an update of the *Patient Blood Management Guidelines: Module 1 Critical Bleeding/ Massive Transfusion* (2011) and forms part of a series of Patient Blood Management Guidelines. At the time of development there was limited evidence to make

recommendations on blood component ratios, timing and dose of blood components and blood conservation strategies. Since its release there have been several clinical trials and international guidelines published *[240][239]*. These address some of the evidence gaps in the management of people with critical bleeding and major haemorrhage, however more research is still needed. The National Blood Authority (NBA) identified the need to update the 2011 guideline to ensure the recommendations incorporate the best available evidence.

Scope
The scope of this guideline is to provide clinical guidance to health professionals providing immediate care for people who have critical bleeding resulting in a major haemorrhage. The management of a major haemorrhage is usually only one part of care. The definition of critical bleeding for the purpose of this guideline is outlined in Definitions. The recommendations and good practice statements have been developed for adults in both trauma and non-trauma settings. While paediatric, perioperative and obstetric settings were included in the literature search, recommendations for specific settings were only made where there was sufficient evidence and consensus among the reference group. For recommendations specific to different populations see the Patient Blood Management Guideline specific to the patient population group.

Neonates (up to 28 days following birth) and individuals with hereditary bleeding disorders were excluded from the literature search.

Structure of the guideline
The guideline consists of two layers:

1. the recommendations and good practice statements
2. the supporting information.

1. Recommendations and good practice statements
Recommendations based on a systematic review are graded as either strong or weak and for/or against an intervention. Statements based on indirect evidence are referred to as good practice statements. The process of developing recommendations and good practice statements following the GRADE process are described in Methodology.

2. Supporting information
Under each recommendation are several tabs which contain information that supports the recommendation. These are outlined below.

Section heading: Can be expanded by clicking on the heading. This section contains information on the research question and some general information about any treatment or test described in the section.

Research evidence tab: Contains a summary of the evidence used to make the recommendation. Each recommendation may have a different number of options depending on the number of comparators assessed in the systematic review. The evidence for the intervention versus each comparator is presented in outcomes, graphical view, and summary.

- **Outcomes:** a tabular view of the overall effect estimates for each outcome assessed in the systematic review. For further information or a detailed description of the outcome, study results and certainty of the evidence, click on the eye icon in the top right-hand corner of the relevant cell.
- **Graphical view:** graphical representation of the effect of the intervention versus comparator for each outcome.
- **Summary:** overview and brief review of the underlying evidence.

Evidence to decision tab: Gives a summary of the factors that the reference group considered relevant under each GRADE domain:

- benefits and harms
- certainty of the evidence
- values and preferences
- resources
- equity
- acceptability
- feasibility

Rationale tab: Describes how the reference group combined the factors in the evidence to decision process to develop the overall direction and strength of the recommendation.

Practical information tab: Provides information for health professionals to implement the recommendation including recommended doses, timing and monitoring.

Feedback tab: If you are logged in as a user, you can comment here on specific recommendations. Your feedback will be entered into a feedback register maintained by the National Blood Authority.

References tab: Lists the studies used to develop the recommendation.

Related material
The technical report that underpins this document is available from the NBA website in three volumes:

- Volume 1 contains background information and the results of the systematic reviews pertaining to the clinical questions posed within this guideline
- Volume 2 contains appendixes that document the literature searches, list of excluded studies and critical appraisal of the included studies
- Volume 3 presents the data extraction forms for the included studies.

Disclaimer
This document is a general guide to appropriate practice, to be followed subject to the circumstances, health professional's judgement and patient's preference in each individual case. It is designed to provide information to assist decision making. Recommendations and good practice statements contained herein are based on the best available evidence published up to 29 September 2021, with the exception of recombinant activated factor VII which included studies published up until 12 August 2019. The relevance and appropriateness of the information and recommendations in this document depend on the individual circumstances. Moreover, the recommendations and guidelines are subject to change over time.

Each of the parties involved in developing this document expressly disclaims and accepts no responsibility for any undesirable consequences arising from relying on the information or recommendations contained herein.

Acknowledgements and endorsements
This guideline was developed by a multidisciplinary reference group with expertise from a range of clinical settings.

The NBA provided project management oversight and funded all goods and services associated with the development of this guideline. The development of clinical guidance was not influenced by the views or interests of the funding body.

4. Definitions

Critical bleeding
Critical bleeding is a term used to describe a range of clinical scenarios where bleeding may result in significant patient morbidity or mortality *[7]*. Critical bleeding results in decreased circulating volume, loss of oxygen-carrying capacity, and coagulopathy (impaired clot formation). Broadly, critical bleeding falls into one of two categories (which may overlap):

1. major haemorrhage that is life-threatening and is likely to result in the need for massive transfusion
2. haemorrhage of a smaller volume in a critical area or organ (e.g. intracranial, intraspinal or intraocular), resulting in patient morbidity or mortality.

For the purpose of this document, critical bleeding refers only to the first category.

Major haemorrhage protocol
An MHP includes a multidisciplinary approach to haemorrhage control, correction of coagulopathy and normalisation of physiological parameters.

Ratio of red blood cell to components
A predefined, balanced, fixed ratio of RBC:FFP:PLT. A ratio of 2:1:1 of RBC:FFP:PLT is lower than a ratio of 1:1:1, as the number of units of RBC increases without a proportionate increase in FFP or PLT.

5. Methodology

Question Development
Research questions for these guidelines were identified, developed and prioritised by a multidisciplinary reference group, working with an independent systematic review expert and the NBA *[166]*. The clinical questions chosen for evidence review are listed below and were structured according to PICO (population, intervention, comparator and outcome) criteria.

A research protocol was then developed that described the methodology to be used to source the clinical evidence (a systematic search of the literature), select the best available evidence, critically appraise and present the evidence and determine the certainty of the evidence, using a structured assessment of the body of evidence in accordance with Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology *[163]*.

Systematic review process

These evidence-based clinical practice guidelines were developed to NHRMC standards by following the principles proposed by the GRADE Working Group. The process involved developing a set of research questions, systematically reviewing the scientific literature for evidence related to those questions, and then developing and grading recommendations based on a structured assessment of the evidence. The methods used to apply this process are outlined here and are given in full in the accompanying technical reports *[8][171]* that present, in detail, the methodology used to identify the evidence base (clinical questions addressed, systematic literature search undertaken and eligibility criteria described), the characteristics of the evidence found (data extraction and risk of bias forms) and detailed results presented by outcome (evidence summary tables, forests plots).

The systematic review process was based on that described in the *Cochrane handbook for systematic reviews of interventions* and relevant sections in the *JBI Manual for Evidence Synthesis*. Covidence, a web-based platform for producing systematic reviews was used to store data that are compatible with the Cochrane data collection tools. RevMan *[162]* was used for the main analyses and GRADEpro GDT software was used to record decisions and derive an overall certainty of evidence for each outcome (high, moderate, low or very low).

To identify the evidence base for the nine research questions outlined in **Box 1**, a systematic search of published medical literature was conducted. All potentially relevant studies were identified after applying prespecified inclusion and exclusion criteria as outlined in the research protocol. For eligible studies, the risk of bias was assessed, appropriate data was extracted into data extraction tables and the results summarised into appropriate categories according to each question.

Box 1 Systematic review questions

Question 1 – In patients with critical bleeding, which physiologic, biochemical and metabolic (including temperature) parameters should be measured early and frequently and what values of these parameters are indicative of critical physiologic derangement?

Question 2 – In patients with critical bleeding, what is the effectiveness of major haemorrhage protocols (MHPs)?

Question 3 – In patients with critical bleeding, what is the optimal dose, timing and ratio (algorithm) to red blood cells (RBCs), of blood component therapy to reduce morbidity, mortality and transfusion?

Question 4 – In patients at risk of critical bleeding, is the transfusion of increased volumes of RBCs associated with an increased risk of mortality or adverse effects?

Question 5 – In patients with critical bleeding, what is the effect of recombinant activated factor VII (rFVIIa) treatment on morbidity, mortality and transfusion rate?

Question 6 – In patients with critical bleeding, what is the effect of fresh frozen plasma (FFP), cryoprecipitate (CRYO), fibrinogen concentrate (FC), prothrombin complex concentrate (PCC) and/or platelet (PLT) transfusion on RBC transfusion and patient outcomes?

Question 7 – In patients with critical bleeding, what is the effect of antifibrinolytics on blood loss, RBC transfusion and patient outcomes?

Question 8 – In patients with critical bleeding, does the use of viscoelastic haemostatic assays (VHAs) change patient outcomes?

Question 9 – In patients with critical bleeding, what is the effect of cell salvage on patient outcomes?

Study selection criteria

Population

In all questions, the specified population was *people who are critically bleeding*, defined as: people who have decreased circulating volume, loss of oxygen-carrying capacity and coagulopathy due to major haemorrhage that is life-threatening and is likely to result in the need for major transfusion.

- In Question 3, the specific population of interest was people *who have received* a major transfusion.
- In Question 4, the population included people who were *at risk of critical bleeding*, to account for patients with penetration injuries who *may* go on to develop critical bleeding if over-transfused before haemorrhage control.
- In Question 5, the focus was *people who fail to reach adequate haemostasis* and did not include patients with haemophilia or those after cardiopulmonary bypass.
- In Question 9, the focus was on *people in the emergency setting*, and did not include patients in the elective setting.

Intervention (or prognostic factor)
Question 1 and 4 were prognostic questions. For Question 1, studies examining the following parameters as predictors of mortality were eligible for inclusion: temperature, acid-base status, ionised calcium, haemoglobin, platelet count, prothrombin time (PT)/international normalised ratio (INR), activated partial thromboplastin time (APTT), or fibrinogen level. For Question 4, studies examining the volume of RBCs transfused as a predictor for mortality or adverse effects were eligible for inclusion.

All remaining questions (Question 2, 3, 5, 6, 7, 8 and 9) were interventional. Restrictions on the product type, mode of administration, number of doses or dosage were applied for each question and are provided in Volume 1 of the technical report *[8]*.

Outcomes
The critical outcome measure to inform decisions on benefits was all-cause mortality reported at 30-days or at the latest measured timepoint. Other measures related to mortality (e.g. death due to bleeding) were also recorded.

The critical outcome measures to inform decisions on harms were related to morbidity. Data reporting any prespecified adverse event relevant to the included population and typically associated with the intervention such as thromboembolic events (TEs), acute respiratory distress syndrome (ARDS), time on mechanical ventilator, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO) and multiorgan failure (MOF) were extracted.

Other outcome measures related to resource use included the volume of blood component or blood product transfused, wastage of blood components, time to delivery of blood components and length of hospital or intensive care unit (ICU) stay.

Study design features
For prognostic questions, studies with the following design labels were eligible for inclusion *[164]*:

- A systematic review of prospective cohort studies (Level I)
- A prospective cohort study (Level II)
- 'All or none' (Level III-1)
- Analysis of prognostic factors among persons in a single arm of a randomised controlled trial (RCT) (Level III-2)
- A retrospective cohort study (Level III-3)

For interventional question, studies with the following design labels were eligible for inclusion:

- A systematic review of RCTs (Level I)
- An RCT (Level II)
- 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-2)
- A comparative study without concurrent controls – including historical control studies, two or more single arm studies, interrupted time series without a parallel control group (Level III-3).

Assessment of noncomparative interventional studies or case series was not conducted for any research question, irrespective of whether sufficient higher-level evidence was found to address all critical and important outcomes for that question. This is because it is difficult (if not impossible) to attribute observed changes in outcomes at this level.

There were no restrictions applied to age, race or nationality or geographical location.

Literature search
The medical literature was searched on 11 August 2018 to identify relevant systematic reviews and primary studies published from database inception to the literature search date. The searches were repeated on 09 August 2019 and again on 29 September 2021 *[171]* to ensure the most recent and relevant evidence had been identified to inform clinical guidance. Details of the systematic literature search and application of the prespecified inclusion and exclusion criteria are provided in Appendix A of the technical report *[171]*.

The search strategy was developed in Ovid (for Embase and MEDLINE) based on key elements provided in the research questions (PICO/PPO [population, prognostic factor, outcome] criteria). The search strategy was then adapted to suit the Cochrane Library (database of systematic reviews, other reviews, clinical trials, technology assessments, economic evaluations) and PubMed (limited to in-process citations and citations not indexed in MEDLINE).

The search strategy was not limited by language; however, publications in languages other than English were only considered where a full text translation into English was available. No date or geographic limitations were applied when conducting the search. Literature search start dates varied for each question as defined by the reference group and is provided in Volume 1 of the technical report *[170]*. These date limits were applied once citations were imported into the bibliographic management database (Endnote).

The review considered both peer-reviewed and unpublished and grey literature. Ongoing trials and studies published as abstracts only were also included if they provided sufficient information for the outcome of interest.

The study selection process was completed by one systematic reviewer, with a second reviewer crosschecking the screening process to ensure adherence to the prespecified exclusion criteria. Any differences were resolved by discussion with a third reviewer (with advice sought from the reference group as necessary) to confirm study eligibility. Further details are provided in the technical report *[171][171][170]*.

Strengths and limitations of the evidence

The methodological quality of included systematic reviews and the risk of bias of primary studies was assessed using a variety of assessment tools according to the type of study, as outlined in Volume 1 of the technical report *[170]*. Here, the clarity and completeness or reporting, strengths and weaknesses of methods and processes used, as well as the underlying assumptions and limitations of a study was assessed. For each systematic review or primary study, supporting information and a rationale for each judgement is provided in Appendix D of the technical report *[171]*.

Evidence synthesis

After data collection, the available effect estimates (including 95% confidence intervals, *p*-values) for critical and important outcomes and those relating to resource use were presented in evidence summary tables, alongside the population and intervention characteristics. The evidence summary tables were structured by question, comparisons, study design and outcome measure (see technical report *[170]*). All available information was reported, including if the results were incompletely reported (e.g. no effect estimate, but the direction of effect with a *p*-value was reported). Implications of the missing outcome data were considered when interpreting the evidence.

Data synthesis of results within each comparison was performed according to methods described in Chapter 6 of the Cochrane Handbook. Using RevMan 5.4, effect estimates were combined across studies for each outcome using a random effects model, with data from RCTs and observational studies presented separately. Forest plots were used to visually depict the results. If the reported information allowed for direct calculation of effect estimates or imputation of missing statistics (e.g. standard deviations), calculations were performed within the computer program.

Heterogeneity was assessed by visually by inspecting the overlap of confidence intervals on the forest plots, formally testing for heterogeneity using the Chi-squared test (using a significance level of $\alpha = 0.1$) and quantifying heterogeneity using the I^2 statistic.

Indirect treatment comparisons were not conducted.

GRADE Summary of findings

GRADE evidence profiles were developed for each comparison and outcome, with relevance to the Australian context considered at this time. As per GRADE guidance *[163]*, the body of evidence was consolidated and rated across five key domains:

- *risk of bias* – based on the summary assessment across studies for each outcome reported for a comparison
- *inconsistency* – based on heterogeneity in the observed intervention effects across studies that suggests important differences in the effect of the intervention, and whether this can be explained
- *imprecision* – based on interpretation of the upper and lower confidence limits, and whether the intervention has a clinically important effect
- *indirectness* – based on important differences between the review questions and the characteristics of included studies that may lead to important differences in the intervention effects
- *publication bias* – based on the extent to which the evidence is available; such bias would be suspected when the evidence is limited to a small number of small trials

For each domain, a judgement was made about whether there were *serious*, *very serious* or *no concerns*, resulting in an overall grade (high, moderate, low or very low) for the certainty of evidence for each outcome, as detailed in **Box 2**. Scoring of the certainty of the evidence began as 'high' for randomised trials (score=4) and was downgraded by −1 for each domain with serious concerns, or −2 for very serious concerns, with observational studies being a 'low'. Further information is detailed in Volume 1 of the technical report *[170]*.

Box 2 GRADE certainty of evidence

High (⊕⊕⊕⊕) – further research is very unlikely to change the confidence in the estimate of effect.

Moderate (⊕⊕⊕⊖) – further research is likely to have an important impact in the confidence in the estimate of effect.

Low (⊕⊕⊖⊖) – further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low (⊕⊖⊖⊖) – any estimate of effect is very uncertain.

Formulating recommendations

The *evidence to decisions framework* provided within MAGICapp was used to inform translation of the evidence into recommendations for use in the clinical guidance chapter. Recommendations were made after considering the following key concepts:

- Benefits and harms
- Certainty of evidence
- Values and preferences
- Resources
- Equity
- Acceptability
- Feasibility

Recommendations were developed according to the processes outlined by the GRADE working group *[163]*. Recommendations based on a systematic review were graded as either strong or weak and for or against an intervention. Good practice statements were developed using a consensus process and were based on indirect evidence and expert opinion from the reference group. A systematic review was not completed, or there was insufficient evidence, and it was agreed it would be a poor use of the reference groups time to conduct a formal review *[210]*.

A consensus process was used to ensure that the clinical guidance was consistent with the evidence presented. The GRADE certainty of the evidence was used to inform the strength of any evidence-based recommendations that were made, with higher certainty evidence resulting in a strong recommendation for or against a particular action, and lower certainty resulting in a weak or conditional recommendation for or against a particular action as outlined in **Box 3.**

The recommendations and good practice statements were reviewed by the reference group between November 2021 to September 2022, following an update of the literature searches in September 2021.

Box 3 Definition of the strength and direction of recommendations

Strong recommendation for

The guideline reference group is confident that the benefits outweigh the harms for almost everyone. All or nearly all informed people would likely choose this option.

Strong recommendation against

The guideline reference group is confident that the harms outweigh the benefits for almost everyone. All or nearly all people would decline the intervention.

Weak recommendation for

The benefits probably outweigh the harms, but uncertainty exists. Most informed people would likely choose this option.

Weak recommendation against

The harms probably outweigh the benefits, but uncertainty exists. Most informed people would not choose this intervention, however different choices may be appropriate in individual circumstances.

Good Practice Statement

A good practice statement indicates that the reference group had high confidence in the indirect evidence. A systematic review was not completed, or there was insufficient evidence, and it was agreed it would be a poor use of the reference groups time to conduct a formal review.

6. Clinical guidance

6.1 Major haemorrhage protocol

An MHP includes a multidisciplinary approach to haemorrhage control, correction of coagulopathy and normalisation of physiological parameters.

Research question
In patients with critical bleeding, what is the effectiveness of major haemorrhage protocols (MHPs)?

Literature search date: 29 September 2021

Strong recommendation

R1: In patients with critical bleeding, it is recommended that institutions use a major haemorrhage protocol that includes a multidisciplinary approach to haemorrhage control, correction of coagulopathy and normalisation of physiological derangement.

Practical Info

refer to 'Major Haemorrhage Protocol'

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

In the meta-analysis of observational cohort studies that included people with critical bleeding in trauma and non-trauma settings, a large effect on mortality (latest timepoint or all-cause) was demonstrated. The true benefits are unknown due to a very low certainty of evidence. A low certainty of evidence also means the harms are not known.

Certainty of the Evidence

Very low

The overall certainty in effect estimates across outcomes was either very low (benefits) or low (harms).

Values and preferences

No substantial variability expected

There is no plausible reason to suspect that patients who are critically bleeding would not accept treatment via a major haemorrhage protocol as recommended. A subgroup of patients may decline blood components based on personal preference.

Resources

Important issues, or potential issues not investigated

Research evidence
Defined MHPs were not shown to increase or decrease the transfusion volume of RBCs or FFP in trauma patients with critical bleeding *(GRADE: very low certainty of evidence)*

Summary
In the absence of high certainty evidence, the resource implications of major haemorrhage protocols are uncertain.

Equity

Important issues, or potential issues not investigated

It is acknowledged that there is jurisdictional, geographical and/or institutional variability in composition and delivery of major haemorrhage protocols.

Acceptability

No important issues with the recommended alternative

Acceptability of a major haemorrhage protocol was not investigated.

Feasibility

Important issues, or potential issues not investigated

The reference group acknowledged the logistical challenges associated with implementing a major haemorrhage protocols to treat critically bleeding patients. Adaptation of this guidance at a local level is required upon consideration of the resources available.

Rationale

Practical benefits of a major haemorrhage protocol include:

- Allowing blood banks to anticipate needs and provide blood components and products quickly.
- Optimising timing of delivery of blood components and products.
- Optimising administration of blood components and products.

Clinical Question/ PICO

Population:	People with critical bleeding (trauma setting)
Intervention:	Defined major haemorrhage protocol (MHP)
Comparator:	No defined MHP

Summary

What did we find?

Twenty-one observational studies were found that assessed the effects of major haemorrhage protocols (MHPs) in trauma patients with critical bleeding (Brink 2016, Cotton 2009, Dirks 2010, Shaz 2010, Hwang 2018, Maciel 2015, Noorman 2016, Riskin 2009, O'Keefe 2008, Nunn 2017, Simmons 2010, Sinah 2013, Sisak 2012, van der Meij 2019, Champion 2013, Duchesne 2010, Fox 2008, Cotton 2008, Dente 2009, Johansson 2009, Vogt 2009).

Study characteristics

Most studies were carried out at Level I trauma centres in the United States, Canada, Denmark and Australia. The included observational studies were judged by various systematic reviews *[27][176][175][174]* to have moderate or high concerns of bias related to study design, data collection and adjustments for confounding.

What are the main results?

Mortality

Among people with blunt and penetrating trauma, pooled data from the observational studies suggested the rate of mortality at the latest timepoint reported (typically up to 30-days or upon hospital discharge) was lower among those in whom an MHP was triggered (717/2278, 31.5%) compared with those whose transfusions were not guided by an MHP (786/1948, 40.3%) (OR 0.67; 95% CI 0.53, 0.85; p = 0.001; random effect, I^2 = 63%). There was little to no important difference in the 24-hour rate of mortality among patients who had an MHP (131/618, 21.2%) compared with those who did not (122/412, 29.6%) (OR 0.79; 95% CI 0.56, 1.11; p = 0.17; random effect, I^2 = 15%).

RBC transfusion volumes

Among people with blunt and penetrating trauma, there was no difference in the volume of red blood cells transfused among those who received MHPs compared with those who did not, with less than one red cell unit saved. The overall standardised mean difference (SMD) was −0.13 (95% CI −0.33, 0.07; p = 0.20; random effect, I^2 = 77%).

Transfusion volumes, other blood products

Only limited conclusions could be drawn from the available evidence, with inconsistency of reporting among the studies and variances in MHP transfusion triggers. The available data suggested no important difference between groups for volume of FFP and PLTs transfused.

Outcome Timeframe	**Study results and measurements**	**Comparator** No defined MHP	**Intervention** Defined major haemorrhage protocol (MHP)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 24 hours 9 Critical	Odds ratio 0.79 (CI 95% 0.56 — 1.11) Based on data from 1,030 participants in 6 studies. [1] (Observational (non-randomized))	296 per 1000 Difference:	249 per 1000 **47 fewer per 1000** (CI 95% 105 fewer — 22 more)	**Very low** Due to serious risk of bias, Due to serious imprecision [2]	There is little to no association between defined MHPs and lower 24-hour mortality in people with critical bleeding in the trauma setting, but the evidence is very uncertain.
Mortality, all cause latest reported timepoint 9 Critical	Odds ratio 0.67 (CI 95% 0.53 — 0.85) Based on data from 4,226 participants in 19 studies. [3] (Observational (non-randomized))	403 per 1000 Difference:	311 per 1000 **92 fewer per 1000** (CI 95% 140 fewer — 38 fewer)	**Very low** Due to serious risk of bias, Due to serious inconsistency [4]	There is a large association between defined MHPs and lower mortality in people with critical bleeding in the trauma setting but the evidence is very uncertain.
RBC transfusion volume	Measured by: Number of Units Lower better Based on data from 2,493 participants in 10 studies. [5] (Observational (non-randomized))	12 - 25 Units Difference:	11.8 - 24 Units **SMD 0.13 fewer** (CI 95% 0.33 fewer — 0.07 more)	**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision [6]	Defined MHPs may reduce volume of RBC transfused but the evidence is very uncertain and MHPs can be overactivated leading to wastage.

Clinical Question/ PICO

Population: People with critical bleeding (non-trauma setting)
Intervention: Defined major haemorrhage protocol (MHP)
Comparator: No defined MHP

Summary

What did we find?

Four retrospective observational studies were found that assessed the effects of major haemorrhage protocols (MHPs) in a non-trauma setting (Dutta 2017, McDaniel 2013, Martinez-Calle 2016, Johansson 2007). One other retrospective cohort study was also included that assessed the effect of the introduction of an MHP across the whole hospital (Balvers 2015). The included observational studies were judged by review authors *[177]* to be at overall high risk of bias due to study design and confounding.

Study characteristics

The studies were conducted at single centres in the United States, Denmark, The Netherlands and Spain and included patients with bleeding due to obstetric complications (Dutta 2017), ruptured abdominal aortic aneurysm (Johansson 2007), a mixed group patients with postsurgical/procedural complications, or gastrointestinal and vascular emergencies (McDaniel 2013, Martinez-Calle 2016), or patients from a variety of settings including surgery (63%), internal medicine (13%), other (11%), trauma (9%), obstetric (4%) (Balvers 2015). Massive bleeding was defined as those who required 4 or more units of red blood cells (RBCs) (Dutta 2017), 5 or more units of RBCs (Blavers 2015) 10 or more units of RBCs (McDaniel 2013, Johansson 2007) or the replacement of whole blood volume in 24-hours, 50% of volume in 3-hours or blood loss more than 1500 mL in ten minutes (Martinez-Calle 2016).

What are the main results?

Mortality

Among non-trauma patients in whom an MHP was triggered, the mortality rate (latest timepoint) of 30.4% (166/546) was slightly lower than the mortality rate of 34.9% (156/447) observed among patients whose transfusions were not guided by an MHP, but the effect estimates were inconsistent and the lower bound of the confidence interval suggests no important association (OR 0.67; 95% CI 0.35, 1.29; p = 0.23; I^2 = 74%).

RBC transfusion volumes

Among non-trauma patients, data from one study suggested there was no important difference between groups for the volume of red blood cell transfused comparing those who received transfusions guided by an MHP with those who did not (less than one unit saved). The overall standardised mean difference (SMD) was 0.04 (95% CI −0.46, 0.54; p = 0.88).

Transfusion volumes, other blood products

Only limited conclusions could be drawn from the available evidence, due to inconsistency of reporting among the studies and variances in MHP transfusion triggers. Data from one study suggested no important difference between groups for volume of FFP and PLTs transfused.

Outcome Timeframe	**Study results and measurements**	**Comparator** No defined MHP	**Intervention** Defined major haemorrhage protocol (MHP)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 24 hours 7 Critical	Odds ratio 1.05 (CI 95% 0.35 — 3.12) Based on data from 861 participants in 4 studies. [1] (Observational (non-randomized))	**99** per 1000 Difference:	**103** per 1000 **4 more per 1000** (CI 95% 62 fewer — 156 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency [2]	There is little to no association between defined MHPs and lower 24-hour mortality in the non-trauma setting, but the evidence is very uncertain.
Mortality, all cause latest reported timepoint 9 Critical	Odds ratio 0.67 (CI 95% 0.35 — 1.29) Based on data from 993 participants in 5 studies. [3] (Observational (non-randomized))	**349** per 1000 Difference:	**264** per 1000 **85 fewer per 1000** (CI 95% 191 fewer — 60 more)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [4]	There is little to no association between defined MHPs and lower mortality in patients with critical bleeding in the non-trauma settings but the evidence is very uncertain.
RBC transfusion volume	Measured by: Number of Units Lower better Based on data from 462 participants in 4 studies. [5] (Observational (non-randomized))	**12.2** Units (Mean) Difference:	**12.6** Units (Mean) **SMD 0.04 more** (CI 95% 0.46 fewer — 0.54 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency [6]	MHPs have little or no effect on volume of RBCs transfused in patients with critical bleeding in the non-trauma settings but the evidence is very uncertain.

Clinical Question/ PICO

Population: People with critical bleeding (any setting)
Intervention: Defined major haemorrhage protocol (MHP)
Comparator: No defined MHP

Summary

What did we find?

There were 29 nonrandomised cohort studies identified that examined the effects of defined major haemorrhage protocols (MHPs) versus no defined MHPs on mortality and transfusion volumes in patients with critical bleeding across any setting (Brink 2016, Cotton 2009, Dirks 2010, Shaz 2010, Hwang 2018, Maciel 2015, Noorman 2016, Riskin 2009, O'Keefe 2008, Nunn 2017, Simmons 2010, Sinah 2013, Sisak 2012, van der Meij 2019, Champion 2013, Duchesne 2010, Fox 2008, Cotton 2008, Dente 2009, Johansson 2009, Vogt 2009, Dutta 2017, McDaniel 2013, Martinez-Calle 2016, Johansson 2007, Chidester 2013, Hendrickson 2012, Hwu 2016, Balvers 2015).

Study characteristics

Most studies were carried out in single and multicentre medical and trauma centres in the United States (US), Canada, Europe and Australia. Overall, the systematic reviews judged included observational studies to be moderate to high risk of bias due to study design, data collection and adjustments for confounding *[176][27][175][174][177][178][179][180].*

What are the main results?

Mortality, latest timepoint

Pooled data from observational studies included in this review showed the mortality rate (latest timepoint) in patients with critical bleeding to be lower among those who received a MHP (926/2927, 13.6%) compared with those who did not (977/2492, 39.2%) (OR 0.71; 95% CI 0.57, 0.87; p = 0.001; random effect, I^2 = 62%).

FFP transfusion volumes

A meta-analysis of data from observational studies included in this review revealed a nonsignificant reduction in the volume of fresh frozen plasma (FFP) transfusion in patients with critical bleeding who received MHPs (n=1340) compared with those who did not (n=1119), with an overall standardised mean difference (SMD) of −0.09 units observed (95% CI −0.41, 0.23; p = 0.57; random effect, I^2 = 92%). Heterogeneity was substantial with effect estimate largely influenced by three observational studies (O'Keefe 2008, Shaz 2010 and Simmons 2010). Furthermore, differences in triggers activating MHPs varied between studies.

PLT transfusion volumes

A meta-analysis of data from observational studies included in this review revealed a nonsignificant increase in the volume of platelet (PLT) transfusion in patients with critical bleeding who received MHPs (n=2049) compared with those who did not (n=1666), with an overall standardised mean difference (SMD) of 0.54 units observed (95% CI −0.26, 1.33; p = 0.19; random effect, I^2 = 99%). Heterogeneity was substantial with effect estimate likely to be largely influenced by differences between studies for MHP activation.

Outcome Timeframe	**Study results and measurements**	**Comparator** No defined MHP	**Intervention** Defined major haemorrhage protocol (MHP)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint 9 Critical	Odds ratio 0.71 (CI 95% 0.57 — 0.87) Based on data from 5,419 participants in 27 studies. [1] (Observational (non-randomized))	**392** per 1000 Difference:	**314** per 1000 **78 fewer per 1000** (CI 95% 123 fewer — 33 fewer)	**Very low** Due to serious risk of bias, Due to serious inconsistency, [2]	There is a large association between defined MHPs and lower mortality in people with critical bleeding but the evidence is very uncertain.
FFP transfusion volume	Measured by: Number of Units Lower better Based on data from 2,459 participants in 9 studies. [3] (Observational (non-randomized))	**8 - 15** Units Difference:	**8 - 14** Units **SMD 0.09 fewer** (CI 95% 0.41 fewer — 0.23 more)	**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision [4]	Defined MHPs may reduce volume of FFP transfused but the evidence is very uncertain and MHPs can be overactivated leading to wastage.

Outcome Timeframe	Study results and measurements	Comparator No defined MHP	Intervention Defined major haemorrhage protocol (MHP)	Certainty of the Evidence (Quality of evidence)	Plain language summary
PLT transfusion volume	Measured by: Number of Units Lower better Based on data from 3,715 participants in 15 studies. [5] (Observational (non-randomized))	1.7 - 15 Units Difference:	1.1 - 31 Units **SMD 0.54 more** (CI 95% 0.26 fewer — 1.33 more)	Very low Due to serious risk of bias, Due to very serious inconsistency, Due to serious indirectness, Due to serious imprecision [6]	Defined MHPs may increase the volume of platelets transfused but the evidence is very uncertain and MHPs can be overactivated leading to wastage.

6.1.1 Physiological, biochemical and metabolic parameters

Research question
In patients with critical bleeding, which physiologic, biochemical and metabolic (including temperature) parameters should be measured early and frequently and what values of these parameters are indicative of critical physiologic derangement?

Literature search date: 29 September 2021

Strong recommendation

R2: In patients with critical bleeding requiring a major haemorrhage protocol, the following parameters should be measured early and frequently*:

- temperature
- acid–base status
- ionised calcium
- haemoglobin
- platelet count
- PT/INR
- APTT
- fibrinogen level

**in addition to standard continuous physiological monitoring.*

Practical Info

refer to GPS1

See National Safety and Quality Health Care Standards: 8.04 Recognising and Responding to Acute Deterioration Standard

Evidence To Decision

Benefits and harms

Identified cohort studies suggest an association between prognostic factors and an increased risk of mortality. However, the overall certainty of the evidence was very low. The true benefits are unknown due to a very low certainty of evidence. A low certainty of evidence also means the harms are not known.

Certainty of the Evidence

Very low

The overall certainty in the effect across outcomes was either very low (benefits) or low (harms).

Values and preferences

No substantial variability expected

There is no plausible reason to suspect that patients who are critically bleeding would not accept assessment of prognostic factors as recommended.

Resources

No important issues with the recommended alternative

Resource implications associated with measuring prognostic factors are likely to be limited given standard laboratory testing is available, with the exception of fibrinogen which may not be considered standard.

Equity

No important issues with the recommended alternative

Equity is unlikely to be impacted as standard laboratory testing is available, with the exception of fibrinogen which may not be considered standard.

Acceptability

No important issues with the recommended alternative

Acceptability is unlikely to be impacted as standard laboratory testing is available, with the exception of fibrinogen which may not be considered standard.

Feasibility

No important issues with the recommended alternative

Feasibility is unlikely to be impacted as standard laboratory testing is available, with the exception of fibrinogen which may not be considered standard.

Rationale

The early identification and management of derangement in the above parameters may prevent the development or worsening of the lethal triad (hypothermia, coagulopathy, acidosis).

Clinical Question/ PICO

Population: People with critical bleeding (any setting)
Intervention: Temperature
Comparator: N/A

Summary

What did we find?

Three observational studies were found that assessed the association between temperature and mortality in patients with critical bleeding (Lester 2019, Martin 2005, Balvers 2016) and one observational study assessed the association of temperature with transfusion requirements in patients with critical bleeding (Callcut 2011).

Study characteristics

Two studies were carried out in trauma centres in the United States (US) and one study in a trauma centre in the Netherlands. Two studies (Martin 2005, Balvers 2016) were judged by Lilitis 2018 *[201]* to be at high risk of one study (Callcut 2011) was assessed by Shih 2019 *[202]* to have overall low concerns of bias .

Lester 2019 *[173]* was a single-arm analysis of a randomised controlled trial (RCT) that evaluated the association between hypothermia and patient outcomes using the data set collected during the PROPPR RCT (Holcomb 2015). Hypothermia was defined as a temperature less than 36°C and normothermia was considered to be between ≥36°C and 38.5°C. Lester 2019 had several limitations related to measurement of the outcome (no standardised method and variability in devices used), reporting of the outcome (pooling of data across 12 sites) and differences in protocols. Overall, Lester 2019 was judged to be at serious risk of bias due to study design, confounding and reporting.

What are the main results?

Mortality
Identified literature suggests an increased risk of mortality associated with hypothermia among patients with critical bleeding. Three studies in trauma settings contributed mortality data reporting odds ratio (OR) ranges of 2.7 observed at 24 hours and 1.8 – 2.8 observed at 30 days. Hypothermia was generally considered to be below 35.5°C.

Transfusion volume
Only limited conclusions can be drawn from the available evidence. Included studies were in trauma settings and reported an increased risk of transfusion requirements associated with hypothermia in patients with critical bleeding.

Outcome Timeframe	**Study results and measurements**	**Comparator** N/A	**Intervention** Temperature	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint 9 Critical	Based on data from 703,030 participants in 3 studies. [1] (Observational (non-randomized))	All studies found an association between hypothermia and an increased risk of mortality. 24-hour mortality OR range 2.7 and 2.72. 30-day OR range 1.8 and 2.82.		**Very low** Due to serious publication bias, Due to serious indirectness, Due to very serious inconsistency, Due to serious imprecision, Due to serious publication bias [2]	Hypothermia (<35°C) is associated with higher mortality.
Transfusion volume	Based on data from 756 participants in 2 studies. (Observational (non-randomized))	One study found increased transfusion volume requirements with hypothermia (OR 4.0) and one study found no difference (RR 0.90).		**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision, Due to serious publication bias [3]	Hypothermia (<35°C) is associated with higher volume of RBCs transfused.

Clinical Question/ PICO

Population: People with critical bleeding (any setting)
Intervention: Acid-base status
Comparator: N/A

Summary

What did we find?

Three reviews (Baxter 2016, Lilitis 2018, Tran 2018) corresponding to 15 observational studies were identified in the literature. There were 12 studies that assessed the effect of lactate levels on mortality in trauma patients with critical bleeding (Aslar 2004, Callaway 2009, Duane 2008, Lavery 2000, Mizushima 2011, Neville 2011, Odom 2012, Regnier 2012, Vandromme 2010, Gale 2016, Heinonen 2014, Odom 2013) and five studies that assessed the effect of lactate levels on transfusion volume in trauma patients with critical bleeding (Vandromme 2010, Vandromme 2011, Regnier 2012, Baron 2004, Ipecki 2013). The literature search also identified one prospective observational study (Javali 2017) and one retrospective cohort study (Sawamura 2009) that assessed the effect of lactate levels on mortality and transfusion volume in the trauma setting.

Study characteristics

The included studies identified from the systematic reviews were carried out in various trauma centres in the United States (US), France, Switzerland and South Africa. The overall risk of bias was judged to be moderate high due to attrition, confounding and reporting biases *[203][201][204]*.

Javali 2017 was a prospective observational study in 100 trauma patients at risk of haemodynamic compromise in a tertiary care centre emergency department in India. This study was found to be at serious risk of bias due to inadequate control of confounding factors. Additionally, the study included 92 patients in the analysis of base deficit and did not provide justification for patients lost to follow-up.

Sawamura 2009 was a retrospective cohort study conducted in Japan which aimed to assess the impact of disseminated intravascular coagulation (DIC) on patient outcomes. Data obtained at four time points (within 24 hours of arrival to the emergency department) was collected from 314 consecutive severe trauma patients which was further subdivided into 259 survivors and 55 nonsurvivors. This study was found to have critical risk of bias due to lack of blinding and inadequate reporting of follow-up.

What are the main results?

Mortality

Identified literature suggests an association between increased risk of mortality and increasing lactate levels among patients with critical bleeding. Fourteen observational studies in trauma settings contributed mortality data. At high lactate levels (>4 mmol/L), authors reported odds ratio (OR) ranges between 4.2 and 10.58 with statistical difference.

Transfusion volume

Identified literature suggests only limited conclusions can be drawn from the available evidence. Included studies were in trauma settings and reported an increased risk of transfusion requirements associated with increased lactate levels in patients with critical bleeding. High lactate levels were reported above >2.9mmol/L.

Outcome Timeframe	**Study results and measurements**	**Comparator** N/A	**Intervention** Acid-base status	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint 9 Critical	Based on data from 41,328 participants in 14 studies. (Observational (non-randomized))	Studies found an association between high lactate levels and increased risk of mortality. OR ranges across studies vary depending on lactate levels. At levels >4mmol/L studies reported OR range of 3.8 and 10.		**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious indirectness, Due to serious imprecision, Due to serious publication bias [1]	Higher lactate levels are associated with higher mortality.
Transfusion volume	Based on data from 1,193 participants in 6 studies. (Observational	Studies found an association between increased lactate levels and increased transfusion volume		**Very low** Due to serious risk of bias, Due	Higher lactate levels are associated with higher volume of RBCs

Outcome Timeframe	**Study results and measurements**	**Comparator** N/A	**Intervention** Acid-base status	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	(non-randomized))	requirements. Two studies reported OR range of 3.13 and 5.20 (OR values not reported for other studies).		to very serious inconsistency, Due to serious indirectness, Due to serious imprecision, Due to serious publication bias [2]	transfused.

Clinical Question/ PICO

Population: People with critical bleeding (any setting)
Intervention: Ionised calcium
Comparator: N/A

Summary

What did we find?

Three reviews (Vasudeva 2021, Moore 2020, Shih 2019) corresponding to three observational studies (Cherry 2006, Magnotti 2011, Vasudeva 2020) and two single-arm analyses of randomised controlled trials (RCTs) (COMBAT, PAMPer) were identified in the literature. All five studies assessed the effect of ionised calcium on mortality in trauma patients with critical bleeding and four studies assessed the effect of ionised calcium on transfusion volume in trauma patients with critical bleeding (Magnotti 2011, Vasudeva 2020, COMBAT, PAMPer). Overall, studies which reported the effect of ionised calcium on patient outcomes were carried out in trauma centres in the United States (US) and Australia.

Study characteristics

Moore 2020 aimed to evaluate the association between prehospital plasma and hypocalcaemia, which in turn is associated with lower survival. To investigate this, Moore 2020 used data collected from two RCTs, COMBAT (Moore 2018) which included injured adults ≥18 years with acute blood loss and PAMPer (Sperry 2018) which included injured adults at risk of haemorrhagic shock. Moore 2020 did not assess the risk of bias of the two included RCTs. However, review authors noted limitations of the studies for the purposes of the meta-analysis acknowledging that these biases can potentially limit the generalisability of the results. These include biases due to outcome data (lack of ionised calcium measurements for all enrolled patients), preexisting disease severity and survivor bias *[205]*.

Vasudeva 2021 assessed the quality of included studies to be moderate, noting that none of the included studies were blinded nor explicitly stated the utilisation of different reviewers for data collection and cross checking. Shih 2019 did not assess risk of bias of included studies. Overall, risk of bias for included observational studies was judged to be moderate due to limited by sample size and confounding *[206]*.

What are the main results?

Mortality

Identified literature suggests an increased risk of mortality associated with hypocalcaemia. Four observational studies in trauma settings contributed data. One study reported an odds ratio (OR) of 1.92 observed with statistical difference. Hypocalcaemia was considered <1.1mmol/L.

Transfusion volume

Identified literature suggests only limited conclusions can be drawn from the available evidence, with observational studies in trauma settings reporting a significant association between hypocalcaemia and increased transfusion requirements in critically bleeding patients.

Outcome Timeframe	Study results and measurements	Comparator N/A	Intervention	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality, all cause (RCTs) latest reported timepoint 9 Critical	Based on data from 160 participants in 2 studies. (Randomized controlled)	Two studies found no association between ionised calcium levels and mortality (p = 0.26).		**Low** Due to serious imprecision, Due to serious publication bias [1]	Hypocalcaemia (<1mmol/L) is associated with higher mortality.
Mortality, all cause (Coh) latest reported timepoint 9 Critical	Based on data from 1,213 participants in 3 studies. (Observational (non-randomized))	Three studies reported a significant association between low ionised calcium levels and mortality (one study reported OR 1.92, p <0.05. two studies did not report OR).		**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision, Due to serious publication bias [2]	Hypocalcaemia (<1mmol/L) is associated with higher mortality.
Transfusion volume (RCTs)	Based on data from 160 participants in 2 studies. (Randomized controlled)	Two studies found a significant association between low ionised calcium levels and increased transfusion volume (RBCs p = 0.0002, plasma p = 0.007, and cryoprecipitate p = 0.0003).		**Low** Due to serious imprecision, Due to serious publication bias [3]	Hypocalcaemia (<1mmol/L) is associated with higher volume of blood products (RBCs, plasma and CRYO) transfused
Transfusion volume (Coh)	Based on data from 817 participants in 2 studies. (Observational (non-randomized))	Two studies found a significant association between low ionised calcium levels and increased transfusion volumes (only one study reported OR 2.29).		**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision, Due to serious publication bias [4]	Hypocalaemia (<1 mmol/L) is associated with higher volume of RBCs transfused.

Clinical Question/ PICO

Population: People with critical bleeding (any setting)
Intervention: Haemoglobin
Comparator: N/A

Summary

What did we find?

Two reviews (Tran 2018, Shih 2019) corresponding to seven observational studies were identified in the literature (Callcut 2013, Paulus 2014, Vandromme 2011, Callcut 2011, Leemann 2010, Schochl 2011, Schreiber 2007). All studies assessed the effect of haemoglobin on transfusion volume requirement in trauma patients with critical bleeding. No studies assessing the effect of haemoglobin on mortality were identified.

Study characteristics

Studies were carried out in trauma centres in the United States (US), Switzerland, Austria and Iraq. Tran 2018 found the quality of included studies was poor noting the frequent lack of justification, inadequate reporting and

suboptimal handling of missing data. Overall, risk of bias for the included observational studies was judged to be moderate to high due to study design and confounding *[204][202]*.

What are the main results?

Transfusion volume

Identified literature suggests only limited conclusions can be drawn from the available evidence. Seven observational studies in trauma settings contributed data, reporting a positive association between low haemoglobin levels and increased risk of transfusion requirements.

Outcome Timeframe	**Study results and measurements**	**Comparator** N/A	**Intervention** Haemoglobin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint 9 Critical		There were no studies assessing the association between haemoglobin and mortality identified in the literature.			No studies were found that looked at all-cause mortality.
Transfusion volume	Based on data from 2,349 participants in 7 studies. (Observational (non-randomized))	Seven studies reported lower haemoglobin levels associated with increased transfusion volumes required in adult trauma patients. Reported OR range 1.8 - 18.18.		**Very low** Due to serious risk of bias, Due to serious very inconsistency, Due to serious indirectness, Due to serious imprecision, Due to serious publication bias [1]	Lower haemoglobin levels are associated with increased volume of RBCs transfused.

Clinical Question/ PICO

Population: People with critical bleeding (any setting)
Intervention: Platelet count
Comparator: N/A

Summary

What did we find?

Two reviews (Poole 2016, Levy 2017) corresponding to nine observational studies were identified in the literature. Two studies assessed the effect of platelet count on mortality in trauma and perioperative surgical patients with critical bleeding (Hagemo 2014, Mitra 2010). Seven studies assessed the effect of platelet count on transfusion volume requirement in perioperative surgical patients with critical bleeding (Arnold 2006, Fayed 2013, McGrath 2008, Premaratne 2001, Tanaka 2014, Wu 2014, van Hout 2017). The literature search also identified two retrospective cohort studies that assessed effect of platelet count on mortality and transfusion volume (Sawamura 2009, Kawatani 2016) in the trauma and surgical setting.

Study characteristics

The three studies identified in the systematic reviews were carried out in trauma or emergency centres in the United States (US), United Kingdom (UK), Norway and Australia. Eight studies were carried out in surgical settings in the US, Canada, Netherlands and Egypt. Poole 2016 found included studies provided very low evidence, with issues arising

due to variables utilised in prediction models and generalisability or results. Overall, the included observational studies were judged to have high risk of bias due to selection bias and confounding *[187][207]*.

Sawamura 2009 was a retrospective cohort study conducted in Japan which aimed to assess the impact of disseminated intravascular coagulation (DIC) on patient outcomes. Data obtained at four time points (within 24 hours of arrival to the emergency department) was collected from 314 consecutive severe trauma patients which was further subdivided into 259 survivors and 55 nonsurvivors. This study was found to have critical risk of bias due to lack of blinding and inadequate reporting of follow-up.

Kawatani 2016 was a retrospective study of the medical records of 25 patients who underwent endovascular aortic repair (EVAR) for ruptured abdominal aortic aneurysms (rAAA) at Chiba-Nishi General Hospital in Japan between October 2013 and December 2015. Major coagulopathy was defined using INR or activated partial thromboplastin time (APTT) ratio of at least 1.5, or platelet count less than 50 × 10/L. This study was found to have serious risk of bias due to lack of control for confounding factors and lack of blinding.

What are the main results?

Mortality
Identified literature suggests an increased risk of mortality associated with lower platelet count in patients with critical bleeding. Four studies in trauma and surgical settings contributed data reporting no statistical difference in mortality and platelet count.

Transfusion volume
Identified literature suggests only limited conclusions can be drawn from the available evidence. Included studies were in surgical settings and reported an association between platelet count and increased transfusion requirements. Studies included varying measurements of platelet count to trigger transfusion requirements, making it difficult to draw conclusions.

Outcome Timeframe	**Study results and measurements**	**Comparator** N/A	**Intervention**	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint 9 Critical	Based on data from 1,989 participants in 4 studies. (Observational (non-randomized))	Studies found no association between platelet count and mortality (two studies reported OR range of 0.99 and 1.097; two studies reported p >0.1).		**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision, Due to serious publication bias [1]	Lower platelet count is not associated with higher mortality.
Transfusion volume	Based on data from 30,735 participants in 7 studies. (Observational (non-randomized))	Included studies used different measurements to trigger platelet transfusion. Different platelet doses per transfusion were administered in all studies, ranging from 1 to 6-12 units. Heterogeneity between studies was so substantial that quantitative synthesis was not possible.		**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision, Due to serious publication bias [2]	Lower platelet counts are associated with higher volume of RBCs transfused.

Clinical Question/ PICO

Population: People with critical bleeding (any setting)
Intervention: PT/INR
Comparator: N/A

Summary

What did we find?

Five reviews (Lilitis 2018, Poole 2016, Haas 2015, Tran 2018, Shih 2019) corresponding to eight observational studies were identified in the literature. Five studies assessed the effect of prothrombin time (PT)/international normalised ratio (INR) levels on mortality in trauma patients with critical bleeding (Macleod 2003, Hess 2009, Mitra 2007, Hagemo 2014, Mitra 2010). Three studies assessed the effect of PT/INR levels on transfusion volume requirements in trauma patients with critical bleeding (Callcut 2013, Vandromme 2011, Schreiber 2007). The literature search also identified two retrospective cohort studies that assessed effect of PT/INR on mortality (Noorbhai 2016, Kawatani 2016) in the trauma and surgical setting.

Study characteristics

All studies identified in the systematic reviews were carried out in trauma centres in the United States (US), United Kingdom (UK), Norway, Australia and Iraq. Overall, risk of bias for included observational studies was judged to be high for inadequate control for confounding, study design and reporting *[201][187][208][204][202]*.

Noorbhai 2016 was a retrospective cohort study which aimed to assess the correlation between coagulopathy (INR) and mortality in 1000 patients admitted to a level 1 trauma unit in South Africa. Overall, INRs were not recorded in 61 patients and were therefore excluded from the analysis to a total of 939 remaining patients. This study was found to have critical risk of bias due to inadequate reporting of follow-up and lack of control for confounding factors.

Kawatani 2016 was a retrospective study of the medical records of 25 patients who underwent endovascular aortic repair (EVAR) for ruptured abdominal aortic aneurysms (rAAA) at Chiba-Nishi General Hospital in Japan between October 2013 and December 2015. Major coagulopathy was defined using INR or activated partial thromboplastin time (APTT) ratio of at least 1.5, or platelet count less than 50 × 10/L. This study was found to have serious risk of bias due to lack of control for confounding factors and lack of blinding.

What are the main results?

Mortality

Identified literature suggests an increased risk of mortality associated with abnormal PT/INR levels among patients with critical bleeding. Included studies contributing data were in trauma and surgical settings, reporting odds ratio (OR) ranges between 1.35 and 3.68 observed for elevated PT/INR levels compared to normal levels with statistical difference.

Transfusion volume

Identified literature suggests only limited conclusions can be drawn from the available evidence. Included studies were in trauma settings, reporting increased PT/INR levels were associated with increased transfusion requirements in patients with critical bleeding (OR ranges between 2.1 and 5.9 observed).

Outcome Timeframe	**Study results and measurements**	**Comparator** N/A	**Intervention** PT/INR	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint 9 Critical	Based on data from 45,693 participants in 7 studies. (Observational (non-randomized))	Six studies reported an association between high PT/INR levels and mortality (three studies reported OR range 1.35 and 1.65, one study reported adjusted RR 1.92, one study did not report risk data). One study reported no significant difference (p >0.07).		**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious indirectness, Due to serious imprecision, Due to serious publication bias [1]	Abnormal PT/INR (INR >1.2) is associated with higher mortality.
Transfusion volume	Based on data from participants in 3 studies.	Studies found an association between PT/INR and increased transfusion volume requirement. Studies reported OR range 2.1 and 5.9. Participant numbers not		**Very low** Due to serious risk of bias, Due to very serious inconsistency,	Abnormal PT/INR (>1.2) is associated with higher volume of RBCs transfused.

Outcome Timeframe	**Study results and measurements**	**Comparator** N/A	**Intervention** PT/INR	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		reported.		Due to serious indirectness, Due to serious imprecision, Due to serious publication bias [2]	

Clinical Question/ PICO

Population: People with critical bleeding (any setting)
Intervention: APTT
Comparator: N/A

Summary

What did we find?

Three reviews (Poole 2016, Lilitis 2018, Haas 2015) corresponding to seven observational studies were identified in the literature. Five studies assessed the effect of APTT levels on mortality in trauma patients with critical bleeding (Rourke 2012, Macleod 2003, Sambavisan 2011, Ciavarella 2987, Mitra 2007). Two studies assessed the effect of activated partial thromboplastin time (APTT) levels on transfusion volume requirement in trauma patients with critical bleeding (Mannucci 1982, Murray 1998). The literature search also identified one retrospective cohort study that assessed effect of APTT on mortality (Kawatani 2016) in the surgical setting.

Study characteristics

All studies identified in the systematic reviews were carried out in trauma centres in the United States (US), United Kingdom (UK), Norway, Italy and Australia. Overall, risk of bias for included observational studies was judged to be unclear to high due to study design, reporting and control for confounding *[187][201][208]*.

Kawatani 2016 was a retrospective study of the medical records of 25 patients who underwent endovascular aortic repair (EVAR) for ruptured abdominal aortic aneurysms (rAAA) at Chiba-Nishi General Hospital in Japan between October 2013 and December 2015. Major coagulopathy was defined using international normalised ratio (INR) or APTT ratio of at least 1.5, or platelet count less than 50 × 10/L. This study was found to have serious risk of bias due to lack of control for confounding factors and lack of blinding.

What are the main results?

Mortality

Identified literature suggests an increased risk of mortality associated with abnormal APTT levels among patients with critical bleeding. Six studies in trauma and surgical settings contributed data reporting odds ratio (OR) ranges between 1.01 and 4.26 observed for elevated APTT levels compared to normal APTT levels.

Transfusion volume

Identified literature suggests only limited conclusions can be drawn from the available evidence, with studies in trauma and surgical settings reporting an association between increased APTT levels and transfusion requirements in patients with critical bleeding.

Outcome Timeframe	Study results and measurements	Comparator N/A	Intervention APTT	Certainty of the Evidence (Quality of evidence)	Plain language summary
Mortality, all cause latest reported timepoint 9 Critical	Based on data from 9,516 participants in 6 studies. (Observational (non-randomized))	Five studies reported an association between high APTT levels and mortality (four studies reported OR range 1.01 and 4.26, one study reported no risk data).		**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision, Due to serious publication bias [1]	Higher APTT levels are associated with higher mortality.
Transfusion volume	Based on data from participants in 2 studies. (Observational (non-randomized))	Studies reported an association between high APTT levels and the need for increased transfusion volume. No risk data reported.		**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision, Due to serious publication bias [2]	Higher APTT levels are associated with higher volume of RBCs transfused.

Clinical Question/ PICO

Population: People with critical bleeding (any setting)
Intervention: Fibrinogen levels
Comparator: N/A

Summary

What did we find?

Three reviews (Poole 2016, Abdul-Kadir 2014, Shih 2019) corresponding to seven observational studies were identified in the literature. Two studies assessed the effect of fibrinogen levels on mortality in trauma patients with critical bleeding (Hagemo 2014, Rourke 2012). Five studies assessed the effect of fibrinogen levels on transfusion volume requirements in trauma and obstetric patients with critical bleeding (Charbit 2007, Cortet 2012, Peyvandi 2012, Rouse 2006, Nakamura 2017). The literature search also identified one prospective observational study (Gaessler 2021) and one retrospective observational study (Sawamura 2009) that was not identified in the included systematic reviews that assessed the effect of fibrinogen levels on mortality and transfusion volume in trauma patients.

Study characteristics

The four studies identified in the systematic reviews were carried out in obstetric settings in the US, France and Italy and three studies were carried out in trauma centres in the United States (US), United Kingdom (UK), Norway, and Japan. Overall, included studies was judged to be high risk of bias due to study design, confounding and reporting biases *[187][209][202]*.

Gaessler 2021 was a single centre prospective observational study conducted in Germany which aimed to assess the impact of coagulopathy in 148 injured patients who were medical treated by the Helicopter Emergency Medical Service (HEMS) and transported to Level 1 trauma centres. This study was found to be at serious risk of bias due to lack of blinding.

Sawamura 2009 was a retrospective cohort study conducted in Japan which aimed to assess the impact of disseminated intravascular coagulation (DIC) on patient outcomes. Data obtained at four time points (within 24 hours of arrival to the emergency department) was collected from 314 consecutive severe trauma patients which was further subdivided into 259 survivors and 55 nonsurvivors. This study was found to have critical risk of bias due to lack of blinding and inadequate reporting of follow-up.

What are the main results

Mortality
Identified literature suggests the risk of mortality significantly increased with low fibrinogen levels among patients with critical bleeding. Three studies in trauma settings contributed data reporting odds ratio (OR) ranges between 0.08 and 0.989 observed for low compared to high fibrinogen levels. Definitions of low fibrinogen levels varied across the studies but were generally considered to be levels less than 1.5 g/L.

Transfusion volume
Identified literature suggests only limited conclusions can be drawn from the available evidence. Five observational studies in trauma settings contributed data, with three studies reporting a positive association between low fibrinogen levels and increased transfusion requirements in patients with critical bleeding. Definitions of low fibrinogen levels were commonly considered less than 2 g/L.

Outcome Timeframe	**Study results and measurements**	**Comparator** N/A	**Intervention**	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint 9 Critical	Based on data from 2,112 participants in 4 studies. (Observational (non-randomized))	Three studies reported an association between low fibrinogen levels and transfusion volume (OR range 0.08 and 0.99). One study reported no data on prognostic factor.		**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious indirectness, Due to serious imprecision, Due to serious publication bias [1]	Lower fibrinogen levels are associated with higher mortality.
Transfusion volume	Based on data from 625 participants in 5 studies. (Observational (non-randomized))	Four studies reported an association between low fibrinogen levels and mortality (one study reported OR 0.931, three studies did not report risk data). One study was unable to determine an association. Participant numbers for four studies not reported.		**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious indirectness, Due to serious imprecision, Due to serious publication bias [2]	Lower fibrinogen levels are associated with higher volume of RBCs transfused.

Good practice statement

GPS1: Values indicative of critical physiological derangement include:

- temperature < 35°C
- pH < 7.2, base excess < −6 mEq/L, lactate > 4 mmol/L
- ionised calcium < 1 mmol/L
- PT > 1.5 × upper limit of normal
- INR > 1.5
- APTT > 1.5 × upper limit of normal
- fibrinogen level < 2.0 g/L

The reference group agreed that is it good practice to monitor the above parameters and include a full blood count and coagulation profile upon initiation of a major haemorrhage protocol and at least after administration of every 4 units of RBC.

Rationale

Direct evidence about the relationship between values indicative of physiologic derangement and mortality is weak, but the reference group has provided guidance to ensure patient care. The changes in full blood count (including haemoglobin and platelet count) during critical bleeding is dynamic and should be monitored frequently to allow targeted therapy.

Note: Haemoglobin and platelet count may remain elevated during the initial stages of critical bleeding.

refer to R2

6.1.2 Red blood cell to component ratio, timing and dose

A ratio of 2:1:1 of RBC:FFP:PLT is lower than a ratio of 1:1:1, as the number of units of RBC increases without a proportionate increase in FFP or PLT.

Research questions
In patients with critical bleeding, what is the optimal dose, timing and ratio (algorithm) to red blood cells (RBCs), of blood component therapy to reduce morbidity, mortality and transfusion?

In patients at risk of critical bleeding, is the transfusion of increased volumes of RBCs associated with an increased risk of mortality or adverse effects?

Literature search date: 29 September 2021

Weak recommendation

R3: In patients with critical bleeding, the implementation of a major haemorrhage protocol with a high ratio of RBC:FFP:PLT* may be beneficial, although there is insufficient evidence to support a 1:1:1 ratio over a 2:1:1 ratio^.

**1 adult unit of pooled or apheresis platelets in Australia is equivalent to platelets derived from 4 single whole blood donor units.*

^A ratio of 2:1:1 of RBC:FFP:PLT is lower than a ratio of 1:1:1, as the number of units of RBC increases without a proportionate increase in FFP or PLT.

Practical Info

See GPS2 and GPS3

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

In the meta-analysis of randomised controlled trials comparing 1:1:1 versus 2:1:1 ratios, no effect on mortality has been demonstrated. In the meta-analysis of observational cohort studies a large effect on mortality was demonstrated, however, the certainty of the evidence was very low. Based on the available evidence the true benefit is unknown.

In the meta-analysis of randomised controlled trials, thromboembolic events and multiple organ failure rates did not differ among populations that received higher ratios of blood components or products compared to those who received lower ratios. Based on the available evidence the harms are not known.

Certainty of the Evidence

Very low

The overall certainty in effect estimates across outcomes was either very low (benefits) or low (harms).

Values and preferences

No substantial variability expected

There is no plausible reason to suspect that patients who are critically bleeding would not accept ratios of blood components as recommended. A subgroup of patients may decline blood components based on personal preference.

Resources

Important issues, or potential issues not investigated

In the absence of high certainty evidence, the resource implications of 1:1:1 ratio of blood components are uncertain.

Equity

Important issues, or potential issues not investigated

The reference group acknowledged that there is jurisdictional, geographical and/or institutional variability in the availability of blood components.

Acceptability

No important issues with the recommended alternative

The acceptability of a ratio at least 2:1:1 of RBC:FFP:PLT was not investigated.

Feasibility

Important issues, or potential issues not investigated

The reference group acknowledged the logistical challenges associated with providing ratios of blood components to treat critically bleeding patients. Adaptation of this guidance at a local level is required upon consideration of the resources available.

Rationale

The evidence supports a ratio of 2:1:1.

Clinical Question/ PICO

Population: People with critical bleeding (trauma setting)
Intervention: High ratio (1:1:1) of blood components
Comparator: Lower ratios of blood components

Summary

What did we find?

There were two randomised controlled trials (RCTs) (Holcomb 2015, Nascimento 2013) and 11 nonrandomised cohort studies (Balvers 2017, Duchesne 2008, Duchesne 2009, Hatimeier 2017, Holcomb 2011, Maegele 2008, Perkins 2009, Sambasivan 2011, Vulliamy 2017, Wafaisade 2011, Zink 2009) identified in the trauma setting that evaluated different blood product ratios on patient outcomes.

Study characteristics

Two RCTs (Holcomb 2015, Nascimento 2013) compared the effect of high (1:1:1) red blood cell (RBC): fresh frozen plasma (FFP): platelet (PLT) transfusion ratios to lower ratios on the 28-day mortality in trauma patients (≥15 years) requiring massive transfusion. The two included RCTs were carried out in trauma centres in the United States (US). Overall, the included RCTs were judged to be at high risk of bias with blinding being the main sources of bias. Holcomb 2015 was the only RCT that attempted to minimise bias from lack of blinding by having each death adjudicated by a clinician blinded to group assignment *[181]*.

Five cohort studies (Vulliamy 2017, Wafaisade 2011, Duchesne 2009, Maegele 2008, Duchesne 2008) assessed RBC:FFP ratios, two cohort studies (Holcomb 2011, Perkins 2009) assessed RBC: platelet (PLT) ratios and four cohort studies (Hatimeier 2017, Balvers 2017, Sambasivan 2011, Zink 2009) assessed both RBC:FFP and RBC:PLT ratios. All cohort studies included adult trauma patients and were carried out in trauma settings in the US, United Kingdom (UK), Germany, Netherlands, Denmark and Iraq. Overall, the risk of bias of included studies was judged to be moderate with concerns arising due to confounding *[182][183][184][185][27][186][187][188][189]*.

What are the main results?

Mortality

A meta-analysis of data from RCTs included in this review showed the mortality rate (latest timepoint) in patients with critical bleeding to be comparable among those who received high ratios of blood components compared to those who received lower ratios with the relative risk (RR) of 1.26 observed (95% CI 0.49, 3.22; p = 0.64). Neither of the included RCTs were powered to detect differences in mortality.

Among patients with blunt and penetrating trauma, a total of 308 patients received a high (1:1:1) ratio of blood components compared with 922 patients who received lower ratios, with significant difference observed (24.3% vs 31.4%, OR 0.38; 95% CI 0.22, 0.69; p = 0.001).

Morbidity

Holcomb (2015) reported no significant difference in thromboembolic events (deep vein thrombosis, pulmonary embolus) between patients who received high ratio of blood components (39/338, 11.5%) compared with those who did not (37/342, 10.8%).

Meta-analysis of two RCTs found no significant difference in multiorgan failure (MOF) between patients who received a high ratio of blood components (21/375, 5.6%) compared with patients who received a low ratio (15/374, 4%) (RR 1.39, 95% CI 0.73, 2.63; p = 0.32).

RBC transfusion volumes

A meta-analysis of data from two RCTs in the trauma setting showed no significant difference in median volume of RBCs transfused in the first 24-hours between patients receiving a high ratio of blood components compared to patients receiving a low ratio (SMD -0.1; 95% CI -0.24, 0.05; p = 0.18, random effect, I^2 = 0%).

Transfusion volume, other blood products

A meta-analysis of data from two RCTs in the trauma setting showed a significant difference in median volume of FFP transfused in the first 24-hours between patients receiving a high ratio of blood components compared to patients receiving a low ratio (SMD 0.3; 95% CI 0.15, 0.44; p <0.0001, random effect, I^2 = 0%).

Outcome Timeframe	**Study results and measurements**	**Comparator** Lower ratios of blood components	**Intervention** High ratio (1:1:1) of blood components	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (RCTs) latest reported timepoint	Relative risk 1.26 (CI 95% 0.49 — 3.22) Based on data from 755 participants in 2 studies.	249 per 1000	314 per 1000	**Very low** Due to very serious inconsistency,	High (1:1:1) RBC:FFP:PLT ratio may result in little or no difference in mortality

Outcome Timeframe	**Study results and measurements**	**Comparator** Lower ratios of blood components	**Intervention** High ratio (1:1:1) of blood components	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical	[1] (Randomized controlled)	Difference:	**65 more per 1000** (CI 95% 127 fewer — 553 more)	Due to very serious imprecision [2]	in trauma patients with critical bleeding but we are very uncertain about the evidence.
Mortality, all cause (Coh) latest reported timepoint 9 Critical	Odds ratio 0.38 (CI 95% 0.22 — 0.69) Based on data from 4,203 participants in 10 studies. [3] (Observational (non-randomized))	314 per 1000 Difference:	148 per 1000 **166 fewer per 1000** (CI 95% 223 fewer — 74 fewer)	**Very low** Due to serious risk of bias, Due to very serious inconsistency [4]	High (1:1:1) RBC:FFP:PLT ratio may reduce mortality in trauma patients with critical bleeding but we are very uncertain about the evidence.
Morbidity, thromboembolic events 9 Critical	Relative risk 1.07 (CI 95% 0.7 — 1.63) Based on data from 680 participants in 1 studies. [5] (Randomized controlled)	108 per 1000 Difference:	116 per 1000 **8 more per 1000** (CI 95% 32 fewer — 68 more)	**Low** Due to very serious imprecision [6]	High (1:1:1) RBC:FFP:PLT ratio may have little or no difference on thromboembolic events in trauma patients with critical bleeding.
Morbidity, multiple organ failure 9 Critical	Relative risk 1.39 (CI 95% 0.74 — 2.64) Based on data from 749 participants in 2 studies. [7] (Randomized controlled)	40 per 1000 Difference:	56 per 1000 **16 more per 1000** (CI 95% 10 fewer — 66 more)	**Low** Due to very serious imprecision [8]	High (1:1:1) RBC:FFP:PLT ratio may have little or no difference on multiorgan failure in trauma patients with critical bleeding.
RBC transfusion volume	Measured by: Number of Units Lower better Based on data from 749 participants in 2 studies. [9] (Randomized controlled)	9 - 10.3 Units Difference:	7.7 - 9.7 Units **SMD 0.1 lower** (CI 95% 0.24 lower — 0.05 higher)	**Low** Due to serious imprecision [10]	High (1:1:1) RBC:FFP:PLT ratio may slightly reduce RBC transfusion volume in trauma patients with critical bleeding.
Transfusion volume, other blood products	Measured by: Number of Units Lower better Based on data from 749 participants in 2 studies. [11] (Randomized controlled)	5 - 5.7 Units Difference:	6 - 7.7 Units **SMD 0.3 higher** (CI 95% 0.15 higher — 0.44 higher)	**Low** Due to serious imprecision [12]	High (1:1:1) RBC:FFP:PLT ratio may slightly increase transfusion volume of other blood products in trauma patients with critical bleeding.

Clinical Question/ PICO

Population: People with critical bleeding (surgical setting)

Intervention: High ratio (1:1:1) of blood components
Comparator: Lower ratios of blood components

Summary

What did we find?

There were seven nonrandomised cohort studies (Hall 2013, Henriksson 2012, Johansson 2007, Johansson 2008, Kauvar 2011, Mell 2010, Tadlock 2010) identified in the surgical setting that evaluated different blood product ratios on patient outcomes.

Study characteristics

All studies included patients with ruptured abdominal aortic aneurysms (rAAAs). Five studies (Hall 2013, Henriksson 2012, Johansson 2007, Johansson 2008, Tadlock 2010) defined a high ratio of fresh frozen plasma (FFP): packed red blood cells (pRBC) as 1:1 and two studies (Kauvar 2011, Mell 2010) did not define a high ratio. All seven studies were carried out in single-centre surgical settings in North America and Denmark. Overall, review authors judged included studies as serious risk of bias, with a significant amount of bias arising from confounding and patient selection *[190]*.

What are the main results?

Mortality

Among patients with ruptured abdominal aortic aneurysms, the observed mortality rate of 23.6% (88/373) among patients receiving a high ratio was significantly different to the mortality rate of 46.4% (143/308) among patients receiving lower ratios. This corresponded to an odds ratio (OR) of 0.41 (95% CI 0.26, 0.63; p <0.0001).

Outcome Timeframe	**Study results and measurements**	**Comparator** Lower ratios of blood components	**Intervention** High ratio (1:1:1) of blood components	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (Coh) latest reported timepoint 9 Critical	Odds ratio 0.41 (CI 95% 0.26 — 0.63) Based on data from 681 participants in 6 studies. [1] (Observational (non-randomized))	464 per 1000 Difference:	262 per 1000 **202 fewer per 1000** (CI 95% 280 fewer — 111 fewer)	**Very low** Due to serious risk of bias [2]	High (1:1:1) RBC:FFP:PLT ratio may reduce mortality in the surgical setting but the evidence is very uncertain.

Clinical Question/ PICO

Population: People at risk of critical bleeding (any setting)
Intervention: Increased RBC transfusion volumes
Comparator: Normal RBC transfusion volumes

Summary

What did we find?

There were 10 prospective and 12 retrospective studies identified in the trauma setting and one retrospective cohort study in the medical setting that investigated the effect of transfusion of increased volumes of red blood cells (RBCs) in patients at risk of clinical bleeding.

Among the included prospective cohort studies identified in the systematic review, there were four studies (Bochicchio 2008, Silverboard 2005, Dunne 2004, Malone 2003) that assessed the effect of RBC on mortality, four studies (Ciesla 2005, Johnson 2010, Moore 1997, Sauaia 1994) that assessed the effect of RBC on multiorgan failure (MOF) and one study (Edens 2010) that assessed the effect of RBC on acute lung injury (ALI). One additional study

was identified (Liu 2018) which investigated the association between RBC transfusion and mortality and hospital length of stay (LOS) in the trauma setting.

Among the included retrospective cohort studies identified in the trauma setting, there were 10 studies (Barbosa 2011, Chaiwat 2009, Mahambrey 2009, Murrell 2005, Phelan 2010, Robinson 2005, Spinella 2008, Croce 2005, Teixeira 2008, Weinberg 2008) that assessed the effect of RBC on mortality, one study (Cotton 2009) that assessed the effect of RBC on MOF and three studies (Plurad 2007, Weinberg 2008, Croce 2005) that assessed the effect of RBC on acute respiratory distress syndrome (ARDS). One additional study was identified (Hassainien 2015) which assessed the effect of RBC on mortality among 70 patients with liver cirrhosis and hepatocellular carcinoma presenting with acute upper gastrointestinal bleeding.

Study characteristics

The included observational cohort studies identified in the systematic review were conducted in the trauma settings and commonly queried trauma databases or registries, resulting in most studies having good representativeness. Overall, the studies were considered to have no serious risk of bias of included studies when conducting a GRADE assessment. However, authors note that observational studies are prone to bias and adjusting for confounding (particularly in relation to the injury severity scores). Review authors attempted to mitigate confounding by only including studies that attempted to adjust for injury severity in the pooled analysis *[191]*.

Liu 2018 was a single centre prospective cohort study conducted in the United States (US) that investigated the association between RBC transfusion and mortality and hospital LOS in the trauma setting. Included trauma patients (predominantly due to assault and motor vehicle accidents) were over 18 years and had received between 0 and 87 units of packed RBC within 24 hours of injury. The study was considered to be at serious risk of bias due to inadequate adjustment for confounders, a lack of details regarding blinding and study design.

Hassanein 2015 was a retrospective hospital-based study conducted in Egypt. The study included 70 patients with liver cirrhosis and hepatocellular carcinoma presenting with acute upper gastrointestinal bleeding. Patients must meet criteria of either hematemesis or melena with a diagnostic esophagogastroduodenoscopy, or both. The study was considered to be at moderate risk of bias due to a lack of details regarding blinding and study design.

What are the main results?

Mortality

Nine studies assessed the effect of RBC transfusion on mortality as a continuous variable. Identified literature suggests transfusion of increased RBCs is associated with an increased risk of mortality among patients at risk of critical bleeding in the trauma setting. Pooled analysis showed an increased in the odds of mortality associated with each additional RBC unit transfused (OR 1.07; 95% CI 1.04, 1.10; *p* <0.001).

Morbidity

Three studies assessed the effect of RBC transfusion on MOF as a continuous variable. Pooled analysis showed a significant increase in the odds of MOF associated with each additional RBC unit transfused (OR 1.08; 95% CI 1.02, 1.14; *p* = 0.012).

Two studies assessed the effect of RBC transfusion on ARDS as a continuous variable. Pooled analysis showed a significant increase in the odds of ARDS or ALI associated with each additional RBC unit transfused (OR 1.06; 95% CI 1.03, 1.10; *p* <0.001).

Outcome Timeframe	**Study results and measurements**	**Comparator** Normal RBC transfusion volumes	**Intervention** Increased RBC transfusion volumes	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (Coh) latest reported timepoint 9 Critical	Based on data from 18,009 participants in 9 studies. [1] (Observational (non-randomized))	The odds of mortality increases with each additional RBC unit transfused (OR range 0.83-1.16).		**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [2]	Each additional RBC unit transfused is associated with higher mortality.

Outcome Timeframe	Study results and measurements	Comparator Normal RBC transfusion volumes	Intervention Increased RBC transfusion volumes	Certainty of the Evidence (Quality of evidence)	Plain language summary
Morbidity, multiorgan failure (Coh) Any timepoint 9 Critical	Based on data from 3,050 participants in 3 studies. (Observational (non-randomized))	The odds of multiorgan failure increases with each additional RBC unit transfused (OR range 2.90-8.60).		**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [3]	Each additional RBC unit transfused is associated with higher risk of multiorgan failure.
Morbidity, ARDS (Coh) Any timepoint 9 Critical	Based on data from 14,136 participants in 2 studies. (Observational (non-randomized))	The odds of acute respiratory distress syndrome or acute lung injury increases with each additional RBC unit transfused (OR range 1.06-1.09).		**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [4]	Each additional RBC unit transfused is associated with higher risk of acute respiratory distress syndrome or acute lung injury.

Good practice statement

GPS2: In patients with critical bleeding, the reference group agreed that it is good practice for the ratio of RBC:FFP:PLT be no lower than 2:1:1 for a major haemorrhage protocol.

Refer to R3

Rationale

Direct evidence regarding the optimal dose of RBC:FFP:PLT is weak, but guidance is provided for patient care.

Clinical Question/ PICO

Population: People with critical bleeding (trauma setting)
Intervention: High ratio (1:1:1) of blood components
Comparator: Lower ratios of blood components

Summary

What did we find?

There were two randomised controlled trials (RCTs) (Holcomb 2015, Nascimento 2013) and 11 nonrandomised cohort studies (Balvers 2017, Duchesne 2008, Duchesne 2009, Hatimeier 2017, Holcomb 2011, Maegele 2008, Perkins 2009, Sambasivan 2011, Vulliamy 2017, Wafaisade 2011, Zink 2009) identified in the trauma setting that evaluated different blood product ratios on patient outcomes.

Study characteristics

Two RCTs (Holcomb 2015, Nascimento 2013) compared the effect of high (1:1:1) red blood cell (RBC): fresh frozen plasma (FFP): platelet (PLT) transfusion ratios to lower ratios on the 28-day mortality in trauma patients (≥15 years) requiring massive transfusion. The two included RCTs were carried out in trauma centres in the United States (US). Overall, the included RCTs were judged to be at high risk of bias with blinding being the main sources of bias. Holcomb 2015 was the only RCT that attempted to minimise bias from lack of blinding by having each death adjudicated by a clinician blinded to group assignment *[181]*.

Five cohort studies (Vulliamy 2017, Wafaisade 2011, Duchesne 2009, Maegele 2008, Duchesne 2008) assessed RBC:FFP ratios, two cohort studies (Holcomb 2011, Perkins 2009) assessed RBC: platelet (PLT) ratios and four

cohort studies (Hatimeier 2017, Balvers 2017, Sambasivan 2011, Zink 2009) assessed both RBC:FFP and RBC:PLT ratios. All cohort studies included adult trauma patients and were carried out in trauma settings in the US, United Kingdom (UK), Germany, Netherlands, Denmark and Iraq. Overall, the risk of bias of included studies was judged to be moderate with concerns arising due to confounding *[182][183][184][185][27][186][187][188][189]*.

What are the main results?

Mortality

A meta-analysis of data from RCTs included in this review showed the mortality rate (latest timepoint) in patients with critical bleeding to be comparable among those who received high ratios of blood components compared to those who received lower ratios with the relative risk (RR) of 1.26 observed (95% CI 0.49, 3.22; p = 0.64). Neither of the included RCTs were powered to detect differences in mortality.

Among patients with blunt and penetrating trauma, a total of 308 patients received a high (1:1:1) ratio of blood components compared with 922 patients who received lower ratios, with significant difference observed (24.3% vs 31.4%, OR 0.38; 95% CI 0.22, 0.69; p = 0.001).

Morbidity

Holcomb (2015) reported no significant difference in thromboembolic events (deep vein thrombosis, pulmonary embolus) between patients who received high ratio of blood components (39/338, 11.5%) compared with those who did not (37/342, 10.8%).

Meta-analysis of two RCTs found no significant difference in multiorgan failure (MOF) between patients who received a high ratio of blood components (21/375, 5.6%) compared with patients who received a low ratio (15/374, 4%) (RR 1.39, 95% CI 0.73, 2.63; p = 0.32).

RBC transfusion volumes

A meta-analysis of data from two RCTs in the trauma setting showed no significant difference in median volume of RBCs transfused in the first 24-hours between patients receiving a high ratio of blood components compared to patients receiving a low ratio (SMD -0.1; 95% CI -0.24, 0.05; p = 0.18, random effect, I^2 = 0%).

Transfusion volume, other blood products

A meta-analysis of data from two RCTs in the trauma setting showed a significant difference in median volume of FFP transfused in the first 24-hours between patients receiving a high ratio of blood components compared to patients receiving a low ratio (SMD 0.3; 95% CI 0.15, 0.44; p <0.0001, random effect, I^2 = 0%).

Outcome Timeframe	**Study results and measurements**	**Comparator** Lower ratios of blood components	**Intervention** High ratio (1:1:1) of blood components	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (RCTs) latest reported timepoint 9 Critical	Relative risk 1.26 (CI 95% 0.49 — 3.22) Based on data from 755 participants in 2 studies. [1] (Randomized controlled)	249 per 1000 Difference:	314 per 1000 **65 more per 1000** (CI 95% 127 fewer — 553 more)	**Very low** Due to very serious inconsistency, Due to very serious imprecision [2]	High (1:1:1) RBC:FFP:PLT ratio may result in little or no difference in mortality in trauma patients with critical bleeding but we are very uncertain about the evidence.
Mortality, all cause (Coh) latest reported timepoint 9 Critical	Odds ratio 0.38 (CI 95% 0.22 — 0.69) Based on data from 4,203 participants in 10 studies. [3] (Observational (non-randomized))	314 per 1000 Difference:	148 per 1000 **166 fewer per 1000** (CI 95% 223 fewer — 74 fewer)	**Very low** Due to serious risk of bias, Due to very serious inconsistency [4]	High (1:1:1) RBC:FFP:PLT ratio may reduce mortality in trauma patients with critical bleeding but we are very uncertain about the evidence.

Outcome Timeframe	**Study results and measurements**	**Comparator** Lower ratios of blood components	**Intervention** High ratio (1:1:1) of blood components	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Morbidity, thromboembolic events 9 Critical	Relative risk 1.07 (CI 95% 0.7 — 1.63) Based on data from 680 participants in 1 studies. [5] (Randomized controlled)	108 per 1000 Difference:	116 per 1000 **8 more per 1000** (CI 95% 32 fewer — 68 more)	**Low** Due to very serious imprecision [6]	High (1:1:1) RBC:FFP:PLT ratio may have little or no difference on thromboembolic events in trauma patients with critical bleeding.
Morbidity, multiple organ failure 9 Critical	Relative risk 1.39 (CI 95% 0.74 — 2.64) Based on data from 749 participants in 2 studies. [7] (Randomized controlled)	40 per 1000 Difference:	56 per 1000 **16 more per 1000** (CI 95% 10 fewer — 66 more)	**Low** Due to very serious imprecision [8]	High (1:1:1) RBC:FFP:PLT ratio may have little or no difference on multiorgan failure in trauma patients with critical bleeding.
RBC transfusion volume	Measured by: Number of Units Lower better Based on data from 749 participants in 2 studies. [9] (Randomized controlled)	9 - 10.3 Units Difference:	7.7 - 9.7 Units **SMD 0.1 lower** (CI 95% 0.24 lower — 0.05 higher)	**Low** Due to serious imprecision [10]	High (1:1:1) RBC:FFP:PLT ratio may slightly reduce RBC transfusion volume in trauma patients with critical bleeding.
Transfusion volume, other blood products	Measured by: Number of Units Lower better Based on data from 749 participants in 2 studies. [11] (Randomized controlled)	5 - 5.7 Units Difference:	6 - 7.7 Units **SMD 0.3 higher** (CI 95% 0.15 higher — 0.44 higher)	**Low** Due to serious imprecision [12]	High (1:1:1) RBC:FFP:PLT ratio may slightly increase transfusion volume of other blood products in trauma patients with critical bleeding.

Clinical Question/ PICO

Population: People with critical bleeding (surgical setting)
Intervention: High ratio (1:1:1) of blood components
Comparator: Lower ratios of blood components

Summary

What did we find?

There were seven nonrandomised cohort studies (Hall 2013, Henriksson 2012, Johansson 2007, Johansson 2008, Kauvar 2011, Mell 2010, Tadlock 2010) identified in the surgical setting that evaluated different blood product ratios on patient outcomes.

Study characteristics

All studies included patients with ruptured abdominal aortic aneurysms (rAAAs). Five studies (Hall 2013, Henriksson 2012, Johansson 2007, Johansson 2008, Tadlock 2010) defined a high ratio of fresh frozen plasma (FFP): packed red blood cells (pRBC) as 1:1 and two studies (Kauvar 2011, Mell 2010) did not define a high ratio. All seven studies

were carried out in single-centre surgical settings in North America and Denmark. Overall, review authors judged included studies as serious risk of bias, with a significant amount of bias arising from confounding and patient selection *[190]*.

What are the main results?

Mortality

Among patients with ruptured abdominal aortic aneurysms, the observed mortality rate of 23.6% (88/373) among patients receiving a high ratio was significantly different to the mortality rate of 46.4% (143/308) among patients receiving lower ratios. This corresponded to an odds ratio (OR) of 0.41 (95% CI 0.26, 0.63; p <0.0001).

Outcome Timeframe	**Study results and measurements**	**Comparator** Lower ratios of blood components	**Intervention** High ratio (1:1:1) of blood components	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (Coh) latest reported timepoint 9 Critical	Odds ratio 0.41 (CI 95% 0.26 — 0.63) Based on data from 681 participants in 6 studies. [1] (Observational (non-randomized))	464 per 1000 Difference:	262 per 1000 **202 fewer per 1000** (CI 95% 280 fewer — 111 fewer)	Very low Due to serious risk of bias [2]	High (1:1:1) RBC:FFP:PLT ratio may reduce mortality in the surgical setting but the evidence is very uncertain.

Clinical Question/ PICO

Population: People at risk of critical bleeding (any setting)
Intervention: Increased RBC transfusion volumes
Comparator: Normal RBC transfusion volumes

Summary

What did we find?

There were 10 prospective and 12 retrospective studies identified in the trauma setting and one retrospective cohort study in the medical setting that investigated the effect of transfusion of increased volumes of red blood cells (RBCs) in patients at risk of clinical bleeding.

Among the included prospective cohort studies identified in the systematic review, there were four studies (Bochicchio 2008, Silverboard 2005, Dunne 2004, Malone 2003) that assessed the effect of RBC on mortality, four studies (Ciesla 2005, Johnson 2010, Moore 1997, Sauaia 1994) that assessed the effect of RBC on multiorgan failure (MOF) and one study (Edens 2010) that assessed the effect of RBC on acute lung injury (ALI). One additional study was identified (Liu 2018) which investigated the association between RBC transfusion and mortality and hospital length of stay (LOS) in the trauma setting.

Among the included retrospective cohort studies identified in the trauma setting, there were 10 studies (Barbosa 2011, Chaiwat 2009, Mahambrey 2009, Murrell 2005, Phelan 2010, Robinson 2005, Spinella 2008, Croce 2005, Teixeira 2008, Weinberg 2008) that assessed the effect of RBC on mortality, one study (Cotton 2009) that assessed the effect of RBC on MOF and three studies (Plurad 2007, Weinberg 2008, Croce 2005) that assessed the effect of RBC on acute respiratory distress syndrome (ARDS). One additional study was identified (Hassainien 2015) which assessed the effect of RBC on mortality among 70 patients with liver cirrhosis and hepatocellular carcinoma presenting with acute upper gastrointestinal bleeding.

Study characteristics

The included observational cohort studies identified in the systematic review were conducted in the trauma settings and commonly queried trauma databases or registries, resulting in most studies having good representativeness.

Overall, the studies were considered to have no serious risk of bias of included studies when conducting a GRADE assessment. However, authors note that observational studies are prone to bias and adjusting for confounding (particularly in relation to the injury severity scores). Review authors attempted to mitigate confounding by only including studies that attempted to adjust for injury severity in the pooled analysis *[191]*.

Liu 2018 was a single centre prospective cohort study conducted in the United States (US) that investigated the association between RBC transfusion and mortality and hospital LOS in the trauma setting. Included trauma patients (predominantly due to assault and motor vehicle accidents) were over 18 years and had received between 0 and 87 units of packed RBC within 24 hours of injury. The study was considered to be at serious risk of bias due to inadequate adjustment for confounders, a lack of details regarding blinding and study design.

Hassanein 2015 was a retrospective hospital-based study conducted in Egypt. The study included 70 patients with liver cirrhosis and hepatocellular carcinoma presenting with acute upper gastrointestinal bleeding. Patients must meet criteria of either hematemesis or melena with a diagnostic esophagogastroduodenoscopy, or both. The study was considered to be at moderate risk of bias due to a lack of details regarding blinding and study design.

What are the main results?

Mortality

Nine studies assessed the effect of RBC transfusion on mortality as a continuous variable. Identified literature suggests transfusion of increased RBCs is associated with an increased risk of mortality among patients at risk of critical bleeding in the trauma setting. Pooled analysis showed an increased in the odds of mortality associated with each additional RBC unit transfused (OR 1.07; 95% CI 1.04, 1.10; p <0.001).

Morbidity

Three studies assessed the effect of RBC transfusion on MOF as a continuous variable. Pooled analysis showed a significant increase in the odds of MOF associated with each additional RBC unit transfused (OR 1.08; 95% CI 1.02, 1.14; p = 0.012).

Two studies assessed the effect of RBC transfusion on ARDS as a continuous variable. Pooled analysis showed a significant increase in the odds of ARDS or ALI associated with each additional RBC unit transfused (OR 1.06; 95% CI 1.03, 1.10; p <0.001).

Outcome Timeframe	**Study results and measurements**	**Comparator** Normal RBC transfusion volumes	**Intervention** Increased RBC transfusion volumes	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (Coh) latest reported timepoint 9 Critical	Based on data from 18,009 participants in 9 studies. [1] (Observational (non-randomized))	The odds of mortality increases with each additional RBC unit transfused (OR range 0.83-1.16).		**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [2]	Each additional RBC unit transfused is associated with higher mortality.
Morbidity, multiorgan failure (Coh) Any timepoint 9 Critical	Based on data from 3,050 participants in 3 studies. (Observational (non-randomized))	The odds of multiorgan failure increases with each additional RBC unit transfused (OR range 2.90-8.60).		**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [3]	Each additional RBC unit transfused is associated with higher risk of multiorgan failure.
Morbidity, ARDS (Coh) Any timepoint	Based on data from 14,136 participants in 2 studies. (Observational (non-randomized))	The odds of acute respiratory distress syndrome or acute lung injury increases with each additional RBC unit transfused (OR range 1.06-1.09).		**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious	Each additional RBC unit transfused is associated with higher risk of acute respiratory distress syndrome or acute lung injury.

Outcome Timeframe	**Study results and measurements**	**Comparator** Normal RBC transfusion volumes	**Intervention** Increased RBC transfusion volumes	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical				imprecision [4]	

Good practice statement

GPS3: The reference group agreed that the ratio of RBC:FFP:PLT of at least 2:1:1 be activated as soon as possible and be maintained throughout resuscitation. Do not use a reactive approach to blood component resuscitation.

Refer to R1

Rationale

Evidence regarding the timing of RBC:FFP:PLT was not evaluated, but guidance is provided for patient care.

Clinical Question/ PICO

Population: People with critical bleeding (trauma setting)
Intervention: High ratio (1:1:1) of blood components
Comparator: Lower ratios of blood components

Summary

What did we find?

There were two randomised controlled trials (RCTs) (Holcomb 2015, Nascimento 2013) and 11 nonrandomised cohort studies (Balvers 2017, Duchesne 2008, Duchesne 2009, Hatimeier 2017, Holcomb 2011, Maegele 2008, Perkins 2009, Sambasivan 2011, Vulliamy 2017, Wafaisade 2011, Zink 2009) identified in the trauma setting that evaluated different blood product ratios on patient outcomes.

Study characteristics

Two RCTs (Holcomb 2015, Nascimento 2013) compared the effect of high (1:1:1) red blood cell (RBC): fresh frozen plasma (FFP): platelet (PLT) transfusion ratios to lower ratios on the 28-day mortality in trauma patients (≥15 years) requiring massive transfusion. The two included RCTs were carried out in trauma centres in the United States (US). Overall, the included RCTs were judged to be at high risk of bias with blinding being the main sources of bias. Holcomb 2015 was the only RCT that attempted to minimise bias from lack of blinding by having each death adjudicated by a clinician blinded to group assignment *[181]*.

Five cohort studies (Vulliamy 2017, Wafaisade 2011, Duchesne 2009, Maegele 2008, Duchesne 2008) assessed RBC:FFP ratios, two cohort studies (Holcomb 2011, Perkins 2009) assessed RBC: platelet (PLT) ratios and four cohort studies (Hatimeier 2017, Balvers 2017, Sambasivan 2011, Zink 2009) assessed both RBC:FFP and RBC:PLT ratios. All cohort studies included adult trauma patients and were carried out in trauma settings in the US, United Kingdom (UK), Germany, Netherlands, Denmark and Iraq. Overall, the risk of bias of included studies was judged to be moderate with concerns arising due to confounding *[182][183][184][185][27][186][187][188][189]*.

What are the main results?

Mortality

A meta-analysis of data from RCTs included in this review showed the mortality rate (latest timepoint) in patients with critical bleeding to be comparable among those who received high ratios of blood components compared to those who received lower ratios with the relative risk (RR) of 1.26 observed (95% CI 0.49, 3.22; p = 0.64). Neither of the included RCTs were powered to detect differences in mortality.

Among patients with blunt and penetrating trauma, a total of 308 patients received a high (1:1:1) ratio of blood

components compared with 922 patients who received lower ratios, with significant difference observed (24.3% vs 31.4%, OR 0.38; 95% CI 0.22, 0.69; *p* = 0.001).

Morbidity
Holcomb (2015) reported no significant difference in thromboembolic events (deep vein thrombosis, pulmonary embolus) between patients who received high ratio of blood components (39/338, 11.5%) compared with those who did not (37/342, 10.8%).

Meta-analysis of two RCTs found no significant difference in multiorgan failure (MOF) between patients who received a high ratio of blood components (21/375, 5.6%) compared with patients who received a low ratio (15/374, 4%) (RR 1.39, 95% CI 0.73, 2.63; p = 0.32).

RBC transfusion volumes
A meta-analysis of data from two RCTs in the trauma setting showed no significant difference in median volume of RBCs transfused in the first 24-hours between patients receiving a high ratio of blood components compared to patients receiving a low ratio (SMD -0.1; 95% CI -0.24, 0.05; *p* = 0.18, random effect, I^2 = 0%).

Transfusion volume, other blood products
A meta-analysis of data from two RCTs in the trauma setting showed a significant difference in median volume of FFP transfused in the first 24-hours between patients receiving a high ratio of blood components compared to patients receiving a low ratio (SMD 0.3; 95% CI 0.15, 0.44; *p* <0.0001, random effect, I^2 = 0%).

Outcome Timeframe	**Study results and measurements**	**Comparator** Lower ratios of blood components	**Intervention** High ratio (1:1:1) of blood components	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (RCTs) latest reported timepoint 9 Critical	Relative risk 1.26 (CI 95% 0.49 — 3.22) Based on data from 755 participants in 2 studies. [1] (Randomized controlled)	249 per 1000 Difference:	314 per 1000 **65 more per 1000** (CI 95% 127 fewer — 553 more)	**Very low** Due to very serious inconsistency, Due to very serious imprecision [2]	High (1:1:1) RBC:FFP:PLT ratio may result in little or no difference in mortality in trauma patients with critical bleeding but we are very uncertain about the evidence.
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Outcome Timeframe	**Study results and measurements**	**Comparator** Lower ratios of blood components	**Intervention** High ratio (1:1:1) of blood components	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical	controlled)		**1000** (CI 95% 10 fewer — 66 more)		trauma patients with critical bleeding.
RBC transfusion volume	Measured by: Number of Units Lower better Based on data from 749 participants in 2 studies. [9] (Randomized controlled)	**9 - 10.3** Units Difference:	**7.7 - 9.7** Units **SMD 0.1 lower** (CI 95% 0.24 lower — 0.05 higher)	**Low** Due to serious imprecision [10]	High (1:1:1) RBC:FFP:PLT ratio may slightly reduce RBC transfusion volume in trauma patients with critical bleeding.
Transfusion volume, other blood products	Measured by: Number of Units Lower better Based on data from 749 participants in 2 studies. [11] (Randomized controlled)	**5 - 5.7** Units Difference:	**6 - 7.7** Units **SMD 0.3 higher** (CI 95% 0.15 higher — 0.44 higher)	**Low** Due to serious imprecision [12]	High (1:1:1) RBC:FFP:PLT ratio may slightly increase transfusion volume of other blood products in trauma patients with critical bleeding.

Clinical Question/ PICO

Population: People with critical bleeding (surgical setting)
Intervention: High ratio (1:1:1) of blood components
Comparator: Lower ratios of blood components

Summary

What did we find?

There were seven nonrandomised cohort studies (Hall 2013, Henriksson 2012, Johansson 2007, Johansson 2008, Kauvar 2011, Mell 2010, Tadlock 2010) identified in the surgical setting that evaluated different blood product ratios on patient outcomes.

Study characteristics

All studies included patients with ruptured abdominal aortic aneurysms (rAAAs). Five studies (Hall 2013, Henriksson 2012, Johansson 2007, Johansson 2008, Tadlock 2010) defined a high ratio of fresh frozen plasma (FFP): packed red blood cells (pRBC) as 1:1 and two studies (Kauvar 2011, Mell 2010) did not define a high ratio. All seven studies were carried out in single-centre surgical settings in North America and Denmark. Overall, review authors judged included studies as serious risk of bias, with a significant amount of bias arising from confounding and patient selection *[190]*.

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Outcome Timeframe	Study results and measurements	Comparator Lower ratios of blood components	Intervention High ratio (1:1:1) of blood components	Certainty of the Evidence (Quality of evidence)	Plain language summary
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Clinical Question/ PICO

Population: People at risk of critical bleeding (any setting)
Intervention: Increased RBC transfusion volumes
Comparator: Normal RBC transfusion volumes

Summary

What did we find?

There were 10 prospective and 12 retrospective studies identified in the trauma setting and one retrospective cohort study in the medical setting that investigated the effect of transfusion of increased volumes of red blood cells (RBCs) in patients at risk of clinical bleeding.

Among the included prospective cohort studies identified in the systematic review, there were four studies (Bochicchio 2008, Silverboard 2005, Dunne 2004, Malone 2003) that assessed the effect of RBC on mortality, four studies (Ciesla 2005, Johnson 2010, Moore 1997, Sauaia 1994) that assessed the effect of RBC on multiorgan failure (MOF) and one study (Edens 2010) that assessed the effect of RBC on acute lung injury (ALI). One additional study was identified (Liu 2018) which investigated the association between RBC transfusion and mortality and hospital length of stay (LOS) in the trauma setting.

Among the included retrospective cohort studies identified in the trauma setting, there were 10 studies (Barbosa 2011, Chaiwat 2009, Mahambrey 2009, Murrell 2005, Phelan 2010, Robinson 2005, Spinella 2008, Croce 2005, Teixeira 2008, Weinberg 2008) that assessed the effect of RBC on mortality, one study (Cotton 2009) that assessed the effect of RBC on MOF and three studies (Plurad 2007, Weinberg 2008, Croce 2005) that assessed the effect of RBC on acute respiratory distress syndrome (ARDS). One additional study was identified (Hassainien 2015) which assessed the effect of RBC on mortality among 70 patients with liver cirrhosis and hepatocellular carcinoma presenting with acute upper gastrointestinal bleeding.

Study characteristics

The included observational cohort studies identified in the systematic review were conducted in the trauma settings and commonly queried trauma databases or registries, resulting in most studies having good representativeness. Overall, the studies were considered to have no serious risk of bias of included studies when conducting a GRADE assessment. However, authors note that observational studies are prone to bias and adjusting for confounding (particularly in relation to the injury severity scores). Review authors attempted to mitigate confounding by only including studies that attempted to adjust for injury severity in the pooled analysis *[191]*.

Liu 2018 was a single centre prospective cohort study conducted in the United States (US) that investigated the association between RBC transfusion and mortality and hospital LOS in the trauma setting. Included trauma patients (predominantly due to assault and motor vehicle accidents) were over 18 years and had received between 0 and 87 units of packed RBC within 24 hours of injury. The study was considered to be at serious risk of bias due to inadequate adjustment for confounders, a lack of details regarding blinding and study design.

Hassanein 2015 was a retrospective hospital-based study conducted in Egypt. The study included 70 patients with liver cirrhosis and hepatocellular carcinoma presenting with acute upper gastrointestinal bleeding. Patients must meet criteria of either hematemesis or melena with a diagnostic esophagogastroduodenoscopy, or both. The study was considered to be at moderate risk of bias due to a lack of details regarding blinding and study design.

What are the main results?

Mortality

Nine studies assessed the effect of RBC transfusion on mortality as a continuous variable. Identified literature suggests transfusion of increased RBCs is associated with an increased risk of mortality among patients at risk of critical bleeding in the trauma setting. Pooled analysis showed an increased in the odds of mortality associated with each additional RBC unit transfused (OR 1.07; 95% CI 1.04, 1.10; *p* <0.001).

Morbidity

Three studies assessed the effect of RBC transfusion on MOF as a continuous variable. Pooled analysis showed a significant increase in the odds of MOF associated with each additional RBC unit transfused (OR 1.08; 95% CI 1.02, 1.14; *p* = 0.012).

Two studies assessed the effect of RBC transfusion on ARDS as a continuous variable. Pooled analysis showed a significant increase in the odds of ARDS or ALI associated with each additional RBC unit transfused (OR 1.06; 95% CI 1.03, 1.10; *p* <0.001).

Outcome Timeframe	**Study results and measurements**	**Comparator** Normal RBC transfusion volumes	**Intervention** Increased RBC transfusion volumes	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (Coh) latest reported timepoint 9 Critical	Based on data from 18,009 participants in 9 studies. [1] (Observational (non-randomized))	The odds of mortality increases with each additional RBC unit transfused (OR range 0.83-1.16).		**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [2]	Each additional RBC unit transfused is associated with higher mortality.
Morbidity, multiorgan failure (Coh) Any timepoint 9 Critical	Based on data from 3,050 participants in 3 studies. (Observational (non-randomized))	The odds of multiorgan failure increases with each additional RBC unit transfused (OR range 2.90-8.60).		**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [3]	Each additional RBC unit transfused is associated with higher risk of multiorgan failure.
Morbidity, ARDS (Coh) Any timepoint 9 Critical	Based on data from 14,136 participants in 2 studies. (Observational (non-randomized))	The odds of acute respiratory distress syndrome or acute lung injury increases with each additional RBC unit transfused (OR range 1.06-1.09).		**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [4]	Each additional RBC unit transfused is associated with higher risk of acute respiratory distress syndrome or acute lung injury.

6.1.3 Blood components and/or products

Blood components and products

Fresh frozen plasma (FFP)

FFP contains all coagulation factors so can be used for the treatment, or prevention of bleeding in patients with a coagulopathy where a specific therapy or factor concentrate is not appropriate or unavailable.

Platelets
Pooled or apheresis platelets can be used for the treatment of bleeding in patients who develop thrombocytopenia due to increased platelet consumption or dilution, or have abnormal platelet function (eg anti-platelet medications).

Cryoprecipitate
Cryoprecipitate is prepared by thawing whole blood derived FFP and recovering the precipitate. The cold-insoluble precipitate is refrozen and contains Factor VIII, von Willebrand factor (VWF), fibrinogen, Factor XIII and fibronectin.

Cryoprecipitate can be used for the treatment of fibrinogen deficiency or dysfibrinogenaemia when there is critical bleeding or disseminated intravascular coagulation (DIC).

Fibrinogen concentrate (FC)
FC is a lyophilised preparation of plasma derived fibrinogen indicated for the treatment of congenital afibrinogenemia and hypofibrinogenemia.

Prothrombin complex concentrate (PCC)
Prothrombinex-VF® is the current PCC available in Australia. It is a coagulation factor concentrate containing Factor II, IX and X and a small amount of Factor VII.

Prothrombinex-VF® is used management of patients with single or multiple congenital deficiencies of Factor II or X, and in patients with single or multiple acquired factor II, IX and X deficiencies caused by vitamin K antagonists (warfarin) requiring partial or complete reversal.

Research question
In patients with critical bleeding, what is the effect of fresh frozen plasma (FFP), cryoprecipitate (CRYO), fibrinogen concentrate (FC), prothrombin complex concentrate (PCC) and/or platelet (PLT) transfusion on RBC transfusion and patient outcomes?

Literature search date: 29 September 2021

Weak recommendation

R4: In patients with critical bleeding, the following initial doses of FFP and PLT are suggested:

- FFP: a minimum 1 unit per 2 units of RBC
- PLT*: a minimum of 1 adult unit per 8 units of RBC

**1 adult unit of pooled or apheresis platelets in Australia is equivalent to platelets derived from 4 single whole blood donor units.*

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The clinical heterogeneity in the trials and studies precludes a strong recommendation on the dose and/or timing of FFP, PLT, PCC, CRYO or FC. The effect of blood components or blood products is uncertain and therefore makes it difficult to make recommendations with regard to timing and/or dose of FC, CRYO or PCC for patients who are critically bleeding.

Certainty of the Evidence

Very low

The overall certainty in effect estimates across outcomes was either very low (benefits) or low (harms).

Values and preferences

No substantial variability expected

There is no plausible reason to suspect that patients who are critically bleeding would not accept blood components as recommended. A subgroup of patients may decline blood components based on personal preference.

Resources

Important issues, or potential issues not investigated

In the absence of high certainty evidence, the effect of blood components on resources (transfusion volume, length of hospital stay) is not clear.

Equity

Important issues, or potential issues not investigated

The reference group acknowledged that there is jurisdictional, geographical and/or institutional variability in the availability of blood components.

Acceptability

Important issues, or potential issues not investigated

Feasibility

Important issues, or potential issues not investigated

The reference group acknowledged the logistical challenges associated with providing blood components to treat critically bleeding patients. Adaptation of this guidance at a local level is required upon consideration of the resources available.

Rationale

RBC units contain negligible amounts of coagulation factors or platelets.

Clinical Question/ PICO

Population: People with critical bleeding (trauma setting)
Intervention: Fresh frozen plasma
Comparator: No fresh frozen plasma (or varying administration of)

Summary

What did we find?

There were two randomised controlled trials (RCTs) (Moore 2018, Sperry 2018) and four nonrandomised cohort studies (Innerhofer 2013, O'Reilly 2014 Holcomb 2017, Shackelford 2017) identified in the trauma setting that assessed the effect of fresh frozen plasma (FFP) versus no FFP (or varying administration of) on patient outcomes.

Study characteristics

Both RCTs were conducted in trauma centres in the United States (US) and enrolled severely injured adults (aged 18 – 90 years) with systolic blood pressure 70 mmHg or lower or 71–90 mmHg and heart rate 108 beats per min thought to be due to acute blood loss, either before the arrival of air medical transport or before arrival at the trauma centre. The RCTs assessed the use of 2 units of FFP compared with the standard resuscitation protocol according to local rules. Moore (2018) included a total of 125 patients in the analysis and Sperry (2018) included 501 patients. Both RCTs reported on the outcomes of mortality and morbidity (including acute lung injury and multiple organ failure) and were judged by the systematic review authors to be at low risk of bias *[192][193]*.

Innerhofer 2013 was a single-centre, prospective cohort study conducted in Austria that assessed the effect of FFP in 144 patients with blunt major trauma. All patients in the study received fibrinogen concentrate (FC) and prothrombin complex concentrate (PCC); 78 patients additionally received FFP transfusions and constitute the interventional arm in this analysis. Review authors judged the study as high risk of bias due to small sample sizes, inadequate follow-up and lacked rigorous analyses *[196][195][194]*.

Holcomb 2017 was a multi-centre, prospective cohort study conducted in the US that assessed the effect of prehospital transfusion of FFP, RBC, or FFP in addition to red blood cell (RBC) transfusion compared with standard of care in 109 patients with penetrating trauma. A total of 26 patients received FFP only, 8 patients received RBC only and 75 patients received both FFP and RBC and constitute the interventional arm in this analysis. The study was found to be at high risk of bias due to imbalances in baseline characteristics which limited matching *[193]*.

Two cohort studies investigated the effect of prehospital transfusion of FFP compared to standard of care in military trauma patients in Afghanistan with gunshot wounds or explosive trauma (O'Reilly 2014, Shackelford 2017). O'Reilly 2014 was a retrospective cohort study that assessed prehospital blood transfusion in 194 patients. A total of 97 patients received a median of 1 unit RBC and 2 units of FFP and 97 patients received standard of care. Shackelford 2017 was a retrospective cohort study of 386 US military combat casualties who received prehospital blood transfusion between 2012 to 2015. A total of 54 patients received RBC and FFP; 332 patients received standard of care. Review authors judged the study as high risk of bias due to retrospective analyses and a lack of uniform guidelines for initiating pre-hospital blood transfusion which makes it difficult to determine the effect of individual blood components *[193]*.

What are the main results?

Mortality

A meta-analysis of data from studies included in this review showed no significant difference in mortality at the latest reported timepoint between patients who received FFP compared to those who did not.

Two RCTs (Moore 2018, Sperry 2018) and four cohort studies (Holcomb 2017, Innerhofer 2013, O'Reilly 2014, Shackelford 2017) reported on the effect of FFP on the outcome of mortality, latest timepoint. All six studies were conducted in the trauma setting. Combined data from the two RCTs showed the mortality rate to be 26.4% (78/295) among those who received FFP compared to 31.4% (104/331) among those who did not. The difference was not statistically significant (RR 0.95; 95% CI 0.56, 1.59; p = 0.83; random effects, I^2 = 38%), with moderate statistical heterogeneity observed.

Combined data from the four cohort studies suggested a significant association between FFP and mortality among trauma patients with critical bleeding (RR 0.65, 95%CI 0.43, 0.98; p = 0.04; random effects, I^2 = 0%) with the rate of mortality observed among those who received FFP (19.3%, 106/549) being lower than the mortality rate of those who did not receive FFP (24.4%, 218/892).

Morbidity

One cohort study (Innerhofer 2013) reported a lower rate of thromboembolic events among patients who received FFP (7.7%, 6/78) compared with those who did not (9.0%, 6/66), but the difference between groups was not significant (RR 0.85, 95% CI 0.29, 2.50; p = 0.76).

A meta-analysis of data from the included studies showed an increased risk of multiple organ failure among patients who received FFP (179/373, 48.0%) compared with those who did not (169/397, 42.6%). The difference between groups was not significant (RR 1.56, 95% CI 0.2, 2.96; p = 0.17; random effects; I^2 = 68%); noting statistical heterogeneity is substantial. The results were not substantially different when only RCT evidence was considered (RR 1.76, 95% CI 0.40, 7.68); p = 0.45; random effects; I^2 = 58%).

RBC transfusion volume

One small cohort study (Innerhofer 2013) reported that the median (interquartile range [IQR]) volume of RBCs transfused (units to 24 hours) among the 78 patients who received FFP was 7 (4, 11) units, which was significantly higher than the median 2 (0, 6) units of RBCs transfused among the 66 patients who did not receive FFP (p = 0.001).

Transfusion volume, other blood products

One small cohort study (Innerhofer 2013) reported that the median (IQR) volume of platelets (PLTs) transfused (units to 24 hours) among the 78 patients who received FFP was 0 (0, 1) units, which was significantly higher than the median 0 (0, 0) units of PLTs transfused among the 66 patients who did not receive FFP (p = 0.003).

There was no significant difference between treatment groups reported for the outcome of FC transfusion volumes (units to 24 hours) and PCC transfusion volumes (units to 24 hours).

Length of stay, hospital or ICU

One small cohort study (Innerhofer 2013) reported the median duration of hospital stay to be 29 days (IQR 16, 50) among 78 patients who received FFP which was longer than the median 24 days (IQR 12, 35) reported for the 66 patients who did not receive FFP. The difference was not statistically significant (p = 0.074).

One small cohort study (Innerhofer 2013) reported the median duration of ICU stay to be 14 days (IQR 7, 30) among 78 patients who received FFP which was longer than the median 12 days (IQR 6, 24) reported for the 66 patients who did not receive FFP. The difference was not statistically significant (p = 0.217).

Outcome Timeframe	**Study results and measurements**	**Comparator** No fresh frozen plasma (or varying administration of)	**Intervention** Fresh frozen plasma (or varying administration of)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (RCTs) latest reported timepoint 9 Critical	Relative risk 0.95 (CI 95% 0.56 — 1.59) Based on data from 626 participants in 2 studies. [1] (Randomized controlled)	**314** per 1000 Difference:	**298** per 1000 **16 fewer per 1000** (CI 95% 138 fewer — 185 more)	**Low** Due to serious inconsistency, Due to serious imprecision [2]	The evidence suggests FFP may have little or no effect on 30-day mortality in trauma patients with critical bleeding.
Mortality, all cause (Coh) latest reported timepoint 9 Critical	Relative risk 0.65 (CI 95% 0.43 — 0.98) Based on data from 815 participants in 4 studies. [3] (Observational (non-randomized))	**203** per 1000 Difference:	**132** per 1000 **71 fewer per 1000** (CI 95% 116 fewer — 4 fewer)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision [4]	FFP appears to reduce 30-day mortality in trauma patients with critical bleeding but the evidence is very uncertain.
Morbidity, thromboembolic events 9 Critical	Relative risk 0.85 (CI 95% 0.29 — 2.5) Based on data from 144 participants in 1 studies. [5] (Observational (non-randomized))	**91** per 1000 Difference:	**77** per 1000 **14 fewer per 1000** (CI 95% 65 fewer — 137 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision [6]	The evidence is very uncertain about the effect of FFP on thromboembolic events in trauma patients with critical bleeding.
Morbidity, multiple organ failure 9 Critical	Relative risk 1.76 (CI 95% 0.4 — 7.68) Based on data from 626 participants in 2 studies. [7] (Randomized controlled)	**476** per 1000 Difference:	**838** per 1000 **362 more per 1000** (CI 95% 286 fewer — 3,180 more)	**Low** Due to serious inconsistency, Due to serious imprecision [8]	FFP may have little to no effect on multiple organ failure in trauma patients with critical bleeding but the evidence is very uncertain.
RBC transfusion volume	Based on data from 144 participants in 1 studies. [9] (Observational (non-randomized))	The median (IQR) volume of RBCs transfused (units to 24 hours) among patients who received FFP was 7 (4, 11) compared with a median volume of 2 (0, 6) among those who did not receive FFP (p = 0.001).		**Very low** Due to serious risk of bias, Due to serious imprecision [10]	The evidence is very uncertain about the effect of FFP on the volume of RBCs transfused in trauma patients with critical bleeding.
Transfusion volume, other blood products 4 Important	Based on data from 144 participants in 1 studies. [11] (Observational (non-randomized))	The median (IQR) volume of PLTs transfused (units to 24 hours) was higher among patients who received FFP compared with those who did not received FFP (p = 0.003). There was no significant difference between treatment groups for the volume of FC or PCC transfused (units to 24 hours).		**Very low** Due to serious risk of bias, Due to very serious imprecision [12]	The evidence is very uncertain about the effect of FFP on the volume of PLTs, FC, or PCC transfused in trauma patients with critical bleeding.

Outcome Timeframe	**Study results and measurements**	**Comparator** No fresh frozen plasma (or varying administration of)	**Intervention** Fresh frozen plasma (or varying administration of)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Length of stay, hospital or ICU Days 4 Important	Based on data from 144 participants in 1 studies. [13] (Observational (non-randomized))	No significant difference in the median length of hospital or ICU stay among patients who received FFP compared to patients who did not.		**Very low** Due to serious risk of bias, Due to very serious imprecision [14]	The evidence is very uncertain about the effect of FFP on hospital or ICU length of stay in trauma patients with critical bleeding.

Clinical Question/ PICO

Population: People with critical bleeding (trauma setting)
Intervention: Cryoprecipitate (CRYO)
Comparator: No CRYO (or varying administration of)

Summary

What did we find?

There was one randomised controlled trial (RCT) (Curry 2015) identified in the trauma setting that assessed the effect of cryoprecipitate (CRYO) versus no CRYO (or varying administration of) on patient outcomes.

Study characteristics

Curry (2015) evaluated the effect of CRYO on mortality, morbidity and transfusion volume in trauma patients with major haemorrhage requiring activation of the major haemorrhage protocol. The study included a total of 44 patients and was carried out in two civilian trauma centres in the United Kingdom (UK). Risk of bias was judged by review authors as unclear due to small sample size and lack of blinding of participants, clinical staff and research staff *[181]*.

What are the main results?

Mortality
One RCT (Curry 2015) reported a lower rate of mortality among patients who received CRYO (2/20, 10.0%) compared with those who did not (6/21, 28.6%). The difference between treatment groups was not statistically significant (RR 0.35, 95% CI 0.08, 1.54; p = 0.14).

Morbidity
One RCT (Curry 2015) reported no thromboembolic events among critically bleeding trauma patients who received CRYO compared with a total of three events in the placebo group. Specifically, a lower rate of deep vein thrombosis (DVT) was observed among patients who received CRYO (0/20, 0%) compared with those who did not (1/21, 4.8%). The event rates for this outcome were not significantly different (DVT: RR 0.35, 95% CI 0.02, 8.10; p = 0.51).

One RCT (Curry 2015) reported a higher rate of multiple organ failure among critically bleeding trauma patients who received CRYO (1/20, 5%) compared with those who did not (0/21, 0%), corresponding to a RR of 3.14 (95% CI 0.14, 72.92; p = 0.48).

RBC transfusion volume
One small RCT (Curry 2015) reported no significant difference in the volume of RBCs transfused up to 6 hours, 24 hours or 28 days among patients who received CRYO compared to those who did not. At 24-hours, participants in the control group had received a median (IQR) of 7 (6, 9) units of red blood cells (RBCs) compared to 8 (5,11) units given to those randomised to the CRYO group.

Transfusion volume, other blood products
One small RCT (Curry 2015) reported no significant difference in the volume of fresh frozen plasma (FFP), platelets (PLTs), or CRYO transfused up to 6 hours, 24 hours or 28 days among patients who received CRYO compared to those who did not. At 24-hours, participants in the control group had received a median (IQR) of 6 (3, 8) units of FFP compared to 7 (4, 8) units given to those randomised to the CRYO group. At 24-hours, participants in the control

group had received a median (IQR) of 1 (1, 2) unit of PLTs compared to 1 (0, 2) unit given to those randomised to the CRYO group. At 24-hours, participants in the control group had received a median (IQR) of 2 (0, 2) unit of CRYO compared to 2 (2, 4) units given to those randomised to the CRYO group.

Length of stay, hospital or ICU
One RCT (Curry 2015) reported the median (interquartile range [IQR]) duration of hospital length of stay (LOS) to be 31 days (29, 33) among 20 patients who received CRYO compared to 30 days (22, 38) among the 21 patients who did not receive CRYO. The difference was not statistically significant (p = 0.66).

One RCT (Curry 2015) reported the median (IQR) duration of intensive care unit (ICU) LOS to be 11 days (5, 17) among 20 patients who received CRYO compared to 18 days (16, 20) among the 21 patients who did not receive CRYO. The difference was not statistically significant (p = 0.56).

Outcome Timeframe	**Study results and measurements**	**Comparator** No CRYO (or varying administration of)	**Intervention** Cryoprecipitate (CRYO)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (RCTs) latest reported timepoint 9 Critical	Relative risk 0.35 (CI 95% 0.08 — 1.54) Based on data from 41 participants in 1 studies. [1] (Randomized controlled)	286 per 1000 Difference:	100 per 1000 **186 fewer per 1000** (CI 95% 263 fewer — 154 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision [2]	CRYO may have little or no effect on mortality in trauma patients with critical bleeding but the evidence is very uncertain.
Morbidity, thromboembolic events 9 Critical	Relative risk 0.35 (CI 95% 0.02 — 8.1) Based on data from 41 participants in 1 studies. [3] (Randomized controlled)	95 per 1000 Difference:	33 per 1000 **62 fewer per 1000** (CI 95% 93 fewer — 675 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision [4]	There were too few who experienced the outcome to determine whether CRYO made a difference on thromboembolic events (including DVT, MI, PE, Stroke) in trauma patients with critical bleeding.
Morbidity, multiple organ failure 9 Critical	Relative risk 3.14 (CI 95% 0.14 — 72.92) Based on data from 41 participants in 1 studies. [5] (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	**Very low** Due to serious risk of bias, Due to very serious imprecision [6]	There were too few who experienced the outcome to determine whether CRYO made a difference on MOF (or other adverse events including sepsis and ARDS) in trauma patients with critical bleeding.
RBC transfusion volume	Based on data from 41 participants in 1 studies. [7] (Randomized controlled)	No significant difference in the median volume of RBCs transfused (to 24 hours or 28 days) among patients who received CRYO compared to patients who did not.		**Very low** Due to serious risk of bias, Due to very serious imprecision [8]	We are very uncertain about the effect of CRYO on the volume of RBCs transfused in trauma patients with critical bleeding.

Outcome Timeframe	Study results and measurements	Comparator No CRYO (or varying administration of)	Intervention Cryoprecipitate (CRYO)	Certainty of the Evidence (Quality of evidence)	Plain language summary
Transfusion volume, other blood products	Based on data from 41 participants in 1 studies. [9] (Randomized controlled)	No significant difference in the median volume of FFP, CRYO, or PLTs transfused (to 24 hours or 28 days) among patients who received CRYO compared to patients who did not.		Very low Due to serious risk of bias, Due to very serious imprecision [10]	We are very uncertain about the effect of CRYO on the volume of FFP, PLTs, or CRYO transfused in trauma patients with critical bleeding.
Length of stay, hospital or ICU	Based on data from 41 participants in 1 studies. [11] (Randomized controlled)	No significant difference in the median length of hospital or ICU stay among patients who received CRYO compared to patients who did not.		Very low Due to serious risk of bias, Due to very serious imprecision [12]	We are very uncertain about the effect of CRYO on the length of hospital or ICU stay in trauma patients with critical bleeding.

Clinical Question/ PICO

Population: People with critical bleeding (trauma setting)
Intervention: Fibrinogen concentrate (FC)
Comparator: No FC (or varying administration of)

Summary

What did we find?

There were five RCTs (Innerhofer 2017, Curry 2018, Nascimento 2016, Akbari 2017, Lucena 2020) and five cohort studies (Wafaisade 2013, Almskog 2020, Schochl 2011, Nienaber 2011, Inokuchi 2017) identified in the trauma setting that assessed the use of FC vs no FC (or varying administration of) on patient outcomes.

Study characteristics

The five RCTs conducted in the trauma setting were performed in Austria, UK, Canada, Iran and Brazil and all assessed the use of FC in adult patients with severe trauma. Three RCTs (Curry 2018, Nascimento 2016, Lucena 2020) compared the use of FC with saline or no FC, one RCT (Akbari 2017) compared FC to an active (FFP) and an inactive (no coagulation factor) comparator, and one RCT (Innerhofer 2017) compared FC to an active comparator (FFP) only. For the purpose of this review, only the inactive comparator in Akbari (2017) was considered. The studies were assessed to be at overall moderate risk of bias due to lack of allocation concealment, blinding of study personnel and outcome assessors, incomplete outcome data and selective reporting *[197][198]*.

Five cohort studies were conducted in Europe and Japan and examined the effect of FC in trauma patients with critical bleeding. Two studies reported the comparator to be no FC (Wafaisade 2013, Almskog 2020), while the remaining three cohort studies reported the comparator to be FFP (Schochl 2011, Nienaber 2011, Inokuchi 2017). The cohort studies were judged by systematic reviews to be at high risk of bias due to missing data, absence of a clear objective criterion for the activation of massive transfusion protocol (MTP) and lack of control for potential confounders *[198]*.

What are the main results?

Mortality

Among critically bleeding trauma patients, a meta-analysis of data from the included RCTs showed the mortality rate (latest timepoint) among those who received FC (26/144, 18.1%) to be comparable to those who did not (25/139, 18.0%) with a RR of 1.12 observed (95% CI 0.53, 2.35; p = 0.77). Statistical heterogeneity was moderate.

Data from the included cohort studies suggests a non-significant association with higher mortality among trauma patients who received FC (131/615, 21.3%) compared with those who did not (152/1130, 13.5%) with the RR of 1.39 observed (95% CI 0.91, 2.13; p = 0.13).

Morbidity
Among patients with critical bleeding in the trauma setting, a meta-analysis of data from four RCTs showed that the rate of thromboembolic events was comparable between patients who received FC (12/107, 11.2%) and those who did not (12/103, 11.7%). This corresponds to a RR of 0.90 (95% CI 0.42, 1.91; *p* = 0.78), noting there was no statistical heterogeneity.

A meta-analysis of data from the RCTs showed that the rate of MOF was lower among patients who received FC (29/97, 30%) compared with those who did not (38/98, 38.8%), but the difference did not reach statistical significance (RR 0.74; 95% CI 0.53, 1.03; *p* = 0.07.

RBC transfusion volume
One RCT and four cohort studies reported the effect of FC on RBC transfusion volume in trauma patients with critical bleeding. Data from Wafaisade 2013 suggested a higher volume of RBCs was required for patients who received FC (n=294) compared with those who did not (n=294), but the difference was not significant (SMD 0.12; 95% CI -0.04, 0.28; *p* = 0.14). The other four studies (one RCT, three cohort studies) reporting median [IQR] values suggested there was no significant difference in the volume of RBCs transfused (comparing patients who received FC compared with those who did not). Reported median values ranged from 3 to 12.8 units (FC) and 3 to 12.5 units (no FC).

Transfusion volume, other blood products
One RCT and four cohort studies reported on the effect of FC on the volume of FFP transfused in the trauma setting. Data from Wafaisade 2013 showed a statistically significant increase in the volume of FFP transfused among patients who received FC (n=294) compared with those who did not (n=294) (SMD 0.19, 95% CI 0.03, 0.35; *p* = 0.02). Among the other four studies (one RCT, three cohort studies), two studies reporting median [IQR] values suggested there was no significant difference in the volume of FFP transfused between patients who received FC compared with those who did not (Inokuchi 2017, Nascimento 2016). One study found a decrease in the volume of FFP transfused among patients who received FC compared with those who did not (Nienaber 2011) and one study did not report comparative data for this outcome.

One RCT and three cohort studies reported on the effect of FC on the volume of PLT transfused in the trauma setting. Among the three studies that reported comparative data, two studies suggested there was no significant difference in the volume of PLT transfused between patients who received FC compared with those who did not (Nascimento 2016, Inokuchi 2017). One cohort study (Nienaber 2011) reported a significant reduction ($p < 0.005$) in platelet transfusion among patients who received FC compared with those who did not, but no further data was provided.

One RCT reported on the effect of FC on the volume of CRYO transfused in the trauma setting and found no significant difference between treatment groups (*p* = 0.18).

Length of stay, hospital
Four RCTs and three cohort studies reported the effect of FC on hospital LOS in the trauma setting. Data were available for two studies (reported as mean [SD]), that showed FC has no significant impact on the duration of hospital stay comparing patients who received FC with those who did not (RR −1.30; 95% CI −6.76, 4.16; *p* = 0.64), noting the heterogeneity was substantial. The remaining studies reported data as median (IQR) that also suggested there is no significant difference in hospital LOS between patients who received FC and those who did not.

Length of stay, ICU
Two RCTs and four cohort studies reported the effect of FC on ICU LOS (days) in the trauma setting. Complete data were not available, but five of the six studies suggested that there is no significant difference in the duration of ICU stay for patients who received FC compared to those who did not. One RCT (Lucena 2020) suggested that the length of ICU stay among patients who received FC was lower (*p* = 0.021) than the length of ICU stay among patients who did not.

Outcome Timeframe	**Study results and measurements**	**Comparator** No fibrinogen concentrate (or varying administration of)	**Intervention** Fibrinogen concentrate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all	Relative risk 1.12	180	202	Very low	The evidence is very

Outcome Timeframe	**Study results and measurements**	**Comparator** No fibrinogen concentrate (or varying administration of)	**Intervention** Fibrinogen concentrate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
cause (RCTs) latest reported timepoint 9 Critical	(CI 95% 0.53 — 2.35) Based on data from 283 participants in 5 studies. [1] (Randomized controlled)	per 1000 Difference:	per 1000 **22 more per 1000** (CI 95% 85 fewer — 243 more)	Due to serious indirectness, Due to very serious imprecision [2]	uncertain about the effect of fibrinogen concentrate on mortality in trauma patients with critical bleeding.
Mortality, all cause (Coh) latest reported timepoint 9 Critical	Relative risk 1.39 (CI 95% 0.91 — 2.13) Based on data from 1,745 participants in 5 studies. [3] (Observational (non-randomized))	135 per 1000 Difference:	188 per 1000 **53 more per 1000** (CI 95% 12 fewer — 153 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision [4]	The evidence is very uncertain about the effect of fibrinogen concentrate on mortality in trauma patients with critical bleeding.
Morbidity, thromboembolic events (RCTs) 9 Critical	Relative risk 0.9 (CI 95% 0.42 — 1.91) Based on data from 210 participants in 4 studies. [5] (Randomized controlled)	117 per 1000 Difference:	105 per 1000 **12 fewer per 1000** (CI 95% 68 fewer — 106 more)	**Low** Due to very serious imprecision [6]	The evidence suggests that fibrinogen concentrate may have little or no difference on thromboembolic events in trauma patients with critical bleeding.
Morbidity, multiple organ failure (RCTs) 9 Critical	Relative risk 0.74 (CI 95% 0.53 — 1.03) Based on data from 195 participants in 3 studies. [7] (Randomized controlled)	388 per 1000 Difference:	287 per 1000 **101 fewer per 1000** (CI 95% 182 fewer — 12 more)	**Low** Due to very serious imprecision [8]	The evidence suggests that fibrinogen concentrate may have little or no difference on multiple organ failure in trauma patients with critical bleeding.
RBC transfusion volume Units	Based on data from 1,574 participants in 5 studies. (Observational (non-randomized))	No significant difference observed for volume of RBCs transfused among patients who received FC compared with those who did not. Reported median values ranged from 3 to 12.8 units (FC) and 3 to 12.5 units (no FC).		**Very low** Due to serious risk of bias, Due to serious imprecision [9]	The evidence is very uncertain about the association of fibrinogen concentrate on the volume of RBCs transfused in trauma patients with critical bleeding.
Transfusion volume, other blood products Units	Based on data from 1,574 participants in 5 studies. (Observational (non-randomized))	No significant difference observed for volume of FFP transfused among patients who received FC compared with those who did not. Reported median values ranged from 0 to 10.6 units (FC) and 1.75 to 10 units (no FC).		**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision, Due to serious publication bias [10]	The evidence is very uncertain about the association of fibrinogen concentrate on the volume of FFP transfused in trauma patients with critical bleeding.

Outcome Timeframe	**Study results and measurements**	**Comparator** No fibrinogen concentrate (or varying administration of)	**Intervention** Fibrinogen concentrate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Length of stay, hospital Days	Based on data from 1,491 participants in 7 studies. [11] (Observational (non-randomized))	No significant difference observed for hospital LOS among patients who received FC compared with those who did not.		**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency [12]	Fibrinogen concentrate may have little or no difference on hospital length of stay in the trauma setting but the evidence is very uncertain.
Length of stay, ICU Days	Based on data from 1,647 participants in 6 studies. [13] (Observational (non-randomized))	Five out of six studies reported no significant difference in ICU LOS among patients who received FC compared with those who did not.		**Very low** Due to serious risk of bias, Due to serious imprecision [14]	Fibrinogen concentrate may have little or no difference on hospital length of stay in the trauma setting but the evidence is very uncertain.

Clinical Question/ PICO

Population: People with critical bleeding (surgical setting)
Intervention: Fibrinogen concentrate (FC)
Comparator: No FC (or varying administration of)

Summary

What did we find?

There were four RCTs (Bilicen 2017, Rahe-Meyer 2013, Rahe-Meyer 2016, Tanaka 2014) and three nonrandomised cohort studies (Bilicen 2013, Rahe-Meyer 2009a, Rahe-Meyer 2009b) identified in the surgical setting that assessed the use of FC vs no FC (or varying administration of) on patient outcomes.

Study characteristics

Four RCTs were conducted in the Netherlands, Germany and US and evaluated the therapeutic use of FC in the cardiac surgery setting. Three RCTs (Bilicen 2017, Rahe-Meyer 2013, Rahe-Meyer 2016) compared the use of FC with saline while one RCT (Tanaka 2014) compared the use of FC with 1 unit of PLTs. All four RCTs were assessed by the systematic review authors to be at an overall low risk of bias, however no trial was considered to be at a low risk of bias for all domains. Domains with high risk of bias included allocation concealment, blinding, incomplete outcome data and selective reporting *[197]*.

Three cohort studies were identified in the surgical setting that evaluated the use of FC in patients with massive haemorrhage (Bilicen 2013, Rahe-Meyer 2009a, Rahe-Meyer 2009b). All three cohort studies were assessed to be at high risk of bias, predominately due to failure to in blinding, lack of information on the allocation of groups and insufficient information about comparability of groups at baseline and at the analysis stage *[194]*.

Bilicen (2013) was a single-centre prospective cohort study that assessed 1075 patients who underwent complex cardiac surgery in the Netherlands. A total of 264 patients received a median dose of 2g FC; the 811 patients that did not receive FC represent the control group. The authors note that due to the nonrandomised design of the study, the association between the infusion of FC and each of the outcomes were likely biased by potential confounders *[194]*.

Rahe-Meyer (2009a) was a pilot cohort study that prospectively enrolled 15 patients undergoing aortic valve operation and ascending aorta replacement surgery in Germany. Five patients received transfusion according to the pre-defined blood products transfusion algorithm while the remaining 10 patients received FC before being transfused according to the algorithm. Rahe-Meyer (2009b) was a retrospective group analysis of 18 patients who underwent elective thoracoabdominal aortic aneurysm surgery. All patients in the study were treated with allogenic

blood products according to a predetermined algorithm; six patients also received a mean (SD) dose of 7.8g (2.7) FC as a first step therapy. Both cohort studies were underpowered due to small sample sizes *[194]*.

What are the main results?

Mortality
Among critically bleeding patients in the surgical setting, a meta-analysis of data from the included RCTs showed no significant difference in the rate of mortality (latest timepoint) between patients who received FC (4/177, 2.3%) compared to patients who did not (9/176, 5.1%) with a RR of 0.48 observed (95%CI 0.08, 2.83; $p = 0.42$), noting the event rate was low across both treatment groups and statistical heterogeneity was moderate.

Data from the included cohort studies also suggested a non-significant association with higher mortality in patients who received FC (18/280, 6.4%) compared with those who did not (35/898, 3.9%), with a RR of 1.58 observed (95% CI 0.65, 3.85; $p = 0.31$).

Morbidity
Among patients with critical bleeding in the surgical setting the rate of thromboembolic events was higher in patients who received FC (8/99, 8.0%) compared with those who did not (4/102, 3.9%) but the difference was not statistically significant (RR 2.03; 95% CI 0.63, 6.58). It is noted that the evidence for thromboembolic events was limited by small patient numbers, with the included studies not sufficiently powered to detect important differences in event rates.

RBC transfusion volume
Two cohort studies reported the effect of FC on RBC transfusion volume in the surgical setting. Data from Rahe-Meyer 2009a suggested that patients who received FC had a lower volume of RBCs transfused compared with patients who did not receive FC (SMD −1.69, 95% CI −2.49, -0.88; $p < 0.0001$). The other study (Rahe-Meyer 2009b) reported that there were significantly fewer ($p < 0.05$) median units of RBCs transfused to 24 hours in patients who received FC compared with those who did not.

Transfusion volume, other blood products
Among critically bleeding patients in the surgical setting, there was a significant reduction in the volume of FFP transfused among patients who received FC compared to those who did not (SMD -4.78, 95%CI -7.04, -2.51; $p < 0.0001$). Two cohort studies also found a statistically significant reduction in the volume of PLT and PCC transfused among patients who received FC compared to those who did not ($p < 0.05$).

Length of stay, ICU
There was one cohort study in the surgical setting (Rahe-Meyer 2009b) that reported on ICU LOS (hours) which suggested FC is associated with a reduction in the length of ICU stay among patients who received FC compared with those who did not (MD − 3.27, 95% CI −4.82, −1.71; $p < 0.0001$; [hours converted to days]); however, the sample size is small and survivorship bias may have influenced the results.

Outcome Timeframe	**Study results and measurements**	**Comparator** No FC (or varying administration of)	**Intervention** Fibrinogen concentrate (FC)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (RCTs) latest reported timepoint 9 Critical	Relative risk 0.48 (CI 95% 0.08 — 2.83) Based on data from 353 participants in 4 studies. [1] (Randomized controlled)	51 per 1000 Difference:	24 per 1000 **27 fewer per 1000** (CI 95% 47 fewer — 93 more)	**Low** Due to very serious imprecision [2]	There were too few who experienced the outcome to determine whether fibrinogen concentrate made a difference on mortality in patients with critical bleeding in the surgical setting.
Mortality, all cause (Coh) latest reported timepoint	Relative risk 1.58 (CI 95% 0.65 — 3.85) Based on data from 1,178 participants in 3	39 per 1000	62 per 1000	**Very low** Due to serious risk of bias, Due to very serious	The evidence is very uncertain about the effect of fibrinogen concentrate on

Outcome Timeframe	**Study results and measurements**	**Comparator** No FC (or varying administration of)	**Intervention** Fibrinogen concentrate (FC)	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
9 Critical	studies. [3] (Observational (non-randomized))	Difference:	**23 more per 1000** (CI 95% 14 fewer — 111 more)	imprecision [4]	mortality in patients with critical bleeding in the surgical setting.
Morbidity, thromboembolic events (RCTs) 9 Critical	Relative risk 2.03 (CI 95% 0.63 — 6.58) Based on data from 201 participants in 3 studies. [5] (Randomized controlled)	**39** per 1000 Difference:	**79** per 1000 **40 more per 1000** (CI 95% 14 fewer — 218 more)	**Low** Due to very serious imprecision [6]	There were too few who experienced the outcome to determine whether fibrinogen concentrate made a difference on thromboembolic events in patients with critical bleeding in the surgical setting.
Transfusion volume, other blood products Units	Based on data from 33 participants in 2 studies.	Two studies found a significant reduction in the volume of FFP transfused among patients who received FC compared with those who did not. One study reported SMD -4.78.		**Very low** Due to serious risk of bias, Due to very serious imprecision [7]	There were too few who experienced the outcome to determine whether fibrinogen concentrate made a difference on the volume of FFP transfused in patients with critical bleeding in the surgical setting.
RBC transfusion volume Units	Based on data from 33 participants in 2 studies.	Two studies found a significant reduction in the volume of RBCs transfused among patients who received FC compared with those who did not. One study reported SMD -1.69.		**Low** Due to very serious imprecision [8]	There were too few who experienced the outcome to determine whether fibrinogen concentrate made a difference on the volume of RBCs transfused in patients with critical bleeding in the surgical setting.
Length of stay, ICU 4 Important	Based on data from 18 participants in 1 studies. [9] (Observational (non-randomized))	One small cohort study suggested FC is associated with a reduction in the length of stay in the ICU (MD −3.27, 95% CI −4.82, −1.71; p < 0.0001); however, the sample size is small and survivorship bias may have influenced the results.		**Very low** Due to serious risk of bias, Due to very serious imprecision [10]	There were too few who experienced the outcome to determine whether fibrinogen concentrate made a difference on ICU length of stay in patients with critical bleeding in the surgical setting.

Clinical Question/ PICO

Population: People with critical bleeding (trauma setting)
Intervention: Prothrombin complex concentrate (PCC)
Comparator: No PCC (or varying administration of)

Summary

What did we find?

There were four nonrandomised cohort studies (Jehan 2018, Zeeshan 2019, Joseph 2014, Joseph 2016) identified in the trauma setting that assessed the use of PCC and FFP versus FFP alone on patient outcomes.

Study characteristics

The four cohort studies were conducted in trauma patients presenting to the emergency department (total sample size 924). Two studies (Jehan 2018, Zeeshan 2019) investigated the effect of 4-factor PCC plus FFP compared to FFP only and two studies (Joseph 2014, Joseph 2016) investigated the effect of 3-factor PCC plus FFP compared to FFP only. Dose of PCC administered was 25 IU/kg for three studies and indication for administration was by clinical judgement for all four studies.

The studies were judged to have moderate risk of bias due to the retrospective study design, in which PCC was administered based on clinical judgement and may have resulted in confounding and bias. It was also noted that considerable variety in the type and dose for PCC could lead to under or overrepresentation of the actual effects of PCC on the outcomes *[200]*.

What are the main results?

Mortality

A meta-analysis of data from the four retrospective cohort studies revealed a significant reduction in mortality among patients who received PCC (72/364, 19.8%) compared with those who did not (159/557, 28.5%), representing an odds ratio (OR) of 0.64 (95%CI 0.46, 0.88; p = 0.007).

Morbidity

A meta-analysis of data from the four retrospective cohort studies showed no significant difference in thromboembolic events between treatment groups (OR 0.90, 95%CI 0.49, 1.67; p = 0.74).

RBC transfusion volume

A meta-analysis of data from the four retrospective cohort studies showed a significant reduction in the volume of RBCs transfused among patients that received PCC compared with those who did not (standardised MD −0.65; 95%CI −0.98, −0.32; p = 0.0001), noting the heterogeneity was substantial.

Outcome Timeframe	**Study results and measurements**	**Comparator** No prothrombin complex concentrate	**Intervention** Prothrombin complex concentrate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint 9 Critical	Odds ratio 0.64 (CI 95% 0.46 — 0.88) Based on data from 921 participants in 4 studies. [1] (Observational (non-randomized))	285 per 1000 Difference:	203 per 1000 **82 fewer per 1000** (CI 95% 130 fewer — 25 fewer)	**Very low** Due to serious risk of bias [2]	The use of prothrombin complex concentrate in trauma patients with critical bleeding may reduce mortality but the evidence is very uncertain.
Morbidity, thromboembolic events 9 Critical	Odds ratio 0.9 (CI 95% 0.49 — 1.67) Based on data from 921 participants in 4 studies. [3] (Observational (non-randomized))	48 per 1000 Difference:	43 per 1000 **5 fewer per 1000** (CI 95% 24 fewer — 30 more)	**Very low** Due to serious risk of bias, Due to serious imprecision [4]	The evidence is very uncertain about the effect of prothrombin complex concentrate on thromboembolic events in trauma patients with critical bleeding.

Outcome Timeframe	Study results and measurements	Comparator No prothrombin complex concentrate	Intervention Prothrombin complex concentrate	Certainty of the Evidence (Quality of evidence)	Plain language summary
RBC transfusion volume	Measured by: Number of Units Lower better Based on data from 921 participants in 4 studies. [5] (Observational (non-randomized))	5.4 - 10 Units Difference:	3.2 - 7 Units **SMD 0.65 lower** (CI 95% 0.98 lower — 0.32 lower)	Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [6]	The use of prothrombin complex concentrate in trauma patients with critical bleeding may reduce the volume of RBCs transfused but the evidence is very uncertain.

Good practice statement

GPS4: For other blood components and products, the reference group agreed that the following doses are a guide:

- Fibrinogen replacement: 8-10 units of whole blood cryoprecipitate, or 4-5 units of apheresis cryoprecipitate, or 3-4 grams fibrinogen concentrate*
- Prothrombin complex concentrate for warfarin reversal^: 25 to 50 IU/kg

There is insufficient evidence to provide a recommendation about timing and/or dose of these blood components or products.

**Fibrinogen concentrate is approved in Australia for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenaemia and hypofibrinogenaemia. Use of fibrinogen concentrate outside these indications (including critical bleeding) is considered 'off-label.'*

^refer to An update of consensus guidelines for warfarin reversal

Rationale

Refer to Research evidence under R4

Clinical Question/ PICO

Population: People with critical bleeding (trauma setting)
Intervention: Prothrombin complex concentrate (PCC)
Comparator: No PCC (or varying administration of)

Summary

What did we find?

There were four nonrandomised cohort studies (Jehan 2018, Zeeshan 2019, Joseph 2014, Joseph 2016) identified in the trauma setting that assessed the use of PCC and FFP versus FFP alone on patient outcomes.

Study characteristics

The four cohort studies were conducted in trauma patients presenting to the emergency department (total sample size 924). Two studies (Jehan 2018, Zeeshan 2019) investigated the effect of 4-factor PCC plus FFP compared to FFP only and two studies (Joseph 2014, Joseph 2016) investigated the effect of 3-factor PCC plus FFP compared to FFP only. Dose of PCC administered was 25 IU/kg for three studies and indication for administration was by clinical

judgement for all four studies.

The studies were judged to have moderate risk of bias due to the retrospective study design, in which PCC was administered based on clinical judgement and may have resulted in confounding and bias. It was also noted that considerable variety in the type and dose for PCC could lead to under or overrepresentation of the actual effects of PCC on the outcomes *[200]*.

What are the main results?

Mortality
A meta-analysis of data from the four retrospective cohort studies revealed a significant reduction in mortality among patients who received PCC (72/364, 19.8%) compared with those who did not (159/557, 28.5%), representing an odds ratio (OR) of 0.64 (95%CI 0.46, 0.88; p = 0.007).

Morbidity
A meta-analysis of data from the four retrospective cohort studies showed no significant difference in thromboembolic events between treatment groups (OR 0.90, 95%CI 0.49, 1.67; p = 0.74).

RBC transfusion volume
A meta-analysis of data from the four retrospective cohort studies showed a significant reduction in the volume of RBCs transfused among patients that received PCC compared with those who did not (standardised MD −0.65; 95%CI −0.98, −0.32; p = 0.0001), noting the heterogeneity was substantial.

Outcome Timeframe	**Study results and measurements**	**Comparator** No prothrombin complex concentrate	**Intervention** Prothrombin complex concentrate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint 9 Critical	Odds ratio 0.64 (CI 95% 0.46 — 0.88) Based on data from 921 participants in 4 studies. [1] (Observational (non-randomized))	285 per 1000 Difference:	203 per 1000 **82 fewer per 1000** (CI 95% 130 fewer — 25 fewer)	**Very low** Due to serious risk of bias [2]	The use of prothrombin complex concentrate in trauma patients with critical bleeding may reduce mortality but the evidence is very uncertain.
Morbidity, thromboembolic events 9 Critical	Odds ratio 0.9 (CI 95% 0.49 — 1.67) Based on data from 921 participants in 4 studies. [3] (Observational (non-randomized))	48 per 1000 Difference:	43 per 1000 **5 fewer per 1000** (CI 95% 24 fewer — 30 more)	**Very low** Due to serious risk of bias, Due to serious imprecision [4]	The evidence is very uncertain about the effect of prothrombin complex concentrate on thromboembolic events in trauma patients with critical bleeding.
RBC transfusion volume	Measured by: Number of Units Lower better Based on data from 921 participants in 4 studies. [5] (Observational (non-randomized))	5.4 - 10 Units Difference:	3.2 - 7 Units **SMD 0.65 lower** (CI 95% 0.98 lower — 0.32 lower)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [6]	The use of prothrombin complex concentrate in trauma patients with critical bleeding may reduce the volume of RBCs transfused but the evidence is very uncertain.

Good practice statement

GPS5: The reference group agreed that it is good practice to administer blood components through a blood warming device whenever possible and aim to maintain the patient core temperature ≥ 35°C.

Rationale

Evidence regarding the warming of blood components was not evaluated, but guidance is provided for patient care.

Good practice statement

GPS6: The reference group agreed that it is good practice to administer group specific blood components as soon as possible.*

*refer to *ANZSBT Guidelines for transfusion and immunohaematology laboratory practice*

Rationale

RBC units contain negligible amounts of coagulation factors or platelets.

6.2 Blood conservation strategies

6.2.1 Recombinant activated factor VII

rFVIIa is indicated for the treatment or prevention of bleeding in patients with inhibitors to coagulation factors FVIII or FIX, congenital factor VII deficiency and Glanzmann's thrombasthenia.

Research question
In patients with critical bleeding, what is the effect of recombinant activated factor VII (rFVIIa) treatment on morbidity, mortality and transfusion rate?

Literature search date: 12 August 2019. Research in this area is not expected to substantially evolve so this question was retired in March 2021.

Weak recommendation against

R5: The reference group suggest against the use of rFVIIa in patients with critical bleeding*.

rFVIIa is approved in Australia and New Zealand for the control of bleeding and prophylaxis for surgery in patients with specific bleeding disorders. Use of rFVIIa outside these indications (including critical bleeding after trauma) is considered 'off-label' and is associated with harm.

Use of rFVIIa should only be considered in exceptional circumstance where all other available measures to control bleeding have been exhausted.

Evidence To Decision

Benefits and harms

There was no significant survival benefits observed in critically bleeding patients who received rFVIIa and evidence for

harms (thromboembolic events) was limited. In a large and comprehensive meta-analysis of placebo-controlled trials of rFVIIa, treatment with high doses of rFVIIa on an off-label basis significantly increased the risk of arterial but not venous thromboembolic events *[169]*.

Certainty of the Evidence

Very low

The overall certainty in effect estimates across outcomes was either very low (benefits) or low (harms).

Values and preferences

We expect few to want the intervention

The use of rFVIIa in patients with critical bleeding has been declining, and the urgency to address the 'off-label' use of this product has waned.

Resources

Important issues, or potential issues not investigated

The intervention is considered costly.

Equity

Important issues, or potential issues not investigated

While the intervention is considered costly, equity is unlikely to be impacted as there is no recommended change to current practice.

Acceptability

No important issues with the recommended alternative

While the intervention is considered costly, acceptability is unlikely to be impacted as there is no recommended change to current practice.

Feasibility

No important issues with the recommended alternative

While the intervention is considered costly, feasibility is unlikely to be impacted as there is no recommended change to current practice.

Rationale

The use of rFVIIa in patients with critical bleeding requiring a major haemorrhage protocol is not recommended because of its lack of effect on mortality and variable effect on morbidity. The ‘off-label’ use of rFVIIa in patients with critical bleeding has declined.

Clinical Question/ PICO

Population: People with critical bleeding, specifically those with ongoing bleeding who fail to achieve adequate haemostasis despite surgical management and appropriate blood component therapy (trauma setting)

Intervention: recombinant activated factor VII

Comparator: standard best practice care without rFVIIa

Summary

What did we find?

Three RCTs were found that examined the effect of rFVIIa in patients with critical bleeding after blunt or penetrating trauma *[24][60]*. There were high concerns of bias in all studies, with high threats to validity due to lack of details (selective reporting) *[24]* or unclear blinding of outcome assessment *[60]*, which may have favoured the intervention *[117]*.

Post-hoc analyses on the effect of rFVIIa on coagulopathic patients *[101]*, on trauma patients who survived the first 48 hours after randomisation *[23]*, and exploring the association between poorer outcomes and baseline haematologic and coagulation parameters *[82]* were also identified. As is extended safety data on patients enrolled in CONTROL *[41]*.

Study characteristics

Two parallel, double blind RCTs were run simultaneously that enrolled patients with haemorrhage from a blunt (Boffard 2005a) or penetrating (Boffard 2005b) traumatic injury requiring a least six unit of RBCs within four hours of hospitalisation and published in the one article *[24]*. The studies were sponsored by the manufacturer and enrolled 301 patients (143 blunt and 134 penetrating) from 32 centres across eight countries (including Australia, Canada, France, Germany, Israel, Singapore, South Africa and the UK). Both RCTs censored deaths that occurred within 48 hours (comprising nearly 20% of patients) as the primary outcomes were RBC transfusion needs during the 48-hour observation period, which indicates that some end-stage use of rFVIIa may have occurred. Mortality and morbidity (ARDS, TEs) were also reported, noting the studies were not powered to detect a difference in these outcomes.

The double blind RCT published by Hauser 2010 (CONTROL) enrolled patients with blunt or penetrating trauma who, despite strict damage control resuscitation and operative management had continued bleeding after receiving 4 units of RBC within 12 hours of injury *[60]*. The study was sponsored by the manufacturer and enrolled 573 patients (481 blunt and 92 penetrating) from 150 hospitals in 26 countries. Subgroup analyses on patients with blunt (Hauser 2010a) and penetrating (Hauser 2010b) trauma were also conducted. The aim of the study was to detect a 16.7% mortality reduction with rFVIIa, assuming a 30% mortality in placebo patients, however, the study was terminated early due to unexpectedly low mortality in the placebo group detected during planned interim futility analysis.

The three RCTs evaluated a total dose of 400 µg/kg intravenous rFVIIa administered in three doses (200 µg/kg at 0 hour, 100 µg/kg at 1 hour and 3 hours); which is higher than that reported among trauma patients in the Australian and New Zealand Haemostasis Registry, with 76% of patients (352/461) receiving only a single dose (median first dose of 95 µg/kg; IQR 80 to 108) *[137]*. Patients enrolled in Hauser 2010 received the first dose earlier during the resuscitation period (after the fourth unit of RBCs) and required participating hospitals to use a prespecified resuscitation protocol.

What are the main results?

Mortality

Among patients with blunt and penetrating trauma, a total of 409 patients received rFVIIa compared with 428 patients who did not, with no difference in mortality observed (16.6% vs 17.1%, RR 0.96; 95% CI 0.71, 1.29; $p = 0.71$; fixed effect, $I^2 = 0\%$).

Morbidity

Among patients with blunt and penetrating trauma who received rFVIIa, 10.8% (44/409) had a thromboembolic event compared with 10.0% (43/428) in the placebo group, corresponding to a nonsignificant difference between treatment groups (RR 1.10; 95% CI 0.74, 1.63; $p = 0.63$, fixed effect, $I^2 = 0\%$). Still, the evidence for thromboembolic events is limited with variance for methods for detection of thromboembolic event noted.

Transfusion volume

Among patients with blunt and penetrating trauma, a significant reduction in the volume of RBC transfused was observed among those who received rFVIIa compared with those who did not (MD −2.35; 95% CI −3.70, −1.00; $p = 0.0007$). It was noted that these data are confounded by the exclusion of trauma patients who died within 48 hours of admission to hospital.

Outcome Timeframe	**Study results and measurements**	**Comparator** standard best practice care without rFVIIa	**Intervention** recombinant activated factor VII	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint 9 Critical	Relative risk 0.96 (CI 95% 0.71 — 1.29) Based on data from 837 participants in 3 studies. [1] (Randomized controlled)	171 per 1000 Difference:	164 per 1000 **7 fewer per 1000** (CI 95% 50 fewer — 50 more)	**Low** Due to serious risk of bias, Due to serious imprecision [2]	The evidence suggests that the use of rFVIIa in patients with critical bleeding due to blunt or penetrating trauma may have little or no difference in mortality compared with placebo or no rFVIIa.
Morbidity, thromboembolic events 9 Critical	Relative risk 1.1 (CI 95% 0.74 — 1.63) Based on data from 837 participants in 3 studies. [3] (Randomized controlled)	100 per 1000 Difference:	110 per 1000 **10 more per 1000** (CI 95% 26 fewer — 63 more)	**Very low** Due to serious risk of bias, , Due to serious indirectness, Due to serious imprecision [4]	The use of rFVIIa in patients with critical bleeding due to blunt or penetrating trauma may have little or no difference on thromboembolic events compared with placebo but we are very uncertain about the evidence.
Morbidity, acute respiratory distress syndrome 9 Critical	Relative risk 0.39 (CI 95% 0.22 — 0.71) Based on data from 837 participants in 3 studies. [5] (Randomized controlled)	89 per 1000 Difference:	35 per 1000 **54 fewer per 1000** (CI 95% 69 fewer — 26 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision [6]	The evidence suggests rFVIIa may result in a slight reduction in ARDS in patients with critical bleeding due to blunt or penetrating trauma.
Morbidity, multiorgan failure 9 Critical	Relative risk 0.56 (CI 95% 0.32 — 0.97) Based on data from 837 participants in 3 studies. [7] (Randomized controlled)	79 per 1000 Difference:	44 per 1000 **35 fewer per 1000** (CI 95% 54 fewer — 2 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision [8]	The evidence suggests rFVIIa may result in a slight reduction in MOF in patients with critical bleeding due to blunt or penetrating trauma.
RBC transfusion volume from dosing to 48 hour	Measured by: Number of Units Lower better Based on data from 713 participants in 3 studies. [9] (Randomized controlled)	6.8 - 10.9 Units Difference:	4.5 - 7.8 Units **MD 2.35 fewer** (CI 95% 3.7 fewer — 1 fewer)	**Very low** Due to very serious risk of bias, Due to serious imprecision [10]	rFVIIa may slightly reduce the volume of RBCs transfused in patients with critical bleeding due to blunt or penetrating trauma, but we are very uncertain about the evidence.
Transfusion volume, other blood products	Based on data from 410 participants in 1 studies. [11] (Randomized controlled)	Fewer units of FFP were used in patients in the rFVIIa group compared with placebo (MD -2.14; 95% CI -3.54, -0.73), while no reduction in platelets, fibrinogen concentrate, or cryoprecipitate observed.		**Low** Due to serious risk of bias, Due to serious imprecision [12]	rFVIIa may slightly reduce the volume of FFP transfused, but not PLTs, FC, or CRYO, in patients with critical bleeding due to blunt or penetrating trauma, but we are very uncertain

Outcome Timeframe	Study results and measurements	Comparator standard best practice care without rFVIIa	Intervention recombinant activated factor VII	Certainty of the Evidence (Quality of evidence)	Plain language summary
					about the evidence.

Clinical Question/ PICO

Population: People with critical bleeding, specifically those with ongoing bleeding who fail to achieve adequate haemostasis despite surgical management and appropriate blood component therapy (medical emergency)

Intervention: recombinant activated factor VII

Comparator: standard best practice care without rFVIIa

Summary

What did we find?

Two RCTs *[25][26]* evaluated the therapeutic use of rFVIIa in the medical emergency setting, both of which were assessed to have some concerns of bias, predominantly due to lack of clear detail and poor reporting in the published reports *[117]*.

Study characteristics

The RCT reported by Bosch 2004 *[26]* was conducted in 245 cirrhotic patients with upper gastrointestinal bleeding (UGIB) enrolled from 26 centres in Europe. Subject were administered 100 µg/kg rFVIIa eights times *before* first endoscopy (t0), then at 2, 4, 6, 12, 18, 24, and 30 hours *after* endoscopy (total dose: 800 µg/kg total), with follow-up of patients occurring through to 42 days.

In the second RCT reported by Bosch 2008 *[25]*, 256 patients with advanced cirrhosis and active variceal bleeding were enrolled from 31 hospitals across Europe and Asia. Patients were randomised to receive 200 µg/kg rFVIIa initially as soon as possible *after* endoscopy, then either 4 x 100 µg/kg (total dose: 600 µg/kg) or a single 100 µg/kg (total dose: 300 µg/kg), or placebo; with the subsequent doses given at 2, 8, 14, and 20 hours after the first dose.

The primary outcome measures in both trials was a composite of failure to control UGIB within 24 hours after first dose, failure to prevent rebleeding between 24 hours and day 5, or death within 5 days. Outcomes of relevance for this review were transfusion requirements within 5 days (at discharge), and mortality and thromboembolic events recorded at latest follow-up.

In both trials, the total dose of rFVIIa was notably higher than that reported among patients with UGIB in the Australian and New Zealand Haemostasis Registry, with 74% of patients (140/189) receiving only a single dose (median first dose of 89 µg/kg; IQR 67 to 104) *[137]*.

What are the main results?

Mortality

Among patients with UGIB who received rFVIIa, the mortality rate of 19.2% (55/286) was not significantly different from the mortality rate of 17.5% (36/206) observed among those who did not receive rFVIIa. This corresponded to a RR of 1.02 (95% CI 0.55, 1.90; p = 0.95; random effects, I^2 = 56%).

Morbidity

Among patients with UGIB, the rate of thromboembolic events in patients who received rFVIIa was also not significantly different from those who did not (5.4% vs 6.6%, RR 0.80; 95% CI 0.40, 1.60, p = 0.54, fixed effect, I^2 = 0%).

Transfusion volumes

Among patients with UGIB who received rFVIIa, no difference in RBC transfusion volumes was observed when compared with those who did not receive rFVIIa (MD −0.24, 95% CI −1.17, 0.69; p = 0.61, I^2 = 62%).

Outcome Timeframe	**Study results and measurements**	**Comparator** standard best practice care without rFVIIa	**Intervention** recombinant activated factor VII	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint 9 Critical	Relative risk 1.02 (CI 95% 0.55 — 1.9) Based on data from 492 participants in 2 studies. [1] (Randomized controlled)	175 per 1000 Difference:	179 per 1000 **4 more per 1000** (CI 95% 79 fewer — 158 more)	**Very low** Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision [2]	rFVIIa may have little or no effect on mortality in patients with severe gastrointestinal bleeding but we are very uncertain about the evidence.
Morbidity, thromboembolic events 9 Critical	Relative risk 0.8 (CI 95% 0.4 — 1.6) Based on data from 507 participants in 2 studies. [3] (Randomized controlled)	67 per 1000 Difference:	54 per 1000 **13 fewer per 1000** (CI 95% 40 fewer — 40 more)	**Low** Due to serious indirectness, Due to serious imprecision [4]	The evidence suggests that the use of rFVIIa may have little or no difference on thromboembolic events in patients with severe gastrointestinal bleeding.
RBC transfusion volume	Measured by: Number of Units Lower better Based on data from 393 participants in 2 studies. [5] (Randomized controlled)	1.3 - 3.3 Units Difference:	1.5 - 2.55 Units **MD 0.24 fewer** (CI 95% 1.17 fewer — 0.69 more)	**Very low** Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision [6]	rFVIIa may have little to no effect on the volume of RBC transfused in patients with severe gastrointestinal bleeding but we are very uncertain about the evidence.

Clinical Question/ PICO

Population: People with critical bleeding, specifically those with ongoing bleeding who fail to achieve adequate haemostasis despite surgical management and appropriate blood component therapy (haematology/ oncology setting)

Intervention: recombinant activated factor VII

Comparator: standard best practice care without rFVIIa

Summary

What did we find?

One multicentre RCT evaluated the use of rFVIIa in 100 patients with moderate or severe bleeding complications following hematopoietic stem cell transplantation (+2 to +180 weeks post-transplant) *[96]*.

Study characteristics

Patients with bleeding (52 gastrointestinal; 26 haemorrhagic cystitis; seven pulmonary; one cerebral; 14 other) were randomised to receive seven doses of rFVIIa at 40, 80 or 160 µg/kg (total dose: 280, 560, or 1120 µg/kg) or placebo every six hours. The primary efficacy endpoint was the change in bleeding score between the first administration and 38 hours. The study was at high risk of bias due to baseline difference observed between treatment groups, suggesting randomisation or allocation concealment was compromised *[117]*.

One RCT conducted in 25 paediatric patients with active bleeding due to dengue fever was identified in the literature *[30]*. Patients were administered 100 µg/kg rFVIIa with repeat dose at 30 minutes if ongoing bleeding was observed. The study was small and not sufficiently powered to detect differences in any outcomes and was considered to be at high risk of bias *[117]*.

What are the main results?

Mortality
Among patients with uncontrolled bleeding due to other medical conditions (after HSCT, Dengue fever), the mortality rate was 25.8% (24/93) among those who received rFVIIa, compared with 21.9% (7/32) in those who did not, corresponding to a RR of 1.02 (95% CI 0.51, 2.07; *p* = 0.95; fixed effects, I^2 = not applicable [one study]) (GRADE: very low).

Morbidity
Among patients with uncontrolled bleeding after HSCT, the risk of thromboembolic events was higher in the group who received rFVIIa (8/93, 10.4%) compared with those who did not (0/23, 0%) (RR 5.23; 95% CI 0.31, 87.34; *p* = 0.25).

Transfusion volumes
The volume of RBC transfused was not reported in the RCT conducted in patients with uncontrolled bleeding after HCST. Among paediatric patients with dengue haemorrhagic fever, no difference in RBC transfusion volumes was observed between treatment groups (MD 0.10, 95% CI −1.24, 1.44; *p* = 0.88).

Outcome Timeframe	**Study results and measurements**	**Comparator** standard best practice care without rFVIIa	**Intervention** recombinant activated factor VII	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint 9 Critical	Relative risk 1.02 (CI 95% 0.51 — 2.07) Based on data from 125 participants in 2 studies. [1] (Randomized controlled)	219 per 1000 Difference:	223 per 1000 **4 more per 1000** (CI 95% 107 fewer — 234 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness [2]	The use of rFVIIa in patients with critical bleeding after HSCT may result in little or no difference in mortality but we are very uncertain about the evidence.
Morbidity, thromboembolic events 9 Critical	Relative risk 5.23 (CI 95% 0.31 — 87.34) Based on data from 125 participants in 2 studies. [3] (Randomized controlled)	0 per 1000 Difference:	0 per 1000 **0 fewer per 1000** (CI 95% 0 fewer — 0 fewer)	Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision [4]	rFVIIa may result in a slight increase in thromboembolic events in patient with critical bleeding after HSCT but we are very uncertain about the evidence.
RBC transfusion volume		No studies reported this outcome			The effect of rFVIIa on RBC transfusion volume in patients with critical bleeding after HSCT is unknown.

Clinical Question/ PICO

Population: People with critical bleeding, specifically those with ongoing bleeding who fail to achieve adequate haemostasis despite surgical management and appropriate blood component therapy (cardiac setting)
Intervention: recombinant activated factor VII
Comparator: standard best practice care without rFVIIa

Summary

What did we find?

One small Phase II dose-escalation study conducted in 13 countries in Africa, Asia, Europe, South America and US was identified that evaluated the therapeutic use of rFVIIa in patients with intractable bleeding after cardiac surgery *[51]*.

Study characteristics

Patients were randomised to receive either 40 µg/kg (n= 35) or 80 µg/kg (n=69) rFVIIa or placebo (n=68) after cardiopulmonary bypass (CPB) as treatment for excessive post-operative bleeding in the ICU. The trial was terminated in November 2007 without proceeding to the highest dosing cohort (160 µg/kg) as it was determined to no longer reflect common clinical practice. The primary outcome was the incidence of critical serious adverse events at 30 days. The study was assessed to be at overall low to unclear risk of bias *[117]*.

What are the main results?

Mortality

Among patients with intractable bleeding after cardiac surgery, the mortality rate among those who received rFVIIa (9.6%) was higher than that observed among those who did not receive rFVIIa (5.9%). This difference was not significant (RR 1.63; 95% CI 0.53, 5.00; p = 0.95; fixed effects, I^2 = not applicable [one study]). It was noted the mortality rate among patients administered 40 and 80 µg/kg rFVIIa was 11.4% (4/35) and 8.7% (6/69), respectively.

Morbidity

Among patients with uncontrolled bleeding due after cardiac surgery, the risk of thromboembolic events was higher in the group who received rFVIIa (7/104, 6.7%) compared with those who did not (1/68, 1.5%). The difference was not significant (RR 4.58; 95% CI 0.58, 36.38; p = 0.15), noting the study was not large enough to detect important differences.

Transfusion volumes

The volume of RBC transfused was not reported in the RCT conducted in patients with intractable bleeding after cardiac surgery.

Outcome Timeframe	**Study results and measurements**	**Comparator** standard best practice care without rFVIIa	**Intervention** recombinant activated factor VII	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint 9 Critical	Relative risk 1.63 (CI 95% 0.53 — 5) Based on data from 172 participants in 1 studies. [1] (Randomized controlled)	**59** per 1000 Difference:	**96** per 1000 **37 more per 1000** (CI 95% 28 fewer — 236 more)	**Low** Due to very serious imprecision [2]	The evidence suggests that the use of rFVIIa in patients with critical bleeding after cardiac surgery results in little to no difference in mortality compared with no rFVIIa
Morbidity, thromboembolic events 9 Critical	Relative risk 4.58 (CI 95% 0.58 — 36.38) Based on data from 172 participants in 1 studies. [3] (Randomized controlled)	**15** per 1000 Difference:	**69** per 1000 **54 more per 1000** (CI 95% 6 fewer — 531 more)	**Low** Due to very serious imprecision [4]	The evidence suggests rFVIIa results in a slight increase in thromboembolic events in patient with critical bleeding after cardiac surgery.
RBC transfusion volume		No studies reported this outcome			The effect of rFVIIa on RBC transfusion volume in patients admitted to intensive care with

Outcome Timeframe	**Study results and measurements**	**Comparator** standard best practice care without rFVIIa	**Intervention** recombinant activated factor VII	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
					intractable bleeding after cardiac surgery is unknown.

6.2.2 Antifibrinolytics

Antifibrinolytics include tranexamic acid, aprotinin*, or 6-aminocaproic acid (EACA)^. The focus of this review was on tranexamic acid. Tranexamic acid acts as an antifibrinolytic by competitively inhibiting the activation of plasminogen to plasmin, a molecule responsible for the degradation of fibrin.

Research question
In patients with critical bleeding, what is the effect of antifibrinolytics on blood loss, RBC transfusion and patient outcomes?

Latest search date: 29 September 2021

*Aprotinin is on the Australian Register of Therapeutic Goods but is not being supplied or marketed by an Australian sponsor.

^EACA is not available or registered for use in Australia.

Weak recommendation

R6: In trauma patients with critical bleeding, the reference group suggest the early use (within 3 hours of injury) of tranexamic acid as part of a major haemorrhage protocol.

Practical Info

A commonly used dose in clinical trials involving trauma patients is 1g tranexamic bolus over 10 minutes and consideration of subsequent 1 g infusion over 8 hours.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

The evidence suggests tranexamic acid may provide a small benefit. The effects on harms are uncertain.

Certainty of the Evidence

Very low

The overall certainty in effect estimates across outcomes was either very low (benefits) or low (harms).

Values and preferences

No substantial variability expected

There is no plausible reason to suspect that patients who are critically bleeding would not accept tranexamic acid as recommended.

Resources

No important issues with the recommended alternative

While tranexamic acid is not funded under the national blood arrangements, the reference group did not expect its recommended use to have a significant impact on resources.

Equity

No important issues with the recommended alternative

Equity of implementation was not investigated but was not considered to be an issue.

Acceptability

No important issues with the recommended alternative

The acceptability of implementation was not investigated but was not considered to be an issue.

Feasibility

No important issues with the recommended alternative

Feasibility of implementation was not investigated but was not considered to be an issue.

Rationale

The CRASH-2 trial supported the use of tranexamic acid in trauma patients, however the evidence is not directly generalisable to the Australian and New Zealand settings where there are advanced trauma centres *[227]*.

The results of the PATCH-Trauma Study were not included in the evidence base as it was completed after the literature search cut-off date.

Clinical Question/ PICO

Population: People with critical bleeding (trauma setting)
Intervention: Antifibrinolytics
Comparator: Placebo or no antifibrinolytics

Summary

What did we find?

Three RCTs (Guyette 2020, Kakaei 2017, CRASH-2) were found that examined the effect of TXA in civilian trauma patients with critical bleeding. The key risk of bias concerns with the largest study (CRASH-2) (contributes more than 97% of the data) included reporting bias (no systematic adverse event reporting, making it difficult to interpret results relating to thrombotic risk, and reporting of blood loss and injury severity), and potential for confounding and measurement error (few patients came from countries with early access to blood products or availability of state-of-the-art trauma care).

There were 16 included cohort studies that examined the effect of TXA in patients with critical bleeding after trauma (mixed combat and civilian trauma, including one paediatric trauma). All had concerns of bias relating to confounding (related to the co-administration of other products) and patient selection bias. There was also concerns for reporting bias with a lack of detail regarding injury severity, and protocols for adverse event reporting.

Study characteristics

CRASH-2 was a large multicentre study that enrolled over 20 000 patients from over 40 countries. Participants had to be classified as being at risk of significant bleeding, in addition to being diagnosed with major haemorrhage. Enrolled participants had a wide range of injury severities, with less than 50% of participants receiving a blood transfusion or requiring surgery.

Guyette 2020 was a multicentre RCT conducted in the US that assessed prehospital administration of TXA in injured patients with hypotension (systolic blood pressure ≤ 90 mmHg) or tachycardia (heart rate ≥ 110/min) before arrival at a level 1 trauma centers.

Kakaei 2017 was a small, single centre study conducted in Iran that enrolled civilian trauma patients with potentially

life-threatening injuries or evidence of critical illness (which could include respiratory and cardiac arrest).

In all studies, participants were typically administered a loading dose of 1 g TXA as soon possible, followed by a maintenance dose of 1 g TXA over eight hours.

What are the main results?

Mortality
The RCT evidence showed a slight decrease in the risk of mortality (latest timepoint) among trauma patients who received TXA (1503/10 537, 14.26%) compared with those who did not 1660/10 550, 15.73%) (RR 0.91; 95% CI 0.85, 0.97; p = 0.003; random effect, I^2 = 0%) *(GRADE: Low)*.

Among the cohort studies, the risk of mortality was not different between groups (19.4% vs 17.26%, RR 0.97; 95%CI 0.75, 1.25; p = 0.80, I^2 = 90%) *(GRADE: Very low)*. Noting there was substantial heterogeneity with a wide variety of injury severity and bleeding risk in the included studies, with the results likely to differ after adjustments for confounders across all studies (e.g., patients who received TXA had higher incidence of shock, blood loss, or transfusion requirements).

Morbidity
The RCT evidence (CRASH-2) suggested there was little to no difference on the incidence of vascular events in trauma patients who received TXA (168/10 060, 1.67%) compared with those who did not receive TXA (201/ 10 067, 1.99%) (RR 0.84, 95% CI 0.68, 1.02; p = 0.08; random effect) (*GRADE: very low*).

Among the cohort studies, the risk of vascular events was higher among those who received TXA (106/1801, 5.89%) compared with those who did not receive TXA (122/ 3157, 3.86%) (RR 1.63; 95%CI 1.17, 2.29; p = 0.23, I^2 = 23%) *(GRADE: Very low)*. Noting there was a wide variety of injury severity and bleeding risk in the included studies, with the likelihood a missing data relating to inconsistencies in the measurement of the outcome.

Transfusion volumes
The RCT evidence in critically bleeding trauma patients (CRASH-2) suggested there was little to no difference on the volume of RBCs transfused in patients who received TXA (mean 6.06 units) compared with those who did not receive TXA (mean 6.29 units) (SMD −0.02, 95%CI −0.02, 0.02; p = 0.25; random effect) (*GRADE: low*).

Among the cohort studies that reported data, the volume of RBCs transfused was higher among patients who received TXA (range 4.42 units to 22 units) compared with those who did not receive TXA (range 2 to 16 units) (SMD 0.53; 95%CI 0.22, 0.85; p = 0.001, I^2 = 90%) *(GRADE: Very low)*. Noting there was substantial heterogeneity with a wide variety of injury severity and bleeding risk in the included studies, with the results likely to differ after adjustments for confounders across all studies (e.g., patients who received TXA had higher incidence of shock, blood loss, and transfusion needs).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or no antifibrinolytics	**Intervention** Antifibrinolytics	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (RCTs) [1] latest reported timepoint 9 Critical	Relative risk 0.91 (CI 95% 0.85 — 0.97) Based on data from 21,087 participants in 3 studies. [2] (Randomized controlled)	**157** per 1000 Difference:	**143** per 1000 **14 fewer per 1000** (CI 95% 24 fewer — 5 fewer)	**Low** Due to very serious indirectness [3]	The evidence suggests antifibrinolytics may slightly reduce mortality in trauma patients with critical bleeding.
Mortality, all cause (Coh) [4] latest reported timepoint 9 Critical	Relative risk 0.97 (CI 95% 0.75 — 1.25) Based on data from 11,369 participants in 15 studies. [5] (Observational (non-randomized))	**144** per 1000 Difference:	**140** per 1000 **4 fewer per 1000** (CI 95% 36 fewer — 36 more)	**Very low** Due to very serious risk of bias, Due to serious inconsistency, Due to serious	We are very uncertain about the association of antifibrinolytics on all-cause mortality in trauma patients with critical bleeding.

Outcome Timeframe	Study results and measurements	Comparator Placebo or no antifibrinolytics	Intervention Antifibrinolytics	Certainty of the Evidence (Quality of evidence)	Plain language summary
				indirectness, Due to serious imprecision [6]	
Morbidity, thromboembolic event (RCTs) 9 Critical	Relative risk 0.84 (CI 95% 0.68 — 1.02) Based on data from 20,127 participants in 1 studies. [7] (Randomized controlled)	**20** per 1000 Difference:	**17** per 1000 **3 fewer per 1000** (CI 95% 6 fewer — 0 fewer)	**Very low** Due to very serious indirectness, Due to serious imprecision [8]	Antifibrinolytics appear to have little to no effect on vascular (thromboembolic) events, but we are very uncertain about the evidence.
Morbidity, thromboembolic events (Coh) 9 Critical	Relative risk 1.63 (CI 95% 1.17 — 2.29) Based on data from 4,958 participants in 10 studies. [9] (Observational (non-randomized))	**39** per 1000 Difference:	**64** per 1000 **25 more per 1000** (CI 95% 7 more — 50 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision, Due to serious inconsistency [10]	We are very uncertain about the association of antifibrinolytics on thromboembolic events in trauma patients with critical bleeding.
RBC transfusion volume (RCTs)	Measured by: Number of Units Lower better Based on data from 10,227 participants in 1 studies. [11] (Randomized controlled)	**6.29** Units (Mean) Difference:	**6.06** Units (Mean) **SMD 0.02 fewer** (CI 95% 0.06 fewer — 0.02 more)	**Low** Due to very serious indirectness [12]	The evidence suggests that antifibrinolytics may have little or no difference on the volume of RBCs transfused in trauma patients with critical bleeding.
RBC transfusion volume (Coh)	Measured by: Number of Units Lower better Based on data from 2,095 participants in 4 studies. [13] (Observational (non-randomized))	**2 - 20.1** Units Difference:	**4.43 - 22** Units **SMD 0.53 more** (CI 95% 0.22 more — 0.85 more)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision [14]	We are very uncertain about the association of antifibrinolytics on the volume of RBCs transfused in trauma patients with critical bleeding.

Weak recommendation

R7: In obstetric patients with critical bleeding, the early use (within 3 hours of the onset of haemorrhage) of tranexamic acid may be considered as part of a major haemorrhage protocol.

Practical Info

A commonly used dose in clinical trials involving obstetric patients is 1g tranexamic bolus over 10 minutes and a second 1g dose after 30 minutes if bleeding continued.

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

An assessment of harms is difficult due to the underlying low number of women who have died from postpartum haemorrhage (PPH) in Australia. In 2018, there were 15 maternal deaths in Australia. Only one was attributable to bleeding (AIHW 2020).

Certainty of the Evidence

Very low

The overall certainty in effect estimates across outcomes was either very low (benefits) or low (harms).

Values and preferences

No substantial variability expected

There is no plausible reason to suspect that maternity patients who are critically bleeding would not accept tranexamic acid as recommended.

Resources

No important issues with the recommended alternative

While tranexamic acid is not funded under the national blood arrangements, the reference group did not expect its recommended use to have a significant impact on resources.

Equity

No important issues with the recommended alternative

Equity of implementation was not investigated but was not considered to be an issue.

Acceptability

No important issues with the recommended alternative

The acceptability of implementation was not investigated but was not considered to be an issue.

Feasibility

No important issues with the recommended alternative

Feasibility of implementation was not investigated but was not considered to be an issue.

Rationale

The WOMAN trial supported the use of tranexamic acid in critically bleeding obstetric patients, but no difference was observed for the primary outcome of hospital mortality *[228]*.

Clinical Question/ PICO

Population: People with critical bleeding (obstetrics and maternity)
Intervention: Antifibrinolytics
Comparator: Placebo or no antifibrinolytics

Summary

What did we find?

Two RCTs (Ducloy-Bouthors 2011, WOMAN) assessed the safety and effectiveness of TXA given to women with primary postpartum haemorrhage (PPH).

Study characteristics

The largest study (WOMAN) enrolled ~20,000 women aged 16 years or older with clinically diagnosed PPH (estimated blood loss after vaginal birth > 500 mL, or > 1000 mL after caesarean section or estimated blood loss enough to compromise the haemodynamic status of the woman). Participants were typically administered a loading dose of 1 g TXA as soon possible after randomisation, and if bleeding continued after 30 minutes, or stopped and restarted within 24 hours after first dose, a second dose could be given. Approximately 50% of participants had an estimated volume of blood loss less than 1000 mL and 41% had no clinical signs of haemodynamic instability. Around 54% of women received a blood product. There was no systematic adverse event reporting, making it difficult to interpret results relating to thrombotic risk and blood loss.

What are the main results?

Mortality
The RCT evidence (see Figure 4.45) suggested the mortality rate among women who received TXA (227/10 111, 2.2%) was comparable to the mortality rate among women who did not receive TXA (255/10 051, 2.5%). This corresponded to a RR of 0.89 (95% CI 0.74, 1.06; *p* = 0.18; random effect, I^2 = not applicable) *(GRADE: Low)*.

Morbidity
The RCT evidence (WOMAN) suggested there was little to no difference on the incidence of vascular events in women with major obstetric haemorrhage who received TXA (31/10 034, 0.31%) compared with those who did not receive TXA (34/ 9977, 0.34%) (RR 0.91, 95% CI 0.56, 1.47; *p* = 0.69; random effect) (*GRADE: very low*).

There was also no difference between women with major obstetric haemorrhage who received TXA compared with those who did not for the outcomes of multiple organ failure (RR 0.94, 95% CI 0.71, 1.23; *p* = 0.65; random effect), respiratory failure (RR 0.87, 95% CI 0.67, 1.12; *p* = 0.27; random effect), or renal failure (RR 1.09; 95% CI 0.85, 1.39; *p* = 0.51; random effect) (*GRADE: very low*).

Outcome Timeframe	**Study results and measurements**	**Comparator** Placebo or no antifibrinolytics	**Intervention** Antifibrinolytics	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint 9 Critical	Relative risk 0.89 (CI 95% 0.74 — 1.06) Based on data from 20,011 participants in 2 studies. [1] (Randomized controlled)	25 per 1000 Difference:	22 per 1000 **3 fewer per 1000** (CI 95% 6 fewer — 2 more)	**Low** Due to very serious indirectness [2]	The evidence suggests that antifibrinolytics may have no difference on all-cause mortality in women with major obstetric haemorrhage
Morbidity, thromboembolic events 9 Critical	Relative risk 0.91 (CI 95% 0.56 — 1.47) Based on data from 20,011 participants in 1 studies. [3] (Randomized controlled)	3 per 1000 Difference:	3 per 1000 **0 fewer per 1000** (CI 95% 1 fewer — 1 more)	**Very low** Due to very serious indirectness, Due to serious imprecision [4]	Antifibrinolytics may have little or no effect on thromboembolic events in women with major obstetric haemorrhage but the evidence is very uncertain.
Morbidity, multiple organ failure 9 Critical	Relative risk 0.94 (CI 95% 0.71 — 1.23) Based on data from 20,168 participants in 2 studies. [5] (Randomized controlled)	10 per 1000 Difference:	9 per 1000 **1 fewer per 1000** (CI 95% 3 fewer — 2 more)	**Very low** Due to very serious indirectness, Due to serious imprecision [6]	Antifibrinolytics may have little or no effect on multiple organ failure in women with major obstetric haemorrhage but the evidence is very uncertain.
Morbidity,	Relative risk 0.87	12	10	**Very low**	Antifibrinolytics may

Outcome Timeframe	Study results and measurements	Comparator Placebo or no antifibrinolytics	Intervention Antifibrinolytics	Certainty of the Evidence (Quality of evidence)	Plain language summary
respiratory failure 9 Critical	(CI 95% 0.67 — 1.12) Based on data from 20,018 participants in 1 studies. [7] (Randomized controlled)	per 1000 Difference:	per 1000 **2 fewer per 1000** (CI 95% 4 fewer — 1 more)	Due to very serious indirectness, Due to serious imprecision [8]	have little or no effect on respiratory failure in women with major obstetric haemorrhage but the evidence is very uncertain.
Morbidity, renal failure 9 Critical	Relative risk 1.09 (CI 95% 0.85 — 1.39) Based on data from 20,169 participants in 2 studies. [9] (Randomized controlled)	12 per 1000 Difference:	13 per 1000 **1 more per 1000** (CI 95% 2 fewer — 5 more)	Very low Due to very serious indirectness, Due to serious imprecision [10]	Antifibrinolytics may have little or no effect on renal failure in women with major obstetric haemorrhage but the evidence is very uncertain.
RBC transfusion volume	Based on data from 20,060 participants in 1 studies. (Randomized controlled)	The mean number of blood units transfused did not differ significantly between patients in the tranexamic and placebo groups, but data were not provided.		Very low Due to very serious indirectness, Due to serious imprecision [11]	Antifibrinolytics may have little or no effect on the volume of RBCs transfused in women with major obstetric haemorrhage but the evidence is very uncertain.

6.2.3 Viscoelastic haemostatic assays

VHAs are whole blood tests designed to provide a functional assessment of clot formation, clot strength and degradation. VHAs can be used in patients with critical bleeding to detect coagulopathy and guide blood component therapy as part of a major haemorrhage protocol.

Research question
In patients with critical bleeding, does the use of viscoelastic haemostatic assays (VHAs) change patient outcomes?

Latest search date: 29 September 2021

Good practice statement

GPS7: The reference group agreed that the use of viscoelastic haemostatic assays* may be beneficial in patients with critical bleeding. There is insufficient evidence to provide a recommendation.

If viscoelastic haemostatic assays are used in the assessment of patients with critical bleeding they must be used in conjunction with a major haemorrhage protocol.

**Interpretation of results requires specific expertise and training.*

Evidence To Decision

Benefits and harms

Substantial net benefits of the recommended alternative

In the meta-analysis of randomised controlled trials a large effect on mortality was demonstrated. In the meta-analysis of observational cohort studies a moderate effect on mortality was demonstrated, however, the certainty of the evidence was very low. Based on the available evidence the true benefit is unknown.

Certainty of the Evidence

Very low

The overall certainty in effect estimates across outcomes was either very low (benefits) or low (harms).

Values and preferences

No substantial variability expected

There is no plausible reason to suspect that patients who are critically bleeding would not accept viscoelastic haemostatic assays as part of a major haemorrhage protocol as recommended in this guideline.

Resources

Important negative issues

The reference group acknowledged there are significant additional resources associated with the implementation and use of viscoelastic haemostatic assays as part of a major haemorrhage protocol.

Equity

Important issues, or potential issues not investigated

The reference group acknowledged that there is jurisdictional, geographical and/or institutional variability in the availability of viscoelastic haemostatic assays as part of a major haemorrhage protocol.

Acceptability

Important issues, or potential issues not investigated

The reference group acknowledged that there may be jurisdictional, geographical and/or institutional variability in acceptability of viscoelastic haemostatic assays as part of a major haemorrhage protocol.

Feasibility

Important issues, or potential issues not investigated

The reference group acknowledged that there may be jurisdictional, geographical and/or institutional variability in implementing viscoelastic haemostatic assays as part of a major haemorrhage protocol.

Rationale

VHAs may be used as part of a major haemorrhage protocol in critically bleeding patients. However, there is insufficient evidence to support a recommendation. In addition to the certainty of evidence, the reference group considered the onset costs, logistical challenges, and jurisdictional, geographic and institutional variability associated with providing VHAs with an MHP. The reference group anticipates minimal variation in patient preferences for this intervention.

Implementation

Expertise is required to undertake and interpret the test.

Research Needs

Further well designed RCTs are required to confirm potential benefits associated with VHAs.

Clinical Question/ PICO

Population: People with critical bleeding (any setting)
Intervention: Viscoelastic haemostatic assays
Comparator: Standard best practice care (blood component therapy guided by MTP protocol or standard laboratory tests)

Summary

What did we find?

There were seven RCTs identified that examined the effects of TEG or ROTEM in patients *with* critical bleeding. Two of the included studies used a TEG-guided transfusion algorithm *[54][92]*, four studies *[71][131][88][94]* used a ROTEM-guided transfusion algorithm, and one multicenter RCT (ITACTIC) *[170]* examined the effect of TEG or ROTEM.

There were also 15 nonrandomised cohort studies that examined the effects of TEG or ROTEM in guiding blood component therapy in patients *with* critical bleeding and were considered relevant to this review. Six of the included cohort studies used a TEG-guided transfusion algorithm (Guth 2019, Unruh 2019, Wang 2017, Barinov 2015, Tapia 2013, Kashuk 2012), and nine studies (McNamara 2019, Snegovskikh 2018, Prat 2017, Nardi 2015, Fassl 2013, Görlinger 2012, Hanke 2012, Nienaber 2011, Schöchl 2011) used a ROTEM-guided transfusion algorithm.

Study characteristics

The overall risk of bias for included RCTs was judged to be high. Most concerns were related to little or no allocation concealment or blinding of clinical personnel, which contributed to the high procedural bias favouring the intervention. Reporting bias was also considered high for blood loss, FFP transfusion and PLT transfusion due to incomplete reporting of outcome data, with no explanations given for missing data.

Three RCTs were stopped early. One (Paniagua 2011) was terminated early due to slow recruitment and included eight of 52 patients that did not meet the inclusion criteria. One (Weber 2012) was stopped at an interim analysis due to clear benefits, and another study (NCT00772239) was stopped early due to futility (no data available).

Many of the included observational cohort studies were at serious risk of bias. This is because they were often conducted before and after the introduction of the intervention into clinical practice, introducing concerns with procedural bias that would favour the intervention. The use of historical controls introduces issued with changes in clinical practices that occur over time. The studies also had issues with incomplete report of outcome data, short follow-up, and small sample size.

What are the main results?

Mortality

The use of viscoelastic tests to guide blood component therapy may provide a small survival benefit in patients with coagulopathy or critical bleeding at study inclusion (regardless of clinical setting).

Pooled data including both RCT and cohort studies showed the mortality rate (latest timepoint) among patients who are critically bleeding to be lower when blood component therapy was guided by TEG or ROTEM compared with haemostatic management guided by an MHP or standard laboratory tests (16.2% vs 18.9%; RR 0.75; 95% CI 0.64, 0.88; p = 0.004; random effect, I^2 = 0%).

Data from the included RCTs suggested the mortality rate to be lower in the TEG or ROTEM groups (19.8%) when compared with management that was not guided by a viscoelastic haemostatic assay (28.1%) (RR 0.61; 95% CI 0.37, 1.02; p = 0.06; random effect, I^2 = 44%). The difference did not reach statistically significance but was considered clinically important.

Data from the included cohort studies, suggested that TEG or ROTEM guided protocols were associated with reduced mortality compared with haemostatic management not guided by TEG or ROTEM (RR 0.75; 95% CI 0.62, 0.94; p = 0.004; I^2 = 0%).

Morbidity

In a meta-analysis of data from the included RCTs, the rate of thromboembolic events in patients with critical bleeding who received blood component therapy guided by TEG or ROTEM was 7.2% (24/333) compared with 9.4% (30/318) among patients in the comparator group. This corresponds to a nonsignificant difference between treatment groups (RR 0.83; 95% CI 0.41, 1.66; p = 0.60, I^2= 26%).

RBC transfusion volumes

Available data from the RCTs included in this review suggested that the volume of RBCs transfused was not different between patients who received blood component therapy guided by TEG or ROTEM (n=81) compared with those

who received treatment guided by an MHP or standard laboratory tests (n=72) (SMD −0.06; 95% CI −0.38, 0.26; p = 0.73, I^2= 0%). Data from two studies were not able to be included in the analysis (both suggested an effect favouring TEG or ROTEM).

Among the included observational cohort studies, a statistically significant reduction in the volume of RBC transfused was observed between patients who received blood component therapy guided by TEG or ROTEM (n=588) compared with those who received treatment guided by an MHP or standard laboratory tests (n=1017) (SMD −0.46; 95% CI -0.92, -0.28; p = 0.0005; I^2= 78%).

Transfusion volumes, other blood products
Available data from the RCTs suggested that the volume of FFP transfused was not different between groups (SMD 0.02; 95% CI −0.30, 0.33; p = 0.93; I^2= 0%) but data were not able to be included for two studies that suggested an effect favouring TEG or ROTEM. Among the included observational cohort studies, a statistically significant reduction in the volume of FFP transfused was observed between patients who received blood component therapy guided by TEG or ROTEM (n=513) compared with those who received treatment guided by an MHP or standard laboratory tests (n=500) (SMD −0.82; 95% CI −1.51, −0.12; p = 0.02; I^2= 96%).

Available data from the RCTs suggested that the volume of PLTs transfused was not different between groups (SMD 0.02; 95% CI −0.59, 0.64; p = 0.94; I^2 = 65%) but data were not able to be included for two studies that suggested an effect favouring TEG or ROTEM. Among the observational cohort studies, the available data suggested there a non-significant reduction in the volume of PLTs transfused (around 1 unit saved) among patients who received blood component therapy guided by TEG or ROTEM (n=284) compared with those who received treatment guided by an MHP or standard laboratory tests (n=284) (SMD −0.31; 95% CI −0.64, 0.03; p = 0.07; I^2= 96%).

Outcome Timeframe	**Study results and measurements**	**Comparator** standard best practice care	**Intervention** Viscoelastic haemostatic assays	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (RCTs) [1] latest reported timepoint 9 Critical	Relative risk 0.61 (CI 95% 0.37 — 1.02) Based on data from 650 participants in 4 studies. [2] (Randomized controlled)	**281** per 1000 Difference:	**171** per 1000 **110 fewer per 1000** (CI 95% 177 fewer — 6 more)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [3]	The use of TEG or ROTEM to guide blood component therapy may reduce mortality in patients with critical bleeding (any setting) but the evidence is very uncertain.
Mortality, all cause (Coh) latest reported timepoint 9 Critical	Relative risk 0.75 (CI 95% 0.62 — 0.92) Based on data from 2,175 participants in 9 studies. [4] (Observational (non-randomized))	**166** per 1000 Difference:	**125** per 1000 **41 fewer per 1000** (CI 95% 63 fewer — 13 fewer)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [5]	The use of TEG or ROTEM to guide blood component therapy may be associated with reduced mortality in patients with critical bleeding (any setting) but the evidence is very uncertain.
Morbidity, thromboembolic events 9 Critical	Relative risk 0.83 (CI 95% 0.41 — 1.66) Based on data from 651 participants in 4 studies. [6] (Randomized controlled)	**91** per 1000 Difference:	**76** per 1000 **15 fewer per 1000** (CI 95% 54 fewer — 60 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias [7]	The use of TEG or ROTEM to guide blood component therapy may have no difference on thromboembolic events in patients with critical bleeding (any setting) but the evidence is very uncertain.

Outcome Timeframe	**Study results and measurements**	**Comparator** standard best practice care	**Intervention** Viscoelastic haemostatic assays	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
RBC transfusion volume (RCTs)	Measured by: Number of Units Lower better Based on data from 153 participants in 2 studies. [8] (Randomized controlled)	6.42 - 15.65 Units Difference:	7.1 - 13.96 Units **SMD 0.06 fewer** (CI 95% 0.38 fewer — 0.26 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias [9]	The evidence suggests use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding (any setting) may have little or no difference in the volume of RBCs transfused.
RBC transfusion volume (Coh)	Measured by: Number of Units Lower better Based on data from 1,605 participants in 7 studies. [10] (Observational (non-randomized))	2 - 11 Units Difference:	2 - 6.5 Units **SMD 0.46 fewer** (CI 95% 0.72 fewer — 0.2 fewer)	**Very low** Due to serious risk of bias, Due to serious inconsistency [11]	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding (any setting) may be associated with a slight reduction in the volume of RBCs transfused but the evidence is very uncertain.
Transfusion volume, other blood components	[12] (Observational (non-randomized))	The use of TEG or ROTEM did not demonstrate a statistically significant reduction the volume of FFP or PLTs transfused across patients in trauma, cardiothoracic or obstetrics settings. There was little evidence reported relating to fibrinogen replacement therapy.		**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency [13]	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding (any setting) may be associated with little or no difference in the volume of FFP or PLTs transfused but the evidence is very uncertain.

Clinical Question/ PICO

Population: People with critical bleeding (trauma setting)

Intervention: Viscoelastic haemostatic assays

Comparator: Standard best practice care (blood component therapy guided by MTP protocol or standard laboratory tests)

Summary

What did we find?

There were two RCTs identified in the trauma setting that examined the effects of TEG or ROTEM in patients *with* critical bleeding. One of the included studies used a TEG-guided transfusion algorithm *[54]* and one multicenter RCT (iTACTIC) examined the effect of haemorrhage protocols that included either TEG or ROTEM.

There were also 10 nonrandomised cohort studies that examined the effects of TEG or ROTEM in guiding blood component therapy in trauma patients *with* critical bleeding and were considered relevant to this review. Five used a TEG-guided transfusion algorithm (Guth 2019, Unruh 2019, Wang 2017, Tapia 2013, Kashuk 2012) and five used a ROTEM-guided transfusion algorithm (Prat 2017, Nardi 2015, Gorlinger 2012, Nienaber 2011, Schöchl 2011)

Study characteristics

Baksaas-Aasen 2020 (iTACTIC) was a multi-centre RCT conducted in Trauma centres located in Denmark, The Netherlands, Norway, Germany and the UK. The study focused on trauma-induced coagulopathy comparing outcomes in 396 patients in whom a local MHP had been initiated, with RBC transfusion guided by VHAs or CCTs. The MHPs included empiric delivery of tranexamic acid, blood components delivered in a 1:1:1 ratio of RBCs, plasma and platelet transfusions and limited infusion of crystalloid fluids.

Gonzalez 2016 was a single centre RCT conducted in the US that enrolled adults patients (aged >18 yrs) with blunt or penetrating trauma sustained less than 6 hours before admission. Patients had to have an injury severity score greater than 15 and were likely to require transfusion of RBC within 6 hours from admission as indicated by clinical assessment. Patients were predominantly male (70.3%0 with a median (IQR) age of 30 (24 to 43). The number of patients with blunt / penetrating trauma was not reported.

Among the cohort studies, five were conducted at single centres (Guth 2019, Wang 2017, Tapia 2013, Görlinger 2012, Kashuk 2012) and involved adult trauma patients (blunt and/or penetrating) with various definitions for injury severity and the timing or need for blood components (i.e., within 6 or 24 hours of admission). Five studies (Unruh 2019 Prat 2017 Nardi 2015 Nienaber 2011 Schöchl 2011) involved the collection of data from trauma registries (civilian and/or combat), with patients being selected based on injury severity (e.g., ISS ≥ 16, base deficit ≥ 2.0 mmol/L) or the need for blood components (e.g., receiving at least 3 units of pRBC within the first 24 hours).

What are the main results?

Mortality

Among trauma patients, the RCT evidence showed the mortality rate (latest timepoint) to be lower when blood component therapy was guided by TEG or ROTEM (23.7%) compared with haemostatic management guided by an MHP or standard laboratory tests (30.1%). The difference, although not statistically significant, was considered clinically important (RR 0.75; 95% CI 0.48, 1.17; p = 0.20; I^2=44%).

Evidence in the cohort studies suggests blood component therapy guided by TEG or ROTEM is associated with a significantly lower mortality rate than treatment guided by an MHP or standard laboratory tests (19.3% vs 17.3%; RR 0.75; 95% CI 0.62, 0.92; p = 0.004; I^2 = 0%).

Morbidity

The RCT evidence suggested that the rate of thromboembolic events in patients who received blood component therapy guided by TEG or ROTEM was 9.3% (24/257), which was comparable with the group guided by an MHP or standard laboratory tests (11.2%, 28/250). The difference was not statistically significant (RR 0.90; 95% CI 0.42, 1.95; p = 0.80, I^2= 46%).

There was no difference in the incidence of multiple organ failure (4.3%, 11/257) among trauma patients who received blood component therapy guided by TEG or ROTEM compared with those whose treatment was guided by an MHP or standard laboratory tests (3.2%, 8/250) (RR 1.33; 95% CI 0.53, 3.34; p = 0.54, I^2=0%).

RBC transfusion volumes

Data from one RCT suggested that the use of TEG or ROTEM to guide blood component therapy does not reduce the volume of RBCs transfused when compared treatment not guided by TEG or ROTEM (SMD −0.13; 95% CI −0.50, 0.25; p = 0.51). Among the cohort studies a significant association was observed (SMD −0.41; 95% CI −0.68, −0.14; p = 0.03; I^2 = 78%).

Transfusion volumes, other blood products

Data from one RCT suggested that the use of TEG or ROTEM to guide blood component therapy did not reduce the volume of FFP transfused when compared treatment not guided by TEG or ROTEM (SMD −0.01; 95% CI −0.39, 0.37; p = 0.96). Among the cohort studies no significant association was observed (SMD −0.39; 95% CI −1.01, 0.23; p = 0.22; I^2 = 95%), noting FFP transfusion volumes were not reported for all studies, possibly due to the p-value or direction of effect being unfavourable for the intervention. Taken together the pooled data from the RCT and cohort studies suggests that the use of TEG or ROTEM to guide blood component therapy does not reduce the volume of FFP transfused when compared treatment not guided by TEG or ROTEM (SMD −0.32; 95% CI −0.86, 0.21; p = 0.23; I^2 = 94%).

Similarly, pooled data from the RCT and cohort studies suggests that the use of TEG or ROTEM to guide blood component therapy does not reduce the volume of FFP transfused when compared treatment not guided by TEG or ROTEM (SMD −0.25; 95% CI −0.66, 0.15; p = 0.22; I^2 = 80%).

Outcome Timeframe	**Study results and measurements**	**Comparator** standard best practice care	**Intervention** Viscoelastic haemostatic assays	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (RCTs) latest reported timepoint 9 Critical	Relative risk 0.75 (CI 95% 0.48 — 1.17) Based on data from 506 participants in 2 studies. [1] (Randomized controlled)	301 per 1000 Difference:	226 per 1000 **75 fewer per 1000** (CI 95% 157 fewer — 51 more)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [2]	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the trauma setting may reduce mortality but the evidence is very uncertain.
Mortality, all cause (Coh) latest reported timepoint 9 Critical	Relative risk 0.75 (CI 95% 0.62 — 0.92) Based on data from 1,920 participants in 8 studies. [3] (Observational (non-randomized))	173 per 1000 Difference:	130 per 1000 **43 fewer per 1000** (CI 95% 66 fewer — 14 fewer)	**Very low** Due to serious risk of bias, Due to serious imprecision [4]	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the trauma setting may be associated with reduced mortality but the evidence is very uncertain.
Morbidity, thromboembolic events 7 Critical	Relative risk 0.9 (CI 95% 0.42 — 1.95) Based on data from 507 participants in 2 studies. [5] (Randomized controlled)	113 per 1000 Difference:	102 per 1000 **11 fewer per 1000** (CI 95% 66 fewer — 107 more)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision, Due to serious publication bias [6]	The use of TEG or ROTEM to guide blood component therapy may have little or no difference on thromboembolic events in patients with critical bleeding in the trauma setting but the evidence is very uncertain.
Morbidity, multiorgan failure 7 Critical	Relative risk 1.75 (CI 95% 0.6 — 5.12) Based on data from 396 participants in 1 studies. [7] (Randomized controlled)	26 per 1000 Difference:	46 per 1000 **20 more per 1000** (CI 95% 10 fewer — 107 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision [8]	The use of TEG or ROTEM to guide blood component therapy may have no difference on multiorgan failure in patients with critical bleeding in the trauma setting but the evidence is very uncertain.
RBC transfusion volume (RCTs)	Measured by: Number of Units Lower better Based on data from 109 participants in 1 studies. [9] (Randomized controlled)	15.65 Units (Mean) Difference:	13.96 Units (Mean) **SMD 0.13 fewer** (CI 95% 0.5 fewer — 0.25 more)	**Low** Due to serious risk of bias, Due to serious imprecision [10]	The evidence suggests the use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding (any setting) may have little to no difference in the volume of RBCs transfused.
RBC transfusion volume (Coh)	Measured by: Number of Units Lower better Based on data from 1,484 participants in 7 studies. [11]	2 - 11 Units Difference:	2 - 6.5 Units **SMD 0.41 fewer** (CI 95% 0.68	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the trauma setting may be

Outcome Timeframe	**Study results and measurements**	**Comparator** standard best practice care	**Intervention** Viscoelastic haemostatic assays	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
	(Observational (non-randomized))		fewer — 0.14 fewer)	inconsistency [12]	associated with a slight reduction in the volume of RBCs transfused but the evidence is very uncertain.
FFP transfusion volume	Measured by: Number of Units Lower better Based on data from 765 participants in 6 studies. [13] (Observational (non-randomized))	1 - 7.57 Units Difference:	1 - 7.49 Units **SMD 0.32 fewer** (CI 95% 0.86 fewer — 0.21 more)	**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision [14]	The use of TEG or ROTEM to guide blood component therapy in patient with critical bleeding in the trauma setting may be associated with little or no difference on the volume of FFP transfused but the evidence is very uncertain.
PLT transfusion volume	Measured by: Number of Units Lower better Based on data from 580 participants in 4 studies. [15] (Observational (non-randomized))	0.95 - 4.2 Units Difference:	0.4 - 2.7 Units **SMD 0.91 fewer** (CI 95% 1.83 fewer — 0.11 more)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [16]	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the trauma setting may be associated with little or no difference in the volume of PLTs transfused but the evidence is very uncertain.

Clinical Question/ PICO

Population: People with critical bleeding (surgical setting)

Intervention: Viscoelastic haemostatic assays

Comparator: Standard best practice care (blood component therapy guided by MTP protocol or standard laboratory tests)

Summary

What did we find?

There were five RCTs (Weber 2012, Paniagua 2011, Kempfert 2011, NCT00772239, Nuttall 2001) and two cohort studies (Fassl 2013, Hanke 2012) identified in the cardiac setting that examined the effects of TEG or ROTEM in patients *with* critical bleeding.

Study characteristics

All five RCTs were single centre studies involving adult patients scheduled for cardiothoracic surgery, with various definitions for enrolment relating to diffuse and/or abnormal bleeding from capillary beds and/or excessive blood loss after surgery. Three studies were stopped early. Paniagua 2011 was terminated early due to slow recruitment and included eight of 52 patients that did not meet the inclusion criteria. Weber 2012 was stopped early at an interim analysis due to clear benefits, and another study (NCT00772239) was stopped early due to futility (no data available).

In the cohort studies, both were conducted at singles centres and included adult patients undergoing urgent

proximal aortic surgery with hypothermic circulatory arrest with major bleeding (Fassl 2013) or adult patients with acute type A aortic dissection and aortic valve replacement (Hanke 2012).

What are the main results?

Evidence to support routine use of viscoelastic testing in people with critical bleeding who fail to achieve adequate haemostasis despite surgical management and appropriate blood component therapy in the surgical setting is of very low certainty.

Mortality
In patients with diffuse and/or abnormal bleeding from capillary beds and/or excessive blood loss after surgery, data from two RCT suggested those who received blood component therapy guided by TEG or ROTEM had a mortality rate of 6.6% (5/76), which was lower than the mortality rate of 20.6% (14/68) observed among those whose management was not guided by TEG or ROTEM (RR 0.33; 95% CI 0.12, 0.91; p = 0.03; I^2= 0%). This outcome was not reported in three studies.

Morbidity
In patients with diffuse and/or abnormal bleeding from capillary beds and/or excessive blood loss after surgery, the rate of thromboembolic events among those who received blood component therapy guided by TEG or ROTEM was 0% (0/76) compared with 2.9% (2/68) in the comparator group. The difference was not statistically significant (RR 0.20; 95% CI 0.01, 4.06; p = 0.29). Only one study contributed data.

RBC transfusion volumes
Data from one small RCT suggested that there was no difference in volume of RBCs transfused comparing blood component therapy guided by TEG or ROTEM with routine transfusion therapy based on standard laboratory tests (SMD 0.12; 95% CI −0.48, 0.72; p = 0.69). Data were not reported in two studies and two other studies suggested an effect favouring TEG or ROTEM but did not provide suitable data for analysis.

Transfusion volumes, other blood products
Data from one small RCT and one small cohort study suggested that there was no difference in volume of FFP transfused comparing blood component therapy guided by TEG or ROTEM with routine transfusion therapy based on standard laboratory tests (SMD −0.05; 95% CI −1.91, 0.91; p = 0.49; I^2 = 70%). Similarly, there was no difference in volume of PLTs transfused comparing blood component therapy guided by TEG or ROTEM with routine transfusion therapy based on standard laboratory tests (SMD −0.33; 95% CI −0.94, 0.27; p = 0.28). Data were not reported in two studies and two studies suggested an effect favouring TEG or ROTEM but did not provide suitable data for analysis.

Outcome Timeframe	**Study results and measurements**	**Comparator** standard best practice care	**Intervention** Viscoelastic haemostatic assays	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (RCTs) [1] latest reported timepoint 9 Critical	Relative risk 0.33 (CI 95% 0.12 — 0.91) Based on data from 144 participants in 2 studies. [2] (Randomized controlled)	**206** per 1000 Difference:	**68** per 1000 **138 fewer per 1000** (CI 95% 181 fewer — 19 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision [3]	The evidence suggests the use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the surgical setting (cardiothoracic) may reduce mortality.
Morbidity, thromboembolic events 7 Critical	Relative risk 0.2 (CI 95% 0.01 — 4.06) Based on data from 144 participants in 2 studies. [4] (Randomized controlled)	**29** per 1000 Difference:	**6** per 1000 **23 fewer per 1000** (CI 95% 29 fewer — 89 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision [5]	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the surgical setting (cardiothoracic) may be associated with little or no difference on the incidence of thromboembolic events but the evidence is very

Outcome Timeframe	**Study results and measurements**	**Comparator** standard best practice care	**Intervention** Viscoelastic haemostatic assays	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
					uncertain.
RBC transfusion volume (RCTs)	Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies. [6] (Randomized controlled)	6.42 Units (Mean) Difference:	7.1 Units (Mean) **SMD 0.12 more** (CI 95% 0.48 fewer — 0.72 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias [7]	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the surgical setting (cardiothoracic)) may have little or no difference on the volume of RBCs transfused but the evidence is very uncertain.
FFP transfusion volume	Measured by: Number of Units Lower better Based on data from 54 participants in 2 studies. [8] (Randomized controlled)	2.8 - 9.2 Units Difference:	1.6 - 3.2 Units **SMD 0.5 fewer** (CI 95% 1.91 fewer — 0.91 more)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision, Due to very serious publication bias [9]	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the surgical setting (cardiothoracic) may have little or no difference on the volume of FFP transfused but the evidence is very uncertain.
PLT transfusion volume	Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies. [10] (Randomized controlled)	1.34 Units (Mean) Difference:	0.85 Units (Mean) **SMD 0.33 fewer** (CI 95% 0.94 fewer — 0.27 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias [11]	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the surgical setting (cardiothoracic) may have little or no difference on the volume of PLTs transfused but the evidence is very uncertain.

6.2.4 Cell salvage

Cell salvage is the process that allows blood lost from surgical procedures to be collected, filtered, and washed for re-transfusion to the patient to minimise or prevent allogeneic red cell transfusion.

Research question
In patients with critical bleeding, what is the effect of cell salvage on patient outcomes?

Latest search date: 29 September 2021

Good practice statement

GPS8: The reference group agreed that the use of cell salvage* in patients with critical bleeding may be considered as part of a major haemorrhage protocol. There is insufficient evidence to provide a recommendation.

**The use of cell salvage requires specific expertise and training.*

Evidence To Decision

Benefits and harms

Small net benefit, or little difference between alternatives

In a meta-analysis of observational cohort studies little to no effect on mortality was demonstrated and evidence for harms were uncertain.

Certainty of the Evidence

Very low

For most bleeding patients there is no substantial survival benefit and no clear substantial harms associated with cell salvage. The overall certainty in effect estimates across outcomes was very low (benefits and harms).

Values and preferences

No substantial variability expected

There is no plausible reason to suspect that patients who are critically bleeding would not accept cell salvage as part of a major haemorrhage protocol as recommended. A subgroup of patients may decline cell salvage based on personal preference.

Resources

Important negative issues

There are costs associated with the implementation and use of cell salvage as part of a major haemorrhage protocol. However a formal health economic analysis was not conducted as part of this review.

Equity

Important issues, or potential issues not investigated

The reference group acknowledged that there is jurisdictional, geographical and/or institutional variability in the availability of cell salvage as part of a major haemorrhage protocol.

Acceptability

Important issues, or potential issues not investigated

Feasibility

Important issues, or potential issues not investigated

The reference group acknowledged the logistical challenges associated with providing cell salvage as part of a major haemorrhage protocol in critically bleeding patients. Adaptation of this guidance at a local level is required upon consideration of the resources available.

Rationale

Direct evidence about the benefits of cell salvage in critically bleeding patients is weak. The reference group agrees cell salvage may be considered as part of an MHP. The reference group considered the onset costs, logistical challenges, and institutional variability associated with providing cell salvage. The reference group anticipates minimal variation in patient preferences for this intervention.

Clinical Question/ PICO

Population: People with critical bleeding (trauma setting)
Intervention: Cell salvage
Comparator: No cell salvage

Summary

What did we find?

One small RCT (Bowley 2006) examining the effect of cell salvage in patients with critical bleeding was identified in the included systematic reviews. No additional RCTs were identified through the systematic review and hand-searching process.

Study characteristics

Bowley 2006 enrolled adult patients (aged > 18 years) presenting to emergency with penetrating torso injury requiring laparotomy and had exhibited hypotension (< 90 mm Hg) either prehospital or on arrival and in whom there was significant blood loss. All but four patients were male (91%, 40/44). The study was conducted in South Africa within the Johannesburg Hospital Trauma Unit.

What are the main results?

Mortality
In patients with penetrating trauma, there were 14 deaths among the 21 patients (66.7%) who received cell salvage compared with 15 deaths among the 23 patients (65.2%) who received standard care. The results suggest no difference between groups for the outcome of mortality (RR 1.02; 95% CI 0.67, 1.56; p = 0.92).

Morbidity
For most bleeding patients there are no clear substantial harms associated with cell salvage, but the evidence is very uncertain. Data from the identified RCT suggested that the risk of sepsis was comparable between those who received cell salvage and those who did not (RR 0.78; 95% CI 0.29, 2.09; p = 0.62).

Transfusion volumes
In patients with penetrating trauma, evidence from the small RCT suggests a significant reduction in the volume of RBC transfused (around 4.7 red cell units saved) favouring cell salvage (SMD −0.82; 95% CI −1.44, −0.20; p = 0.009). There was no difference in the the volume of FFP (SMD 0.16; 95% CI −0.44, 0.75; p = 0.61) or PLTs transfused (SMD 0.26; 95% CI −0.33, 0.85; p = 0.39).

Costs
In patients with penetrating trauma, there were no difference between study groups with regards to overall costs (MD −178.17, 95% CI −453.20 to 96.86) (2002 British Pound Sterling).

Outcome Timeframe	**Study results and measurements**	**Comparator** No cell salvage	**Intervention** Cell salvage	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (RCTs) latest reported timepoint 9 Critical	Relative risk 1.02 (CI 95% 0.67 — 1.56) Based on data from 44 participants in 1 studies. [1] (Randomized controlled)	652 per 1000 Difference:	665 per 1000 **13 more per 1000** (CI 95% 215 fewer — 365 more)	**Very low** Due to serious indirectness, Due to very serious imprecision [2]	Cell salvage may have little or no difference on mortality in trauma patients with critical bleeding but the evidence is very uncertain.
Morbidity, postoperative complications sepsis	Relative risk 0.78 (CI 95% 0.29 — 2.09) Based on data from 44 participants in 1 studies. [3] (Randomized controlled)	304 per 1000 Difference:	237 per 1000 **67 fewer per 1000**	**Very low** Due to serious indirectness, Due to very serious imprecision [4]	Cell salvage may have little or no difference in morbidity (sepsis) in trauma patients with critical bleeding but the evidence is very

Outcome Timeframe	Study results and measurements	Comparator No cell salvage	Intervention Cell salvage	Certainty of the Evidence (Quality of evidence)	Plain language summary
7 Critical			(CI 95% 216 fewer — 331 more)		uncertain.
RBC transfusion volume	Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies. [5] (Randomized controlled)	11.17 Units (Mean) Difference:	6.47 Units (Mean) **SMD 0.82 fewer** (CI 95% 1.44 fewer — 0.2 fewer)	**Very low** Due to serious indirectness, Due to very serious imprecision [6]	Cell salvage may reduce the volume of allogenic RBCs transfused slightly in trauma patients with critical bleeding but the evidence is very uncertain.
FFP transfusion volume	Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies. [7] (Randomized controlled)	4.04 Units (Mean) Difference:	4.76 Units (Mean) **SMD 0.16 more** (CI 95% 0.44 fewer — 0.75 more)	**Very low** Due to serious indirectness, Due to very serious imprecision [8]	Cell salvage may have no difference on the volume of FFP transfused in trauma patients with critical bleeding but evidence is very uncertain.
PLT transfusion volume	Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies. [9] (Randomized controlled)	0.56 Units (Mean) Difference:	1 Units (Mean) **SMD 0.26 more** (CI 95% 0.33 fewer — 0.85 more)	**Very low** Due to very serious indirectness, Due to serious imprecision [10]	Cell salvage may have no difference on the volume of PLTs transfused in trauma patients with critical bleeding but the evidence is very uncertain.

Clinical Question/ PICO

Population: People with critical bleeding (medical emergency)
Intervention: Cell salvage
Comparator: No cell salvage

Summary

What did we find?

Five nonrandomised studies (Markovic 2009, Tawfick 2008, Serricino-Inglott 2005, Shuhaiber 2003, Poscaioglu 2002) involving urgent AAA repair were identified and considered relevant to this review.

None of the above studies were randomised, due to the unpredictability and urgency of admissions and difficulties with ethical approval. All studies had important problems relating to patient selection bias, outcome assessment and reporting bias.

Study characteristics

Markovic 2009 retrospectively reviewed clinical and financial outcomes relating to abdominal aortic surgery among 90 patients who received intraoperative cell salvage compared with 90 patients who did not receive intraoperative cell salvage at a single institution in Serbia. The patients were subdivided according to the type of operation, being aortoiliac occlusive disease (AOD), elective AAA repair, or ruptured AAA repair. Only the ruptured AAA repair was relevant to this review.

Tawfick 2008 retrospectively reviewed ruptured AAA over a 9-year period (between June 1997 and June 2006) at a single hospital in Ireland. The study included both emergency open AAA repair and scheduled or elective AAA repair. The mean age for all patients who received cell salvage was 72 years, which was significantly higher (p = 0.01) than that of the control group (69 years). All other factors (preoperative cardiac, pulmonary, and renal status, smoking, diabetes, mean preoperative haemoglobin) were comparable between groups. Only the group receiving emergency open AAA repair was relevant to this review.

Serracino-Inglott 2005 was a prospective cohort study that examined 154 ruptured AAA repairs reported to a regional vascular audit database in the UK over a 4-year period (January 2000 to June 2004). The two groups were matched for age, cardiac and respiratory symptoms, cardiac medication, incidence of myocardial infarction, and diabetes.

Shuhaiber 2003 was a small retrospective cohort study conducted at a single centre in the UK among 128 patients who underwent AAA repair between 1992 and 1999 by a single vascular surgeon. Only 25 patients had emergency AAA repair (Group B), with the other 93 patients receiving elective AAA repair (Group A). Among patients in Group B, the mean age was 74.3 years (range 58 to 84), all but 2 patients were male (23/25; 92%).

Posacioglu 2002 retrospectively reviewed mortality, postoperative morbidity and blood loss in 56 patients with suprarenal and infrarenal ruptured AAA repairs by a single surgeon in Turkey. There were no differences in baseline characteristics (98% [55/56] were male), with the mean age being 68 ± 8 years.

What was are the main results?

Mortality

Among patients requiring urgent abdominal aortic aneurysm repair, there were fewer deaths among those who received cell salvage (47/141, 33%) compared with those who did not (87/209, 42%). An effect favouring cell salvage is suggested (RR 0.74; 95% CI 0.55, 1.01; p = 0.05; I^2 = 0%); however, there were concerns of reporting bias for this outcome with some studies excluding patients who died in the operative theatre and other reporting combined mortality data (across treatment groups).

Morbidity

Postoperative complications

Not including the studies that reporting combined data for elective and urgent abdominal aortic aneurysm repair, the risk of postoperative respiratory complications was higher among patients who received cell salvage (16/84, 19%) compared with those who did not (2/151, 1.3%); but the difference did not reach statistical significance (RR 3.20, 95% CI 0.83, 12.35; p = 0.09). Similar data were observed for postoperative renal complications (12% vs 1.3%; RR 2.00, 95% CI 00.49, 8.14; p = 0.33) and postoperative gastrointestinal complications (4.8% vs 0.7%; RR 1.60, 95% CI 0.19, 13.24; p = 0.66).

Transfusion volumes

Among patients requiring urgent AAA repair, the volume of RBCs transfused was not significantly different between groups (SMD −0.36; 95% CI −0.87, −0.14; p = 0.16). There was also no difference between groups in the the volume of FFP transfused (SMD 0.21; 95% CI −0.97, 1.40; p = 0.72). There was no data relating to the volume of PLTs transfused (if any).

Costs

None of the included studies reported costs associated with cell salvage or allogenic transfusions specific to the emergency AAA patient population.

Outcome Timeframe	**Study results and measurements**	**Comparator** No cell salvage	**Intervention** Cell salvage	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint 9 Critical	Relative risk 0.74 (CI 95% 0.55 — 1.01) Based on data from 350 participants in 5 studies. [1] (Observational (non-randomized))	416 per 1000 Difference:	308 per 1000 **108 fewer per 1000** (CI 95% 187 fewer — 4 more)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [2]	Cell salvage may be associated with little or no difference in mortality in patients undergoing urgent AAA repair but the evidence is very uncertain.

Outcome Timeframe	Study results and measurements	Comparator No cell salvage	Intervention Cell salvage	Certainty of the Evidence (Quality of evidence)	Plain language summary
Morbidity, respiratory complications 9 Critical	Relative risk 3.2 (CI 95% 0.83 — 12.35) Based on data from 235 participants in 3 studies. [3] (Observational (non-randomized))	13 per 1000 Difference:	42 per 1000 **29 more per 1000** (CI 95% 2 fewer — 148 more)	Very low Due to serious risk of bias, Due to serious imprecision [4]	The evidence is very uncertain about the association of cell salvage with postoperative respiratory complications in patients undergoing urgent AAA repair.
Morbidity, renal complications 9 Critical	Relative risk 2 (CI 95% 0.49 — 8.14) Based on data from 235 participants in 3 studies. [5] (Observational (non-randomized))	13 per 1000 Difference:	26 per 1000 **13 more per 1000** (CI 95% 7 fewer — 93 more)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious risk of bias [6]	The evidence is very uncertain about the association of cell salvage with postoperative renal complications in patients undergoing urgent AAA repair.
Morbidity, gastrointestinal complications 9 Critical	Relative risk 1.6 (CI 95% 0.19 — 13.24) Based on data from 235 participants in 3 studies. [7] (Observational (non-randomized))	6 per 1000 Difference:	10 per 1000 **4 more per 1000** (CI 95% 5 fewer — 73 more)	Very low Due to serious risk of bias, Due to serious imprecision [8]	The evidence is very uncertain about the association of cell salvage with postoperative gastrointestinal complications in patients undergoing urgent AAA repair.
RBC transfusion volume	Measured by: Number of Units Lower better Based on data from 350 participants in 5 studies. [9] (Observational (non-randomized))	3.63 - 12.6 Units Difference:	4 - 11.2 Units **SMD 0.36 fewer** (CI 95% 0.87 fewer — 0.14 more)	Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision [10]	Cell salvage may be associated with little or no difference on the volume of allogenic RBCs transfused in patients undergoing urgent AAA repair but the evidence is very uncertain.

7. Cost considerations

Blood components and blood products are a critical aspect of health care. The NBA manages the national blood supply to ensure that health service organisations and health professionals have reliable and efficient access to blood components and blood products needed for patient care, and that value for money is achieved.

Governments, through the NBA, spend over $1.6 billion per annum funding the supply of blood components and blood products. They are provided to patients free of charge and based on clinical need and appropriate clinical practice.

The reference group did not explicitly include search strategies to identify evidence related to cost–effectiveness or resource implications in the systematic review process, except for the research question investigating the effect of cell savage on patient outcomes. However, where the literature searches found information on cost-effectiveness or economic evaluations, this information was reviewed by the reference group.

The reference group considered resource issues during the evidence to decision process for all research questions. For example, during

the reference group's consideration of blood component ratios, members considered whether the existing guidance to implement a MHP with a 2:1:1 (RBC:FFP:PLT) ratio was still appropriate or whether a higher ratio of 1:1:1 should be considered. While the reference group acknowledged that the implementation of an MHP with a 1:1:1 ratio may be beneficial, there was insufficient evidence to recommend implementing an MHP with a 1:1:1: ratio. Therefore, the updated MHP has retained a 2:1:1 ratio. However, if the MHP template is modified by health service organisations to include a 1:1:1 ratio, the costs associated with a change in blood component ratios should be considered.

The updated guideline also includes new guidance on the use of cell salvage and VHAs. The reference group agreed that the use of cell salvage and VHAs in patients with critical bleeding may be considered as part of an MHP. However, there was insufficient evidence to present the reference group's guidance as evidence-based recommendations in both cases. The guidance on the use of cell salvage and VHAs has been presented as expert consensus-based good practice statements instead. The reference group acknowledged that the use of these interventions requires specific expertise and training. Costs associated with implementation, use and ongoing expertise should be considered.

8. Supply considerations

In Australia, the supply of blood components and blood products are managed by the NBA under the *National Blood Authority Act 2003* *[215]* and National Blood Agreement.

The supply of blood components and blood products rely on the donation of blood. In Australia, Lifeblood is responsible for all blood collections under a contract with the NBA. Ensuring supply requires collection of over one million donations per annum by Lifeblood. Most plasma derived products used in Australia are manufactured by CSL Behring from plasma collected by Lifeblood under the National Fractionation Agreement for Australia. In addition, security of the blood supply also relies on the NBA procuring blood products from overseas. These products are either not manufactured in Australia or the Australian system is unable to produce enough product to meet demand. The challenges associated with a reliance on blood donations is explored in Challenges.

A summary of the blood components, blood products and blood-related services discussed in the guideline is presented below:

- **Fresh frozen plasma** contains all coagulation factors so can be used for the treatment, or prevention of bleeding in patients with a coagulopathy where a specific therapy or factor concentrate is not appropriate or unavailable.
- **Platelets** pooled or apheresis platelets can be used for the treatment of bleeding in patients who develop thrombocytopenia due to increased platelet consumption or dilution, or have abnormal platelet function (eg anti-platelet medications).
- **Cryoprecipitate** is prepared by thawing whole blood derived FFP and recovering the precipitate. The cold-insoluble precipitate is refrozen and contains Factor VIII, von Willebrand factor, fibrinogen, Factor XIII and fibronectin. Cryoprecipitate can be used for the treatment of fibrinogen deficiency or dysfibrinogenaemia when there is critical bleeding or disseminated intravascular coagulation.
- **Fibrinogen concentrate** is a lyophilised preparation of plasma derived fibrinogen indicated for the treatment of congenital afibrinogenemia and hypofibrinogenemia.
- **Recombinant activated factor VII** is indicated for the treatment or prevention of bleeding in patients with inhibitors to coagulation factors FVIII or FIX, congenital factor VII deficiency and Glanzmann's thrombasthenia.
- **Antifibrinolytics** include tranexamic acid which acts as an antifibrinolytic by competitively inhibiting the activation of plasminogen to plasmin, a molecule responsible for the degradation of fibrin.
- **Prothrombin complex concentrate** Prothrombinex-VF® is the current PCC available in Australia. It is a coagulation factor concentrate containing Factor II, IX and X and a small amount of Factor VII. Prothrombinex-VF® is used management of patients with single or multiple congenital deficiencies of Factor II or X, and in patients with single or multiple acquired factor II, IX and X deficiencies caused by vitamin K antagonists (warfarin) requiring partial or complete reversal.
- **Cell salvage** is the process that allows blood lost from surgical procedures to be collected, filtered, and washed for re-transfusion to the patient to minimise or prevent allogeneic red cell transfusion.
- **Viscoelastic haemostatic assays** are whole blood tests designed to provide a functional assessment of clot formation, clot strength and degradation. VHAs can be used in patients with critical bleeding to detect coagulopathy and guide blood component therapy as part of a MHP.

The National Blood Agreement describes the process for determining the products which are supplied and funded under the national blood arrangements. Products which are agreed by Health Ministers under the National Blood Agreement are funded 63% by the Commonwealth and 37% by the states and territories.

The blood components and blood products supplied under the national blood arrangements are listed in the National Product Price List on the NBA website. The list also shows the price of the products for the current financial year. The list is updated when products change.

Not all the recommended interventions in the guideline are funded under the national blood arrangements. In some cases, the product is funded under its registered indications but not in settings considered 'off label'. The guideline suggests or notes the potential 'off label' use of rFVIIa, FC and PCC. The reference group also suggested or acknowledged the potential benefits of interventions not provided under the national blood arrangements in any setting i.e. tranexamic acid, cell salvage and VHA.

It may be possible for these products and services to be purchased directly from the supplier. However, payments for these purchases must be arranged separately

The NBA works closely with all Australian governments, Lifeblood, commercial suppliers of blood products, health professionals, patient groups and many other stakeholders to ensure there is no national blood supply shortage and that Australians continue to have access to the safe, secure and affordable supply of blood components and blood products required to meet clinical demand. However, there are instances where geographical and organisational constraints may present challenges in maintaining an inventory of blood components and blood products in quantities suggested in this guideline. These issues are explored in Challenges.

The COVID-19 pandemic has also challenged the NBA, our suppliers, partners and stakeholders, in relation to the critical work required to ensure a safe, secure and affordable supply of blood components, blood products and services. However, Australia remains in a good position, with the effectiveness of our national blood arrangements continuing to demonstrate their importance and value.

9. Adverse reactions

Transfusion risks in the context of patient blood management
It is acknowledged that under certain circumstances blood transfusion may benefit patients. The benefit of transfusion must always be balanced against the potential adverse effects of this therapeutic intervention.

The risk of transmission of infectious diseases through blood transfusion has reduced significantly in recent years, through improved manufacturing and laboratory processes *[233]*. However, there remains a potential for transfusion of an infectious agent *[232]*.

There is also a risk of serious non-viral adverse consequences including TACO and TRALI *[231]*. These conditions may occur with a higher frequency than previously reported *[234][235]*. Transfusion-related immunomodulation is also recognised as potentially harmful under certain circumstances.

Despite improvements in systems management, there exists a risk of transfusion-related harm due to administrative process or laboratory error *[241]*. Process errors have the potential to result in acute haemolytic reaction from ABO incompatibility which carries a significant risk of mortality.

If it is considered a patient may benefit from therapy for anaemia, thrombocytopaenia or coagulopathy, the decision as to whether transfusion is the optimal approach should:

- consider the full range of available therapies
- balance the evidence for efficacy and improved clinical outcome against the risks
- consider patient values and preferences.

The health professional offering transfusion is responsible for obtaining informed consent from the patient or nominated decision maker. All elements of the consent process should reflect local state, territory or national requirements. See Patient consent.

The table below summarises transfusion risks *[225]*. The estimates for transfusion risk may change over time. Refer to Lifeblood website for the most recent risk estimates.

TRANSFUSION RISK	ESTIMATED RATE[a] (HIGHEST TO LOWEST RISK)	CALMAN RATING[b]
Transfusion-associated circulatory overload (iatrogenic)	Up to 1 in 100 transfusions	High
Transfusion-related acute lung injury	1 in 1200–190,000	Low to minimal
Haemolytic reactions	Delayed: 1 in 2500–11,000 Acute: 1 in 76,000 Fatal: Less than 1 in 1.8 million	Low to very low Very low Negligible

TRANSFUSION RISK	ESTIMATED RATE[a] (HIGHEST TO LOWEST RISK)	CALMAN RATING[b]
Anaphylactoid reactions or anaphylaxis (usually due to Immunoglobulin A deficiency)	1 in 20,000–50,000	Very low
Bacterial sepsis: platelets	At least 1 in 75,000	Very low
Bacterial sepsis: red blood cells	At least 1 in 500,000	Minimal
Hepatitis B virus	Approximately 1 in 468,000	Minimal
Hepatitis C virus	Less than 1 in 1 million	Negligible
Human immunodeficiency virus	Less than 1 in 1 million	Negligible
Human T-lymphotropic virus (types 1 and 2)	Less than 1 in 1 million	Negligible
Malaria	Less than 1 in 1 million	Negligible
Variant Creutzfeldt-Jakob disease (not tested)	Possible, not yet reported in Australia	Negligible
Transfusion-associated graft-versus-host disease	Rare	Negligible
Transfusion-related immune modulation	Not quantified	Unknown

[a] Risk per unit transfused unless otherwise specified

[b] See Calman 1996 *[226]*

Adverse Event and Haemovigilance Reporting

Under the NSQHS Standards for Blood Management, there are several actions that health service organisations are required to meet relating to reporting adverse events and haemovigilance. Refer to Australian Commission on Safety and Quality in Health Care.

An adverse event, adverse reaction or near miss is an incident where the patient experienced actual or potential harm. Adverse reactions, adverse events and near misses relating to blood and blood products often go unrecognised and unreported *[221][222].*

Health service organisations should capture transfusion-related incidents, including near misses, in the incident management and investigation system under a category for incidents relating to blood and blood products. This information should be routinely reported to the blood management governance group for analysis. This analysis feeds into the assessment of risks and implementation of risk mitigation strategies.

Health service organisations should participate in relevant haemovigilance activities to improve the effective and appropriate management of blood and blood products, and to ensure the safety of people receiving and donating blood.

10. Patient consent

The NSQHS Standards *[216]* require health service organisations to partner with patients for their own care, and to ensure that patients and carers are informed about the risks and benefits of using blood, blood components and blood products, and all available treatment options.

The NSQHS Standards define informed consent as “a process of communication between a patient and health professional about options for treatment, care processes or potential outcomes. This communication results in the patient’s authorisation or agreement to undergo a specific intervention or participate in planned care. The communication should ensure that the patient understands the care they will receive, all the available options and the expected outcomes, including success rates and side effects for each option” *[216].*

In accordance with Action 2.05 of NSQHS Standard 2 (Partnering with Consumers), health service organisations are required to:

- ensure that its informed consent processes comply with local, state/territory and national requirements and best practice; and

- have processes to identify:
  - the capacity of a patient to make decisions about their own care
  - a substitute decision maker if a patient does not have the capacity to make decisions for themselves *[217]*.

If a patient does not have the capacity to make decisions about their own care, such as an unconscious critically bleeding patient, a substitute decision-maker may be appointed. Local legislation and best-practice guidelines should be consulted to identify who is authorised to provide substitute decision-making in the state or territory. Examples of substitute decision-makers are a nominated carer, a health attorney, or a person nominated under an enduring power of attorney or guardianship arrangement. A list of appropriate substitute decision-makers should be incorporated into the health service organisation's informed consent policy *[216]*.

When a patient regains the capacity to be an active partner in the design and delivery of their care, the treating health professional should involve them in the planning, communication, goal-setting and decision-making for their current and future care *[218]*.

In the process of obtaining informed consent, wherever possible a health professional should allow the patient or substitute decision maker sufficient time to ask questions and should answer those questions. If the patient or substitute decision maker is unable to speak or understand English, the health professional may need to involve an interpreter. In certain contexts, a trained medical interpreter may be required (rather than a family member or a friend).

11. Challenges

This section outlines potential challenges in implementing the recommendations and good practice statements within this guideline and meeting the requirements of the NSQHS Standards, in particular the Blood Management Standard.

Variation in healthcare governance
The key aim of PBM is to improve patient outcomes. While a consequence of this aim may be less blood being transfused, PBM is not technically about inventory management or reducing wastage of blood and blood products. It is a patient-centred (rather than a product focussed) approach that requires actions to be undertaken by health professionals in primary, secondary and tertiary care settings.

The patient's care and their outcomes are optimised if this care is coordinated. However, in Australia there is wide range of practices and processes for the management of critical bleeding. This variation can be attributed to a range of challenges including geographical (metropolitan, regional and remote locations) and resource (eg access to blood components) limitations.

The operational and cultural change required to implement best practice at a health professional level is significant and sometimes requires complex changes in business process and clinical practice. There are also a wide range of environmental challenges confronting jurisdictions, health service organisations and health professionals seeking to implement change.

The reference group suggested that there are jurisdictional, geographical and/or institutional variability in composition and delivery of MHPs throughout Australia.

The use of blood components in MHPs differs across the country and the impact of implementing this guideline is unclear. Changes in product ratios may increase or decrease RBC use, wastage and use of other components. Maintaining platelet supplies in remote settings might present a challenge secondary to the lack of services and equipment for platelet storage which may influence the local MHP strategy.

Health service organisations should have local policies and procedures determining the composition and delivery for MHPs which are appropriate for their requirements, product and patient outcomes.

Patient Consent
As discussed in Patient consent, health service organisations are required to have processes to identify a substitute decision maker if a patient lacks capacity to make decisions regarding their own care. This is particularly relevant in settings where critically bleeding patients are likely to be compromised.

Health professionals may be required to administer an MHP to patients who are critically bleeding and are unable to consent. When this occurs, information should be provided to the patient when they have the capacity to make decisions, or to a substitute decision maker once appointed. This information should include the process, the products, the risks, and the outcomes of any MHP administered, to ensure the patient understands and is able to obtain feedback on their care. All elements of the consent process should be consistent with local state, territory, or national policies.

Donors and Supply Issues
The Australian Red Cross Lifeblood (Lifeblood) collects blood from donors to ensure that the Australian demand for blood components is achieved. The clinical need for blood components and supply from blood donations to meet this need has always been a focus of

Lifeblood ensuring patient needs are met. However, during the COVID-19 pandemic the demand and supply of blood components and plasma, both in Australia and globally, has been affected.

Lifeblood has been managing ongoing supply for blood components, requiring 33,000 donations every week to meet the needs of Australians. Lifeblood is continually seeking eligible donors. Closer management and rationalisation of group O Rhesus (RhD) negative red blood cell inventory and use, including its use in emergency transfusion, provides significant benefit, minimising pressure on group O RhD negative RBC donors and supplies.

Group O RhD negative RBC have traditionally been used for all emergency transfusions where the patient's blood group was unknown. Whilst only 6.5% of the Australian population are group O RhD negative *[223]*, group O RhD negative RBC has represented as high as 17% of total RBC issued to Australian health providers *[224]*.

In 2022, the NBA formed a working group to develop a joint *National Statement for the Emergency Use of Group O Red Blood Cells* (National Statement) and provide guidance on inventory management and emergency practices. The National Statement encourages the use of group O RhD positive RBC in MHPs for male adults and females over the age of 50 years.

Inventory management encompasses all the activities associated with ordering, storing, handling, and issuing of blood products. Good inventory management is necessary to ensure appropriate use of a precious resource. Maintaining inadequate product may potentially adversely impact patients or disrupt routine services. Maintaining excess product may deplete products held by the supplier and increase the age of blood at transfusion or increase wastage.

Good inventory management practices ensuring blood components are appropriately used and not wasted are essential to ensure sufficient blood components are available for use in MHPs.

Changing clinical practice in line with an evolving evidence base
Health professionals may be unwilling to change long-standing and established prescribing patterns.

Health care system strategies have a wide reach and as such, can be used to set clinical practice expectations, manage demand for therapeutic goods/services and influence specific clinical decisions/practices, including those recommended in the evidence based PBM Guidelines. Clinical decisions might be influenced by health system regulation, accreditation, and funding.

Implementing changes to the health care systems can minimise health professional reluctance to adopt new clinical practice and enable them to continue making decisions that optimise individual patient outcomes.

Health care systems should be monitored to ensure that poor practice is not being inadvertently incentivised or based on an outdated evidence base.

Measuring the uptake of these guidelines
The uptake of this guideline will be measured under a comprehensive evaluation of the 2017-2024 National Patient Blood Management Implementation Strategy, which includes the following objectives:

- Increase awareness and understanding of PBM by engaging with patients, consumers and healthcare professionals through effective communication, education, and training
- Consolidate, review, and evaluate existing activities for PBM to identify gaps in knowledge and care
- Implement effective PBM practices through consultation and collaboration across healthcare settings to ensure appropriate prescribing, authorising, dispensing and administration of blood and blood products
- Implement effective systems and processes for appropriate prescribing, authorising, dispensing and administration are in place
- Improve national reporting on adverse events to reduce the number of transfusion related complications and improve patient safety
- Implement nationally coordinated measures and outcomes for PBM
- Reduce variation in clinical practice through benchmarking and reporting
- Achieve consensus on a national research agenda for PBM
- Facilitate the development of frameworks to support the sustainability of PBM initiatives
- Simplify for health service organisations to access reference documents for PBM

The evaluation will mirror the objectives and supporting activities outlined in the strategy and will be designed to provide an overview of progress towards PBM and appropriate use of blood and blood products in Australia. This may reflect a combination of initiatives implemented by many groups.

The evaluation will use indicators that:

- Provide quantitative data on the PBM and appropriate use initiatives
- Research the use of qualitative data on health professional and consumer understanding of PBM initiatives and blood product transfusion

12. Evidence gaps and potential research priorities

The review of evidence identified a number of areas where the evidence is uncertain or unknown. These areas, which are listed below, may present avenues for further research regarding the composition, effectiveness and impact of major haemorrhage protocols:

- indications for initiation and cessation of a major haemorrhage protocol
- patient specific parameters such as physiological and biochemical triggers and endpoints for intervention
- the optimal strategy for storage and use of blood components and products including, but not limited to:
  - whole blood
  - plasma
  - platelets
  - fibrinogen
  - factor concentrates
- adjuvant interventions, for example
  - viscoelastic haemostatic assay guided major haemorrhage protocols
  - cell salvage
- novel methods for assessment of oxygen delivery and tissue perfusion
- alternatives to blood components and products
- variations in assessment and management of critical bleeding for age-specific subgroups, such as paediatric and older patients

13. Implementing, evaluation and maintaining the guideline

Communication and education
This guideline will be available within the public domains of the NBA website and on MAGICapp.

The availability of the guideline will be communicated with all relevant clinical colleges and societies and a summary of the development process and clinical guidance will be published in a clinical journal.

To support implementation of the guideline at a health service organisation level, the NBA, in collaboration with the PBM Steering Committee has developed a National Patient Blood Management Implementation Strategy (the Strategy). The Strategy describes and reports on the development of communication and educational resources designed to support the implementation of PBM practice in the clinical setting. All resources are developed with the help of a network of health professionals with an interest in PBM.

Under the Strategy, the NBA has established a partnership with BloodSafe eLearning to develop online educational resources based on the PBM guidelines. The existing Critical Bleeding education module *[220]* will be updated in line with this guideline.

Review of the guideline
Ongoing review of the guideline will be necessary to reduce variation in practice patterns, support appropriate use of blood component therapy and reduce inappropriate exposure of patients to blood components. *[219]*

The recommendations in this guideline will be included in a database containing the recommendations across the entire suite of PBM guidelines. Once the recommendations and their associated research questions are prioritised in consultation with clinical stakeholders, updated clinical guidance will be developed and published incrementally in accordance with the priority list.

Feedback
Feedback on the guideline may be submitted to the NBA via:

Email: guidelines@blood.gov.au

Mail: Guidelines

National Blood Authority

Locked Bag 8430

Canberra ACT 2601

Advice on any emerging changes to clinical practice in this setting is also welcomed.

Any correspondence should be addressed to the project manager for consideration in the next scheduled review.

14. Abbreviations and acronyms

Abbreviation	Definition
ALI	acute lung injury
ANZSBT	Australia & New Zealand Society of Blood Transfusion
APTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
CCT	conventional coagulation tests
CI	confidence interval
CPB	cardiopulmonary bypass
CRG	Clinical/Consumer Reference Group
CRYO	cryoprecipitate
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
EVAR	endovascular aortic repair
FC	fibrinogen concentrate
FFP	fresh frozen plasma
GPS	good practice statement
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICU	intensive care unit
INR	international normalised ratio
IQR	interquartile range
IU	international unit
LOS	length of stay
MD	mean difference
MHP	major haemorrhage protocol
MOF	multiorgan failure
MTP	massive transfusion protocol
NBA	National Blood Authority
NHMRC	National Health and Medical Research Council
NZ	New Zealand
OR	odds ratio
PBM	Patient Blood Management

Abbreviation	Definition
PCC	prothrombin complex concentrate
PICO	population, intervention, comparator, outcome
PLT	platelet
PPH	postpartum haemorrhage
PPO	population, prognostic factor, outcome
pRBC	packed red blood cell
PT	prothrombin time
R	recommendation
rAAA	ruptured abdominal aortic aneursyms
RBC	red blood cell
RCT	randomised controlled trial
rFVIIa	recombinant activated factor VII
ROTEM	rotational thromboelastometry
RR	relative risk
SMD	standardised mean difference
TACO	transfusion-associated circulatory overload
TEG	thromboelastography
TRALI	transfusion-related acute lung injury
TXA	tranexamic acid
UK	United Kingdom
US	United States
VHA	viscoelastic haemostatic assay

15. Governance and process

Blood sectors

Australian blood sector
Health Ministers' Meeting (HMM) (formerly the Council of Australian Governments (COAG))
The HMM enables health ministers to progress collaborative decisions and actions on issues of national importance. The HMM forum focuses on issues outside the Health National Cabinet Reform Committee (HNCRC) remit.

Through the HMM, health ministers:

- consider legal and regulatory health matters covered under national law and provide governance on issues agreed to in national agreements
- oversee work administered by ministerial authorities on behalf of government
- deliver national health improvement strategies outlined in annual work plans
- progress matters as delegated by National Cabinet, outside of the HNCRC remit.

Health Chief Executives Forum (HCEF)
The HCEF is an intergovernmental forum for joint decision-making and strategic policy discussions that helps to efficiently deliver health services in Australia. It is made up of the health department chief executive officer from each state and territory and the Australian Government.

Jurisdictional Blood Committee (JBC)
The JBC is a committee of senior government officials with representation from the Australian Government, the six state governments and two territory governments. The JBC is responsible for all jurisdictional issues relating to the national blood supply, including planning, production, supply and budgeting. The JBC approved the process and expenditure to update the guideline.

National Blood Authority Board (Board)

The Board and its roles are established under the *National Blood Authority Act 2003*.[1] The Board is by nature an advisory rather than a governance body. Its principal ongoing role is to give advice to the General Manager about the performance of the NBA's functions.

National Blood Authority (NBA)
The NBA was established in 2003 as an Australian Government agency within the health and ageing portfolio. It is responsible for ensuring the adequate, safe, secure and affordable supply of blood and blood products. The role of the NBA is outlined in the *National Blood Authority Act 2003*[1] and the National Blood Agreement.

Therapeutic Goods Administration (TGA)
The TGA is the regulator for blood and blood products in Australia, and is responsible for:

- regulating the sector in terms of the safety and quality of blood and blood products under the *Therapeutic Goods Act 1989*
- auditing good manufacturing practice
- issuing product recalls
- modifying safety standards
- issuing directives such as donor deferral

Australian Red Cross Lifeblood (Lifeblood) (formerly the Australian Red Cross Blood Service)
Lifeblood was established as a national organisation in 1996 (then the Australian Red Cross Blood Service). It is responsible for collecting, processing and distributing blood and blood components sourced from voluntary donors in Australia. Lifeblood works alongside Australian regulators, government departments, and commercial and professional organisations, and with international bodies, to constantly review and improve the safety and provision of blood and blood components in Australia. Lifeblood also has significant transfusion medicine expertise and clinical involvement

New Zealand blood sector
New Zealand Blood Service (NZBS)
The NZBS was established in 1998 under the *New Zealand Public Health and Disability Act 2000* and is an appointed entity pursuant to section 63 of the Human Tissue Act 2008 being primarily responsible for the performance of functions in relation to blood and controlled human substances in New Zealand.

NZBS is a Crown Entity under the *Crown Entities Act 2004*. Pursuant to section 7 of the *Crown Entities Act 2004*, NZBS is required to give effect to Government policy when directed by the responsible Minister, the Minister of Health.

NZBS is also classified a Public Benefit Entity as its primary objective is to support the New Zealand healthcare community through managing the collection, processing and supply of blood, controlled human substances and related services.

Medsafe
Medsafe is the **New Zealand Medicines and Medical Devices Safety Authority** and is responsible for:

- regulating the sector in terms of the safety and quality of blood and blood products under the *Medicines Act 1981* and *Medicines Regulations 1984*
- auditing and licensing blood centres in accordance with good manufacturing practice
- issuing product recalls
- approving changes to the NZBS Collection and Manufacturing Standards.

Consensus process
In circumstances where no or insufficient evidence was identified, clinical guidance was developed by members of the reference group through a consensus-based process.

The consensus process was used where:

- the systematic review found insufficient evidence to address the clinical question
- the reference group determined that additional clinical practice guidance was required for the evidence-based recommendations
- the development of clinical commentary was required.

The consensus process followed is presented below.

Stage 1 – Introduction
The consensus process, participants' roles and responsibilities, ground rules and guiding principles are provided to members.

Stage 2 – Open discussion
The Chair opens the floor to a general discussion and suggestions for expert opinion or commentary wording. The Chair provides an opportunity for concerns or issues to be raised.

Stage 3 – Resolve concerns
The Chair has the first option to resolve concerns by clarifying or changing the wording, or seeing whether those with concerns will stand aside. Where concerns are not resolved and the time is short, the discussion will be carried over to a later meeting.

Stage 4 – First call for consensus
The Chair calls for consensus. If consensus is not reached, the reference group will consider the consensus process guiding principles and values, before the Chair calls for consensus again.

Stage 5 – Second call for consensus
If consensus is not reached:

- the member stands aside and the differing schools of thought are documented
- the member is not willing to withdraw the concern or stand aside, and the reference group declares itself blocked – the proposed clinical guidance is not accepted
- the member withdraws their concern and consensus is reached.

Conflict of Interest
All members of the reference group were asked to declare any interests before starting work on the guideline.

Members were advised that the NBA regards a conflict of interest as referring to any situation where any professional, commercial, financial, personal or other interest or duty of the reference group member means that:

- the reference group member may not participate in the activity in a fair and impartial way; or
- the reference group member may have the opportunity to gain an improper benefit or advantage (for themselves or another person or organisation) because of participating in the activity.

Reference group members were asked to take a broad and conservative view and were provided with a conflict of interest form to draw out the domains and topics that could provide a source of a conflict of interest and subsequently affect proceedings within the reference group. Members were asked to declare both pecuniary and non-pecuniary interests:

- **Pecuniary interests** are possible financial advantages or disadvantages of participating in a process associated with businesses or companies that are providers of products, viewpoints or information that could be relevant to the reference group.
- **Non-pecuniary interests** can include the notions of reputation, pursuing a particular favoured practice or supporting a particular viewpoint of a group with whom members are affiliated.

New declarations were required to be declared to the NBA and Chair before the start of each meeting as a standing agenda item on each day of a meeting. The NBA kept a register of all declared interests. If an interest was declared, and the Chair decided that it should be considered by the reference group, the reference group decided by consensus whether it affected the proceedings. If the interest was competing or in conflict, the Chair directly managed the participation of that member in relation to discussions and decisions pertaining to the declared interest.

All perceived or actual conflict of interest declarations made in confidence and subsequent management action plans are treated as sensitive personal information and, as such, are not made public and are not published in the guideline.

The declarations listed below were made during the guideline development process.

Dr Don Campbell	Dr Campbell receives income from Queensland Health.
A/Prof Shannon Farmer	A/Prof Farmer is an independent researcher and consultant in PBM and a member of the Executive Committee, Western Australia PBM Group within The University of Western Australia. A/Prof Farmer has received:

	• PBM lectures and consultancy fees through involvement with the International Foundation for PBM • PBM lecture honoraria Ethicon Biosurgery • PBM webinar honorarium Pfizer Australia • PBM in a pandemic webinar honorarium Baxter Australia A/Prof Farmer has memberships or affiliations with: • Executive Committee, Western Australia Patient Blood Management Group, The University of Western Australia • Scientific Associate, International Foundation of PBM • 2021 World Health Organization (WHO) External Working Group to develop a PBM Policy Brief • 2022 WHO External Steering Committee for development of the WHO Guidance for implementation of PBM A/Prof Farmer has almost 50 peer-reviewed publications, 32 abstracts, 8 book chapters, and two books on PBM and transfusion appropriateness, thresholds, and outcomes.
A/Prof Craig French	A/Prof French received NHMRC funding for transfuse study blood care. A/Prof French is a member of the Blood Service Advisory Committee, is recognised as clinical leader in PBM in critical care and has given numerous presentations.
A/Prof Nichole Harvey	A/Prof Harvey is employed at James Cook University and is a member of both the Australian College of Nursing and the Australian College of Midwifery.
Dr Anthony Holley	Dr Anthony Holley is a member of the ANZICS Board. He has also served as the Treasurer and President of the ANZICS Board.
Dr Anastazia Keegan	Dr Keegan is employed at PathWest Laboratory Medicine, King Edward Memorial Hospital and the Australian Red Cross Lifeblood, Transfusion Policy and Education. Dr Keegan has memberships or affiliations with ANZSBT, ISBT, RCPA, RACP. Dr Keegan was awarded an ANZSBT Research Grant in 2019 and an NBA grant for the RATIONAL study in 2016.
Prof Biswadev Mitra (Chair)	Prof Mitra has received seed funding from the National Blood Authority for a pilot pre-hospital trial on lyophilised plasma; and NHMRC funding for the PATCH Trauma trial: A double blinded placebo controlled trial of tranexamic acid for trauma. Prof Mitra's spouse owns shares in CSL Ltd through a managed fund. Prof Mitra is a member of the Australian Red Cross Lifeblood advisory committee.
Prof Michael Parr	Prof Parr has received benefits from the: • CONTROL study (Efficacy and safety of recombinant activated Factor VII in the management of refractory traumatic haemorrhage) Steering Committee (funded by NovoNorsisk). • Chinese Care Society (funded by CSL). Prof Parr was an advisory committee member to NovoNordisk from 2004-2009. Prof Parr was a lecturer/advisor to CSL on albumin use in ICU in 2019. Prof Parr lectures on haemorrhage, coagulopathy, MTPs, albumin use in ICU and trauma management guidelines.
Prof Michael Reade	Prof Reade has received travel funds to consult for Hospira Pty Ltd and Bard Pty Ltd on pharmaceuticals/devices that are not related to blood transfusion (fees did not exceed A$1000). Prof Reade was the Co-CI in the NHMRC Blood Synergy grant held by Monash University and the

	CI-A in the NHMRC funded CLIP-II trial of cryopreserved platelets. Prof Reade has written and spoken several times in the general area of blood transfusion.
Ms Cindy Schultz-Ferguson	Ms Schultz-Ferguson is a Board member of Dhelkaya Health.
Dr Richard Seigne	Dr Seigne receives income from the Canterbury District Health Board. Dr Seigne prescribes blood and blood components as part of his role as Anaesthetist. Dr Seigne has served as the vice-chair of the Canterbury District Health Board Transfusion Committee. This role includes reviewing appropriateness of blood use ensuring systems are in place to ensure this occurs. This role also requires close working relationships with employees of the New Zealand Blood Service. He has also performed regular blood utilisation audits as part of his roles. Dr Seigne has an interest in the appropriate use of blood and blood components and has presented lectures on the PBM Guidelines to meetings of Anaesthetists. Dr Seigne is a member of ANZSBT and the Canterbury District Health Board Transfusion Committee.
Dr James Winearls	Dr Winearls receives income from Queensland Health. Dr Winearls received a CSL Travel Grant in 2015.

Public consultation

Public consultation was conducted for 6 weeks from 28 September 2022 to 9 November 2022, during which time the draft guideline was available on the NBA website. The NBA also sent direct notification to relevant organisations.

XX submissions were received. The reference group met on 23-24 November 2022 to consider all the public consultation submissions and, where necessary, revise the guideline in accordance with the feedback received. Changes were made to the guideline to address comments and concerns raised in submissions, and to improve clarity.

Appraisal of the guideline

The Appraisal of Guidelines for REsearch & Evaluation (AGREE) II instrument was developed to address the issue of variability in guideline quality and assesses the methodological rigour and transparency in which a guideline is developed. The draft guideline was sent to two Australian reviewers, independent to the guideline development process, who used the AGREE II tool to assess the quality and usability of the guideline against international quality standards.

The AGREE II assessor/s recommended [recommendation will be inserted following public consultation].

Membership of bodies involved

A multitiered governance framework was established by the NBA for the development of the guideline. The framework is depicted in Figure 1.

Figure 1: Governance arrangements

The **JBC** is a committee of senior government officials with representation from the Australian Government, the six state governments and two territory governments. The JBC is responsible for all jurisdictional issues relating to the national blood supply, including planning, production, supply and budgeting. The JBC approved the process and expenditure to develop the guideline.

The **JBC Working Group** for the review and update of the PBM Guidelines was established to:

- provide guidance on the process and related funding options for the project
- review and provide advice on the project plan outlining the issues to be researched and investigated by the NBA, including but not limited to, potential partnerships with national and international organisations, IT platforms, horizon scanning and update triggers, and engagement of clinical and methodological expertise
- review the updated research questions and PICO prior to the systematic review of evidence
- provide advice and contribute to performance improvement activities intended to streamline the guideline update process, by reviewing information and identifying, proposing and actioning opportunities for continuous improvement

The **NBA** provided project management oversight and managed the procurement of all goods and services associated with the development of the guideline.

A multidisciplinary **reference group** was established by the NBA to provide expert knowledge and input, with members representing a range of clinical colleges, societies and organisations. Members of the reference group:

- identified and developed the research questions and research parameters (ie PICO criteria and search terms) for the systematic review
- provided advice on the type of evidence review required to support the update
- reviewed the list of abstracts compiled by the systematic review team and advised which articles should be retained in the evidence base for data extraction and analyses
- provided advice and clinical interpretation to guide the systematic review team
- reviewed the findings from the systematic review, with support from the systematic reviewer
- provided advice on current clinical practices in specific areas of expertise
- drafted the clinical guidance, with support from a medical writer
- reviewed public consultation feedback and revised the guideline accordingly
- proposed tools and strategies to support implementation.

A **subgroup of the reference group,** comprising a subset of reference group members was established to streamline the review and appraisal of the systematic review findings and translation of evidence into clinical guidance. A draft evidence to decision framework for all questions was completed by the subgroup and presented to the reference group for consideration and consensus.

A **systematic review team** was contracted by the NBA to conduct systematic reviews of the scientific literature and provide technical writing services to produce the guideline and associated technical report in collaboration with the reference group.

Membership

Clinical/Consumer Reference Group

Dr Don Campbell	Australasian College for Emergency Medicine
A/Prof Shannon Farmer	Independent researcher and consultant
A/Prof Craig French	College of Intensive Care Medicine
A/Prof Nichole Harvey	Australian College of Nursing Australian College of Midwives
Dr Anthony Holley	Australian and New Zealand Intensive Care Society
Dr Anastazia Keegan	Australasian and New Zealand Society of Blood Transfusion
Prof Biswadev Mitra (Chair)	Australasian College for Emergency Medicine
Prof Michael Parr	Australian and New Zealand College of Anaesthetists Australian Resuscitation Council (a Society)
Prof Michael Reade	Military expertise representative
Ms Cindy Schultz-Ferguson	Consumer representative
Dr Richard Seigne	Australian & New Zealand Society of Blood Transfusion
Dr James Winerals	College of Intensive Care Medicine

Systematic review team (HTAnalysts)

Dr Margaret Jorgensen	Project lead and methodological oversight
Ms Alison Miles	Senior Project Manager 2021-2022
Ms Stephanie Allerdice	Senior Project Manager 2018-2019
Ms Jessica Shi Mr Jack Hide	Consultants 2021-2022
Ms Aiya Taylor Mr Adrian Peacock Mr Kevin Phan	Consultants 2018-2019

Project management and committee secretariat (National Blood Authority)

Ms Sandra Cochrane	Project sponsor
Ms Donna Cassoni Ms Brooke Porter	Project management
Ms Natalie Walton	Project support

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