The background of the cover is a solid purple color. Overlaid on this background are numerous red blood cells, depicted in a 3D style with a reddish-purple hue. They are scattered across the entire page, with some appearing in the foreground and others in the background, creating a sense of depth. The cells are of various sizes and orientations, some showing their biconcave disc shape clearly.

# Patient blood management guideline for adults with critical bleeding

2023

**v1.7: 29/05/2024**

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### 1. Guideline Amendments

When changes are made to this guideline a new version is created.

Changes that are made that do not impact clinical guidance, are recorded as a minor version eg v1.1, v1.2, and changes that are made to clinical guidance, are recorded as a major version eg v2.0, v3.0.

Details of major guideline versions are captured in the Info box below. Should you wish to see publication dates of both major and minor versions, click the (!) button above and select 'Version history and subscription'.

## Info Box

Major Version No.	Release date	Section Updated	Details	Last date of evidence search
v1.0	8 August 2023	Guideline Release		29 September 2021

## 2. Summary of recommendations and good practice statements

For this guideline, critical bleeding refers to major haemorrhage that is life-threatening and is likely to result in the need for massive transfusion (greater than or equal to 5 units of red blood cells in 4 hours) [104] [109]. Critical bleeding is resolved when life-threatening haemorrhage is controlled.

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			
<b>R1</b>	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.  <i>(Strong recommendation, very low certainty about the evidence).</i>		7.1
<b>GPS1</b>	The reference group agreed that it is essential to identify the cause of bleeding and control it as soon as possible.  *Refer to MHP template.		7.1
<b>R2</b>	In patients with critical bleeding requiring activation of a major haemorrhage protocol, it is recommended that the following parameters be measured early and frequently*:  <ul style="list-style-type: none"> <li>• temperature</li> <li>• acid–base status</li> <li>• ionised calcium</li> <li>• haemoglobin</li> <li>• platelet count</li> <li>• PT/INR</li> <li>• APTT</li> <li>• fibrinogen level.</li> </ul> *in addition to standard continuous physiological monitoring.		7.1.1

Table 1.1: Recommendations and good practice statements		Section
	<i>(Strong recommendation, low or very low certainty about the evidence).</i>	
<b>GPS2</b>	<p>Values indicative of critical physiological derangement include:</p> <ul style="list-style-type: none"> <li>• temperature &lt; 35°C</li> <li>• pH &lt; 7.2, base excess &lt; -6 mmol/L, lactate &gt; 4 mmol/L</li> <li>• ionised calcium &lt; 1 mmol/L</li> <li>• PT &gt; 1.5 × upper limit of normal</li> <li>• INR &gt; 1.5</li> <li>• APTT &gt; 1.5 × upper limit of normal</li> <li>• fibrinogen level &lt; 2.0 g/L.</li> </ul> <p>The reference group agreed that it is good practice to monitor the above parameters and include a full blood count on, or prior to, activation of a major haemorrhage protocol. Consider repeating after administration of every 4 units of red blood cells.</p>	7.1.1
<b>R3</b>	<p>In patients with critical bleeding managed with a ratio-based major haemorrhage protocol, 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<sup>^</sup>.</p> <p>*1 adult unit of apheresis or pooled platelets in Australia is equivalent to platelets derived from 4 single whole blood donor units. A transfusion ratio of 1:1:1 would equate to 4 units of red blood cells, 4 units of FFP and 1 adult unit of platelets.</p> <p><sup>^</sup>A transfusion ratio of 2:1:1 of RBC:FFP:PLT is lower than a transfusion ratio of 1:1:1, as the number of units of red blood cells increases without a proportionate increase in FFP or platelets. A transfusion ratio of 2:1:1 would equate to 8 units of red blood cells, 4 units of FFP and 1 adult unit of platelets.</p> <p><i>(Weak recommendation, low or very low certainty about the evidence).</i></p>	7.1.2
<b>GPS3</b>	<p>The reference group agreed that in a ratio-based major haemorrhage protocol, it is good practice for the transfusion ratio of RBC:FFP:PLT to be no lower than 2:1:1.</p> <p>Refer to R3.</p>	7.1.2
<b>GPS4</b>	<p>The reference group agreed that in a ratio-based major haemorrhage protocol, it is good practice that the ratio of RBC:FFP:PLT of at least 2:1:1 be achieved as soon as possible and be maintained until critical bleeding is controlled. In addition, assess fibrinogen and replace as required.</p> <p>Refer to R2.</p> <p>Refer to R3.</p>	7.1.2
<b>R4</b>	<p>In patients with critical bleeding, the following initial doses of FFP and platelets are suggested:</p> <ul style="list-style-type: none"> <li>• FFP: a minimum of 1 unit with every 2 units of red blood cells</li> <li>• Platelets*: a minimum of 1 adult unit with every 8 units of red blood cells</li> </ul>	7.1.3

Table 1.1: Recommendations and good practice statements		Section
	<p>*1 adult unit of apheresis or pooled platelets in Australia is equivalent to platelets derived from 4 single whole blood donor units.</p> <p><i>(Weak recommendation, low or very low certainty about the evidence).</i></p>	
<b>GPS5</b>	<p>For other blood components and products, the reference group agreed that the following doses are a guide:</p> <ul style="list-style-type: none"> <li>Fibrinogen replacement: 3-4 g of fibrinogen concentrate which may be achieved using fibrinogen concentrate* or cryoprecipitate (10 units of whole blood cryoprecipitate, or 4 units of apheresis cryoprecipitate in Australia, or 1 unit of cryoprecipitate/30 kg body weight in New Zealand)</li> <li>Prothrombin complex concentrate for warfarin reversal<sup>^</sup>: 25 to 50 IU/kg.</li> </ul> <p>There is insufficient evidence to provide recommendations for the optimal timing and/or dose of these blood components or products.</p> <p>*Fibrinogen concentrate is approved in Australia and New Zealand for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency. Use of fibrinogen concentrate outside these indications (including critical bleeding) is considered 'off-label.'</p> <p><sup>^</sup>Refer to <a href="#">An update of consensus guidelines for warfarin reversal</a>.</p>	7.1.3
<b>GPS6</b>	The reference group agreed that it is good practice to administer red blood cells through a blood warming device whenever possible and aim to maintain the patient's core temperature $\geq 35^{\circ}\text{C}$ .	7.1.3
<b>GPS7</b>	<p>The reference group agreed that it is good practice to administer group specific blood components as soon as possible.*</p> <p>*Refer to ANZSBT Guidelines for transfusion and immunohaematology laboratory practice.</p>	7.1.3
<b>GPS8</b>	When critical bleeding is controlled, the reference group agreed that it is good practice to cease the major haemorrhage protocol and proceed to targeted optimisation of coagulation, physiological and biochemical parameters and continued patient assessment.	7.1.3
<b>Blood conservation strategies</b>		
<b>R5</b>	<p>In patients with critical bleeding, the reference group suggests against the routine use of recombinant activated factor VII*.</p> <p>*Recombinant activated factor VII is approved in Australia and New Zealand for the control of bleeding and surgical prophylaxis in patients with:</p> <ul style="list-style-type: none"> <li>inhibitors to coagulation Factors VIII or IX</li> <li>congenital FVII deficiency</li> <li>Glanzmann's Thrombasthenia who have antibodies to GPIIb-IIIa and/or HLA who present with refractoriness to platelet transfusions.</li> </ul>	7.2.1

Table 1.1: Recommendations and good practice statements		Section
	<p>Use of recombinant activated factor VII outside these indications (including critical bleeding after trauma) is considered 'off-label' and is associated with harm.</p> <p>Use of recombinant activated factor VII should only be considered in exceptional circumstance where all other available measures to control bleeding have been exhausted.</p> <p><i>(Weak recommendation against, low or very low certainty about the evidence).</i></p>	
<b>R6</b>	<p>In trauma patients with critical bleeding, the reference group suggests the early use (within 3 hours of injury) of tranexamic acid as part of a major haemorrhage protocol.</p> <p><i>(Weak recommendation, low certainty of evidence about the evidence).</i></p>	7.2.2
<b>GPS9</b>	<p>The reference group agreed that there is insufficient evidence to provide a recommendation on the use of tranexamic acid in patients with critical gastrointestinal bleeding.</p>	7.2.2
<b>R7</b>	<p>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.</p> <p><i>(Weak recommendation, low certainty of evidence about the evidence).</i></p>	7.2.2
<b>GPS10</b>	<p>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.</p> <p>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.</p> <p>*Interpretation of results requires specific expertise and training.</p>	7.2.3
<b>GPS11</b>	<p>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.</p> <p>*The use of cell salvage requires specific expertise and training.</p>	7.2.4

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, PT: prothrombin time, R: recommendation, RBC:FFP:PLT: red blood cells: fresh frozen plasma: platelets.

### 3. Major haemorrhage protocol (MHP)

The reference group developed an MHP template to update the massive transfusion protocol (MTP) 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.

You can download the MHP template [here](#).

## 4. Introduction

Patient blood management (PBM) 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 consider the full range of available treatments and balance the evidence for efficacy and improved outcomes against the potential risks.

Critical bleeding, for the purpose of this guideline, is defined as a major haemorrhage that is life threatening and is likely to result in the need for a massive transfusion (greater than or equal to 5 units of red blood cells in 4 hours) [104][109]. See Definitions. Critical bleeding is a clinical emergency associated with significant morbidity and mortality. This guideline recommends health service organisations use an MHP to guide the management of people with critical bleeding. More research is needed to continue to inform future guideline updates and clarify the ideal timing and ratio of blood components and products, and the benefits of strategies to conserve a person's own blood. The content in this guideline and associated MHP are a guide only; health professionals should use clinical judgement and consider the clinical circumstances and patient preferences, to determine the appropriateness of these guidelines for an individual patient.

This guideline supersedes the *Patient Blood Management Guidelines: Module 1 Critical Bleeding/ Massive Transfusion* (2011). The reference group used the results of multiple systematic reviews to inform the development of recommendations using Grading of Recommendations Assessment, Development and Evaluation (GRADE) [15]. Good practice statements were developed where the reference group had high confidence in the indirect evidence [91].

The literature review used to develop this guideline included studies published from data base inception up to 29 September 2021 for all questions except for the off-label use of recombinant activated factor VII (also known as eptacog alfa) which included studies published up to 12 August 2019. Complete details on the systematic literature review are provided in the technical reports [11][12][13].

### Background

Major haemorrhage can occur in surgical, medical, obstetric, or trauma patients and often requires the administration of large volumes of blood components and products. The management of major haemorrhage is clinically and logistically complex and is associated with significant morbidity and mortality [106]. 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 [102]. Over the past two decades there has been considerable evidence published evaluating different strategies to improve patient outcomes in major haemorrhage [101]. Despite this, substantial evidence gaps remain and applicability of results across trauma and non-trauma settings is unclear [101]. 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 [106].

### Clinical need for this guideline

When *Patient Blood Management Guidelines: Module 1 Critical Bleeding/ Massive Transfusion* was published in 2011, there was limited evidence to make recommendations on blood component ratios, timing and dose of blood components, blood products and blood conservation strategies. Since its release there have been several clinical trials and international guidelines published [105][103][256]. These address some of the evidence gaps in the management of adults 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 guideline is intended for health professionals providing immediate in-hospital care for adults who have critical bleeding resulting in a major haemorrhage.



The clinical focus of the guideline is on the use of an MHP to guide the use of blood components, blood products and blood conservation strategies as part of the overall management of an adult patient with critical bleeding.

The following were considered out of scope of the guideline: Individuals with hereditary bleeding disorders, neonates (up to 28 days following birth), prehospital management, surgical, radiological and endoscopic interventions, the use of crystalloids for fluid resuscitation, the use of whole blood, and reversal of direct oral anticoagulants.

While surgical interventions are out of scope for this guideline, it is acknowledged that in circumstances of active bleeding following trauma or surgery, the management priority is to stop the bleeding whilst the blood replacement protocols recommended in this guideline are followed, and the management of this situation is not blood replacement alone.

While the literature searches included adult and paediatric patients with critical bleeding, the reference group narrowed the scope of the guideline to adults only following the appraisal of evidence.

The recommendations and good practice statements have been developed for both trauma and non-trauma settings based on available evidence. Recommendations for specific patient populations and settings, such as critically bleeding obstetric patients and patients with critical gastrointestinal bleeding were only made where there was sufficient evidence and consensus among the reference group. Any guidance for a specific patient population or setting is clearly stated. For recommendations specific to different populations see the PBM Guideline specific to the patient population group.

The scope of this guideline will be updated according to the results of ongoing literature surveillance, emergence of novel therapies and recommendation prioritisation.

## Structure of the guideline

The guideline consists of 2 sections:

### 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 informed by the GRADE approach 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 intervention 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 guidance on 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 NBA.

**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 3 volumes:

- Volume 1 contains background information and the results of the systematic reviews pertaining to the clinical questions posed within this guideline [11]
- Volume 2 contains appendixes that document the literature searches, list of excluded studies and critical appraisal of the included studies [12]
- Volume 3 presents the data extraction forms for the included studies [13].

### **Disclaimer**

This guideline 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 in this guideline 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. The recommendations and good practice statements are subject to change over time.

Each of the parties involved in developing this guideline expressly disclaims and accepts no responsibility for any undesirable consequences arising from relying on the information, recommendations or good practice statements contained in this guideline.

### **Acknowledgements and endorsements**

This guideline was developed by a multidisciplinary reference group with members representing a range of clinical colleges, societies and organisations. Reference group members and their affiliations are listed in Governance and process.

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

## **5. Definitions**

### **Critical bleeding**

Critical bleeding is a term used to describe a range of clinical scenarios where bleeding may result in significant morbidity or mortality. Critical bleeding results in decreased circulating volume, loss of oxygen-carrying capacity, and may result in coagulopathy (impaired

clot formation). Broadly, critical bleeding falls into one of 2 categories (which may overlap):

1. Major haemorrhage that is life-threatening and is likely to result in the need for massive transfusion (greater than or equal to 5 units of red blood cells in 4 hours) [104][109].
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. Critical bleeding is resolved when life-threatening haemorrhage is controlled.

### **Major haemorrhage protocol**

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

### **Ratio of red blood cells to components**

A predefined or 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 red blood cells increases without a proportionate increase in FFP or PLT.

### **Transfusion Laboratory**

The term transfusion laboratory (or blood bank) is used in the guideline to refer to a pathology provider or transfusion medicine laboratory that performs pretransfusion testing on blood samples and issues blood components and products for transfusion. The transfusion laboratory may be located within or separate to a health service organisation.

## **6. 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 [10]. The clinical questions chosen for evidence review are listed below and were structured according to PPO/PICO (population, prognostic factor, outcome/population, intervention, comparator, 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 GRADE methodology [15].

### **Systematic review process**

These evidence-based clinical practice guidelines were developed to National Health and Medical Research Council (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 [11][12][13] 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 *JBIM 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 [48] 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 9 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.

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### 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?

*Question 3* – In patients with critical bleeding, what is the optimal dose, timing and ratio (algorithm) to red blood cells, 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 red blood cells 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 treatment on morbidity, mortality and transfusion rate?

*Question 6* – In patients with critical bleeding, what is the effect of fresh frozen plasma (FFP), cryoprecipitate, fibrinogen concentrate, prothrombin complex concentrate and/or platelet transfusion on red blood cell transfusion and patient outcomes?

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

*Question 8* – In patients with critical bleeding, does the use of viscoelastic haemostatic assays 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 or 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 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 failed to achieve 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 red blood cells transfused as a predictor for mortality or adverse outcomes were eligible for inclusion.

All remaining questions (Question 2, 3, 5, 6, 7, 8 and 9) were interventional. Restrictions on the component or 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 [9].

## 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 was based on morbidity. Data reporting any prespecified adverse outcome relevant to the included population and typically associated with the intervention such as thromboembolic events, acute respiratory distress syndrome (ARDS), time on mechanical ventilator, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO) and multiple organ failure (MOF) were extracted.

Other outcome measures related to resource use included the volume of blood component or product transfused, wastage of blood components, time to delivery of blood components or product 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 [49]:

- 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 questions, 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, 2 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, ethnicity or geographical location.

## Literature search

The 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 [12] 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 [12].

The search strategy was developed in Ovid (for Embase and MEDLINE) based on key elements provided in the research questions (i.e. population, intervention, prognostic factor). 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 [11]. 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 [11][12][13].

### 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 [11]. Here, the clarity and completeness of 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 [12].

### Evidence synthesis

After data collection, the available effect estimates (including 95% confidence intervals (CI), 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 [11]). 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 inspecting the overlap of confidence intervals on the forest plots, formally testing for heterogeneity using the chi-square test (using a significance level of  $\alpha = 0.1$ ) and quantifying heterogeneity using the  $I^2$  statistic.

Data reported under the main results refer to the available measure of effect (mean difference (MD), relative risk (RR), odds ratio (OR)) and include the 95% CI and P value relating to the effect.

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 and New Zealand context considered at this time. As per GRADE guidance [15], the body of evidence was consolidated and rated across 5 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 [11].

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## 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.

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## Formulating recommendations

The *evidence to decisions framework* provided within MAGICapp was used to inform translation of the evidence into recommendations for use in the guideline. 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 [15][24]. 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. This occurred when the evidence was insufficient or when a systematic review was not completed and it was agreed it would be a poor use of the reference group's time to conduct a formal review [91].

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 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.

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## 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 group's time to conduct a formal review.

## 7. Clinical guidance

### 7.1 MHP

#### Research question

**In patients with critical bleeding, what is the effectiveness of major haemorrhage protocols?**

Literature search date: 29 September 2021

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

Strong recommendation , Very low certainty evidence

**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 'MHP template'

#### 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 an MHP as part of a multidisciplinary approach to haemorrhage control. 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 an MHP 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 an MHP.

## Acceptability

No important issues with the recommended alternative

Acceptability of an MHP was not investigated.

## Feasibility

Important issues, or potential issues not investigated

The reference group acknowledged the logistical challenges associated with implementing an MHP to treat adult patients who are critically bleeding. Adaptation of this guidance at a local level is required upon consideration of the resources available.

## Rationale

Practical benefits of an MHP include:

- assisting the transfusion laboratory to anticipate needs and provide blood components and products rapidly
- 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 MHP

**Comparator:** No defined MHP

## Summary

Refer to the technical reports for further information on individual studies.

### What did we find?

Four systematic reviews (Cannon 2017 [52], Vogt 2012 [53], Mitra 2013 [54], Consunji 2020 [55]) were found that included evidence from 21 observational studies that assessed the effects of an MHP 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 [52][53][54][55] to have moderate or high concerns about risk 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 that mortality at the latest timepoint reported (typically up to 30-days or upon hospital discharge) was lower among those who were managed using an MHP (717/2278, 31.5%) compared with those who were not managed using 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 24-hour 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,  $I^2 = 15\%$ ).

#### Red blood cell transfusion volumes

Among people with blunt and penetrating trauma, there was no difference in the volume of red blood cells transfused among those who were managed using an MHP compared with those who were 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 components/products

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

Outcome Timeframe	Study results and measurements	Comparator No defined MHP	Intervention Defined MHP	Certainty of the Evidence (Quality of evidence)	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. <sup>1</sup> (Observational (non-randomized))	296 per 1000  Difference:	249 per 1000  <b>47 fewer per 1000</b> ( CI 95% 105 fewer — 22 more )	Very low Due to serious risk of bias, Due to serious imprecision <sup>2</sup>	There is little to no association between a defined MHP and lower 24-hour mortality in people with critical bleeding in the trauma setting, but the evidence is very uncertain.
Mortality, all cause	Odds ratio 0.67 (CI 95% 0.53 — 0.85) Based on data from	403 per 1000	311 per 1000	Very low Due to serious risk of bias, Due	There is a large association between a defined MHP and lower

Outcome Timeframe	Study results and measurements	Comparator No defined MHP	Intervention Defined MHP	Certainty of the Evidence (Quality of evidence)	Summary
latest reported timepoint  9 Critical	4,226 participants in 19 studies. <sup>3</sup> (Observational (non-randomized))	Difference:	<b>92 fewer per 1000</b> ( CI 95% 140 fewer — 38 fewer )	to serious inconsistency <sup>4</sup>	mortality in people with critical bleeding in the trauma setting, but the evidence is very uncertain.
Red blood cell transfusion volume	Measured by: Number of Units Lower better Based on data from 2,493 participants in 10 studies. <sup>5</sup> (Observational (non-randomized))	<b>12 - 25</b> Units  Difference:	<b>11.8 - 24</b> Units  <b>SMD 0.13 fewer</b> ( 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 <sup>6</sup>	A defined MHP may reduce volume of red blood cells transfused but the evidence is very uncertain.

1. Systematic review [1] with included studies: Cotton 2009 (Coh, trauma), Sisak 2012 (Coh, trauma), O'Keeffe 2008 (Coh, trauma), Noorman 2016 (Coh, trauma), van der Meij 2019 (Coh, trauma), Shaz 2010 (Coh, trauma). **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Several comparative observational studies with concerns of bias due to patient selection, data collection and reporting that weaken the confidence in the results. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** The available evidence is in United States, Netherlands, Denmark surgical, obstetrics and non-trauma patients and could be sensibly applied to the Australian context. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals (upper and lower bounds overlap with no important difference). Certainty of evidence downgraded. **Publication bias: no serious.**
3. Systematic review [1] with included studies: van der Meij 2019 (Coh, trauma), Sinha 2013 (Coh, trauma), Sisak 2012 (Coh, trauma), Hwang 2018 (Coh, trauma), O'Keeffe 2008 (Coh, trauma), Campion 2013 (Coh, trauma), Noorman 2016 (Coh, trauma), Simmons 2010 (Coh, trauma), Cotton 2009 (Coh, trauma), Johansson 2009 (Coh, trauma), Duchesne 2010 (Coh, trauma), Dente 2009 (Coh, trauma), Dirks 2010 (Coh, trauma), Cotton 2008 (Coh, trauma), Maciel 2015 (Coh, trauma), Riskin 2009 (Coh, trauma), Shaz 2010 (Coh, trauma), Nunn 2017 (Coh, trauma), Brinck 2016 (Coh, trauma). **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Several comparative observational studies with concerns of bias due to patient selection, data collection and reporting that weaken the confidence in the results. Certainty of evidence downgraded. **Inconsistency: serious.** Significant heterogeneity with substantial variability in effect estimates ( $I^2 > 50\%$ ). Point estimates vary widely. Certainty of evidence downgraded. **Indirectness: no serious.** The available evidence is in United States, Netherlands, Denmark trauma patients and could be sensibly applied to the Australian trauma population and healthcare context. Certainty of evidence not downgraded. **Imprecision: no serious. Publication bias: no serious.**
5. Systematic review [1] with included studies: Vogt 2009 (Coh, trauma), Johansson 2009 (Coh, trauma), Shaz 2010 (Coh, trauma), Cotton 2008 (Coh, trauma), Fox 2008 (Coh, trauma), Riskin 2009 (Coh, trauma), Simmons 2010 (Coh, trauma), O'Keeffe 2008 (Coh, trauma), Sinha 2013 (Coh, trauma), Sisak 2012 (Coh, trauma). Two studies (total 605 participants) not included in RevMan. Median (IQR) data reported. No significant differences reported between RBC transfusion volume in the MHP and no MHP groups.. **Baseline/comparator:** Systematic review.
6. **Risk of Bias: serious.** Several comparative observational studies with concerns of bias due to patient

selection, data collection and reporting that weaken the confidence in the results. Certainty of evidence downgraded. **Inconsistency: very serious.** Point estimates vary widely with high statistical heterogeneity ( $I^2 = 77\%$ ). Certainty of evidence downgraded 2 levels. **Indirectness: no serious.** The available evidence is in United States and Denmark trauma patients and could be sensibly applied to the Australian trauma and non-trauma population and healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals (lower bound overlaps with no important difference). Certainty of evidence downgraded. **Publication bias: no serious.**

## References

1. HTANALYSTS, Jorgensen M, Miles A, Shi J. Massive transfusion protocols for critical bleeding. RevMan 5.4 2022.
52. Cannon JW, Khan MA, Raja AS, Cohen MJ, Como JJ, Cotton BA, et al. Damage control resuscitation in patients with severe traumatic hemorrhage: A practice management guideline from the Eastern Association for the Surgery of Trauma. *Journal of Trauma and Acute Care Surgery* 2017;82(3):605-617 [Journal](#)
53. Vogt KN, Van Koughnett JA, Dubois L, Gray DK, Parry NG. The use of trauma transfusion pathways for blood component transfusion in the civilian population: a systematic review and meta-analysis. *Transfusion Medicine (Oxford, England)* 2012;22(3):156-66 [Pubmed Journal](#)
54. Mitra B, O'Reilly G, Cameron PA, Zatta A, Gruen RL. Effectiveness of massive transfusion protocols on mortality in trauma: a systematic review and meta-analysis. *ANZ Journal of Surgery* 2013;83(12):918-23 [Pubmed Journal](#)
55. Consunji R, Elseed A, El-Menyar A, Sathian B, Rizoli S, Al-Thani H, et al. The effect of massive transfusion protocol implementation on the survival of trauma patients: a systematic review and meta-analysis. *Blood transfusion = Trasfusione del Sangue* 2020;18(6):434-445 [Pubmed Journal](#)

## Clinical question/ PICO

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

## Summary

Refer to the technical reports for further information on individual studies.

### What did we find?

One systematic review (Sommer 2019 [56]) was found that included evidence from 4 retrospective observational studies that assessed the effects of an MHP in a non-trauma setting (Dutta 2017, Martinez-Calle 2016, McDaniel 2013, Johansson 2007). The systematic review authors [56] also included evidence from one retrospective cohort study (Balvers 2015) that assessed the effect of the introduction of an MHP across the hospital system (including both trauma and non-trauma patients).

### 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 (rAAA) (Johansson 2007), a mixed group of patients with postsurgical/procedural complications, or gastrointestinal and vascular emergencies (Martinez-Calle 2016, McDaniel 2013), or patients from a variety of settings including surgery (63%), internal medicine (13%), other (11%), trauma (9%), obstetric (4%) (Balvers 2015). Major bleeding was defined as those who required 4 or more units of red blood cells (Dutta 2017), 5 or more units of red blood cells (Balvers 2015), 10 or more units of red blood cells (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 10 minutes (Martinez-Calle 2016).

The included observational studies were judged by review authors [56] to be at overall high risk of bias due to study design and confounding.

### What are the main results?

#### Mortality

Among non-trauma patients who were managed using an MHP, the mortality rate (latest reported timepoint) of 30.4% (166/546) was slightly lower than the mortality rate of 34.9% (156/447) observed among patients who were not managed using an MHP, but the effect estimates were inconsistent and the lower bound of the CI suggests no important association (OR 0.67; 95% CI 0.35, 1.29;  $P = 0.23$ ;  $I^2 = 74\%$ ).

#### Red blood cell transfusion volumes

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

#### Transfusion volumes, other blood components/products

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

Outcome Timeframe	Study results and measurements	Comparator No defined MHP	Intervention Defined MHP	Certainty of the Evidence (Quality of evidence)	Summary
Mortality 24 hours  9 Critical	Odds ratio 1.05 (CI 95% 0.35 — 3.12) Based on data from 861 participants in 4 studies. <sup>1</sup> (Observational (non- randomized))	99 per 1000  Difference:	103 per 1000  <b>4 more per 1000</b> ( CI 95% 62 fewer — 156 more )	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious	There is little to no association between a defined MHP and lower 24-hour mortality in the non-trauma setting, but the evidence is very uncertain.

Outcome Timeframe	Study results and measurements	Comparator No defined MHP	Intervention Defined MHP	Certainty of the Evidence (Quality of evidence)	Summary
				inconsistency <sup>2</sup>	
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. <sup>3</sup> (Observational (non- randomized))	349 per 1000  Difference:	264 per 1000  <b>85 fewer per 1000</b> ( CI 95% 191 fewer — 60 more )	Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision <sup>4</sup>	There is little to no association between a defined MHP and lower mortality in patients with critical bleeding in the non-trauma setting, but the evidence is very uncertain.
Red blood cell transfusion volume	Measured by: Number of Units Lower better Based on data from 462 participants in 4 studies. <sup>5</sup> (Observational (non- randomized))	12.2 Units (Mean)  Difference:	12.6 Units (Mean)  <b>SMD 0.04 more</b> ( CI 95% 0.46 fewer — 0.54 more )	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency <sup>6</sup>	An MHP has little or no effect on volume of red blood cells transfused in patients with critical bleeding in the non- trauma setting, but the evidence is very uncertain.

1. Systematic review [1] with included studies: Balvers 2015 (RCoh, 9% trauma, 63% surgical), Martinez-Calle 2016 (RCoh, surgical & nonsurgical), McDaniel 2013 (RCoh, non-trauma), Dutta 2017 (RCoh, Obstetrics). **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** Several comparative observational studies with concerns of bias due to patient selection, data collection and reporting that weaken the confidence in the results. Certainty of evidence downgraded. **Inconsistency: serious.** Point estimates vary widely. The magnitude of statistical heterogeneity was high ( $I^2 = 62\%$ ). Certainty of evidence downgraded. **Indirectness: no serious.** The available evidence is in United States, Netherlands, Denmark trauma and non trauma patients (general medicine/surgical/obstetrics) and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals (upper and lower bounds overlap with no important difference). Certainty of evidence downgraded. **Publication bias: no serious.**
3. Systematic review [1] with included studies: Martinez-Calle 2016 (RCoh, surgical & nonsurgical), McDaniel 2013 (RCoh, non-trauma), Johansson 2007 (RCoh, ruptured AAA), Balvers 2015 (RCoh, 9% trauma, 63% surgical), Dutta 2017 (RCoh, Obstetrics). **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Several comparative observational studies with concerns of bias due to patient selection, data collection and reporting that weaken the confidence in the results. Certainty of evidence downgraded. **Inconsistency: serious.** Point estimates vary widely. The magnitude of statistical heterogeneity was high ( $I^2 = 74\%$ ). Certainty of evidence downgraded. **Indirectness: no serious.** The available evidence is in United States, Netherlands, Denmark trauma and non trauma patients (general medicine/surgical/obstetrics) and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals (upper and lower bounds overlap with no important difference). Certainty of evidence downgraded. **Publication bias: no serious.**
5. Systematic review [1] with included studies: McDaniel 2013 (RCoh, non-trauma), Johansson 2007 (RCoh, ruptured AAA), Dutta 2017 (RCoh, Obstetrics), Martinez-Calle 2016 (RCoh, surgical & nonsurgical). Three studies (total 398 participants) were not included in the RevMan. Studies reported median (IQR).

Two studies reported no significant difference in volume of RBCs transfused between the MHP and.

**Baseline/comparator:** Control arm of reference used for intervention.

6. **Risk of Bias: serious.** More than one comparative observational studies with concerns of bias due to patient selection, data collection and reporting that weaken the confidence in the results. Certainty of evidence downgraded. **Inconsistency: serious.** Clinical heterogeneity between studies due to differences in MHP and thresholds for transfusion. Certainty of evidence downgraded. **Indirectness: no serious.** The available evidence is in United States non trauma (general medicine/surgical/obstetrics) patients and could be sensibly applied to the Australian non-trauma population and healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals (upper and lower bounds overlap with both effect and no effect). Certainty of evidence downgraded. **Publication bias: no serious.**

## References

1. HTANALYSTS, Jorgensen M, Miles A, Shi J. Massive transfusion protocols for critical bleeding. RevMan 5.4 2022.

56. Sommer N, Schnüriger B, Candinas D, Haltmeier T. Massive transfusion protocols in nontrauma patients: A systematic review and meta-analysis. The Journal of Trauma and Acute Care Surgery 2019;86(3):493-504 [Pubmed Journal](#)

## Clinical question/ PICO

**Population:** People with critical bleeding (any setting)

**Intervention:** Defined MHP

**Comparator:** No defined MHP

## Summary

Refer to the technical reports for further information on individual studies.

### What did we find?

Eight systematic reviews (Cannon 2017 [52], Vogt 2012 [53], Mitra 2013 [54], Consunji 2020 [55], Sommer 2019 [56], Kinslow 2020 [57], Kamyszek 2019 [58], Maw 2018 [59]) were found that included evidence from 29 non-randomised cohort studies that examined the effects of a defined MHP versus no defined MHP 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, Canada, Europe and Australia. Overall, the observational studies were judged by the included systematic review authors [52][53][54][55][56][57][58][59] to be at moderate to high risk of bias due to study design, data collection



and adjustments for confounding.

### 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 were managed using an MHP (926/2927, 31.6%) compared with those who were 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 FFP transfusion in patients with critical bleeding who were managed using an MHP ( $n=1340$ ) compared with those who were not ( $n=1119$ ), with an overall 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 3 observational studies (O'Keefe 2008, Shaz 2010 and Simmons 2010). Furthermore, differences in thresholds activating MHPs varied between studies.

#### Platelet transfusion volumes

A meta-analysis of data from observational studies included in this review revealed a nonsignificant increase in the volume of platelet transfusion in patients with critical bleeding who were managed using an MHP ( $n=2049$ ) compared with those who were not ( $n=1666$ ), with an overall 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 MHP	Certainty of the Evidence (Quality of evidence)	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. <sup>1</sup> (Observational (non-randomized))	392 per 1000  Difference:	314 per 1000  <b>78 fewer per 1000</b> ( CI 95% 123 fewer — 33 fewer )	Very low Due to serious risk of bias, Due to serious inconsistency <sup>2</sup>	There is a large association between a defined MHP 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. <sup>3</sup> (Observational (non-randomized))	8 - 15 Units  Difference:	8 - 14 Units  <b>SMD 0.09 fewer</b> ( 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 <sup>4</sup>	A defined MHP may reduce volume of FFP transfused but the evidence is very uncertain.



Outcome Timeframe	Study results and measurements	Comparator No defined MHP	Intervention Defined MHP	Certainty of the Evidence (Quality of evidence)	Summary
Platelet transfusion volume	Measured by: Number of Units Lower better Based on data from 3,715 participants in 15 studies. <sup>5</sup> (Observational (non-randomized))	1.7 - 15 Units  Difference:	1.1 - 31 Units  <b>SMD 0.54 more</b> ( CI 95% 0.26 fewer — 1.33 more )	Very low Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision <sup>6</sup>	A defined MHP may increase the volume of platelets transfused but the evidence is very uncertain.

1. Systematic review [1] with included studies: O'Keeffe 2008 (Coh, trauma), Dente 2009 (Coh, trauma), McDaniel 2013 (RCoh, non-trauma), Hendrickson 2012 (Coh, paediatric trauma), Duchesne 2010 (Coh, trauma), Brinck 2016 (Coh, trauma), Sinha 2013 (Coh, trauma), Riskin 2009 (Coh, trauma), Dirks 2010 (Coh, trauma), Johansson 2007 (RCoh, ruptured AAA), Maciel 2015 (Coh, trauma), Cotton 2009 (Coh, trauma), Chidester 2012 (Coh, paediatric trauma), Champion 2013 (Coh, trauma), Dutta 2017 (RCoh, Obstetrics), Balvers 2015 (RCoh, 9% trauma, 63% surgical), Sisak 2012 (Coh, trauma), van der Meij 2019 (Coh, trauma), Nunn 2017 (Coh, trauma), Shaz 2010 (Coh, trauma), Johansson 2009 (Coh, trauma), Hwu 2016 (Coh, paediatric trauma), Simmons 2010 (Coh, trauma), Noorman 2016 (Coh, trauma), Hwang 2018 (Coh, trauma), Martinez-Calle 2016 (RCoh, surgical & nonsurgical), Cotton 2008 (Coh, trauma). **Baseline/comparator:** Control arm of reference used for intervention.

2. **Risk of Bias: serious.** Several comparative observational studies with concerns of bias due to patient selection, data collection and reporting that weaken the confidence in the results. Certainty of evidence downgraded. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. Certainty of evidence downgraded. **Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**

3. Systematic review [1] with included studies: Simmons 2010 (Coh, trauma), Cotton 2008 (Coh, trauma), Shaz 2010 (Coh, trauma), McDaniel 2013 (RCoh, non-trauma), Riskin 2009 (Coh, trauma), Vogt 2009 (Coh, trauma), O'Keeffe 2008 (Coh, trauma), Johansson 2009 (Coh, trauma), Sisak 2012 (Coh, trauma). One study (77 participants not recorded in RevMan) did not report standard deviation data.. **Baseline/comparator:** Control arm of reference used for intervention.

4. **Risk of Bias: serious.** Several comparative observational studies with concerns of bias due to patient selection, data collection and reporting that weaken the confidence in the results. Certainty of evidence downgraded. **Inconsistency: very serious.** The magnitude of statistical heterogeneity was high ( $I^2 > 50\%$ ). Point estimates vary widely. The direction of the effect is not consistent between the included studies. Certainty of evidence downgraded 2 levels. **Indirectness: no serious.** The available evidence is in United States, Netherlands, Denmark trauma and non trauma (general medicine/surgical/obstetrics) patients and could be sensibly applied to the Australian trauma and non-trauma population and healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence interval (upper and lower bounds overlap with both effect and no effect). Certainty of evidence downgraded. **Publication bias: no serious.**

5. Systematic review [1] with included studies: Martinez-Calle 2016 (RCoh, surgical & nonsurgical), McDaniel 2013 (RCoh, non-trauma), Cotton 2008 (Coh, trauma), Sisak 2012 (Coh, trauma), O'Keeffe 2008 (Coh, trauma), Johansson 2009 (Coh, trauma), Riskin 2009 (Coh, trauma), Shaz 2010 (Coh, trauma), Sinha 2013 (Coh, trauma), Dutta 2017 (RCoh, Obstetrics), Dirks 2010 (Coh, trauma), Johansson 2007 (RCoh, ruptured AAA), Vogt 2009 (Coh, trauma), Balvers 2015 (RCoh, 9% trauma, 63% surgical), Simmons 2010 (Coh, trauma). Seven studies (total 1333 participants) not recorded in RevMan. Six studies reported median (IQR), with little or no significant difference in PLT transfusion volume between MHP and no MHP.

One study did not report standard deviation data.. **Baseline/comparator:** Control arm of reference used for intervention.

6. **Risk of Bias: serious.** Several comparative observational studies with concerns of bias due to patient selection, data collection and reporting that weaken the confidence in the results. Certainty of evidence downgraded. **Inconsistency: very serious.** The magnitude of statistical heterogeneity was high ( $I^2 = 99\%$ ). Point estimates vary widely. The confidence interval of some of the studies do not overlap with the point estimate of some of the included studies. Certainty of evidence downgraded 2 levels. **Indirectness: no serious.** The available evidence is in United States, Netherlands, Denmark trauma and non trauma patients (general medicine/surgical/obstetrics) and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals (upper and lower bounds overlap with no important difference). Certainty of evidence downgraded. **Publication bias: no serious.**

## References

1. HTANALYSTS, Jorgensen M, Miles A, Shi J. Massive transfusion protocols for critical bleeding. RevMan 5.4 2022.
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53. Vogt KN, Van Koughnett JA, Dubois L, Gray DK, Parry NG. The use of trauma transfusion pathways for blood component transfusion in the civilian population: a systematic review and meta-analysis. Transfusion Medicine (Oxford, England) 2012;22(3):156-66 [Pubmed Journal](#)
54. Mitra B, O'Reilly G, Cameron PA, Zatta A, Gruen RL. Effectiveness of massive transfusion protocols on mortality in trauma: a systematic review and meta-analysis. ANZ Journal of Surgery 2013;83(12):918-23 [Pubmed Journal](#)
55. Consunji R, Elseed A, El-Menyar A, Sathian B, Rizoli S, Al-Thani H, et al. The effect of massive transfusion protocol implementation on the survival of trauma patients: a systematic review and meta-analysis. Blood transfusion = Trasfusione del Sangue 2020;18(6):434-445 [Pubmed Journal](#)
56. Sommer N, Schnüriger B, Candinas D, Haltmeier T. Massive transfusion protocols in nontrauma patients: A systematic review and meta-analysis. The Journal of Trauma and Acute Care Surgery 2019;86(3):493-504 [Pubmed Journal](#)
57. Kinslow K, McKenney M, Boneva D, Elkbuli A. Massive transfusion protocols in paediatric trauma population: A systematic review. Transfusion Medicine 2020. [Website](#)
58. Kamyszek RW, Leraas HJ, Reed C, Ray CM, Nag UP, Poisson JL, et al. Massive transfusion in the pediatric population: A systematic review and summary of best-evidence practice strategies. The Journal of Trauma and Acute Care Surgery 2019;86(4):744-754 [Pubmed Journal](#)
59. Maw G, Furyk C. Pediatric Massive Transfusion: A Systematic Review. Pediatric Emergency Care 2018;34(8):594-598 [Pubmed Journal](#)

#### Good practice statement

**GPS1:** The reference group agreed that it is essential to identify the cause of bleeding and control it as soon as possible \*

\*Refer to MHP template

### Practical info

Haemorrhage control includes:

- early identification of cause of bleeding
- temporary control of bleeding, using:
  - compression
  - packing
  - tourniquet
  - pelvic binder
- assessment and definitive haemorrhage control:
  - early surgery or angiography to stop bleeding.

### Rationale

R1 is a strong recommendation supporting a multidisciplinary approach to haemorrhage control as part of an MHP. The reference group developed a good practice statement to reinforce the importance of early identification of cause of bleeding and haemorrhage control. Some suggested strategies for haemorrhage control are in Practical info tab.

Details regarding specific strategies for haemorrhage control are outside the scope of this guideline.

## 7.1.1 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 , Very low certainty evidence**

**R2:** In patients with critical bleeding requiring activation of a major haemorrhage protocol, it is recommended that the following parameters 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 GPS2.

See National Safety and Quality Health Service (NSQHS) Standard: 8 Recognising and Responding to Acute Deterioration Standard.

**Evidence to decision****Benefits and harms**

Identified cohort studies suggest there is an association between prognostic factors and an increased risk of mortality. However, the overall certainty of the evidence was low. The true benefits are unknown due to a very low certainty of evidence.

**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 physiological, biochemical and metabolic prognostic factors as recommended.

**Resources**

No important issues with the recommended alternative

Resource implications associated with measuring physiological, biochemical and metabolic prognostic factors are likely to be limited given routine 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 routine 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 routine 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 routine 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 physiological, biochemical and metabolic parameters may prevent the development or worsening of the lethal triad of critical bleeding (hypothermia, coagulopathy, acidosis).

**Clinical question/ PICO**

**Population:** People with critical bleeding (any setting)

**Intervention:** Temperature

**Comparator:** N/A

**Summary**

Refer to the technical reports for further information on individual studies.

**What did we find?**

Two systematic reviews (Lilitis 2018 [82], Shih 2019 [83]) were found that included evidence from 3 studies (Balvers 2016, Callcut 2011, Martin 2005) examining the association between body temperature and mortality or transfusion requirements in patients with critical bleeding. Two additional studies were found in this review (Lester 2019 [61], McQuilten 2017a [219]).

**Study characteristics**

Three retrospective cohort studies (Balvers 2016, Callcut 2011, Martin 2005) were carried out in trauma centres in either the United States or the Netherlands. Hypothermia was generally considered by the included studies to be below 35.5°C. Lilitis 2018 [82] stated general concerns of bias inherent to study design for 2 studies (Balvers 2016, Martin 2005) and one study (Callcut 2011) was considered by Shih 2019 [83] to be of good methodological quality.

Lester 2019 [61] was a single-arm analysis of a RCT that evaluated the association between hypothermia and patient outcomes using the dataset collected during the PROPPR RCT (Holcomb 2015). Hypothermia was defined as a temperature less than 36°C and normothermia was considered to be between  $\geq 36^\circ\text{C}$  and  $38.5^\circ\text{C}$ . Lester 2019

was judged to be at serious risk of bias due to 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.

McQuilten 2017a [219] was a prospective study that assessed the association of low fibrinogen levels with mortality in all adult trauma patients identified through a statewide trauma registry in Victoria (Australia). Variables considered in the stepwise multiple logistic regression models included temperature, pH, Hb, platelet count, INR, APTT (among others). Data were available for 4772 patients who presented to the 2 major trauma hospitals between January 2008 and July 2011 and who had a fibrinogen level measured during initial resuscitation. The study had some concerns of bias relating to measurement of outcomes and missing data.

### What are the main results?

#### Mortality

Identified literature suggests hypothermia (below 35°C) is independently associated with an increased risk of mortality among patients with critical bleeding. Four studies in the trauma setting contributed data, with an adjusted OR around 2.7 observed at 24-hours and the adjusted OR ranging between 1.8 and 2.8 at 30 days.

#### Transfusion volume

Only limited conclusions can be drawn from the available evidence. Among trauma patients, one study reported an increased risk of transfusion of 10 or more units of red blood cells in the first 6 hours (OR 4.0; 95% CI 1.6, 10.1) and one study reported no important association between hypothermia and the volume of red blood cells transfused (RR 0.90; 95% CI 0.89, 0.92).

Outcome Timeframe	Study results and measurements	Comparator N/A	Intervention Temperature	Certainty of the Evidence (Quality of evidence)	Summary
Mortality, all cause latest reported timepoint  9 Critical	Based on data from 707,803 participants in 4 studies. <sup>1</sup> (Observational (non-randomized))	All studies found an association between hypothermia and an increased risk of mortality at 24-hours (OR range 2.7 to 2.72) and at 30-days (OR range 1.8 to 2.8).		Very low Due to serious risk of bias <sup>2</sup>	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 serious imprecision, Due to serious publication bias <sup>3</sup>	Hypothermia (< 35°C) is associated with higher volume of red blood cells transfused.

1. Systematic review Two studies reported OR range 2.7-2.72 for 24 hour mortality and OR range

1.8-2.82 for 30 day mortality.. **Supporting references:** [219], [61],

2. **Risk of Bias: serious.** Four observational studies with concerns of bias due to study design, patient selection and reporting. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** The evidence is in trauma patients enrolled across the United States, United Kingdom, Netherlands, Norway, France and Australia and could be sensibly applied to trauma patients treated in Australia and the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: no serious. Publication bias: no serious.**

3. **Risk of Bias: serious.** Two observational studies with concerns of bias due to study design, patient selection and reporting that seriously weaken the confidence in the results. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** Evidence is across similar healthcare settings such as the United States, United Kingdom, Netherlands, Norway, France and Australia and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: serious.** There is a strong suspicion of non-reporting of results likely to be related to P value, direction or magnitude of effect. Certainty of evidence downgraded.

## References

11. National Blood Authority. Update of the 2011 Patient Blood Management Guidelines for people with critical bleeding: Technical report Volume 1. Canberra: The Commonwealth of Australia as represented by the NBA 2022.

61. Lester ELW, Fox EE, Holcomb JB, Brasel KJ, Bulger EM, Cohen MJ, et al. The impact of hypothermia on outcomes in massively transfused patients. The Journal of Trauma and Acute Care Surgery 2019;86(3):458-463 [Pubmed Journal](#)

82. Lilitsis E, Xenaki S, Athanasakis E, Papadakis E, Syrogianni P, Chalkiadakis G, et al. Guiding Management in Severe Trauma: Reviewing Factors Predicting Outcome in Vastly Injured Patients. Journal of Emergencies, Trauma, and Shock 11(2):80-87 [Pubmed Journal](#)

83. Shih AW, Al Khan S, Wang AY-H, Dawe P, Young PY, Greene A, et al. Systematic reviews of scores and predictors to trigger activation of massive transfusion protocols. The journal of trauma and acute care surgery 2019;87(3):717-729 [Pubmed Journal](#)

219. McQuilten ZK, Wood EM, Bailey M, Cameron PA, Cooper DJ. Fibrinogen is an independent predictor of mortality in major trauma patients: A five-year statewide cohort study. Injury 2017;48(5):1074-1081 [Pubmed Journal](#)

## Clinical question/ PICO

**Population:** People with critical bleeding (any setting)

**Intervention:** Acid-base status

**Comparator:** N/A

## Summary

Refer to the technical reports for further information on individual studies.

**What did we find?**

Three systematic reviews (Lilitis 2018 [82], Baxter 2016 [84], Tran 2018 [85]) were found that included evidence from 15 observational studies (Gale 2016, Heinonen 2014, Odom 2013, Ipecki 2013, Regnier 2012, Odom 2012, Vandromme 2011, Mizushima 2011, Neville 2011, Vandromme 2010, Callaway 2009, Duane 2008, Aslar 2004, Baron 2004, Lavery 2000) that assessed the association between lactate levels and outcomes in patients with critical bleeding. The search also identified 2 additional observational studies (Javali 2017 [205], Sawamura 2009 [209]) that assessed the association between lactate levels on mortality and transfusion volume in the trauma setting.

**Study characteristics**

The included studies identified by the included reviews were carried out in various trauma centres in the United States, France, Switzerland and South Africa. This included 12 studies that assessed the association between lactate levels and mortality (Gale 2016, Heinonen 2014, Odom 2013, Odom 2012, Regnier 2012, Mizushima 2011, Neville 2011, Vandromme 2010, Callaway 2009, Duane 2008, Aslar 2004, Lavery 2000) and 5 studies that assessed the association between lactate levels and transfusion volume (Ipecki 2013, Regnier 2012, Vandromme 2011, Vandromme 2010, Baron 2004). Review authors [82][84][85] reported moderate to high concerns of bias of included studies relating to attrition, confounding and reporting biases.

Javali 2017 [205] was a prospective observational study involving 100 trauma patients at risk of haemodynamic compromise admitted to a tertiary care emergency department in India. The study was judged to be at serious risk of bias due to inadequate control of confounding factors, patient selection and likely reporting bias.

Sawamura 2009 [209] was a retrospective cohort study conducted in Japan that assessed the impact of disseminated intravascular coagulation (DIC) on patient outcomes. Data obtained at 4 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 non-survivors. This study was found to have serious concerns of bias due to study design, likely confounders, and inadequate reporting of data.

**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 data. At high lactate levels (>4 mmol/L), authors reported OR for death ranged from 3.8 to 10.58.

**Transfusion volume**

Only limited conclusions can be drawn from the available evidence. The studies reported increased lactate levels in patients with critical bleeding to be associated with an increased risk of higher red blood cell transfusion volumes, with 2 studies reporting OR ranged from 3.13 to 5.20. High lactate levels were reported above 2.9 mmol/L.



Outcome Timeframe	Study results and measurements	Comparator N/A	Intervention Acid-base status	Certainty of the Evidence (Quality of evidence)	Summary
Mortality, all cause latest reported timepoint  9 Critical	Based on data from 41,328 participants in 14 studies. (Observational (non- randomized))	Studies report an association between high lactate levels and increased risk of mortality. The OR varied across studies depending on lactate levels. At lactate levels > 4 mmol/L the OR ranged between 3.8 and 10.58.		Very low Due to serious risk of bias <sup>1</sup>	Higher lactate levels are associated with higher mortality.
Transfusion volume	Based on data from 1,193 participants in 6 studies. (Observational (non-randomized))	Studies found an association between increased lactate levels and increased volume of red blood cells transfused. Two studies reported OR range of 3.13 and 5.20 (OR values not reported for other studies).		Very low Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias <sup>2</sup>	Higher lactate levels are associated with higher volume of red blood cells transfused.

1. **Risk of Bias: serious.** 14 observational studies with concerns of bias due to study design, patient selection and reporting that seriously weaken the confidence in the results. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: serious.** Evidence is in trauma patients which is generally representative of trauma patients treated in Australia. Certainty of evidence not downgraded. Evidence is in a variety of differing healthcare settings such as the United States, Switzerland, France, South Africa, Japan and India. It is hard to judge whether it could be sensibly applied. Certainty of evidence downgraded. **Imprecision: no serious. Publication bias: no serious.**

2. **Risk of Bias: serious.** One or more observational studies with concerns of bias due to study design, patient selection and reporting that seriously weaken the confidence in the results. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** Evidence is in a variety of differing healthcare settings such as the United States, Switzerland, France, South Africa, Japan and India but could be sensibly applied. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: serious.** There is a strong suspicion of non-reporting of results likely to be related to P value, direction or magnitude of effect. Certainty of evidence downgraded.

## References

11. National Blood Authority. Update of the 2011 Patient Blood Management Guidelines for people with critical bleeding: Technical report Volume 1. Canberra: The Commonwealth of Australia as represented by the NBA 2022.

82. Lilitsis E, Xenaki S, Athanasakis E, Papadakis E, Syrogianni P, Chalkiadakis G, et al. Guiding Management in Severe Trauma: Reviewing Factors Predicting Outcome in Vastly Injured Patients. *Journal of Emergencies, Trauma, and Shock* 11(2):80-87 [Pubmed](#) [Journal](#)

84. Baxter J, Cranfield KR, Clark G, Harris T, Bloom B, Gray AJ. Do lactate levels in the emergency department predict outcome in adult trauma patients? A systematic review. *Journal of Trauma and Acute Care Surgery* 2016. [Website](#)

85. Tran A, Matar M, Lampron J, Steyerberg E, Taljaard M, Vaillancourt C. Early identification of patients requiring massive transfusion, embolization or hemostatic surgery for traumatic hemorrhage: A systematic review and meta-analysis. *The Journal of Trauma and Acute Care Surgery* 2018;84(3):505-516 [Pubmed Journal](#)

205. Javali RH, Ravindra P, Patil A, Srinivasarangan M, Mundada H, Adarsh SB, et al. A Clinical Study on the Initial Assessment of Arterial Lactate and Base Deficit as Predictors of Outcome in Trauma Patients. *Indian journal of critical care medicine : peer-reviewed, official publication of Indian Society of Critical Care Medicine* 2017;21(11):719-725 [Pubmed Journal](#)

209. Sawamura A, Hayakawa M, Gando S, Kubota N, Sugano M, Wada T, et al. Disseminated intravascular coagulation with a fibrinolytic phenotype at an early phase of trauma predicts mortality. *Thrombosis research* 2009;124(5):608-13 [Pubmed Journal](#)

## Clinical question/ PICO

**Population:** People with critical bleeding (any setting)

**Intervention:** Ionised calcium

**Comparator:** N/A

## Summary

Refer to the technical reports for further information on individual studies.

### What did we find?

Two reviews (Shih 2019 [83], Vasudeva 2021 [87]) were found that assessed the association between ionised calcium and outcomes in patients with critical bleeding. The reviews included evidence from 3 observational studies (Vasudeva 2020, Magnotti 2011, Cherry 2006). One additional study was included (Moore 2020 [86]), that assessed the association of hypocalcaemia and patient outcomes among participants enrolled in 2 RCTs.

### Study characteristics

All 5 studies were carried out in trauma centres in the United States and Australia and assessed the effect of ionised calcium on mortality in trauma patients with critical bleeding. Four studies (Vasudeva 2020, Magnotti 2011, Moore 2018, Sperry 2018) also assessed the effect of ionised calcium on transfusion volumes.

Moore 2020 evaluated the association between prehospital plasma and hypocalcaemia with lower survival using data collected from 2 RCTs in patients with blunt or penetrating injuries: COMBAT (Moore 2018 [210]), which enrolled adults aged 18 years or older and acute blood loss and PAMPer (Sperry 2018 [211]), which enrolled injured adults at risk of haemorrhagic shock. The review authors [86] noted limitations of the RCTs for the purposes of their meta-analysis, which included a lack of ionised calcium measurements for all enrolled patients, patient selection bias relating to pre-existing disease severity and survivor bias.

The quality of included observational studies was reported by Vasudeva 2021 [87] to be moderate, noting that none of the included studies were blinded, there was a lack of adjustment for confounders, and sample sizes were limited.

### What are the main results?

#### Mortality

The available evidence suggests hypocalcaemia (ionised calcium < 1.0 mmol/L) is associated with an increased risk of mortality. Four studies conducted in the trauma settings contributed data, with pooled (unadjusted) data suggesting the mortality rate to be 24% among those with hypocalcaemia, compared with 15% among those with normocalcaemia (OR 1.87; 95% CI 1.27, 2.75; P = 0.001; random effects,  $I^2 = 0\%$ ). After adjustment for confounders (age, injury severity score (ISS), Shock index), one study (Moore 2020) suggested hypocalcaemia to be independently associated with survival (hazard ratio (HR) 1.07; 95% CI 1.02, 1.13; P = 0.01).

#### Transfusion volume

Only limited conclusions can be drawn from the available evidence which suggests a significant association between hypocalcaemia and increased volume of red blood cells, plasma and cryoprecipitate transfused. Data from one study found a significant association between low ionised calcium levels and increased volume of red blood cells transfused within 24 hours (P = 0.0002). The same study also suggested a significant association between low ionised calcium levels and increased volume of plasma (P = 0.007) and cryoprecipitate (P = 0.0003) transfused within 24 hours. Two other studies report a significant association between low ionised calcium levels and increased need for massive/multiple transfusions (> 5 or >10 Units of red blood cells transfused).

Outcome Timeframe	Study results and measurements	Comparator N/A	Intervention	Certainty of the Evidence (Quality of evidence)	Summary
Mortality, all cause latest reported timepoint  9 Critical	Based on data from 1,373 participants in 4 studies. <sup>1</sup> (Observational (non-randomized))	A significant association between low ionised calcium levels and mortality observed (OR 1.87; 95% CI 1.27, 2.75; P = 0.001; random effects, $I^2 = 0\%$ )		Very low Due to serious risk of bias, Due to serious imprecision <sup>2</sup>	Hypocalcaemia (<1mmol/L ionised calcium) is associated with higher mortality.
Red blood cell transfusion volume	Based on data from 977 participants in 3 studies. (Observational (non-randomized))	Data from one study suggested a significant association between low ionised calcium levels and increased volume of red blood cells transfused within 24 hours (P = 0.0002). Two other studies report a significant association between low ionised calcium levels and increased need for massive/multiple transfusions (> 5 or >10 units of red blood cells transfused).		Very low Due to serious risk of bias, Due to serious imprecision <sup>3</sup>	Hypocalcaemia (<1 mmol/L ionised calcium) is associated with higher volume of red blood cells transfused.

Outcome Timeframe	Study results and measurements	Comparator N/A	Intervention	Certainty of the Evidence (Quality of evidence)	Summary
Transfusion volume, other blood components/ products	Based on data from 160 participants in 1 studies. <sup>4</sup> (Observational (non- randomized))	Data from one study suggested a significant association between low ionised calcium levels reported and increased volume of plasma (P = 0.007) and cryoprecipitate (P = 0.0003) transfused within 24 hours.		Very low Due to serious risk of bias, Due to serious imprecision <sup>5</sup>	Hypocalcaemia (<1mmol/L ionised calcium) is associated with higher volume of blood components/ products (red blood cells, plasma and cryoprecipitate) transfused.

1. Systematic review **Supporting references:** [211], [210], [86], [83], [87],
2. **Risk of Bias: serious.** Several observational studies with concerns of bias due to study design, patient selection and reporting that seriously weaken the confidence in the results. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** Evidence is across similar healthcare settings such as the United States, United Kingdom, Netherlands, Norway, France and Australia and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.**
3. **Risk of Bias: serious.** Several observational studies with concerns of bias due to study design, patient selection and reporting that seriously weaken the confidence in the results. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** Evidence is across similar healthcare settings such as the United States, United Kingdom, Netherlands, Norway, France and Australia and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Low number of patients. Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.**
4. Systematic review **Supporting references:** [86],
5. **Risk of Bias: serious.** Analysis of single arm data from 2 RCTs. Concerns of bias related to missing data, confounding and survivor bias. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** Evidence is in the United States and Australia and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Low number of patients. Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.**

## References

11. National Blood Authority. Update of the 2011 Patient Blood Management Guidelines for people with critical bleeding: Technical report Volume 1. Canberra: The Commonwealth of Australia as represented by the NBA 2022.
83. Shih AW, Al Khan S, Wang AY-H, Dawe P, Young PY, Greene A, et al. Systematic reviews of scores and predictors to trigger activation of massive transfusion protocols. The journal of trauma and acute care surgery 2019;87(3):717-729 [Pubmed](#) [Journal](#)
86. Moore HB, Tessmer MT, Moore EE, Sperry JL, Cohen MJ, Chapman MP, et al. Forgot calcium? Admission ionized-calcium in two civilian randomized controlled trials of prehospital plasma for traumatic hemorrhagic shock. The Journal of Trauma and Acute Care Surgery 2020;88(5):588-596

### Pubmed Journal

87. Vasudeva M, Mathew JK, Groombridge C, Tee JW, Johnny CS, Maini A, et al. Hypocalcemia in trauma patients: A systematic review. *The Journal of Trauma and Acute Care Surgery* 2021;90(2):396-402 [Pubmed Journal](#)

210. Moore HB, Moore EE, Chapman MP, McVane K, Bryskiewicz G, Blechar R, et al. Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial. *Lancet (London, England)* 2018;392(10144):283-291 [Pubmed Journal](#)

211. Sperry JL, Guyette FX, Brown JB, Yazer MH, Triulzi DJ, Early-Young BJ, et al. Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock. *The New England journal of medicine* 2018;379(4):315-326 [Pubmed Journal](#)

### Clinical question/ PICO

**Population:** People with critical bleeding (any setting)

**Intervention:** Haemoglobin

**Comparator:** N/A

### Summary

Refer to the [technical reports](#) for further information on individual studies.

### What did we find?

Two reviews (Shih 2019 [83], Tran 2018 [85]) were found that included evidence from 5 observational studies (Callcut 2013, Callcut 2011, Leemann 2010, Schöch I 2011, Schreiber 2007) that assessed the association between haemoglobin levels and transfusion volume requirement in trauma patients with critical bleeding. No studies assessed the association between haemoglobin and mortality in patients with critical bleeding.

### Study characteristics

The studies were carried out in trauma centres in the United States, Switzerland, Austria and Iraq. The quality of included studies was poor noting the frequent lack of justification, inadequate reporting and suboptimal handling of missing data [85].

### What are the main results?

#### Transfusion volume

Only limited conclusions can be drawn from the available evidence, which suggests there is a positive association between lower haemoglobin levels (< 11 g/L) and an increased risk of massive transfusion (10 or more red blood cell units within 6 hours) in the trauma setting. Reported OR in each study, ranged from 1.8 (1.3, 2.5) to 18.18 (2.73, 125.00).

Outcome Timeframe	Study results and measurements	Comparator N/A	Intervention Haemoglobin	Certainty of the Evidence (Quality of evidence)	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 5 studies. <sup>1</sup> (Observational (non-randomized))	Studies reported a significant association between lower haemoglobin levels (< 11 g/L) and an increased risk of massive transfusion (10 or more red blood cell units within 6 hours). Reported OR ranged between 1.8 - 18.18.		Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision <sup>2</sup>	Lower haemoglobin levels are associated with increased volume of red blood cells transfused.

1. Systematic review Participant numbers not reported for 2 of the 5 studies.. **Supporting references:** [85], [83],
2. **Risk of Bias: serious.** Several observational studies with concerns of bias related to study design, patient selection and reporting bias. Certainty of evidence downgraded . **Inconsistency: no serious. Indirectness: serious.** Evidence is in a variety of differing healthcare settings such as the United States, Switzerland and Iraq among adult trauma patients. It is hard to judge whether it could be sensibly applied. Certainty of evidence downgraded . **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.**

## References

11. National Blood Authority. Update of the 2011 Patient Blood Management Guidelines for people with critical bleeding: Technical report Volume 1. Canberra: The Commonwealth of Australia as represented by the NBA 2022.
83. Shih AW, Al Khan S, Wang AY-H, Dawe P, Young PY, Greene A, et al. Systematic reviews of scores and predictors to trigger activation of massive transfusion protocols. The journal of trauma and acute care surgery 2019;87(3):717-729 [Pubmed](#) [Journal](#)
85. Tran A, Matar M, Lampron J, Steyerberg E, Taljaard M, Vaillancourt C. Early identification of patients requiring massive transfusion, embolization or hemostatic surgery for traumatic hemorrhage: A systematic review and meta-analysis. The Journal of Trauma and Acute Care Surgery 2018;84(3):505-516 [Pubmed](#) [Journal](#)

## Clinical question/ PICO

**Population:** People with critical bleeding (any setting)  
**Intervention:** Platelet count

**Comparator:** N/A

## Summary

Refer to the technical reports for further information on individual studies.

### What did we find?

Two reviews (Poole 2016 [68], Levy 2017 [88]) were found that included evidence from 9 observational studies (Hagemo 2014, Mitra 2010, Arnold 2006, Fayed 2013, McGrath 2008, Premaratne 2001, Tanaka 2014, Wu 2014, van Hout 2017) that assessed the association between platelet count on mortality or transfusion volumes in patients with critical bleeding. The search also identified 3 additional studies (McQuilten 2017a [219], Kawatani 2016 [207], Sawamura 2009 [209]) that contributed data.

### Study characteristics

Two studies (Hagemo 2014, Mitra 2010) were carried out in trauma or emergency centres in the United States, United Kingdom, Norway and Australia. Seven studies (Arnold 2006, Fayed 2013, McGrath 2008, Premaratne 2001, Tanaka 2014, Wu 2014, van Hout 2017) were carried out in the perioperative surgical settings in the United States, Canada, Netherlands and Egypt. Overall, the included observational studies were considered to be at high risk of bias relating to selection bias and confounding, with issues arising due to variables used in prediction models.

McQuilten 2017a [219] was a prospective study that assessed the association of low fibrinogen levels with mortality in all adult trauma patients identified through a statewide trauma registry in Victoria (Australia). Data were available for 4772 patients who presented to the 2 major trauma hospitals between January 2008 and July 2011 and who had a fibrinogen level measured during initial resuscitation. In-hospital mortality was modelled using multiple logistic regression that included the following variables: age, gender, ISS, pH, temperature, GCS, injury type (blunt, penetrating, other), chest decompression, pulse and systolic BP on admission, time from injury to admission, Hb, platelet count, INR, APTT and fibrinogen level. The study had some concerns of bias relating to measurement of outcomes and missing data.

Kawatani 2016 [207] was a retrospective study of the medical records of 25 patients who underwent endovascular aortic repair (EVAR) for rAAAs at Chiba-Nishi General Hospital in Japan between October 2013 and December 2015. Major coagulopathy was defined using PT/INR or APTT ratio greater than 1.5 times the upper limit of normal, or platelet count less than  $50 \times 10^9/L$ . The study was judged to be at serious risk of bias due to patient selection bias and likely confounding.

Sawamura 2009 [209] was a retrospective cohort study conducted in Japan which aimed to assess the impact of DIC on patient outcomes. Data obtained at 4 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 non-survivors. The study had some concerns of bias relating to study design and inadequate reporting of data.

### What are the main results?



**Mortality**

The association between platelet count and mortality is unclear. Three studies suggested lower platelet counts are not associated with an increased risk of mortality in critically bleeding trauma or surgical patients (adjusted OR ranged between 0.99 and 1.0;  $P > 0.5$ ). One study (McQuilten 2017a) suggested platelet counts below  $100 \times 10^9/L$  to be independently associated with survival (adjusted OR 0.50; 95% CI 0.30, 0.84;  $P = 0.009$ ) (after adjustment for age, ISS, Shock index). One study (Sawamura 2009) suggested lower platelet counts were associated with increased prediction of death (stepwise logistic regression, OR 1.097; 95% CI 1.003, 1.116;  $P = 0.003$ ) (including DIC scores, lactate coagulation and fibrinolysis variables).

**Transfusion volume**

Only limited conclusions can be drawn from the available evidence. Included studies were in surgical settings and reported an association between low 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)	Summary
Mortality, all cause latest reported timepoint  9 Critical	Based on data from 6,762 participants in 5 studies. <sup>1</sup> (Observational (non- randomized))		The association between platelet count and mortality is unclear. Three studies reported no significant association (adjusted OR range between 0.99 and 1.0; $P > 0.5$ ). One study suggested an association with survival (adjusted OR 0.5) and one study suggested increased prediction for death (adjusted OR 1.097)	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency <sup>2</sup>	The association between platelet count and mortality is uncertain.
Transfusion volume	Based on data from 30,735 participants in 7 studies. (Observational (non-randomized))		Included studies used different measurements to trigger 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 serious imprecision <sup>3</sup>	Lower platelet counts are associated with higher volume of red blood cells transfused.

1. Systematic review **Supporting references:** [68], [219], [207], [209],
2. **Risk of Bias: serious.** Several observational studies with concerns of bias due to study design, patient selection and reporting that seriously weaken the confidence in the results. Certainty of evidence downgraded . **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. Certainty of evidence downgraded . **Indirectness: no serious.** Evidence is across similar healthcare settings such as the United States, United Kingdom, Netherlands, Norway, France and Australia and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded . **Imprecision: serious.** Increased uncertainty of precision of results related to platelet count cut-offs and measures. Certainty of evidence downgraded . **Publication bias: no**



**serious.**

3. **Risk of Bias: serious.** Several observational studies with concerns of bias due to study design, patient selection and reporting that seriously weaken the confidence in the results. Certainty of evidence downgraded . **Inconsistency: no serious. Indirectness: no serious.** Evidence is across similar healthcare settings such as the United States, United Kingdom, Netherlands, Norway, France and Australia and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded . **Imprecision: serious.** Confidence intervals not reported. Increased uncertainty of precision of results which reduces confidence in the results. Certainty of evidence downgraded . **Publication bias: no serious.**

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68. Poole D, Cortegiani A, Chierigato A, Russo E, Pellegrini C, De Blasio E, et al. Blood Component Therapy and Coagulopathy in Trauma: A Systematic Review of the Literature from the Trauma Update Group. *PloS One* 2016;11(10):e0164090 [Pubmed Journal](#)

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207. Kawatani Y, Nakamura Y, Kurobe H, Suda Y, Hori T. Correlations of perioperative coagulopathy, fluid infusion and blood transfusions with survival prognosis in endovascular aortic repair for ruptured abdominal aortic aneurysm. *World journal of emergency surgery : WJES* 2016;11:29 [Pubmed Journal](#)

209. Sawamura A, Hayakawa M, Gando S, Kubota N, Sugano M, Wada T, et al. Disseminated intravascular coagulation with a fibrinolytic phenotype at an early phase of trauma predicts mortality. *Thrombosis research* 2009;124(5):608-13 [Pubmed Journal](#)

219. McQuilten ZK, Wood EM, Bailey M, Cameron PA, Cooper DJ. Fibrinogen is an independent predictor of mortality in major trauma patients: A five-year statewide cohort study. *Injury* 2017;48(5):1074-1081 [Pubmed Journal](#)

**Clinical question/ PICO**

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

**Summary**

Refer to the technical reports for further information on individual studies.

**What did we find?**

Five reviews (Shih 2019 [83], Lilitis 2018 [82], Tran 2018 [85], Poole 2016 [68], Haas 2015 [166]) were found that included evidence from 8 observational studies that assessed the association between PT/INR and patient outcomes in patients with critical bleeding (Hagemo 2014, Callcut 2013, Vandromme 2011, Mitra 2010, Hess 2009, Mitra 2007, Schreiber 2007, Macleod 2003). The literature search also identified 3 non-randomised cohort studies that assessed the association between PT/INR and mortality (McQuilten 2017a [219], Kawatani 2016 [207], Noorbhai 2016 [208]) 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, United Kingdom, Norway, Australia and Iraq and typically used an INR value 1.5 times the upper limit of normal as reference. Five studies (Hagemo 2014, Mitra 2010, Hess 2009, Mitra 2007, Macleod 2003) assessed the effect of PT/INR on mortality and 3 studies assessed the effect of PT/INR on transfusion volume requirements in trauma patients with critical bleeding (Callcut 2013, Vandromme 2011, Schreiber 2007). Overall, risk of bias for included observational studies was judged to be high for inadequate control for confounding, study design and reporting.

McQuilten 2017a [219] was a prospective study that assessed the association of low fibrinogen levels with mortality in all adult trauma patients identified through a state-wide trauma registry in Victoria (Australia). Data were available for 4772 patients who presented to the 2 major trauma hospitals between January 2008 and July 2011 and who had a fibrinogen level measured during initial resuscitation. In-hospital mortality was modelled using multiple logistic regression that included the following variables: age, gender, ISS, pH, temperature, GCS, injury type (blunt, penetrating, other), chest decompression, pulse and systolic BP on admission, time from injury to admission, Hb, platelet count, INR, APTT and fibrinogen level. The study had some concerns of bias relating to measurement of outcomes and missing data.

Kawatani 2016 [207] was a retrospective study of the medical records of 25 patients who underwent EVAR for rAAAs at Chiba-Nishi General Hospital in Japan between October 2013 and December 2015. Major coagulopathy was defined using a PT/INR or APTT ratio greater than 1.5 times the upper limit of normal, or platelet count less than  $50 \times 10^9/L$ . This study was found to be at serious risk of bias due to patient selection bias and lack of control for confounding factors.

Noorbhai 2016 [208] was a retrospective cohort study that aimed to assess the correlation between coagulopathy (INR) and mortality in 1000 patients admitted to a level 1 trauma unit in South Africa. INRs were not recorded in 61 patients and were therefore excluded from the analysis to a total of 939 remaining patients. The INR was dichotomised into  $\leq 1.2$  and  $> 1.2$ , then correlated with ISS and in-hospital mortality. This study was found to have serious risk of bias due to inadequate reporting of follow-up and lack of control for confounding factors.

**What are the main results?****Mortality**

Identified literature suggests an increased risk of mortality associated with abnormal PT/INR among patients with

critical bleeding in the trauma setting. Adjusted OR ranged from 1.35 to 3.23 for elevated PT/INR measured against normal (INR < 1.5). One study in patients undergoing EVAR reported no significant association ( $P > 0.05$ ) but there were too few patients for any meaningful analysis.

### Transfusion volume

Only limited conclusions can be drawn from the available evidence. Included studies were in trauma settings, reporting an INR more than 1.5 was associated with an increased risk of massive transfusion (10 or more units of red blood cells) (OR ranged from 2.1 to 5.9).

Outcome Timeframe	Study results and measurements	Comparator N/A	Intervention PT/INR	Certainty of the Evidence (Quality of evidence)	Summary
Mortality, all cause latest reported timepoint  9 Critical	Based on data from 50,466 participants in 7 studies. <sup>1</sup> (Observational (non-randomized))	Seven studies reported an association between high PT/INR and mortality in the trauma setting (adjusted OR ranged between 1.35 to 3.23).		Very low Due to serious risk of bias, Due to serious imprecision <sup>2</sup>	Abnormal PT/INR (INR >1.2) is associated with higher mortality.
Transfusion volume	Based on data from 2,109 participants in 3 studies. <sup>3</sup> (Observational (non-randomized))	Studies found an association between high PT/INR and increased transfusion volumes. OR range 2.1 to 5.9. Participant numbers not reported.		Very low Due to serious risk of bias, Due to serious indirectness <sup>4</sup>	Abnormal PT/INR (>1.5) is associated with higher volume of red blood cells transfused.

1. Systematic review **Supporting references:** [68], [166], [207], [208], [219],
2. **Risk of Bias: serious.** Eight observational studies with concerns of bias due to study design, patient selection and reporting that seriously weaken the confidence in the results. Certainty of evidence downgraded . **Inconsistency: no serious. Indirectness: no serious.** Evidence is in a variety of differing healthcare settings such as the United States, Switzerland, France, South Africa, Japan and India. Certainty of evidence not downgraded . **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded . **Publication bias: no serious.**
3. Systematic review Participant numbers not reported. **Supporting references:** [85], [83],
4. **Risk of Bias: serious.** Three observational studies with concerns of bias due to study design, patient selection and reporting. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** Evidence is in a variety of differing healthcare settings such as the United States, Switzerland, France, South Africa, Japan and India but could be sensibly applied. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded . **Publication bias: no serious.**

### References

11. National Blood Authority. Update of the 2011 Patient Blood Management Guidelines for people

with critical bleeding: Technical report Volume 1. Canberra: The Commonwealth of Australia as represented by the NBA 2022.

68. Poole D, Cortegiani A, Chierigato A, Russo E, Pellegrini C, De Blasio E, et al. Blood Component Therapy and Coagulopathy in Trauma: A Systematic Review of the Literature from the Trauma Update Group. *PloS One* 2016;11(10):e0164090 [Pubmed Journal](#)

82. Lilitsis E, Xenaki S, Athanasakis E, Papadakis E, Syrogianni P, Chalkiadakis G, et al. Guiding Management in Severe Trauma: Reviewing Factors Predicting Outcome in Vastly Injured Patients. *Journal of Emergencies, Trauma, and Shock* 11(2):80-87 [Pubmed Journal](#)

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166. Haas T, Fries D, Tanaka KA, Asmis L, Curry NS, Schöchl H. Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence?. *British Journal of Anaesthesia* 2015;114(2):217-24 [Pubmed Journal](#)

207. Kawatani Y, Nakamura Y, Kurobe H, Suda Y, Hori T. Correlations of perioperative coagulopathy, fluid infusion and blood transfusions with survival prognosis in endovascular aortic repair for ruptured abdominal aortic aneurysm. *World journal of emergency surgery : WJES* 2016;11:29 [Pubmed Journal](#)

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219. McQuilten ZK, Wood EM, Bailey M, Cameron PA, Cooper DJ. Fibrinogen is an independent predictor of mortality in major trauma patients: A five-year statewide cohort study. *Injury* 2017;48(5):1074-1081 [Pubmed Journal](#)

### Clinical question/ PICO

**Population:** People with critical bleeding (any setting)

**Intervention:** APTT

**Comparator:** N/A

### Summary

Refer to the technical reports for further information on individual studies.

**What did we find?**

Three reviews (Poole 2016 [68], Lilitis 2018 [82], Haas 2015 [166]) were found that included evidence from 7 observational studies that assessed the association between APTT and mortality and transfusion volumes in trauma patients with critical bleeding (Rourke 2012, Sambavisan 2011, Mitra 2007, Macleod 2003, Murray 1998, Ciavarella 1987, Mannucci 1982). The literature search also identified one retrospective cohort study (Kawatani 2016 [207]) that reported data for the surgical setting.

**Study characteristics**

Five studies (Rourke 2012, Sambavisan 2011, Mitra 2007, Macleod 2003, Ciavarella 1987) assessed the association between APTT and mortality in trauma patients with critical bleeding. Two studies (Murray 1998, Mannucci 1982) assessed the association between APTT and transfusion volume in trauma patients with critical bleeding. All studies identified in the systematic reviews were carried out in trauma centres in the United States, United Kingdom, Norway, Italy and Australia. Overall, risk of bias for included observational studies was judged to be unclear or high due to study design, reporting and confounding.

Kawatani 2016 [207] was a retrospective study of the medical records of 25 patients who underwent EVAR for rAAAs at Chiba-Nishi General Hospital in Japan between October 2013 and December 2015. Major coagulopathy was defined using a PT/INR or APTT ratio greater than 1.5 times the upper limit of normal, or platelet count less than  $50 \times 10^9/L$ . 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 a prolonged APTT among patients with critical bleeding. Six studies in trauma patients and one study in the surgical setting contributed data reporting OR ranging from 1.01 to 4.26.

**Transfusion volume**

Only limited conclusions can be drawn from the available evidence, with studies in trauma and surgical settings reporting an association between prolonged APTT and increased risk of massive transfusion in patients with critical bleeding.

Outcome Timeframe	Study results and measurements	Comparator N/A	Intervention APTT	Certainty of the Evidence (Quality of evidence)	Summary
Mortality, all	Based on data from	Five studies reported an association		Very low	Prolonged APTT is associated with higher

Outcome Timeframe	Study results and measurements	Comparator N/A	Intervention APTT	Certainty of the Evidence (Quality of evidence)	Summary
cause latest reported timepoint  9 Critical	9,516 participants in 6 studies. (Observational (non-randomized))	between prolonged APTT and mortality (4 studies reported OR range 1.01 and 4.26, one study reported no risk data).		Due to serious risk of bias, Due to serious imprecision <sup>1</sup>	mortality.
Transfusion volume	Based on data from participants in 2 studies. (Observational (non- randomized))	Studies reported an association between prolonged APTT and the need for increased transfusion volume. No risk data reported.		Very low Due to serious risk of bias, Due to serious imprecision <sup>2</sup>	Prolonged APTT is associated with higher volumes of red blood cells transfused.

- 1. Risk of Bias: serious.** Seven observational studies with concerns of bias due to study design, patient selection and reporting that seriously weaken the confidence in the results. Certainty of evidence downgraded . **Inconsistency: no serious. Indirectness: no serious.** Evidence is across similar healthcare settings such as the United States, United Kingdom, Netherlands, Norway, France and Australia and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded . **Imprecision: serious.** Wide confidence intervals. Low number of patients. Certainty of evidence downgraded . **Publication bias: no serious.**
- 2. Risk of Bias: serious.** Two observational studies with concerns of bias due to study design, patient selection and reporting that seriously weaken the confidence in the results. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** Evidence is across similar healthcare settings such as the United States, United Kingdom, Netherlands, Norway, France and Australia and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded . **Imprecision: serious.** Confidence intervals not reported. Increased uncertainty of precision of results which reduces confidence in the results. Certainty of evidence downgraded . **Publication bias: no serious.**

## References

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68. Poole D, Cortegiani A, Chieragato A, Russo E, Pellegrini C, De Blasio E, et al. Blood Component Therapy and Coagulopathy in Trauma: A Systematic Review of the Literature from the Trauma Update Group. *PloS One* 2016;11(10):e0164090 [Pubmed Journal](#)
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166. Haas T, Fries D, Tanaka KA, Asmis L, Curry NS, Schöchl H. Usefulness of standard plasma coagulation tests in the management of perioperative coagulopathic bleeding: is there any evidence?. *British Journal of Anaesthesia* 2015;114(2):217-24 [Pubmed Journal](#)

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## Clinical question/ PICO

**Population:** People with critical bleeding (any setting)

**Intervention:** Fibrinogen levels

**Comparator:** N/A

## Summary

Refer to the technical reports for further information on individual studies.

### What did we find?

Three reviews (Shih 2019 [83], Poole 2016 [68], Abdul-Kadir 2014 [89]) were found that included evidence from 7 observational studies (Nakamura 2017, Hagemo 2014, Cortet 2012, Peyvandi 2012, Rourke 2012, Charbit 2007, Rouse 2006) that assessed the association between fibrinogen levels and mortality, and fibrinogen levels and red blood cell transfusion volume in patients with critical bleeding (Nakamura 2017, Hagemo 2014, Cortet 2012, Peyvandi 2012, Rourke 2012, Charbit 2007, Rouse 2006). The literature search also identified 4 non-randomised cohort studies (Gaessler 2021 [206], McQuilten 2017a [219], McQuilten 2017b [218], Sawamura 2009 [209]) that assessed the association between fibrinogen levels and patient outcomes.

### Study characteristics

Two studies assessed the effect of fibrinogen levels on mortality (Hagemo 2014, Rourke 2012) and 5 studies assessed the effect of fibrinogen levels on red blood cell transfusion volume (Nakamura 2017, Cortet 2012, Peyvandi 2012, Charbit 2007, Rouse 2006). Three studies were carried out in trauma centres in the United States, United Kingdom, Norway, and Japan and 4 studies were carried out in obstetric settings in the United States, France and Italy. Overall, included studies was judged to be high risk of bias due to study design, confounding and reporting biases.

Gaessler 2021 [206] was a prospective observational study conducted at a single centre in Germany that assessed the impact of coagulopathy in 148 injured patients who were treated by the Helicopter Emergency Medical Service and transported to Level 1 trauma centres. This study was found to be at moderate risk of bias related to patient selection bias.

McQuilten 2017a [219] was a prospective cohort study that assessed the association of low fibrinogen levels with mortality in all adult trauma patients identified through a statewide registry that prospectively collects data on all major trauma patients in Victoria (Australia). Data were available for 4772 patients who presented to the 2 major trauma hospitals between January 2008 and July 2011 and who had a fibrinogen level measured during initial resuscitation. Similarly, McQuilten 2017b [218] was a retrospective study that assessed the prognostic value of

fibrinogen levels on mortality and transfusion volume in adult trauma patients who received massive transfusion in hospitals across Australia and New Zealand. Data were available for 2829 patients who received a massive transfusion (defined as 5 or more units of red blood cells within any 4-hour period during admission) between April 2011 and October 2015. Both studies had some concerns of bias relating to measurement of outcomes and missing data.

Sawamura 2009 [209] was a retrospective cohort study conducted in Japan that aimed to assess the impact of DIC on patient outcomes. Data obtained at 4 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 non-survivors. This study was at serious risk of bias due to patient selection, likely confounding and inadequate reporting of data.

### What are the main results?

#### Mortality

The available evidence suggests low fibrinogen levels are associated with an increased risk of mortality among patients with critical bleeding. Definitions of low fibrinogen levels varied across the studies, but levels less than 1.5 g/L were generally considered to have a significant association with mortality. Two studies reported an adjusted OR that ranged between 1.29 and 3.28 for fibrinogen levels lower than 2.0 g/L and 3 studies reported an association with survival (OR ranged between 0.08 to 0.99). One study did not provide usable data.

One study also reported fibrinogen levels above 4 g/L to be associated with an increased risk of mortality (OR 2.03; 95% CI 1.35, 3.40; P = 0.001) in patients who had received a massive transfusion (compared against fibrinogen levels between 2 to 4 g/L).

#### Transfusion volume

Only limited conclusions can be drawn from the available evidence. Evidence was from 6 studies in the trauma and obstetrics setting, with 5 studies reporting a significant 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)	Summary
Mortality, all cause latest reported timepoint  9 Critical	Based on data from 9,714 participants in 6 studies. <sup>1</sup> (Observational (non- randomized))	Five studies reported an association between low fibrinogen levels and survival (adjusted OR range 0.08 to 0.22) or mortality (adjusted OR range 1.29 and 12.5). One study suggested a correlation with mortality but did not provide any data.		Very low Due to serious risk of bias, Due to serious imprecision <sup>2</sup>	Lower fibrinogen levels are associated with higher mortality.



Outcome Timeframe	Study results and measurements	Comparator N/A	Intervention	Certainty of the Evidence (Quality of evidence)	Summary
Transfusion volume	Based on data from 625 participants in 5 studies. (Observational (non-randomized))	Four studies reported an association between low fibrinogen levels and transfusion volume (one study reported OR 0.931, 3 studies did not report risk data). One study was unable to determine an association. Participant numbers for 4 studies not reported.		Very low Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias <sup>3</sup>	Lower fibrinogen levels are associated with higher volume of red blood cells transfused.

1. Systematic review **Supporting references:** [209], [219], [68], [218], [206],
2. **Risk of Bias: serious.** Several observational studies with concerns of bias relating to study design, patient selection and reporting. Certainty of evidence downgraded . **Inconsistency: no serious. Indirectness: no serious.** Evidence is in a variety of differing healthcare settings such as the United States, Switzerland, France, South Africa, Japan and India. Certainty of evidence not downgraded . **Imprecision: serious.** Wide confidence intervals. Low number of patients. Certainty of evidence downgraded . **Publication bias: no serious.**
3. **Risk of Bias: serious.** One or more observational studies with concerns of bias due to study design, patient selection and reporting that seriously weaken the confidence in the results. Certainty of evidence downgraded . **Inconsistency: no serious. Indirectness: no serious.** Evidence was from obstetric patients across similar healthcare settings such as the United States, United Kingdom, Netherlands, Norway, France and Australia and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded . **Imprecision: serious.** Confidence intervals not reported. Increased uncertainty of precision of results which reduces confidence in the results. Certainty of evidence downgraded. **Publication bias: serious.** There is a strong suspicion of non-reporting of results likely to be related to P value, direction or magnitude of effect. Certainty of evidence downgraded.

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#### Good practice statement

**GPS2:** Values indicative of critical physiological derangement include:

- temperature < 35°C
- pH < 7.2, base excess < -6 mmol/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 it is good practice to monitor the above parameters and include a full blood count on, or prior to, activation of a major haemorrhage protocol. Consider repeating after administration of every 4 units of red blood cells.

#### 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 appropriate patient care. The changes in full blood count (including haemoglobin and platelet count) and coagulation profiles during critical bleeding is dynamic and should be monitored frequently to guide additional therapy.

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

Refer to R2

### 7.1.2 Red blood cell to component ratio, timing and dose

**Research questions**

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

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

Literature search date: 29 September 2021

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

Weak recommendation , Very low certainty evidence

**R3:** In patients with critical bleeding managed with a ratio-based major haemorrhage protocol, 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 apheresis or pooled platelets in Australia is equivalent to platelets derived from 4 single whole blood donor units. A transfusion ratio of 1:1:1 would equate to 4 units of red blood cells, 4 units of FFP and 1 adult unit of platelets.*

*^A transfusion ratio of 2:1:1 of RBC:FFP:PLT is lower than a transfusion ratio of 1:1:1, as the number of units of red blood cells increases without a proportionate increase in FFP or platelets. A transfusion ratio of 2:1:1 would equate to 8 units of red blood cells, 4 units of FFP and 1 adult unit of platelets.*

**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 RCTs comparing transfusion ratios of 1:1:1 (high) versus 2:1:1 (low), little or no difference on mortality was demonstrated whereas in the meta-analysis of observational cohort studies a large effect on mortality was suggested. Confidence in the results is very low because the studies are susceptible to bias and there are inconsistencies in the results. Based on the available evidence the optimal ratio for RBC:FFP:PLT in patients with critical bleeding is unknown.

In the meta-analysis of RCTs, thromboembolic events and MOF rates did not differ among populations that received a high transfusion ratio compared to those who received a lower ratio, but the evidence is limited by low patient numbers and inconsistent reporting. 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 transfusion ratios 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 a transfusion ratio of at least 2:1:1 of RBC:FFP:PLT 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

As a ratio-based approach is widely used, the acceptability of a transfusion ratio of at least 2:1:1 of RBC:FFP:PLT was not explored.

## Feasibility

Important issues, or potential issues not investigated

The reference group acknowledged the logistical challenges associated with providing defined ratios of blood components to treat patients who are critically bleeding. Adaptation is required to implement a ratio-based MHP of at least 2:1:1 of RBC:FFP:PLT in facilities that are impacted by logistical requirements to store, supply and administer blood components (including platelets which have a short shelf life).

## Rationale

The evidence supports a transfusion ratio of at least 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

Refer to the technical reports for further information on individual studies.

### What did we find?

Numerous systematic reviews were found [52][60][63][64][65][66][67][68][69][70][212][230][231] that included evidence from 2 RCTs (Holcomb 2015, Nascimento 2013) and 11 non-randomised cohort studies (Balvers 2017, Duchesne 2008, Duchesne 2009, Hatimeier 2017, Holcomb 2011, Maegele 2008, Perkins 2009, Sambasivan 2011, Vulliamy 2017, Wafaisade 2011, Zink 2009) that evaluated different ratios of transfused blood components on patient outcomes in the trauma setting. Studies that assessed ratios of transfused blood components that did not meet the criteria for high (1:1:1) were not included in this review.

### Study characteristics

Two RCTs (Holcomb 2015 [214], Nascimento 2013 [213]) compared the effect of high (1:1:1) RBC:FFP:PLT

transfusion ratios to lower transfusion ratios on the 28-day mortality in trauma patients (aged 15 years or older) requiring massive transfusion. The 2 included RCTs were carried out in trauma centres in the United States and were judged by McQuilten 2018 [60] to be at high risk of bias, with blinding being the main sources of concern. 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.

Five cohort studies (Vulliamy 2017, Wafaisade 2011, Duchesne 2009, Maegele 2008, Duchesne 2008) assessed RBC:FFP ratios, 2 cohort studies (Holcomb 2011, Perkins 2009) assessed RBC:PLT ratios and 4 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 United States, United Kingdom, Germany, Netherlands, Denmark and Iraq. Overall, the risk of bias of included studies was judged by review authors [52][60][63][64][65][66][67][68][69][70][212][230][231] to be moderate with general concerns arising due to confounding.

## **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 transfusion ratios of blood components compared to those who received lower transfusion ratios with the 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 transfusion ratio of blood components (1:1:1) compared with 922 patients who received lower transfusion ratios, with significant difference observed (24.3% vs 31.4%, OR 0.38; 95% CI 0.22, 0.69; P = 0.001).

### **Morbidity**

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

Pooled data from 2 RCTs found no significant difference in MOF between patients who received a high ratio of blood components (21/375, 5.6%) compared with patients who received a lower ratio (15/374, 4%) (RR 1.39, 95% CI 0.73, 2.63; P = 0.32).

### **Red blood cell transfusion volumes**

Pooled data from 2 RCTs showed no significant difference in median volume of red blood cells transfused in the first 24-hours between patients receiving a high transfusion ratio of blood components compared to patients receiving a lower ratio (SMD -0.1; 95% CI -0.24, 0.05; P = 0.18, random effect,  $I^2 = 0\%$ ).

### **Transfusion volume, other blood components/products**

Pooled data from 2 RCTs in the trauma setting showed a significant increase in the volume of FFP transfused in the first 24-hours among patients receiving a high ratio of blood components compared to patients receiving a lower ratio (SMD 0.3; 95% CI 0.15, 0.44; P < 0.0001, random effect,  $I^2 = 0\%$ ).

Holcomb (2015) also suggested an increase in the volume of platelets (median 12 units vs 6 units) and cryoprecipitate (median 0 units vs 0 units) transfused among patients who received high ratio of blood components compared with those who did not, but data were skewed and the true difference is unclear.

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)	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. <sup>1</sup> (Randomized controlled)	249 per 1000  Difference:	314 per 1000  <b>65 more per 1000</b> ( CI 95% 127 fewer — 553 more )	Very low Due to very serious inconsistency, Due to very serious imprecision <sup>2</sup>	High transfusion ratios of (1:1:1) RBC:FFP:PLT 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. <sup>3</sup> (Observational (non- randomized))	314 per 1000  Difference:	148 per 1000  <b>166 fewer per 1000</b> ( CI 95% 223 fewer — 74 fewer )	Very low Due to serious risk of bias, Due to very serious inconsistency <sup>4</sup>	High transfusion ratios of (1:1:1) RBC:FFP:PLT may reduce mortality in trauma patients with critical bleeding but we are very uncertain about the evidence.
Morbidity, thromboemboli c events  6 Important	Relative risk 1.07 (CI 95% 0.7 — 1.63) Based on data from 680 participants in 1 studies. <sup>5</sup> (Randomized controlled)	108 per 1000  Difference:	116 per 1000  <b>8 more per 1000</b> ( CI 95% 32 fewer — 68 more )	Low Due to very serious imprecision <sup>6</sup>	High transfusion ratios of (1:1:1) RBC:FFP:PLT may have little or no difference on thromboembolic events in trauma patients with critical bleeding.
Morbidity, MOF  6 Important	Relative risk 1.39 (CI 95% 0.74 — 2.64) Based on data from 749 participants in 2 studies. <sup>7</sup> (Randomized controlled)	40 per 1000  Difference:	56 per 1000  <b>16 more per 1000</b> ( CI 95% 10 fewer — 66 more )	Low Due to very serious imprecision <sup>8</sup>	High transfusion ratios of (1:1:1) RBC:FFP:PLT may have little or no difference on MOF in trauma patients with critical bleeding.
Red blood cell transfusion volume	Measured by: Number of Units Lower better Based on data from 749 participants in 2 studies. <sup>9</sup> (Randomized controlled)	9 - 10.3 Units  Difference:	7.7 - 9.7 Units  <b>SMD 0.1 lower</b> ( CI 95% 0.24 lower — 0.05 higher )	Low Due to serious imprecision <sup>10</sup>	High transfusion ratios of (1:1:1) RBC:FFP:PLT may slightly reduce red blood cell transfusion volume in the first 24hrs in trauma patients with critical bleeding.

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)	Summary
Transfusion volume, other blood components/ products	Measured by: Number of Units of FFP transfused Lower better Based on data from 749 participants in 2 studies. <sup>11</sup> (Randomized controlled)	5 - 5.7 Units  Difference:	6 - 7.7 Units  <b>SMD 0.3 higher</b> ( CI 95% 0.15 higher — 0.44 higher )	Low Due to serious imprecision <sup>12</sup>	High transfusion ratios of (1:1:1) RBC:FFP:PLT may slightly increase the volume of FFP transfused in the first 24hrs in trauma patients with critical bleeding. The effect on other blood components/ products is unclear.

1. Systematic review [2] with included studies: Holcomb 2015 (RCT), Nascimento 2013 (RCT).

**Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [213], [214],

2. **Risk of Bias: no serious.** One or more randomised studies with overall low risk of bias. Certainty of evidence not downgraded. **Inconsistency: very serious.** Evidence is inconsistent. The magnitude of statistical heterogeneity was high ( $I^2 > 50\%$ ). Certainty of evidence downgraded 2 levels.

**Indirectness: no serious.** Evidence is in United States trauma patients, including both blunt and penetrating trauma and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: very serious.** Wide confidence interval (upper and lower bounds overlap with both effect and no effect). Low event rate in included studies that were not the optimal information size for the outcome of interest, Certainty of evidence downgraded 2 levels.

**Publication bias: no serious.**

3. Systematic review [2] with included studies: Zink 2009, Duchesne 2008, Vulliamy 2017, Perkins 2009, Duchesne 2009, Sambasivan 2011, Holcomb 2011, Wafaisade 2011, Maegele 2008, Haltmeier 2017. **Baseline/comparator:** Control arm of reference used for intervention.

4. **Risk of Bias: serious.** Several comparative observational studies with high concerns of bias due to study design and reporting which reduces confidence in results. Certainty of evidence downgraded.

**Inconsistency: very serious.** The magnitude of statistical heterogeneity was high ( $I^2 = 88\%$ ). Point estimates vary widely. The confidence interval of some of the studies do not overlap with the point estimate of some of the included studies. Certainty of evidence downgraded 2 levels. **Indirectness: no serious.** Evidence is in trauma patients in Germany, United States, United Kingdom and Iraq and includes both blunt and penetrating trauma. Evidence could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: no serious. Publication bias: no serious.**

5. Systematic review [2] with included studies: Holcomb 2015 (RCT). **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [231],

6. **Risk of Bias: no serious.** One randomised study with overall low risk of bias. Certainty of evidence not downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: no serious.** The available evidence is in United States patients with blunt and penetrating trauma and can be sensibly applied to the Australian healthcare context (noting blunt trauma is predominant in Australia). Certainty of evidence not downgraded. **Imprecision: very serious.** Wide confidence intervals and low number of patients. Certainty of evidence is downgraded 2 levels. **Publication bias: no serious.**

7. Systematic review [2] with included studies: Holcomb 2015 (RCT), Nascimento 2013 (RCT).

**Baseline/comparator:** Control arm of reference used for intervention.



8. **Risk of Bias: no serious.** One or more randomised studies with overall low risk of bias. Certainty of evidence not downgraded. **Inconsistency: no serious.** No significant heterogeneity, with no variability in effect estimates ( $I^2 = 0\%$ ). All studies consistent. Certainty of evidence not downgraded.

**Indirectness: no serious.** Evidence is from the United States which could be sensibly applied to the Australian healthcare context. Evidence is in trauma patients, including blunt and penetrating trauma. Blunt trauma is the predominant trauma treated in Australia. Evidence could be sensibly generalised to the Australian trauma population. Certainty of evidence not downgraded. **Imprecision: very serious.** Wide confidence intervals that cross the line of no effect. Confidence in the results is weak. Low event rates unlikely to be sufficiently powered to detect a statistically significant difference. Certainty of evidence is downgraded 2 levels. **Publication bias: no serious.**

9. Systematic review [2] with included studies: Holcomb 2015 (RCT), Nascimento 2013 (RCT).

**Baseline/comparator:** Systematic review [2] with included studies: Holcomb 2015 (RCT), Nascimento 2013 (RCT).

10. **Risk of Bias: no serious.** One or more randomised studies with overall low risk of bias. Certainty of evidence not downgraded. **Inconsistency: no serious.** **Indirectness: no serious.** Evidence is in United States trauma patients, including both blunt and penetrating trauma. The evidence could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded.

**Imprecision: serious.** Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded. **Publication bias: no serious.**

11. Systematic review [2] with included studies: Holcomb 2015 (RCT), Nascimento 2013 (RCT).

**Baseline/comparator:** Systematic review.

12. **Risk of Bias: no serious.** One or more randomised studies with overall low risk of bias. Certainty of evidence not downgraded. **Inconsistency: no serious.** **Indirectness: no serious.** Evidence is in United States trauma patients, including blunt and penetrating trauma which could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded. **Publication bias: no serious.**

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## 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

Refer to the technical reports for further information on individual studies.

### What did we find?

One systematic review (Phillips 2021 [71]) was found that included evidence from 7 non-randomised cohort studies (Hall 2013, Henriksson 2012, Johansson 2007, Johansson 2008, Kauvar 2011, Mell 2010, Tadlock 2010) evaluating the effect of different blood component ratios on patient outcomes in the surgical setting.

### Study characteristics

All studies included patients with rAAAs. Five studies (Hall 2013, Henriksson 2012, Johansson 2007, Johansson 2008, Tadlock 2010) defined a high ratio of FFP: packed red blood cells as 1:1 and 2 studies (Kauvar 2011, Mell 2010) did not define a high transfusion ratio. All 7 studies were carried out in single-centre surgical settings in North America and Denmark. Overall, review authors [71] judged included studies as serious risk of bias, with a significant amount of bias arising from confounding and patient selection.

### What are the main results?

#### Mortality

Among patients with rAAAs, the observed mortality rate of 23.6% (88/373) among patients receiving a high transfusion ratio was significantly different to the mortality rate of 46.4% (143/308) among patients receiving lower transfusion ratios. This corresponded to an 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)	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. <sup>1</sup> (Observational (non- randomized))	464 per 1000  Difference:	262 per 1000  <b>202 fewer per 1000</b> ( CI 95% 280 fewer — 111 fewer )	Very low Due to serious risk of bias <sup>2</sup>	High transfusion ratios of (1:1:1) RBC:FFP:PLT may reduce mortality in the surgical setting but the evidence is very uncertain.

1. Systematic review [2] with included studies: Hall 2013, Johansson 2007, Mell 2010, Henriksson 2012, Johansson 2008, Tadlock 2010. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** One or more comparative observational studies with serious concerns of bias due to study design and reporting which reduces confidence in results. Certainty of evidence downgraded. **Inconsistency: no serious.** No significant statistical heterogeneity ( $I^2 = 15\%$ ). Certainty of evidence not downgraded. **Indirectness: no serious.** Evidence is in United States and Denmark

surgical patients which is generalisable to Australian surgical patients and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: no serious.**  
**Publication bias: no serious.**

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### Clinical question/ PICO

**Population:** People at risk of critical bleeding (any setting)

**Intervention:** Increasing red blood cell transfusion volumes

**Comparator:**

### Summary

Refer to the technical reports for further information on individual studies.

#### What did we find?

One systematic review (Patel 2014 [72]) was found that included evidence from 23 non-randomised cohort studies that investigated the association between the transfusion of increasing volumes of red blood cells and health outcomes in patients at risk of clinical bleeding in the trauma setting. The literature search found 2 additional studies (Liu 2018 [215], Hassainien 2015 [216]) that contributed data.

#### Study characteristics

The systematic review included observational cohort studies that 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 ISS). Review authors attempted to mitigate confounding by only including studies that attempted to adjust for injury severity in the pooled analysis [72].

Among the 10 prospective cohort studies conducted in the trauma setting, 5 studies (Liu 2018, Bochicchio 2008, Silverboard 2005, Dunne 2004, Malone 2003) assessed the association between red blood cell transfusion and mortality, 4 studies (Ciesla 2005, Johnson 2010, Moore 1997, Sauaia 1994) assessed the association between red blood cell transfusion and MOF and one study (Edens 2010) that assessed the association between red blood cell transfusion and acute lung injury. One study (Liu 2018) also investigated the association between red blood cell transfusion and hospital length of stay (LOS).

Among the 13 retrospective cohort studies conducted in the trauma setting, 10 studies (Barbosa 2011, Chaiwat 2009, Mahambrey 2009, Murrell 2005, Phelan 2010, Robinson 2005, Spinella 2008, Croce 2005, Teixeira 2008, Weinberg 2008) examined the association between red blood cell transfusion and mortality, one study (Cotton 2009) assessed the association between red blood cell transfusion and MOF and 3 studies (Plurad 2007, Weinberg 2008, Croce 2005) assessed the association between red blood cell transfusion and ARDS.

Liu 2018 [215] was a prospective cohort study conducted at a single centre in the United States that investigated the association between red blood cell 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 red blood cells 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 [216] was a retrospective cohort study conducted at a single hospital in Egypt. The study included 70 patients with liver cirrhosis and hepatocellular carcinoma presenting with acute upper gastrointestinal bleeding. Patients must have met criteria of either hematemesis or melena with a diagnostic panendoscopy, or both. The study was considered to be at moderate risk of bias due to a lack of details regarding patient selection and study design.

### **What are the main results?**

#### **Mortality**

Nine studies assessed the effect of red blood cell transfusion on mortality as a continuous variable. Identified literature suggests transfusion of increased number of red blood cells 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 red blood cell unit transfused (OR 1.07; 95% CI 1.04, 1.10;  $P < 0.001$ ).

#### **Morbidity**

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

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

Outcome Timeframe	Study results and measurements	Comparator	Intervention Increasing red blood cell transfusion volumes	Certainty of the Evidence (Quality of evidence)	Summary
Mortality, all cause (Coh) latest reported timepoint  9 Critical	Based on data from 18,009 participants in 9 studies. <sup>1</sup> (Observational (non- randomized))	The odds of mortality increases with each additional red blood cell unit transfused OR 1.07 (95% CI 1.04, 1.10).		Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision <sup>2</sup>	Each additional red blood cell unit transfused is associated with higher mortality.
Morbidity, MOF (Coh) Any timepoint  6 Important	Based on data from 3,050 participants in 3 studies. (Observational (non-randomized))	The odds of MOF increases with each additional red blood cell unit transfused OR 1.08 (95% CI 1.02, 1.14).		Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision <sup>3</sup>	Each additional red blood cell unit transfused is associated with higher risk of MOF.
Morbidity, ARDS (Coh) Any timepoint  6 Important	Based on data from 14,136 participants in 2 studies. (Observational (non-randomized))	The odds of ARDS increases with each additional red blood cell unit transfused OR 1.06 (95% CI 1.03, 1.10).		Very low Due to serious risk of bias, Due to serious imprecision <sup>4</sup>	Each additional red blood cell unit transfused is associated with higher risk of ARDS.

1. Systematic review [72].

2. **Risk of Bias: serious.** More than one observational study at risk of bias due to patient selection and comparability which weakens the confidence in the results. Certainty of evidence downgraded.

**Inconsistency: serious.** The magnitude of statistical heterogeneity was high ( $I^2 = 83\%$ ). The direction of the effect is not consistent between the included studies. Certainty of evidence downgraded. **Indirectness: no serious.** Evidence is in United States and Canadian trauma patients which is generalisable to the Australian trauma patient and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.**

3. **Risk of Bias: serious.** More than one observational study at risk of bias due to patient selection and comparability which weakens the confidence in the results. Certainty of evidence downgraded. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high ( $I^2 = 96\%$ ). Certainty of evidence downgraded. **Indirectness: no serious.** Evidence is in United States and Canadian trauma patients which is generalisable to the Australian trauma patient and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.**

4. **Risk of Bias: serious.** Three observational studies with some risk of bias due to patient selection and confounding which weakens the confidence in the results. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** Evidence is in United States and Canadian trauma patients which is generalisable to the Australian trauma patient and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals (upper and lower bounds overlap with both effect and no effect). Certainty of evidence downgraded. **Publication bias: no serious.**

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### Good practice statement

**GPS3:** The reference group agreed that in a ratio-based major haemorrhage protocol, it is good practice for the transfusion ratio of RBC:FFP:PLT to be no lower than 2:1:1.

Refer to R3

## Rationale

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

### Good practice statement

**GPS4:** The reference group agreed that in a ratio-based major haemorrhage protocol, it is good practice that the ratio of RBC:FFP:PLT of at least 2:1:1 be achieved as soon as possible and be maintained until critical bleeding is controlled. In addition, assess fibrinogen and replace as required.

Refer to R2

Refer to R3

## Rationale

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

## 7.1.3 Blood components and products

### Blood component

Blood component is used in reference to red blood cells, platelets, fresh frozen plasma, cryoprecipitate and cryodepleted plasma [225]. For more information about specific blood components visit the Australian Red Cross Lifeblood (Lifeblood)

website or see the Blood Component Information book for more detail.

**Blood product**

Blood product refers to plasma derivative, or plasma derived proteins fractionated from large pools of human plasma under pharmaceutical conditions, such as prothrombin complex concentrate and fibrinogen concentrate [225]. For Australia, in 2023, these products are manufactured or imported by CSL Behring. The Australian Product Information can be found on the CSL Behring Product List. All blood products supplied under the national blood arrangements are listed in the National Product Price List on the NBA website.

**Research question**

**In patients with critical bleeding, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, prothrombin complex and/or platelet transfusion on red blood cell transfusion and patient outcomes?**

Literature search date: 29 September 2021

Weak recommendation , Very low certainty evidence

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

- FFP: a minimum of 1 unit with every 2 units of red blood cells
- Platelets\*: a minimum of 1 adult unit with every 8 units of red blood cells

*\*1 adult unit of apheresis or pooled 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, platelets, prothrombin complex concentrate, cryoprecipitate or fibrinogen concentrate. 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 fibrinogen concentrate, cryoprecipitate or prothrombin complex concentrate 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 and products 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 and products on resources (transfusion volume, hospital LOS) 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 and products.

## 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 and products to treat patients who are critically bleeding. Adaptation of this guidance at a local level is required upon consideration of the resources available.

## Rationale

Red blood cell 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 frozen frozen plasma (or varying administration of)

## Summary

Refer to the technical reports for further information on individual studies.

### What did we find?

Several systematic reviews (Coccolini 2019 [73], Rijnhout 2019 [74], Mengoli 2017 [77], Aubron 2014 [76], Lunde 2014 [75]) were found that included evidence from 2 RCTs (Moore 2018, Sperry 2018) and 4 non-randomised cohort studies (Holcomb 2017, Shackelford 2017, O'Reilly 2014, Innerhofer 2013) that assessed the effect of FFP versus no FFP (or varying administration of) on patient outcomes in the trauma setting.

### Study characteristics

Both RCTs were conducted in trauma centres in the United States and enrolled severely injured adults (aged 18 to 90 years) with systolic blood pressure (SBP) of 70 mmHg or lower or had an SBP of 71–90 mmHg and a heart rate more than 108 beats per minute; 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 guidelines. Moore 2018 [210] included a total of 125 patients in



the analysis and Sperry 2018 [211] included 501 patients. Both RCTs reported on the outcomes of mortality and morbidity (including acute lung injury and MOF) and were judged by systematic review authors [73][74] to be at overall low risk of bias.

Holcomb 2017 [234] was a multicentre, prospective cohort study conducted in the United States that assessed the effect of prehospital transfusion of FFP or red blood cells, or FFP in addition to red blood cell transfusion in 109 patients with penetrating trauma matched to 109 patients who received standard prehospital care. A total of 26 patients received FFP only, 8 patients received red blood cells only and 75 patients received both FFP and red blood cells in the interventional arm. The study was found to be at high risk of bias due to imbalances in baseline characteristics which limited matching [74].

Innerhofer 2013 [41] 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 and/or 4-factor prothrombin complex concentrate; 78 patients additionally received FFP transfusions and constitutes the interventional arm in this analysis. Review authors [75][76][77] judged the study as high risk of bias due to small sample sizes, inadequate follow-up and lack of rigorous analyses.

O'Reilly 2014 [235] and Shackelford 2017 [236] 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 was a retrospective cohort study that assessed prehospital blood transfusion in 194 patients. A total of 97 patients received a median of 1 unit of red blood cells and 2 units of FFP and 97 patients received standard of care. Shackelford 2017 was a retrospective cohort study of 386 United States military combat casualties who received prehospital blood transfusion between 2012 to 2015. A total of 54 patients received red blood cells and FFP; 332 patients received standard of care. Review authors [74] judged the study to be at high risk of bias due to study design and a lack of uniform guidelines for initiating pre-hospital blood transfusion which makes it difficult to determine the effect of individual blood components.

## **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 4 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 6 studies were conducted in the trauma setting. Combined data from the 2 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 4 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 mortality observed among those who received FFP (19.3%, 106/549) being lower than the mortality among 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 MOF 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;  $I^2 = 58\%$ ).

**Red blood cell transfusion volume**

One small cohort study (Innerhofer 2013) reported that the median (interquartile range (IQR)) volume of red blood cells 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 red blood cells transfused among the 66 patients who did not receive FFP ( $P = 0.001$ ).

**Transfusion volume, other blood components/products**

One small cohort study (Innerhofer 2013) reported that the median (IQR) volume of platelets 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 platelets transfused among the 66 patients who did not receive FFP ( $P = 0.003$ ).

There was no significant difference between treatment groups reported for the dose of fibrinogen concentrate (grams to 24 hours) and prothrombin complex concentrate (international units to 24 hours) used.

**LOS, 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 ( $P = 0.22$ ).

Outcome Timeframe	Study results and measurements	Comparator No FFP (or varying administration of)	Intervention FFP (or varying administration of)	Certainty of the Evidence (Quality of evidence)	Summary
Mortality, all cause (RCTs) latest reported timepoint	Relative risk 0.95 (CI 95% 0.56 — 1.59) Based on data from 626 participants in 2 studies. <sup>1</sup> (Randomized controlled)	314 per 1000  Difference:	298 per 1000  <b>16 fewer per 1000</b>	Very low Due to serious inconsistency, Due to very serious imprecision <sup>2</sup>	The evidence is very uncertain about the effect of FFP on 30-day mortality in trauma patients with critical bleeding.

Outcome Timeframe	Study results and measurements	Comparator No FFP (or varying administration of)	Intervention FFP (or varying administration of)	Certainty of the Evidence (Quality of evidence)	Summary
9 Critical			( CI 95% 138 fewer — 185 more )		
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. <sup>3</sup> (Observational (non- randomized))	203 per 1000  Difference:	132 per 1000  <b>71 fewer per 1000</b> ( CI 95% 116 fewer — 4 fewer )	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision <sup>4</sup>	FFP may reduce 30-day mortality in trauma patients with critical bleeding, but the evidence is very uncertain.
Morbidity, thromboemboli c events  9 Critical	Relative risk 0.85 (CI 95% 0.29 — 2.5) Based on data from 144 participants in 1 studies. <sup>5</sup> (Observational (non- randomized))	91 per 1000  Difference:	77 per 1000  <b>14 fewer per 1000</b> ( CI 95% 65 fewer — 137 more )	Very low Due to serious risk of bias, Due to very serious imprecision <sup>6</sup>	The evidence is very uncertain about the effect of FFP on thromboembolic events in trauma patients with critical bleeding.
Morbidity, MOF  9 Critical	Relative risk 1.76 (CI 95% 0.4 — 7.68) Based on data from 626 participants in 2 studies. <sup>7</sup> (Randomized controlled)	476 per 1000  Difference:	838 per 1000  <b>362 more per 1000</b> ( CI 95% 286 fewer — 3,180 more )	Low Due to serious inconsistency, Due to serious imprecision <sup>8</sup>	FFP may have little to no effect on MOF in trauma patients with critical bleeding, but the evidence is very uncertain.
Red blood cell transfusion volume	Based on data from 144 participants in 1 studies. <sup>9</sup> (Observational (non- randomized))	The median (IQR) volume of red blood cells transfused (to 24 hours) among patients who received FFP was 7 units (4, 11) compared with a median volume of 2 units (0, 6) among those who did not receive FFP (P = 0.001).		Very low Due to serious risk of bias, Due to serious imprecision <sup>10</sup>	The evidence is very uncertain about the effect of FFP on the volume of red blood cells transfused in trauma patients with critical bleeding.
Transfusion volume, other blood components/ products	Based on data from 144 participants in 1 studies. (Observational (non- randomized))	The median (IQR) volume of platelets transfused 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 dose of fibrinogen concentrate (grams) or volume of prothrombin complex concentrate transfused (international units to 24 hours).		Very low Due to serious risk of bias, Due to very serious imprecision <sup>11</sup>	The evidence is very uncertain about the effect of FFP on the volume of platelets, fibrinogen concentrate or 4-factor prothrombin complex concentrate transfused in trauma patients with critical bleeding.

Outcome Timeframe	Study results and measurements	Comparator No FFP (or varying administration of)	Intervention FFP (or varying administration of)	Certainty of the Evidence (Quality of evidence)	Summary
LOS, hospital or ICU Days	Based on data from 144 participants in 1 studies. (Observational (non- randomized))	No significant difference in the median hospital or ICU LOS among patients who received FFP compared to patients who did not.		Very low Due to serious risk of bias, Due to very serious imprecision <sup>12</sup>	The evidence is very uncertain about the effect of FFP on hospital or ICU LOS in trauma patients with critical bleeding.

1. Systematic review [4] with included studies: Sperry 2018 (RCT, trauma), Moore 2018 (RCT, trauma). **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [210], [211],

2. **Risk of Bias: no serious.** Two randomised studies with overall low risk of bias. Certainty of evidence not downgraded. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies, some of which can be explained (comparators may differ between studies and may not reflect current standard of care). The magnitude of statistical heterogeneity was moderate ( $I^2 = 38\%$ ). Certainty of evidence downgraded. **Indirectness: no serious.** The available evidence is in trauma patients, with studies conducted in the United States and Austria. The evidence is considered reflective of the Australian trauma patient population and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: very serious.** Wide confidence intervals. Low number of patients. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

3. Systematic review [4] with included studies: Shackelford 2017 (Coh, trauma), O'Reilly 2014 (Coh, trauma), Holcomb 2017 (Coh, trauma), Innerhofer 2013 (Coh, trauma). **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [41], [234], [235], [236],

4. **Risk of Bias: serious.** Several observational studies with concerns of bias related to study design and outcome reporting. Certainty of evidence downgraded. **Inconsistency: no serious.** No statistical heterogeneity ( $I^2 = 0\%$ ). Certainty of evidence not downgraded. **Indirectness: serious.** Evidence is in Austria, the United States and Afghanistan and includes combat trauma which makes it hard to judge whether it could be sensibly applied to the Australian healthcare context. Certainty of evidence downgraded. **Imprecision: serious.** Wide confidence intervals. Only data from one study. Low number of patients. Certainty of evidence downgraded. **Publication bias: no serious.**

5. Systematic review [4] with included studies: Innerhofer 2013 (Coh, trauma). **Baseline/comparator:** Control arm of reference used for intervention.

6. **Risk of Bias: serious.** One observational study with concerns of bias related to study design and outcome measurement. Certainty of evidence downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: no serious.** The evidence is in blunt trauma patients in Austria, which could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: very serious.** Data from one study. Wide confidence intervals. Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

7. Systematic review [4] with included studies: Sperry 2018 (RCT, trauma), Moore 2018 (RCT, trauma). **Baseline/comparator:** Control arm of reference used for intervention.

8. **Risk of Bias: no serious.** Two randomised studies with overall low risk of bias. Certainty of evidence not downgraded. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high ( $I^2 = 58\%$ ). Point estimates vary widely. Certainty of evidence downgraded. **Indirectness: no**

**serious.** The available evidence is in United States trauma patients and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded . **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded . **Publication bias: no serious.**

9. Primary study **Supporting references:** [41],

10. **Risk of Bias: serious.** One observational study with concerns of bias related to study design. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** Evidence is in trauma patients in Austria and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded . **Imprecision: serious.** Only data from one study. Low number of patients. Certainty of evidence downgraded. **Publication bias: no serious.**

11. **Risk of Bias: serious.** One observational study with concerns of bias due to study design. Certainty of evidence downgraded . **Inconsistency: no serious. Indirectness: no serious.** Evidence is in Austrian trauma patients and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded . **Imprecision: very serious.** Only data from one study. Wide confidence intervals. Certainty of evidence downgraded 2 levels . **Publication bias: no serious.**

12. **Risk of Bias: serious.** One cohort study with concerns of bias related to study design. Certainty of evidence downgraded . **Inconsistency: no serious. Indirectness: no serious.** Evidence is in Austrian trauma patients and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded . **Imprecision: very serious.** Wide confidence intervals, data from one study, low number of patients. Certainty of evidence downgraded 2 levels . **Publication bias: no serious.**

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## Clinical question/ PICO

**Population:** People with critical bleeding (trauma setting)

**Intervention:** Cryoprecipitate

**Comparator:** No cryoprecipitate (or varying administration of)

## Summary

Refer to the technical reports for further information on individual studies.

### What did we find?

One systematic review (McQuilten 2018 [60]) was found that included evidence from one RCT (Curry 2015) that assessed the effect of cryoprecipitate versus no cryoprecipitate (or varying administration of) on patient outcomes.

### Study characteristics

Curry 2015 [62] included a total of 44 patients and was carried out in 2 civilian trauma centres in the United Kingdom. The study evaluated the effect of cryoprecipitate on mortality, morbidity and transfusion volume in trauma patients with major haemorrhage requiring activation of an MHP. Risk of bias was judged by review authors [60] to be unclear due to small sample size and lack of blinding of participants, clinical staff and research staff.

### What are the main results?

#### Mortality

One RCT (Curry 2015) reported a lower rate of mortality among patients who received cryoprecipitate (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 cryoprecipitate compared with a total of 3 events in the placebo group (RR 0.15; 95% CI 0.01, 2.73;  $P = 0.20$ ).

Specifically, a lower rate of DVT was observed among patients who received cryoprecipitate (0/20, 0%) compared with those who did not (1/21, 4.8%) and a lower rate of pulmonary embolus (PE) was reported among patients who received cryoprecipitate (0/20, 0%) compared with those who did not (2/21, 9.5%). The event rates for both outcomes were not significantly different (DVT: RR 0.35, 95% CI 0.02, 8.10;  $P = 0.51$ ) and (PE: RR 0.21, 95% CI 0.01, 4.11;  $P = 0.30$ ). There were no events of myocardial infarction or stroke reported in the RCT.

One RCT (Curry 2015) reported a higher rate of MOF among critically bleeding trauma patients who received cryoprecipitate (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;  $P = 0.48$ ).

### **Red blood cell transfusion volume**

One RCT (Curry 2015) reported no significant difference in the volume of red blood cells transfused up to 6 hours, 24 hours or 28 days among patients who received cryoprecipitate 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 compared to 8 (5,11) units given to those randomised to the cryoprecipitate group.

### **Transfusion volume, other blood components/products**

One RCT (Curry 2015) reported no significant difference in the volume of FFP, platelets, or cryoprecipitate transfused up to 6 hours, 24 hours or 28 days among patients who received early cryoprecipitate in addition to an empiric MHP compared to those who received an empiric MHP. 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 cryoprecipitate group. At 24-hours, participants in the control group had received a median (IQR) of 1 (1, 2) unit of platelets compared to 1 (0, 2) unit given to those randomised to the cryoprecipitate group. At 24-hours, participants in the control group had received a median (IQR) of 2 (0, 2) unit of cryoprecipitate compared to 2 (2, 4) units given to those randomised to the cryoprecipitate group.

### **LOS, hospital or ICU**

One RCT (Curry 2015) reported the median (IQR) duration of hospital LOS to be 31 days (29, 33) among 20 patients who received cryoprecipitate compared to 30 days (22, 38) among the 21 patients who did not receive cryoprecipitate. The difference was not statistically significant ( $P = 0.66$ ).

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



Outcome Timeframe	Study results and measurements	Comparator No cryoprecipitate (or varying administration of)	Intervention Cryoprecipitate	Certainty of the Evidence (Quality of evidence)	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. <sup>1</sup> (Randomized controlled)	286 per 1000  Difference:	100 per 1000  <b>186 fewer per 1000</b> ( CI 95% 263 fewer — 154 more )	Very low Due to serious risk of bias, Due to very serious imprecision <sup>2</sup>	Cryoprecipitate may have little or no effect on mortality in trauma patients with critical bleeding, but the evidence is very uncertain.
Morbidity, thromboemboli c events  9 Critical	Relative risk 0.15 (CI 95% 0.01 — 2.73) Based on data from 41 participants in 1 studies. <sup>3</sup> (Randomized controlled)	143 per 1000  Difference:	21 per 1000  <b>122 fewer per 1000</b> ( CI 95% 142 fewer — 247 more )	Very low Due to serious risk of bias, Due to very serious imprecision <sup>4</sup>	There were too few who experienced the outcome to determine whether cryoprecipitate made a difference on thromboembolic events (including DVT, myocardial infarction, PE, stroke) in trauma patients with critical bleeding.
Morbidity, MOF  9 Critical	Relative risk 3.14 (CI 95% 0.14 — 72.92) Based on data from 41 participants in 1 studies. <sup>5</sup> (Randomized controlled)	0 per 1000  Difference:	0 per 1000  <b>0 fewer per 1000</b> ( CI 95% 0 fewer — 0 fewer )	Very low Due to serious risk of bias, Due to very serious imprecision <sup>6</sup>	There were too few who experienced the outcome to determine whether cryoprecipitate made a difference on MOF (or other adverse events including sepsis and ARDS) in trauma patients with critical bleeding.
Red blood cell transfusion volume	Based on data from 41 participants in 1 studies. <sup>7</sup> (Randomized controlled)	No significant difference in the median volume of red blood cells transfused (to 24 hours or 28 days) among patients who received cryoprecipitate compared to patients who did not.		Very low Due to serious risk of bias, Due to very serious imprecision <sup>8</sup>	We are very uncertain about the effect of cryoprecipitate on the volume of red blood cells transfused in trauma patients with critical bleeding.
Transfusion volume, other blood components/ products	Based on data from 41 participants in 1 studies. <sup>9</sup> (Randomized controlled)	No significant difference in the median volume of FFP, cryoprecipitate, or platelets transfused (to 24 hours or 28 days) among patients who received cryoprecipitate compared to patients who did not.		Very low Due to serious risk of bias, Due to very serious imprecision <sup>10</sup>	We are very uncertain about the effect of cryoprecipitate on the volume of FFP, platelets or cryoprecipitate transfused in trauma patients with critical bleeding.



Outcome Timeframe	Study results and measurements	Comparator No cryoprecipitate (or varying administration of)	Intervention Cryoprecipitate	Certainty of the Evidence (Quality of evidence)	Summary
LOS, hospital or ICU	Based on data from 41 participants in 1 studies. <sup>11</sup> (Randomized controlled)	No significant difference in the median hospital or ICU LOS among patients who received cryoprecipitate compared to patients who did not.		Very low Due to serious risk of bias, Due to very serious imprecision <sup>12</sup>	We are very uncertain about the effect of cryoprecipitate on hospital or ICU LOS in trauma patients with critical bleeding.

1. Systematic review [4] with included studies: Curry 2015 (RCT, trauma)). **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: serious.** One RCT with some concerns of bias due to lack of blinding of participants, personnel and outcome assessors, resulting in potential for performance and detection bias. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** Evidence is in United Kingdom trauma patients which is generally representative of the Australian trauma patient population and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: very serious.** Data from one study with low event rate. Wide confidence intervals. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**
3. Systematic review [4] with included studies: Curry 2015 (RCT, trauma)), Curry 2015 (RCT, trauma)). **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [62],
4. **Risk of Bias: serious.** One RCT assessed to have some concerns of bias due to lack of blinding of participants, personnel and outcome assessors, resulting in potential for performance and detection bias. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** Evidence is in United Kingdom trauma patients which is generally representative of the Australian trauma patient population and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: very serious.** Data from one study with low event rate. Wide confidence intervals. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**
5. Systematic review [4] with included studies: Curry 2015 (RCT, trauma)). **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** One RCT assessed to have some concerns of bias due to lack of blinding of participants, personnel and outcome assessors, resulting in potential for performance and detection bias. Certainty of evidence downgraded.. **Inconsistency: no serious. Indirectness: no serious.** Evidence is in United Kingdom trauma patients which is generally representative of the Australian trauma patient population and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded.. **Imprecision: very serious.** Data from one study with low event rate. Wide confidence intervals. Certainty of evidence downgraded 2 levels.. **Publication bias: no serious.**
7. Systematic review **Supporting references:** [62],
8. **Risk of Bias: serious.** One RCT assessed to have some concerns of bias due to lack of blinding of participants, personnel and outcome assessors, resulting in potential for performance and detection bias. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** Evidence is in United Kingdom trauma patients which is generally representative of the Australian trauma patient population and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: very serious.** Data from one study with low event rate. Wide confidence intervals. Certainty of evidence downgraded 2 levels. **Publication bias: no**

**serious.**

9. Systematic review **Supporting references:** [62],

10. **Risk of Bias: serious.** One RCT assessed to have some concerns of bias due to lack of blinding of participants, personnel and outcome assessors, resulting in potential for performance and detection bias. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** Evidence is in United Kingdom trauma patients which is generally representative of the Australian trauma patient population and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: very serious.** Wide confidence intervals. Low number of patients. Only data from one study. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

11. Systematic review **Supporting references:** [62],

12. **Risk of Bias: serious.** The RCT assessed to have some concerns of bias due to lack of blinding of participants, personnel and outcome assessors, resulting in potential for performance and detection bias. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** Evidence is in United Kingdom trauma patients which is generally representative of the Australian trauma patient population and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: very serious.** Low number of patients. Wide confidence intervals. Data from one study. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

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**Clinical question/ PICO**

**Population:** People with critical bleeding (trauma setting)

**Intervention:** Fibrinogen concentrate

**Comparator:** No fibrinogen concentrate (or varying administration of)

**Summary**

Refer to the technical reports for further information on individual studies.

**What did we find?**

Several systematic reviews (Stabler 2020 [79], Zaidi 2020 [80], Coccolini 2019 [73], Rijnhout 2019 [74], Fabes 2018 [78], McQuilten 2018 [60]) were found that included evidence from 5 RCTs (Innerhofer 2017, Curry 2018,

Nascimento 2016, Akbari 2017, Lucena 2020) and 5 non-randomised cohort studies (Wafaisade 2013, Almskog 2020, Schöchl 2011, Nienaber 2011, Inokuchi 2017) that assessed the use of fibrinogen concentrate compared with no fibrinogen concentrate (or varying administration of) on patient outcomes in the trauma setting.

### Study characteristics

The 5 RCTs conducted in the trauma setting were performed in Austria, United Kingdom, Canada, Iran and Brazil and all assessed the use of fibrinogen concentrate in adult patients with severe trauma. Three RCTs (Curry 2018 [237], Nascimento 2016 [238], Lucena 2020 [42]) compared the use of fibrinogen concentrate with saline or no fibrinogen concentrate, one RCT (Akbari 2017 [39]) compared fibrinogen concentrate to an active (FFP) and an inactive (no coagulation factor) comparator, and one RCT (Innerhofer 2017 [37]) compared fibrinogen concentrate to an active comparator (FFP) only. The studies were assessed by Fabes 2018 [78] and Stabler 2020 [79] 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.

Five cohort studies were conducted in Europe and Japan and examined the effect of fibrinogen concentrate in trauma patients with critical bleeding. In 2 studies the comparator was no fibrinogen concentrate (Wafaisade 2013 [47], Almskog 2020 [239]), while the remaining 3 cohort studies examined the effect of including fibrinogen concentrate as part of an MHP compared with an MHP without fibrinogen concentrate (Schöchl 2011 [195], Nienaber 2011 [194], Inokuchi 2017 [240]). The cohort studies were judged by Stabler 2020 [79] to be at high risk of bias due to missing data, absence of a clear objective criterion for the activation of an MHP and lack of control for potential confounders.

### 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 fibrinogen concentrate (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 fibrinogen concentrate (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 4 RCTs showed that the rate of thromboembolic events was comparable between patients who received fibrinogen concentrate (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 fibrinogen concentrate (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;  $P = 0.07$ ).

### **Red blood cell transfusion volume**

One RCT and 4 cohort studies reported the effect of fibrinogen concentrate on red blood cell transfusion volume in trauma patients with critical bleeding. Data from Wafaisade 2013 suggested a higher volume of red blood cells was required for patients who received fibrinogen concentrate ( $n=294$ ) 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 4 studies (one RCT, 3 cohort studies) reporting median (IQR) values suggested there was no significant difference in the volume of red blood cells transfused (comparing patients who received fibrinogen concentrate compared with those who did not). Reported median values ranged from 3 to 12.8 units (fibrinogen concentrate) and 3 to 12.5 units (no fibrinogen concentrate) of red blood cells transfused.

### **Transfusion volume, other blood components/products**

One RCT and 4 cohort studies reported on the effect of fibrinogen concentrate 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 fibrinogen concentrate ( $n=294$ ) compared with those who did not ( $n=294$ ) (SMD 0.19, 95% CI 0.03, 0.35;  $P = 0.02$ ). Among the other 4 studies (one RCT, 3 cohort studies), 2 studies reporting median (IQR) values suggested there was no significant difference in the volume of FFP transfused between patients who received fibrinogen concentrate 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 fibrinogen concentrate compared with those who did not (Nienaber 2011) and one study did not report comparative data for this outcome.

One RCT and 3 cohort studies reported on the effect of fibrinogen concentrate on the volume of platelets transfused in the trauma setting. Among the 3 studies that reported comparative data, 2 studies suggested there was no significant difference in the volume of platelets transfused between patients who received fibrinogen concentrate 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 fibrinogen concentrate compared with those who did not, but no further data was provided.

One RCT reported on the effect of fibrinogen concentrate on the volume of cryoprecipitate transfused in the trauma setting and found no significant difference between treatment groups ( $P = 0.18$ ).

### **LOS, hospital**

Four RCTs and 3 cohort studies reported the effect of fibrinogen concentrate on hospital LOS in the trauma setting. Data were available for 2 studies (reported as mean (SD)), that showed fibrinogen concentrate has no significant impact on the duration of hospital stay comparing patients who received fibrinogen concentrate with those who did not (MD -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 fibrinogen concentrate and those who did not.

### **LOS, ICU**

Two RCTs and 4 cohort studies reported the effect of fibrinogen concentrate on ICU LOS (days) in the trauma setting. Complete data were not available, but 5 of the 6 studies suggested that there is no significant difference in

the duration of ICU stay for patients who received fibrinogen concentrate compared to those who did not. One RCT (Lucena 2020) suggested that the length of ICU stay among patients who received fibrinogen concentrate 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)	Summary
Mortality, all cause (RCTs) latest reported timepoint  9 Critical	Relative risk 1.12 (CI 95% 0.53 — 2.35) Based on data from 283 participants in 5 studies. <sup>1</sup> (Randomized controlled)	180 per 1000  Difference:	202 per 1000  <b>22 more per 1000</b> ( CI 95% 85 fewer — 243 more )	Very low Due to serious indirectness, Due to very serious imprecision <sup>2</sup>	The evidence is very 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. <sup>3</sup> (Observational (non- randomized))	135 per 1000  Difference:	188 per 1000  <b>53 more per 1000</b> ( CI 95% 12 fewer — 153 more )	Very low Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision <sup>4</sup>	The evidence is very uncertain about the effect of fibrinogen concentrate on mortality in trauma patients with critical bleeding.
Morbidity, thromboemboli c events (RCTs)  9 Critical	Relative risk 0.9 (CI 95% 0.42 — 1.91) Based on data from 210 participants in 4 studies. <sup>5</sup> (Randomized controlled)	117 per 1000  Difference:	105 per 1000  <b>12 fewer per 1000</b> ( CI 95% 68 fewer — 106 more )	Low Due to very serious imprecision <sup>6</sup>	The evidence suggests that fibrinogen concentrate may have little or no difference on thromboembolic events in trauma patients with critical bleeding.
Morbidity, MOF (RCTs)  9 Critical	Relative risk 0.74 (CI 95% 0.53 — 1.03) Based on data from 195 participants in 3 studies. <sup>7</sup> (Randomized controlled)	388 per 1000  Difference:	287 per 1000  <b>101 fewer per 1000</b> ( CI 95% 182 fewer — 12 more )	Low Due to very serious imprecision <sup>8</sup>	The evidence suggests that fibrinogen concentrate may have little or no difference on MOF in trauma patients with critical bleeding.
Red blood cell transfusion volume Units	Based on data from 1,574 participants in 5 studies. (Observational (non-randomized))	No significant difference observed for volume of red blood cells transfused among patients who received fibrinogen concentrate		Very low Due to serious risk of bias, Due to serious	The evidence is very uncertain about the association of fibrinogen concentrate

Outcome Timeframe	Study results and measurements	Comparator No fibrinogen concentrate (or varying administration of)	Intervention Fibrinogen concentrate	Certainty of the Evidence (Quality of evidence)	Summary
		compared with those who did not. Reported median values ranged from 3 to 12.8 units (fibrinogen concentrate) and 3 to 12.5 units (no fibrinogen concentrate).		imprecision <sup>9</sup>	on the volume of red blood cells transfused in trauma patients with critical bleeding.
Transfusion volume, other blood components/ 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 fibrinogen concentrate compared with those who did not. Reported median values ranged from 0 to 10.6 units (fibrinogen concentrate) and 1.75 to 10 units (no fibrinogen concentrate).		Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision, Due to serious publication bias <sup>10</sup>	The evidence is very uncertain about the association of fibrinogen concentrate on the volume of FFP transfused in trauma patients with critical bleeding.
LOS, hospital Days	Based on data from 1,491 participants in 7 studies. <sup>11</sup> (Observational (non-randomized))	No significant difference observed for hospital LOS among patients who received fibrinogen concentrate compared with those who did not.		Very low Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency <sup>12</sup>	Fibrinogen concentrate may have little or no difference on hospital LOS in the trauma setting but the evidence is very uncertain.
LOS, ICU Days	Based on data from 1,647 participants in 6 studies. <sup>13</sup> (Observational (non-randomized))	Five out of 6 studies reported no significant difference in ICU LOS among patients who received fibrinogen concentrate compared with those who did not.		Very low Due to serious risk of bias, Due to serious imprecision <sup>14</sup>	Fibrinogen concentrate may have little or no difference on ICU LOS in the trauma setting but the evidence is very uncertain.

1. Systematic review [4] with included studies: Nascimento 2016 (RCT, trauma), Innerhofer 2017 (RCT, trauma), Lucena 2020 (RCT, trauma), Akbari 2018 (RCT, trauma), Curry 2018 (RCT, trauma). **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [238], [39], [37], [42], [237],
2. **Risk of Bias: no serious.** Several randomised studies with overall low risk of bias. Certainty of evidence not downgraded. **Inconsistency: no serious.** Moderate statistical heterogeneity ( $I^2$  between 25 to 50%). Some inconsistency that can be explained. Certainty of evidence not downgraded. **Indirectness: serious.** The available evidence is in trauma patients, but the studies were conducted in various healthcare settings including United States, Sweden, Japan and Brazil and it is hard to judge whether it could be sensibly applied to the Australian healthcare context. Certainty of evidence downgraded. **Imprecision: very serious.** Wide confidence intervals. Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**
3. Systematic review [4] with included studies: Inokuchi 2017 (Coh, trauma), Almskog 2020 (Coh, trauma), Wafaisade 2013 (Coh, trauma), Schochl 2011 (Coh, trauma), Nienaber 2011 (Coh, trauma).

**Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [240], [194], [239], [195], [47],

4. **Risk of Bias: serious.** Several comparative observational studies with concerns of bias due to study design and reporting. Certainty of evidence downgraded.. **Inconsistency: no serious.** Moderate statistical heterogeneity ( $I^2$  between 25 to 50%). Some inconsistency that can be explained. Certainty of evidence not downgraded.. **Indirectness: serious.** The available evidence is in trauma patients, but the studies were conducted in various healthcare settings including United States, Sweden, Japan and Brazil and it is hard to judge whether it could be sensibly applied to the Australian healthcare context. Certainty of evidence downgraded.. **Imprecision: very serious.** Wide confidence intervals. Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels.. **Publication bias: no serious.**

5. Systematic review [4] with included studies: Nascimento 2016 (RCT, trauma), Lucena 2020 (RCT, trauma), Curry 2018 (RCT, trauma), Innerhofer 2017 (RCT, trauma). **Baseline/comparator:** Control arm of reference used for intervention.

6. **Risk of Bias: no serious.** Four randomised studies with overall low risk of bias. Certainty of evidence not downgraded. **Inconsistency: no serious.** All studies consistent. No statistical heterogeneity ( $I^2 = 0\%$ ). Certainty of evidence not downgraded. **Indirectness: no serious.** The available evidence is in trauma patients with the studies conducted in various healthcare settings including the United Kingdom, Canada, Austria, Germany and Sweden. The evidence could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded.. **Imprecision: very serious.** Wide confidence intervals. Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

7. Systematic review [4] with included studies: Innerhofer 2017 (RCT, trauma), Akbari 2018 (RCT, trauma), Nascimento 2016 (RCT, trauma). **Baseline/comparator:** Control arm of reference used for intervention.

8. **Risk of Bias: no serious.** Three randomised studies with overall low risk of bias. Certainty of evidence not downgraded. **Inconsistency: no serious.** No statistical heterogeneity ( $I^2 = 0\%$ ). Certainty of evidence not downgraded. **Indirectness: no serious.** The available evidence is in trauma patients with the studies conducted in various healthcare settings including the United Kingdom, Canada, Austria, Germany and Sweden. The evidence could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: very serious.** Wide confidence intervals. Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

9. **Risk of Bias: serious.** Several comparative observational studies with concerns of bias relating to study design and reporting of results. Certainty of evidence downgraded. **Inconsistency: no serious.** **Indirectness: no serious.** The available evidence is in trauma patients with the studies conducted in various healthcare settings including the United Kingdom, Canada, Austria, Germany and Sweden, which could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.**

10. **Risk of Bias: serious.** One RCT and several comparative observational studies with concerns of bias relating to study design, blinding and potential confounders. Certainty of evidence downgraded. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. Heterogeneity between studies in dose and timing of intervention, comparator and outcome measure. Certainty of evidence downgraded. **Indirectness: no serious.** The available evidence is in trauma patients with the studies conducted in various healthcare settings including the United Kingdom, Canada, Austria, Germany and Sweden, which could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals.



Certainty of evidence downgraded. **Publication bias: serious.** Non-reporting bias suspected. Certainty of evidence downgraded.

11. Systematic review Includes both RCT and Coh studies. Data reported as median (IQR) and not able to be included in a meta-analysis.. **Supporting references:** [42], [39], [37],

12. **Risk of Bias: serious.** Three RCTs with overall low risk of bias and 3 comparative observational studies with high concerns of bias relating to study design, blinding and potential confounders.

Certainty of evidence downgraded. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. Certainty of evidence downgraded. **Indirectness: no serious.**

The available evidence is in trauma patients with the studies conducted in various healthcare settings including the United Kingdom, Canada, Austria, Germany and Sweden, which could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.**

Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.**

13. Systematic review **Supporting references:** [195], [47], [194],

14. **Risk of Bias: serious.** Two RCTs with overall low risk of bias and 4 comparative observational studies with concerns of bias due to study design, blinding and potential confounders. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** The available evidence is in trauma patients with the studies conducted in various healthcare settings including the United Kingdom, Canada, Austria, Germany and Sweden, which could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Confidence intervals not reported/calculated, which increases uncertainty in precision of the results. Certainty of evidence downgraded. **Publication bias: no serious.**

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## Clinical question/ PICO

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

## Summary

Refer to the technical reports for further information on individual studies.

### What did we find?

Three systematic reviews (Fabes 2018 [78], Lunde 2014 [75], Warmuth 2012 [233]) were found that included evidence from 4 RCTs (Bilicen 2017, Rahe-Meyer 2016, Rahe-Meyer 2013, Tanaka 2014) and 3 non-randomised cohort studies (Bilicen 2013, Rahe-Meyer 2009a, Rahe-Meyer 2009b) that assessed the use of fibrinogen concentrate compared with no fibrinogen concentrate (or varying administration of) on patient outcomes in the surgical setting.

### Study characteristics

The 4 RCTs were conducted in the Netherlands, Germany and United States and evaluated the use of fibrinogen concentrate in critically bleeding patients undergoing cardiac surgery. Three RCTs (Bilicen 2017 [241], Rahe-Meyer 2013 [244], Rahe-Meyer 2016 [242]) compared the use of fibrinogen concentrate with saline while one RCT (Tanaka 2014 [243]) compared the use of fibrinogen concentrate with 1 unit of platelets. All 4 RCTs were assessed by Fabes 2018 [78] 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 concerns of bias included allocation concealment, blinding, incomplete outcome data and selective reporting.

The 3 cohort studies (Bilicen 2013 [245], Rahe-Meyer 2009a [29], Rahe-Meyer 2009b [45]) evaluated the use of fibrinogen concentrate in patients with critical bleeding in the surgical setting and were assessed by Lunde 2014 [75] to be at high risk of bias, predominately due to failure in blinding, lack of information on the allocation of groups and insufficient information about comparability of groups at baseline and at the analysis stage.

Bilicen 2013 was a prospective cohort study conducted at a single-centre that assessed 1075 patients who underwent complex cardiac surgery in the Netherlands. A total of 264 patients received a median dose of 2 g fibrinogen concentrate; the 811 patients that did not receive fibrinogen concentrate represent the control group. Lunde 2014 [75] noted that due to study design, the association between the infusion of fibrinogen concentrate and each of the outcomes were likely biased by potential confounders.

Rahe-Meyer 2009a was a pilot cohort study that prospectively enrolled 15 patients undergoing aortic valve and ascending aorta replacement surgery in Germany. Five patients received transfusion according to the predefined blood products transfusion algorithm while the remaining 10 patients received fibrinogen concentrate 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 components according to a predetermined algorithm; 6 patients also received a mean (SD) dose of 7.8 g (2.7 g) fibrinogen concentrate as a first step therapy. Both cohort studies were underpowered due to small sample sizes [75].

### 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 fibrinogen concentrate (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 fibrinogen concentrate (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 fibrinogen concentrate (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.

**Red blood cell transfusion volume**

Two cohort studies reported the effect of fibrinogen concentrate on red blood cell transfusion volume in the surgical setting. Data from Rahe-Meyer 2009a suggested that patients who received fibrinogen concentrate had a lower volume of red blood cells transfused compared with patients who did not receive fibrinogen concentrate (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 red blood cells transfused to 24 hours in patients who received fibrinogen concentrate compared with those who did not.

**Transfusion volume, other blood components/products**

Among critically bleeding patients in the surgical setting, there was a significant reduction in the volume of FFP transfused among patients who received fibrinogen concentrate 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 platelets and prothrombin complex transfused among patients who received fibrinogen concentrate compared to those who did not ( $P < 0.05$ ).

**LOS, ICU**

There was one cohort study in the surgical setting (Rahe-Meyer 2009b) that reported on ICU LOS (hours) which suggested fibrinogen concentrate is associated with a reduction in the length of ICU stay among patients who received fibrinogen concentrate 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 fibrinogen concentrate (or varying administration of)	Intervention Fibrinogen concentrate	Certainty of the Evidence (Quality of evidence)	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. <sup>1</sup> (Randomized controlled)	51 per 1000  Difference:	24 per 1000  <b>27 fewer per 1000</b> ( CI 95% 47 fewer — 93 more )	Low Due to very serious imprecision <sup>2</sup>	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  9 Critical	Relative risk 1.58 (CI 95% 0.65 — 3.85) Based on data from 1,178 participants in 3 studies. <sup>3</sup> (Observational (non- randomized))	39 per 1000  Difference:	62 per 1000  <b>23 more per 1000</b> ( CI 95% 14 fewer — 111 more )	Very low Due to serious risk of bias, Due to very serious imprecision <sup>4</sup>	The evidence is very uncertain about the effect of fibrinogen concentrate on mortality in patients with critical bleeding in the surgical setting.
Morbidity, thromboemboli c events (RCTs)  9 Critical	Relative risk 2.03 (CI 95% 0.63 — 6.58) Based on data from 201 participants in 3 studies. <sup>5</sup> (Randomized controlled)	39 per 1000  Difference:	79 per 1000  <b>40 more per 1000</b> ( CI 95% 14 fewer — 218 more )	Low Due to very serious imprecision <sup>6</sup>	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.
Red blood cell transfusion volume Units	Based on data from 33 participants in 2 studies.	Two studies found a significant reduction in the volume of red blood cells transfused among patients who received fibrinogen concentrate compared with those who did not. One study reported SMD -1.69.		Low Due to very serious imprecision <sup>7</sup>	There were too few who experienced the outcome to determine whether fibrinogen concentrate made a difference on the volume of red blood cells transfused in patients with critical bleeding in the surgical setting.
Transfusion volume, other blood components/ 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 fibrinogen concentrate 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 <sup>8</sup>	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

Outcome Timeframe	Study results and measurements	Comparator No fibrinogen concentrate (or varying administration of)	Intervention Fibrinogen concentrate	Certainty of the Evidence (Quality of evidence)	Summary
					the surgical setting.
LOS, ICU	Based on data from 18 participants in 1 studies. <sup>9</sup> (Observational (non-randomized))	One small cohort study suggested fibrinogen concentrate 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 <sup>10</sup>	There were too few who experienced the outcome to determine whether fibrinogen concentrate made a difference on ICU LOS in patients with critical bleeding in the surgical setting.

1. Systematic review [4] with included studies: Rahe-Meyer 2013 (RCT, surgical), Rahe-Meyer 2016 (RCT, surgical), Bilecen 2017 (RCT, surgical), Tanaka 2014 (RCT, surgical). **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [244], [242], [243], [241],
2. **Risk of Bias: no serious.** Several randomised studies with overall low risk of bias. Certainty of evidence not downgraded. **Inconsistency: no serious.** The magnitude of statistical heterogeneity was moderate ( $I^2 = 40\%$ ). Some inconsistency but inconsistency can be explained. Certainty of evidence not downgraded. **Indirectness: no serious.** The available evidence is in surgical patients (cardiac, aortic) with critical bleeding assessed in various healthcare settings including UK, Canada, Austria, Germany and Sweden. This is representative of the target patient population in Australia and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: very serious.** Wide confidence intervals. Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**
3. Systematic review [4] with included studies: Rahe-Meyer 2009b (Coh, surgical), Rahe-Meyer 2009a (Coh, surgical), Bilecen 2013 (Coh, surgical). **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [45], [245], [29],
4. **Risk of Bias: serious.** Comparative observational studies with concerns of bias related to study design and reporting bias. Certainty of evidence downgraded. **Inconsistency: no serious.** Mild statistical heterogeneity ( $I^2 < 25\%$ ). Most studies consistent and inconsistency can be explained. Certainty of evidence not downgraded. **Indirectness: no serious.** The available evidence is in surgical patients (cardiac, aortic) with critical bleeding assessed in various healthcare settings including United Kingdom, Canada, Austria, Germany and Sweden. This is representative of the target patient population in Australia and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: very serious.** Wide confidence intervals. Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**
5. Systematic review [4] with included studies: Rahe-Meyer 2013 (RCT, surgical), Bilecen 2017 (RCT, surgical), Tanaka 2014 (RCT, surgical). **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: no serious.** Three randomised studies with overall low risk of bias. Certainty of evidence not downgraded. **Inconsistency: no serious.** No statistical heterogeneity ( $I^2 = 0\%$ ). Studies are consistent. Certainty of evidence not downgraded. **Indirectness: no serious.** The available

evidence is in surgical patients (cardiac, aortic) with critical bleeding assessed in various healthcare settings including United Kingdom, Canada, Austria, Germany and Sweden. This is representative of the target patient population in Australia and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: very serious.** Only data from one study. Wide confidence intervals. Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

7. **Inconsistency: no serious. Indirectness: no serious. Imprecision: very serious.** Wide confidence intervals. Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

8. **Risk of Bias: serious.** Two comparative observational studies with concerns of bias related to study design and reporting. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** The available evidence is in surgical patients (cardiac, aortic) with critical bleeding assessed in Germany. This is representative of the target patient population in Australia and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: very serious.** Wide confidence intervals. Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

9. Systematic review **Supporting references:** [45],

10. **Risk of Bias: serious.** One observational study with concerns of bias due to study design and reporting. Certainty of evidence downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: no serious.** Evidence is in surgical patients (cardiac, aortic) with studies conducted in various healthcare settings including United Kingdom, Canada, Austria, Germany and Sweden, which could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: very serious.** Confidence intervals not reported/calculated, which increases uncertainty in precision of the results. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

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## Journal

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## Clinical question/ PICO

- Population:** People with critical bleeding (obstetrics and maternity)  
**Intervention:** Fibrinogen concentrate  
**Comparator:** No fibrinogen concentrate (or varying administration of)

## Summary

Refer to the technical reports for further information on individual studies.

### What did we find?

Three systematic reviews (Zaidi 2020 [80], Fabes 2018 [78], Lunde 2012 [75]) were found that included evidence from 2 RCTs (Collins 2017, Wikkelsø 2015) and one non-randomised cohort study (Ahmed 2012) that assessed the use of fibrinogen concentrate compared with no fibrinogen concentrate (or varying administration of) on patient outcomes in the obstetrics and maternity setting.

### Study characteristics

The 2 RCTs (Collins 2017 [46], Wikkelsø 2015 [246]) were conducted in Denmark and the United Kingdom and reported on the outcomes of mortality and morbidity. In both RCTs, adult women with postpartum haemorrhage (PPH) were randomised to receive early fibrinogen concentrate or saline. The RCTs were assessed by the included



systematic reviews [78][80] to be at overall low risk of bias.

One cohort study (Ahmed 2012) evaluated the use of fibrinogen concentrate in women with major obstetric haemorrhage. Among 77 patients, 20 received a mean dose of  $4 \pm 0.8$ g fibrinogen concentrate and 34 received a mean dose of  $2.21 \pm 0.35$  pools of cryoprecipitate. Given both treatment arms represent eligible interventions for this review, fibrinogen concentrate was chosen as the interventional arm for this analysis. Ahmed 2012 was assessed by Lunde 2014 [75] to be at serious risk of bias due to small sample size and inadequate follow-up.

### **What are the main results?**

#### **Mortality**

There were no deaths (up to 30 days) reported in the RCTs that examined the effect of fibrinogen concentrate on mortality in women with major PPH (Collins 2017, Wikkelsø 2015).

#### **Morbidity**

Among women with major PPH, the rate of thromboembolic events was comparable between patients who received fibrinogen concentrate (1/151, 0.7%) and those who did not (1/148, 0.7%); corresponding to a RR of 0.96 (95% CI 0.06, 14.65;  $P = 0.98$ ). The RCTs were small and not sufficiently powered to detect this outcome with one study (Wikkelsø 2015) reporting no thromboembolic events.

#### **RBC transfusion volume**

One cohort study (Ahmed 2012) reported the effect of fibrinogen concentrate on red blood cell transfusion volume among women with major PPH. The study reported a lower volume of red blood cells transfused among women who received fibrinogen concentrate compared with those who did not (SMD  $-0.29$ ; 95% CI  $-0.98$ ,  $0.40$ ;  $P = 0.41$ ) but the difference was not significant.

#### **Transfusion volume, other blood components/products**

Among women with major PPH, no significant difference for blood component/product transfusion between treatment groups was observed.

One systematic review (Zaidi 2020) reported the effect of fibrinogen concentrate on transfusion volume among women with major PPH. The systematic review authors identified one RCT (Collins 2017) that they used to determine the total volume of blood transfused per patient at 7 days (inclusive of red blood cells, FFP, cryoprecipitate, fibrinogen concentrate, platelets and prothrombin complex concentrate) between women who received TEG-guided early administration of fibrinogen concentrate compared with those who did not. An adjusted rate ratio 0.72 (95% CI 0.30, 1.70) was reported ( $P = 0.45$ ).

#### **LOS, hospital or ICU**

Among critically bleeding patients with PPH, 2 cohort studies reported no significant difference for hospital LOS (Collins 2017) or ICU LOS (Ahmed 2012) between patients who received fibrinogen concentrate compared with those 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)	Summary
Mortality, all cause (RCTs) Latest reported timepoint  9 Critical	Relative risk 0  Based on data from 299 participants in 2 studies. <sup>1</sup> (Randomized controlled)	0 per 1000  Difference:	0 per 1000  <b>0 fewer per 1000</b> CI 95% 0 fewer —	Low Due to very serious imprecision <sup>2</sup>	There were too few who experienced the outcome, to determine whether fibrinogen concentrate made a difference on mortality in women with major PPH.
Morbidity, thromboemboli c events  9 Critical	Relative risk 0.96 (CI 95% 0.06 — 14.65) Based on data from 299 participants in 2 studies. <sup>3</sup> (Randomized controlled)	7 per 1000  Difference:	7 per 1000  <b>0 fewer per 1000</b> ( CI 95% 7 fewer — 96 more )	Low Due to very serious imprecision <sup>4</sup>	There were too few who experienced the outcome to determine whether fibrinogen concentrate made a difference in thromboembolic events in women with major PPH.
RBC transfusion volume	Measured by: Number of Units Lower better Based on data from 34 participants in 1 studies. <sup>5</sup> (Observational (non- randomized))	7.2 Units (Mean)  Difference:	5.9 Units (Mean)  <b>SMD 0.29 fewer</b> ( CI 95% 0.98 fewer — 0.4 more )	Very low Due to serious risk of bias, Due to very serious imprecision <sup>6</sup>	The evidence is very uncertain about the effect of fibrinogen concentrate on the volume of RBCs transfused in women with major PPH
Transfusion volume, other blood components/ products	Based on data from 34 participants in 1 studies. <sup>7</sup> (Observational (non- randomized))	There was no significant difference in the volume of FFP, PLT or FC transfused among women who received FC compared to those who received CRYO.		Very low Due to serious risk of bias, Due to very serious imprecision <sup>8</sup>	The evidence is very uncertain about the effect of fibrinogen concentrate on the volume of FFP, PLTs, or FC transfused in women with major PPH
Length of stay	Based on data from 89 participants in 2 studies. <sup>9</sup> (Observational (non- randomized))	There was no significant difference in the length of hospital or ICU stay among women who received FC compared to those who received CRYO.		Very low Due to serious risk of bias, Due to very serious imprecision <sup>10</sup>	The evidence is very uncertain about the effect of fibrinogen concentrate on length of hospital or ICU stay in women with major PPH.

1. Systematic review [4] with included studies: Collins 2017 (RCT, obstetrics), Wikkelsø 2015 (RCT, obstetrics). **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [46], [246],
2. **Risk of Bias: no serious.** Two RCTs with overall low risk of bias. Certainty of evidence not

downgraded . **Inconsistency: no serious. Indirectness: no serious.** The available evidence is in women with major postpartum hemorrhage in various healthcare settings including United Kingdom, Canada, Austria, Germany and Sweden. The evidence can be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded . **Imprecision: very serious.** Only one study contributing data. Wide confidence intervals. Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels .

**Publication bias: no serious.**

3. Systematic review [4] with included studies: Wikkelsø 2015 (RCT, obstetrics), Collins 2017 (RCT, obstetrics). **Baseline/comparator:** Control arm of reference used for intervention.

4. **Risk of Bias: no serious.** Two RCTs with overall low risk of bias. Certainty of evidence not downgraded . **Inconsistency: no serious. Indirectness: no serious.** The available evidence is in women with major postpartum hemorrhage in various healthcare settings including United Kingdom and Denmark. The evidence can be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded . **Imprecision: very serious.** Only one study contributing data. Wide confidence intervals. Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels . **Publication bias: no serious.**

5. Systematic review [4] with included studies: [43]. **Baseline/comparator:** Primary study.

6. **Risk of Bias: serious.** Some concerns of bias due to study design and selective outcome reporting. Certainty of evidence downgraded . **Inconsistency: no serious. Indirectness: no serious.** The available evidence is generalisable to the Australian obstetric population and could be sensibly applied. The study was conducted in the United Kingdom among women with major PPH.

**Imprecision: very serious.** Only one study contributing data. Wide confidence intervals. Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels . **Publication bias: no serious.**

7. Systematic review **Supporting references:** [43],

8. **Risk of Bias: serious.** Some concerns of bias due to study design and selective outcome reporting. Certainty of evidence downgraded . **Inconsistency: no serious.** Heterogeneity not applicable.

**Indirectness: no serious.** The available evidence is generalisable to the Australian obstetric population and could be sensibly applied. The study was conducted in the United Kingdom among women with major PPH. Certainty of evidence not downgraded. **Imprecision: very serious.** Only one study contributing data. Wide confidence intervals. Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels .

**Publication bias: no serious.**

9. Systematic review **Supporting references:** [43],

10. **Risk of Bias: serious.** Two comparative observational studies with some concerns of bias due to study design and reporting. Certainty of evidence downgraded. **Inconsistency: no serious.**

**Indirectness: no serious.** The available evidence is in obstetric patients in various healthcare settings including United Kingdom, Canada, Austria, Germany and Sweden, and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded . **Imprecision: very serious.** Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels . **Publication bias: no serious.**

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## Clinical question/ PICO

**Population:** People with critical bleeding (trauma setting)

**Intervention:** Prothrombin complex

**Comparator:** No prothrombin complex (or varying administration of)

## Summary

Refer to the technical reports for further information on individual studies.

### What did we find?

One systematic review (van den Brink 2020 [81]) was found that included evidence from 4 non-randomised cohort studies (Jehan 2018, Zeeshan 2019, Joseph 2014, Joseph 2016) that assessed the use of different prothrombin complex concentrates and FFP versus FFP alone on patient outcomes in the trauma setting.

### Study characteristics

The 4 cohort studies (total sample size 924) were conducted in trauma patients presenting to the emergency department. Two studies (Jehan 2018 [248], Zeeshan 2019 [251]) investigated the effect of 4-factor prothrombin complex concentrates plus FFP compared to FFP only and 2 studies (Joseph 2014 [249], Joseph 2016 [250]) investigated the effect of 3-factor prothrombin complex concentrates plus FFP compared to FFP only. Dose of prothrombin complex concentrate administered was 25 IU/kg for 3 studies and indication for administration was by clinical judgement for all 4 studies.

The studies were judged by van den Brink 2020 [81] to have moderate risk of bias due to the retrospective study design, in which prothrombin complex concentrate 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 prothrombin complex concentrates could lead to under or overrepresentation of the actual effects of prothrombin complex concentrates on the outcomes.

### What are the main results?

#### Mortality

A meta-analysis of data from the 4 retrospective cohort studies revealed a significant reduction in mortality among patients who received prothrombin complex concentrates in conjunction with FFP (72/364, 19.8%) compared with those who received FFP alone (159/557, 28.5%), representing an OR of 0.64 (95% CI 0.46, 0.88; P = 0.007).

#### Morbidity

A meta-analysis of data from the 4 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).

#### Red blood cell transfusion volume

A meta-analysis of data from the 4 retrospective cohort studies showed a significant reduction in the volume of red blood cells transfused among patients that received prothrombin complex concentrates in conjunction with FFP compared with those who received FFP alone (SMD -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	Intervention Prothrombin complex	Certainty of the Evidence (Quality of evidence)	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. <sup>1</sup> (Observational (non- randomized))	285 per 1000  Difference:	203 per 1000  <b>82 fewer per 1000</b> ( CI 95% 130 fewer — 25 fewer )	Very low Due to serious risk of bias <sup>2</sup>	The use of prothrombin complex concentrates in trauma patients with critical bleeding may reduce mortality but the evidence is very uncertain.
Morbidity, thromboemboli c events  9 Critical	Odds ratio 0.9 (CI 95% 0.49 — 1.67) Based on data from 921 participants in 4 studies. <sup>3</sup> (Observational (non- randomized))	48 per 1000  Difference:	43 per 1000  <b>5 fewer per 1000</b> ( CI 95% 24 fewer — 30 more )	Very low Due to serious risk of bias, Due to serious imprecision <sup>4</sup>	The evidence is very uncertain about the effect of prothrombin complex concentrates on thromboembolic events in trauma patients with critical bleeding.

Outcome Timeframe	Study results and measurements	Comparator No prothrombin complex	Intervention Prothrombin complex	Certainty of the Evidence (Quality of evidence)	Summary
Red blood cell transfusion volume	Measured by: Number of Units Lower better Based on data from 921 participants in 4 studies. <sup>5</sup> (Observational (non- randomized))	5.4 - 10 Units  Difference:	3.2 - 7 Units  <b>SMD 0.65 lower</b> ( CI 95% 0.98 lower — 0.32 lower )	Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision <sup>6</sup>	The use of prothrombin complex concentrates in trauma patients with critical bleeding may reduce the volume of red blood cells transfused but the evidence is very uncertain.

1. Systematic review [4] with included studies: Joseph 2014 (Coh, trauma), Joseph 2016 (Coh, trauma), Zeeshan 2019 (Coh, trauma), Jehan 2018 (Coh, trauma). **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [249], [250], [251], [248],
2. **Risk of Bias: serious.** Several comparative observational studies with some concerns of bias related to study design. Certainty of evidence downgraded. **Inconsistency: no serious.** No statistical heterogeneity ( $I^2 = 0\%$ ). Certainty of evidence not downgraded. **Indirectness: no serious.** Evidence is in United States trauma patients which is generalisable to Australian trauma patients and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: no serious. Publication bias: no serious.**
3. Systematic review [4] with included studies: Joseph 2014 (Coh, trauma), Joseph 2016 (Coh, trauma), Jehan 2018 (Coh, trauma), Zeeshan 2019 (Coh, trauma). **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Several comparative observational studies with some concerns of bias related to study design. Certainty of evidence downgraded. **Inconsistency: no serious.** No statistical heterogeneity ( $I^2 = 0\%$ ). Certainty of evidence not downgraded. **Indirectness: no serious.** Evidence is in United States trauma patients which is generalisable to Australian trauma patients and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.**
5. Systematic review [4] with included studies: Jehan 2018 (Coh, trauma), Joseph 2014 (Coh, trauma), Joseph 2016 (Coh, trauma), Zeeshan 2019 (Coh, trauma). **Baseline/comparator:** Systematic review [4] with included studies: Zeeshan 2019 (Coh, trauma), Joseph 2016 (Coh, trauma), Jehan 2018 (Coh, trauma), Joseph 2014 (Coh, trauma).
6. **Risk of Bias: serious.** Several comparative observational studies with some concerns of bias related to study design. Certainty of evidence downgraded. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high ( $I^2 > 50\%$ ). Certainty of evidence downgraded. **Indirectness: no serious.** Evidence is in United States trauma patients which is generalisable to Australian trauma patients and could be sensibly applied to the Australian healthcare context. Certainty of evidence not downgraded. **Imprecision: serious.** Low event rates. Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.**

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### Clinical question/ PICO

**Population:** People with critical bleeding (any setting)  
**Intervention:** Platelets  
**Comparator:** No platelets (or varying administration of)

### Summary

Refer to the technical reports for further information.

There were no systematic reviews, RCTs or non-randomised cohort studies found that assessed the use of platelets compared to no platelets (or varying administration of) in patients with critical bleeding.

Outcome Timeframe	Study results and measurements	Comparator No platelets (or varying administration of)	Intervention Platelets	Certainty of the Evidence (Quality of evidence)
Mortality, all cause latest reported timepoint  9 Critical		No evidence found		

#### Good practice statement

**GPS5:** For other blood components and products, the reference group agreed that the following doses are a guide:

- Fibrinogen replacement: 3-4 g of fibrinogen concentrate which may be achieved using fibrinogen concentrate\* or cryoprecipitate (10 units of whole blood cryoprecipitate, or 4 units of apheresis cryoprecipitate in Australia, or 1 unit of cryoprecipitate/30 kg body weight in New Zealand).
- Prothrombin complex concentrate for warfarin reversal<sup>^</sup>: 25 to 50 IU/kg

There is insufficient evidence to provide recommendations for the optimal timing and/or dose of these blood components or products.

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

*<sup>^</sup>Refer to [An update of consensus guidelines for warfarin reversal](#)*

#### Rationale

Refer to Research evidence under R4

#### Good practice statement

**GPS6:** The reference group agreed that it is good practice to administer red blood cells through a blood warming device whenever possible and aim to maintain the patient's core temperature  $\geq 35^{\circ}\text{C}$ .

#### Rationale

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

#### Good practice statement

**GPS7:** 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

Transition to ABO identical blood component as soon as possible to ensure optimal stewardship of scarce blood components, especially group O negative red blood cells [217]. Refer to the National Statement for the Emergency Use of Group O Red Blood Cells.

## Good practice statement

**GPS8:** When critical bleeding is controlled, the reference group agreed that it is good practice to cease the major haemorrhage protocol and proceed to targeted optimisation of coagulation, physiological and biochemical parameters and continued patient assessment.

## Rationale

The reference group agreed that evidence supports the initial transfusion of blood components in a fixed ratio of at least 2:1:1 in critically bleeding patients requiring an MHP (refer to R3). The reference group developed a good practice statement to support health professionals to transition to targeted optimisation of coagulation, physiological, and biochemical parameters.

Further management, after critical bleeding is controlled, was outside the scope of this guideline.

## 7.2 Blood conservation strategies

### 7.2.1 Recombinant activated factor VII

#### Research question

**In patients with critical bleeding, what is the effect of recombinant activated factor VII treatment on morbidity, mortality and transfusion rate?**

Literature search date: 12 August 2019.

This question was retired in March 2021 as research in this area is not expected to substantially evolve.

Recombinant activated factor VII is indicated for the treatment or prevention of bleeding in patients with inhibitors to coagulation factor VIII or factor IX, congenital factor VII deficiency and Glanzmann's thrombasthenia.

## Weak recommendation against , Very low certainty evidence

**R5:** In patients with critical bleeding, the reference group suggests against the routine use of recombinant activated factor VII\*.

*\*Recombinant activated factor VII is approved in Australia and New Zealand for the control of bleeding and surgical prophylaxis in patients with*

- *inhibitors to coagulation Factors VIII or IX*
- *congenital FVII deficiency*
- *Glanzmann's Thrombasthenia who have antibodies to GPIIb-IIIa and/or HLA who present with refractoriness to platelet transfusions.*

*Use of recombinant activated factor VII outside these indications (including critical bleeding after trauma) is considered 'off-label' and is associated with harm.*

*Use of recombinant activated factor VII should only be considered in exceptional circumstance where all other available measures to control bleeding have been exhausted.*



## Evidence to decision

### Benefits and harms

Important harms

There was no significant survival benefit observed in patients with critical bleeding who received recombinant activated factor VII and evidence for harms (thromboembolic events) was limited. In a large and comprehensive meta-analysis of RCTs of recombinant activated factor VII, treatment with high doses of recombinant activated factor VII on an off-label basis significantly increased the risk of arterial but not venous thromboembolic events [108].

### 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 recombinant activated factor VII 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 recombinant activated factor VII in patients with critical bleeding requiring an MHP is not recommended because of its lack of effect on mortality and variable effect on morbidity. The 'off-label' use of recombinant activated factor VII 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 without recombinant activated factor VII

## Summary

Refer to the technical reports for further information on individual studies.

### What did we find?

Five systematic reviews (Cannon 2017 [52], McQuilten 2015 [106], Simpson 2012 [123], Curry 2011 [118], Yank 2011 [119]) were found that included evidence from 3 RCTs (Boffard 2005a, Boffard 2005b, Hauser 2010) examining the effect of recombinant activated factor VII in patients with critical bleeding after blunt or penetrating trauma. There were high concerns of bias in all studies [123], with high threats to validity due to lack of details (selective reporting) or unclear blinding of outcome assessment, which may have favoured the intervention.

The search also found several post-hoc subgroup analyses of the identified RCTs that examined the effect of recombinant activated factor VII on coagulopathic patients [128], on trauma patients who survived the first 48 hours after randomisation [126] and exploring the association between poorer outcomes and baseline haematologic and coagulation parameters [129]. Extended safety data on patients enrolled in CONTROL [127] were also identified for inclusion.

### Study characteristics

Two parallel, double-blind RCTs were run simultaneously that enrolled patients with haemorrhage from a blunt (Boffard 2005a [124]) or penetrating (Boffard 2005b [124]) traumatic injury requiring at least 6 units of red blood cells within 4 hours of hospitalisation and published in the one article [124]. The studies were sponsored by the manufacturer and enrolled 301 patients (143 blunt and 134 penetrating) from 32 centres across 8 countries (including Australia, Canada, France, Germany, Israel, Singapore, South Africa and the United Kingdom). Both RCTs censored deaths that occurred within 48 hours (comprising nearly 20% of patients) as the primary outcomes were red blood cell transfusion needs during the 48-hour observation period, which indicates that some end-stage use of recombinant activated factor VII may have occurred. Mortality and morbidity (ARDS, thromboembolic events) 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 [125]) enrolled patients with blunt or penetrating trauma who, despite strict damage control resuscitation and operative management had continued bleeding after receiving 4 units of red blood cells within 12 hours of injury [125]. 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 recombinant activated factor VII, 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 3 RCTs evaluated a total dose of 400 µg/kg intravenous recombinant activated factor VII administered in 3 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) [35]. Patients enrolled in Hauser 2010 received the first

dose earlier during the resuscitation period (after the fourth unit of red blood cells) 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 recombinant activated factor VII 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 recombinant activated factor VII, 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 red blood cells transfused was observed among those who received recombinant activated factor VII 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 without recombinant activated factor VII	Intervention recombinant activated factor VII	Certainty of the Evidence (Quality of evidence)	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. <sup>1</sup> (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 <sup>2</sup>	The evidence suggests that the use of recombinant activated factor VII in patients with critical bleeding due to blunt or penetrating trauma may have little or no difference in mortality compared with placebo or no recombinant activated factor VII.
Morbidity, thromboemboli c events	Relative risk 1.1 (CI 95% 0.74 — 1.63) Based on data from 837 participants in 3 studies. <sup>3</sup> (Randomized	100 per 1000  Difference:	110 per 1000  10 more per	Very low Due to serious risk of bias, Due to serious indirectness, Due	The use of recombinant activated factor VII in patients with critical bleeding due to blunt or penetrating trauma

Outcome Timeframe	Study results and measurements	Comparator standard best practice without recombinant activated factor VII	Intervention recombinant activated factor VII	Certainty of the Evidence (Quality of evidence)	Summary
9 Critical	controlled)		<b>1000</b> ( CI 95% 26 fewer — 63 more )	to serious imprecision <sup>4</sup>	may have little or no difference on thromboembolic events compared with placebo but we are very uncertain about the evidence.
Morbidity, ARDS  9 Critical	Relative risk 0.39 (CI 95% 0.22 — 0.71) Based on data from 837 participants in 3 studies. <sup>5</sup> (Randomized controlled)	<b>89</b> per 1000  Difference:	<b>35</b> per 1000  <b>54 fewer per 1000</b> ( CI 95% 69 fewer — 26 fewer )	Low Due to serious risk of bias, Due to serious imprecision <sup>6</sup>	The evidence suggests recombinant activated factor VII may result in a slight reduction in ARDS in patients with critical bleeding due to blunt or penetrating trauma.
Morbidity, MOF  9 Critical	Relative risk 0.56 (CI 95% 0.32 — 0.97) Based on data from 837 participants in 3 studies. <sup>7</sup> (Randomized controlled)	<b>79</b> per 1000  Difference:	<b>44</b> per 1000  <b>35 fewer per 1000</b> ( CI 95% 54 fewer — 2 fewer )	Low Due to serious risk of bias, Due to serious imprecision <sup>8</sup>	The evidence suggests recombinant activated factor VII may result in a slight reduction in MOF in patients with critical bleeding due to blunt or penetrating trauma.
Red blood cell transfusion volume units up to 48 hours	Measured by: Number of Units Lower better Based on data from 713 participants in 3 studies. <sup>9</sup> (Randomized controlled)	<b>6.8 - 10.9</b> Units  Difference:	<b>4.5 - 7.8</b> Units  <b>MD 2.35 fewer</b> ( CI 95% 3.7 fewer — 1 fewer )	Very low Due to very serious risk of bias, Due to serious imprecision <sup>10</sup>	Recombinant activated factor VII may slightly reduce the volume of red blood cells transfused in patients with critical bleeding due to blunt or penetrating trauma, but we are very uncertain about the evidence.
Transfusion volume, other blood components/ products	Based on data from 410 participants in 1 studies. <sup>11</sup> (Randomized controlled)	Fewer units of FFP were used in patients in the recombinant activated factor VII group compared with placebo (MD -2.14; 95% CI -3.54, -0.73), while no reduction in platelets, fibrinogen concentrate or cryoprecipitate was observed.		Low Due to serious risk of bias, Due to serious imprecision <sup>12</sup>	Recombinant activated factor VII may slightly reduce the volume of FFP transfused, but not platelets, cryoprecipitate or fibrinogen concentrate, in patients with critical bleeding due to blunt or penetrating trauma, but we are very uncertain about the evidence.

1. Systematic review [3] with included studies: Boffard 2005b (penetrating), Hauser 2010a (blunt), Boffard 2005a (blunt), Hauser 2010b (penetrating). **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [126], [124], [125], [127], [129],
2. **Risk of Bias: serious.** Three randomised studies with concerns of bias were considered to seriously affect the observed effect. The concerns relate to censoring of patients with early in-hospital mortality. Certainty of evidence downgraded. **Inconsistency: no serious.** Results were consistent across studies. No significant statistical heterogeneity detected ( $I^2 = 0\%$ ). Point estimates vary widely. Certainty of evidence not downgraded. **Indirectness: no serious.** Evidence is generalisable to bleeding patients admitted to trauma or emergency centres in Australia with few caveats. Applicability is probably similar to the Australian emergency context, however, comparison to 'usual care' is limited and may not reflect current practice (changes in practice since the conduct of studies). Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence interval (upper and lower bounds overlap with both effect and no effect). Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded. **Publication bias: no serious.**
3. Systematic review [3] with included studies: Hauser 2010b (penetrating), Boffard 2005b (penetrating), Boffard 2005a (blunt), Hauser 2010a (blunt). **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Three randomised studies with concerns of bias considered to seriously affect the observed effect. Certainty of evidence downgraded. **Inconsistency: no serious.** Results were consistent across studies. No significant statistical heterogeneity detected ( $I^2 = 0\%$ ). Certainty of evidence not downgraded. **Indirectness: serious.** Evidence is generalisable to bleeding patients admitted to trauma or emergency centres in Australia with few caveats. However, comparison to 'usual care' is limited and may not reflect current practice (changes in practice since the conduct of studies). Certainty of evidence downgraded. **Imprecision: serious.** Wide confidence interval (upper and lower bounds overlap with both effect and no effect). Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded. **Publication bias: no serious.**
5. Systematic review [3] with included studies: Hauser 2010b (penetrating), Boffard 2005a (blunt), Hauser 2010a (blunt), Boffard 2005b (penetrating). **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: serious.** Three randomised studies with concerns of bias were considered to seriously affect the observed effect. Certainty of evidence downgraded. **Inconsistency: no serious.** Results were consistent across studies. No significant statistical heterogeneity detected. ( $I^2 = 0\%$ ). Certainty of evidence not downgraded. **Indirectness: no serious.** Evidence is generalisable to bleeding patients admitted to trauma or emergency centres in Australia with few caveats. Applicability is probably similar to the Australian emergency context, however, comparison to 'usual care' is limited and may not reflect current practice (changes in practice since the conduct of studies). Certainty of evidence not downgraded. **Imprecision: serious.** Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded. **Publication bias: no serious.**
7. Systematic review [3] with included studies: Hauser 2010b (penetrating), Hauser 2010a (blunt), Boffard 2005a (blunt), Boffard 2005b (penetrating). **Baseline/comparator:** Control arm of reference used for intervention.
8. **Risk of Bias: serious.** Three randomised studies with concerns of bias were considered to seriously affect the observed effect. Certainty of evidence downgraded. **Inconsistency: no serious.** Results were consistent across studies. No significant statistical heterogeneity detected ( $I^2 = 0\%$ ). Certainty of evidence not downgraded. **Indirectness: no serious.** Evidence is generalisable to bleeding patients admitted to trauma or emergency centres in Australia with few caveats. Applicability is probably similar to the Australian emergency context, however, comparison to 'usual care' is limited and may

not reflect current practice (changes in practice since the conduct of studies). Certainty of evidence not downgraded. **Imprecision: serious.** Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded. **Publication bias: no serious.**

9. Systematic review [3] with included studies: Boffard 2005b (penetrating), Hauser 2010a (blunt), Hauser 2010b (penetrating), Boffard 2005a (blunt). **Baseline/comparator:** Systematic review [3] with included studies: Boffard 2005a (blunt), Boffard 2005b (penetrating), Hauser 2010b (penetrating), Hauser 2010a (blunt). **Supporting references:** [123],

10. **Risk of Bias: very serious.** Concerns regarding censoring of patients with early in-hospital mortality. Three randomised studies with concerns of bias were considered to seriously affect the observed effect. Certainty of evidence downgraded 2 levels. **Inconsistency: no serious.** Results were consistent across studies. No significant statistical heterogeneity detected ( $I^2 = 0\%$ ). Certainty of evidence not downgraded. **Indirectness: no serious.** Evidence is generalisable to bleeding patients admitted to trauma or emergency centres in Australia with few caveats. Applicability is probably similar to the Australian emergency context, however, comparison to 'usual care' is limited and may not reflect current practice (changes in practice since the conduct of studies). Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.**

11. Systematic review [3].

12. **Risk of Bias: serious.** One randomised study with concerns of bias was considered to seriously affect the observed effect. Certainty of evidence downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: no serious.** Evidence is generalisable to bleeding patients admitted to trauma or emergency centres in Australia with few caveats. Applicability is probably similar to the Australian emergency context, however, comparison to 'usual care' is limited and may not reflect current practice (changes in practice since the conduct of studies). Certainty of evidence not downgraded. **Imprecision: serious.** Only data from one study. Certainty of evidence downgraded. **Publication bias: no serious.**

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## 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 without recombinant activated factor VII

## Summary

Refer to the technical reports for further information on individual studies.

## What did we find?

One systematic review (Simpson 2012 [\[123\]](#)) was found that included evidence from 2 RCTs (Bosch 2004, Bosch 2008) that evaluated the therapeutic use of recombinant activated factor VII in the medical emergency setting, both of which were assessed by Simpson 2012 [\[123\]](#) to have some concerns of bias, predominantly due to lack of clear detail and poor reporting in the published reports.



**Study characteristics**

The RCT reported by Bosch 2004 [131] was conducted in 245 cirrhotic patients with upper gastrointestinal bleeding (UGIB) enrolled from 26 centres in Europe. Patients were administered 100 µg/kg recombinant activated factor VII 8 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 [130], 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 recombinant activated factor VII 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 RCTs 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 RCTs, the total dose of recombinant activated factor VII 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) [35].

**What are the main results?****Mortality**

Among patients with UGIB who received recombinant activated factor VII, 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 recombinant activated factor VII. 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 recombinant activated factor VII 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 recombinant activated factor VII, no difference in red blood cell transfusion volumes was observed when compared with those who did not receive recombinant activated factor VII (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 without recombinant activated factor VII	Intervention recombinant activated factor VII	Certainty of the Evidence (Quality of evidence)	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. <sup>1</sup> (Randomized controlled)	175 per 1000  Difference:	179 per 1000  <b>4 more per 1000</b> ( CI 95% 79 fewer — 158 more )	Very low Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision <sup>2</sup>	Recombinant activated factor VII may have little or no effect on mortality in patients with severe gastrointestinal bleeding, but we are very uncertain about the evidence.
Morbidity, thromboemboli c events  9 Critical	Relative risk 0.8 (CI 95% 0.4 — 1.6) Based on data from 507 participants in 2 studies. <sup>3</sup> (Randomized controlled)	67 per 1000  Difference:	54 per 1000  <b>13 fewer per 1000</b> ( CI 95% 40 fewer — 40 more )	Low Due to serious indirectness, Due to serious imprecision <sup>4</sup>	The evidence suggests that the use of recombinant activated factor VII may have little or no difference on thromboembolic events in patients with severe gastrointestinal bleeding.
Red blood cell transfusion volume	Measured by: Number of Units Lower better Based on data from 393 participants in 2 studies. <sup>5</sup> (Randomized controlled)	1.3 - 3.3 Units  Difference:	1.5 - 2.55 Units  <b>MD 0.24 fewer</b> ( CI 95% 1.17 fewer — 0.69 more )	Very low Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision <sup>6</sup>	Recombinant activated factor VII 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.

1. Systematic review [3] with included studies: Bosch 2004 (GI haemorrhage in cirrhosis), Bosch 2008 (GI haemorrhage in cirrhosis). **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [131], [130],

2. **Risk of Bias: no serious.** Two randomised studies with low concerns of bias. Certainty of evidence not downgraded. **Inconsistency: serious.** Substantial statistical heterogeneity detected ( $I^2 > 50\%$ ). Certainty of evidence downgraded. **Indirectness: serious.** Evidence is generalisable to bleeding patients admitted to trauma or emergency centres in Australia with few caveats. Dosing of recombinant activated factor VII in the included trials not reflective of current practice. Certainty of evidence downgraded. **Imprecision: serious.** Wide confidence interval (upper and lower bounds overlap with both effect and no effect). Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded. **Publication bias: no serious.**

3. Systematic review [3] with included studies: Bosch 2004 (GI haemorrhage in cirrhosis), Bosch 2008 (GI haemorrhage in cirrhosis). **Baseline/comparator:** Control arm of reference used for intervention.

4. **Risk of Bias: no serious.** Two randomised studies with low to unclear risk of bias. Certainty of evidence not downgraded. **Inconsistency: no serious.** Results were consistent across studies. No

significant statistical heterogeneity detected ( $I^2 = 0\%$ ). Certainty of evidence not downgraded.

**Indirectness: serious.** Dosing of recombinant activated factor VII in the included trials not reflective of current practice. Evidence is generalisable to bleeding patients admitted to trauma or emergency centres in Australia with few caveats. Certainty of evidence downgraded. **Imprecision: serious.** Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded. **Publication bias: no serious.**

5. Systematic review [3] with included studies: Bosch 2008 (GI haemorrhage in cirrhosis), Bosch 2004 (GI haemorrhage in cirrhosis). **Baseline/comparator:** Systematic review [3] with included studies: Bosch 2008 (GI haemorrhage in cirrhosis), Bosch 2004 (GI haemorrhage in cirrhosis).

6. **Risk of Bias: no serious.** Two randomised studies with low to unclear risk of bias. Certainty of evidence downgraded. **Inconsistency: serious.** Substantial statistical heterogeneity detected ( $I^2 > 50\%$ ). Certainty of evidence downgraded. **Indirectness: serious.** Dosing of recombinant activated factor VII in the included trials not reflective of current practice. Evidence is generalisable to bleeding patients admitted to trauma or emergency centres in Australia with few caveats. Certainty of evidence downgraded. **Imprecision: serious.** Wide confidence interval (upper and lower bounds overlap with both effect and no effect). Certainty of evidence downgraded. **Publication bias: no serious.**

## References

3. HTANALYSTS, Jorgensen M. rFVIIa for critical bleeding. RevMan 5.4 2019.

123. Simpson E., Lin Y., Stanworth S., Birchall J., Doree C., Hyde C.. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane Database of Systematic Reviews (Online) 3:CD005011 [Journal](#)

130. Bosch J., Thabut D., Albillos A., Carbonell N., Spicak J., Massard J., et al. Recombinant factor VIIa for variceal bleeding in patients with advanced cirrhosis: A randomized, controlled trial. Hepatology 2008;47(5):1604-14 [Journal](#)

131. Bosch J., Thabut D., Bendtsen F., D'Amico G., Albillos A., Gonzalez Abraldes J., et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. Gastroenterology 2004;127(4):1123-30 [Journal](#)

## 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 without recombinant activated factor VII

## Summary

Refer to the technical reports for further information on individual studies.

**What did we find?**

One systematic review (Simpson 2012 [123]) was found that included evidence from 2 RCTs (Pihusch 2005, Chuansumrit 2005) that evaluated the use of recombinant activated factor VII in patients with bleeding.

**Study characteristics**

The RCT reported by Pihusch 2005 [132] evaluated the use of recombinant activated factor VII in 100 patients with moderate or severe bleeding complications following haematopoietic stem cell transplantation (HSCT) (+2 to +180 weeks post-transplant). The study enrolled patients with bleeding (52 gastrointestinal; 26 haemorrhagic cystitis; 7 pulmonary; one cerebral; 14 other) who were randomised to receive 7 doses of recombinant activated factor VII at 40, 80 or 160 µg/kg (total dose: 280, 560, or 1120 µg/kg) or placebo every 6 hours. The primary efficacy endpoint was the change in bleeding score between the first administration and 38 hours. The study was considered by Simpson 2012 [123] to be at high risk of bias due to baseline difference observed between treatment groups, suggesting randomisation or allocation concealment was compromised.

Chuansumrit 2005 [133] was an RCT conducted in 25 paediatric patients with active bleeding due to dengue fever. The study authors administered 100 µg/kg recombinant activated factor VII with repeat dose at 30 minutes to patients if ongoing bleeding was observed. The study was small and not sufficiently powered to detect differences in any outcomes and was considered by Simpson 2012 [123] to be at high risk of bias.

**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 recombinant activated factor VII, 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 recombinant activated factor VII (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 red blood cells transfused was not reported in the RCT conducted in patients with uncontrolled bleeding after HSCT. Among paediatric patients with dengue haemorrhagic fever, no difference in red blood cell 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 without recombinant activated factor VII	Intervention recombinant activated factor VII	Certainty of the Evidence (Quality of evidence)	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. <sup>1</sup> (Randomized controlled)	219 per 1000  Difference:	223 per 1000  <b>4 more per 1000</b> ( CI 95% 107 fewer — 234 more )	Low Due to serious risk of bias, Due to serious imprecision <sup>2</sup>	The evidence suggests recombinant activated factor VII results in little or no difference in mortality in patients with critical bleeding after HSCT.
Morbidity, thromboemboli c events  9 Critical	Relative risk 5.23 (CI 95% 0.31 — 87.34) Based on data from 125 participants in 2 studies. <sup>3</sup> (Randomized controlled)	0 per 1000  Difference:	0 per 1000  <b>0 fewer per 1000</b> ( CI 95% 0 fewer — 0 fewer )	Very low Due to serious risk of bias, Due to very serious imprecision <sup>4</sup>	Recombinant activated factor VII may result in a slight increase in thromboembolic events in patient with critical bleeding after HSCT but we are very uncertain about the evidence.
Red blood cell transfusion volume		No studies reported this outcome			The effect of recombinant activated factor VII on red blood cell transfusion volume in patients with critical bleeding after HSCT is unknown.

1. Systematic review [3] with included studies: Pihusch 2005 (haemorrhage after HSCT), Chuansumrit 2005 (dengue). **Baseline/comparator:** Systematic review [3] with included studies: Pihusch 2005 (haemorrhage after HSCT), Chuansumrit 2005 (dengue). **Supporting references:** [132], [133],
2. **Risk of Bias: serious.** Randomised studies with unclear to high risk of bias that was considered to seriously affect the confidence in the observed effect. Certainty of evidence downgraded.  
**Inconsistency: no serious. Indirectness: no serious.** Evidence is generalisable to patients with critical bleeding after HSCT. Applicability is probably similar to the Australian emergency context, however, comparison to 'usual care' is limited and may not reflect current practice (changes in practice since the conduct of studies). Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals (upper and lower bounds overlap with both effect and no effect). Low event rate in included studies that were not powered to detect the outcome of interest. Certainty of evidence downgraded. **Publication bias: no serious.**
3. Systematic review [3] with included studies: Pihusch 2005 (haemorrhage after HSCT), Chuansumrit 2005 (dengue). **Baseline/comparator:** Control arm of reference used for intervention.
4. **Risk of Bias: serious.** Randomised studies with unclear to high risk of bias that was considered to seriously affect the confidence in the observed effect. Certainty of evidence downgraded.  
**Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: no serious.** Evidence is generalisable to patients with critical bleeding after HSCT. Applicability is probably similar to the Australian emergency context, however, comparison to 'usual

care' is limited and may not reflect current practice (changes in practice since the conduct of studies). Certainty of evidence not downgraded. **Imprecision: very serious.** Only one study contributing data. Wide confidence intervals. Optimal information size not reached. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

### References

3. HTANALYSTS, Jorgensen M. rFVIIa for critical bleeding. RevMan 5.4 2019.

123. Simpson E., Lin Y., Stanworth S., Birchall J., Doree C., Hyde C.. Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia. Cochrane Database of Systematic Reviews (Online) 3:CD005011 [Journal](#)

132. Pihusch M., Bacigalupo A., Szer J., von Depka Prondzinski M., Gaspar-Blaudschun B., Hyveled L., et al. Recombinant activated factor VII in treatment of bleeding complications following hematopoietic stem cell transplantation. J Thromb Haemost 2005;3(9):1935-44 [Journal](#)

133. Chuansumrit A., Wangruangsatid S., Lektrakul Y., Chua MN, Zeta Capeding MR, Bech OM, et al. Control of bleeding in children with Dengue hemorrhagic fever using recombinant activated factor VII: a randomized, double-blind, placebo-controlled study. Blood Coagul Fibrinolysis 2005;16(8):549-55 [Journal](#)

### 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 without recombinant activated factor VII

### Summary

Refer to the [technical reports](#) for further information on individual studies.

### What did we find?

One systematic review (Yank 2011 [119]) was found that included evidence from one small Phase II dose-escalation study (Gill 2009 [134]) that evaluated the therapeutic use of recombinant activated factor VII in patients with intractable bleeding after cardiac surgery.

### Study characteristics

Gill 2009 [134] was conducted across 13 countries in Africa, Asia, Europe, South America and United States. Patients were randomised to receive either 40 µg/kg (n=35) or 80 µg/kg (n=69) recombinant activated factor VII or placebo (n=68) after cardiopulmonary bypass as treatment for excessive post-operative bleeding in the ICU. The study 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 by Yank 2011 [119] to be at overall low to unclear risk of bias.

## What are the main results?

### Mortality

Among patients with intractable bleeding after cardiac surgery, the mortality rate among those who received recombinant activated factor VII (9.6%) was higher than that observed among those who did not receive recombinant activated factor VII (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 after cardiac surgery, the risk of thromboembolic events was higher in the group who received recombinant activated factor VII (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 red blood cells 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 without recombinant activated factor VII	Intervention recombinant activated factor VII	Certainty of the Evidence (Quality of evidence)	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. <sup>1</sup> (Randomized controlled)	59 per 1000  Difference:	96 per 1000  <b>37 more per 1000</b> ( CI 95% 28 fewer — 236 more )	Low Due to very serious imprecision <sup>2</sup>	The evidence suggests that the use of recombinant activated factor VII in patients with critical bleeding after cardiac surgery results in little to no difference in mortality compared with no recombinant activated factor VII
Morbidity, thromboemboli c events	Relative risk 4.58 (CI 95% 0.58 — 36.38) Based on data from 172 participants in 1 studies.	15 per 1000	69 per 1000	Low Due to very serious imprecision <sup>4</sup>	The evidence suggests recombinant activated factor VII results in a slight increase in

Outcome Timeframe	Study results and measurements	Comparator standard best practice without recombinant activated factor VII	Intervention recombinant activated factor VII	Certainty of the Evidence (Quality of evidence)	Summary
9 Critical	<sup>3</sup> (Randomized controlled)	Difference:	<b>54 more per 1000</b> ( CI 95% 6 fewer — 531 more )		thromboembolic events in patient with critical bleeding after cardiac surgery.
Red blood cell transfusion volume		No studies reported this outcome			The effect of recombinant activated factor VII on red blood cell transfusion volume in patients admitted to intensive care with intractable bleeding after cardiac surgery is unknown.

1. Systematic review [3] with included studies: Gill 2009 (treatment). **Baseline/comparator:** Systematic review [3] with included studies: Gill 2009 (treatment). **Supporting references:** [134],
2. **Risk of Bias: no serious.** One randomised study with unclear risk of bias not likely to seriously influence the results. Certainty of evidence not downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: no serious.** Evidence is generalisable to patients admitted to intensive care with intractable bleeding after cardiac surgery. Applicability is probably similar to the Australian emergency context, however, comparison to 'usual care' is limited and may not reflect current practice (changes in practice since the conduct of studies). Certainty of evidence not downgraded. **Imprecision: very serious.** Only data from one study. Wide confidence interval (upper and lower bounds overlap with both effect and no effect). Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**
3. Systematic review [3] with included studies: Gill 2009 (treatment). **Baseline/comparator:** Systematic review [3] with included studies: Gill 2009 (treatment).
4. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: no serious.** Evidence is generalisable to patients admitted to intensive care with intractable bleeding after cardiac surgery. Applicability is probably similar to the Australian emergency context, however, comparison to 'usual care' is limited and may not reflect current practice (changes in practice since the conduct of studies). Certainty of evidence not downgraded. **Imprecision: very serious.** Only data from one study. Wide confidence interval (upper and lower bounds overlap with both effect and no effect). Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

## References

3. HTANALYSTS, Jorgensen M. rFVIIa for critical bleeding. RevMan 5.4 2019.

119. Yank V, Tuohy CV, Logan AC, Bravata DM, Staudenmayer K, Eisenhut R, et al. Systematic



review: benefits and harms of in-hospital use of recombinant factor VIIa for off-label indications. *Annals of Internal Medicine* 2011;154(8):529-40 [Journal](#)

134. Gill R., Herbertson M., Vuylsteke A., Olsen PS, von Heymann C., Mythen M., et al. Safety and efficacy of recombinant activated factor VII: a randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. *Circulation* 2009;120(1):21-7 [Journal](#)

## 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 (obstetrics and maternity setting)

**Intervention:** recombinant activated factor VII

**Comparator:** standard best practice without recombinant activated factor VII

## Summary

Refer to the technical reports for further information on individual studies.

### What did we find?

The literature search found one multicentre RCT (Lavigne-Lissalde 2015 [\[135\]](#)) that assessed the safety and effectiveness of recombinant activated factor VII given to women with severe primary PPH, defined as loss of more than 1500 mL of blood within 24 hours after birth, after sulprostone failure.

### Study characteristics

Lavigne-Lissalde 2015 enrolled women aged over 18 years who had delivered after the end of 27 weeks of gestation by either vaginal or Caesarean section with severe PPH. Patients were randomly assigned to receive a single dose of 60 µg/kg recombinant activated factor VII or not, with the primary outcome being a reduction in the need for specific second-line therapies (inclusive of arterial embolization, hysterectomy). Safety outcomes were also recorded up to 5 days post infusion. The study was assessed as being at high risk of bias due to non-blinding that seriously weakens confidence in the results. The study allowed for compassionate use of recombinant activated factor VII in the comparator arm (8 out of 42 women in the standard care group received late recombinant activated factor VII) so it is also possible that this introduced bias into the subsequent management of patients.

### What are the main results?

#### Mortality

No deaths were observed in the RCT that assessed the effects of recombinant activated factor VII among women with severe PPH with persistent bleeding after sulprostone treatment and the included RCT was not large enough to detect differences in mortality.



**Morbidity**

Among patients with PPH, the risk of thromboembolic events was higher in the group who received recombinant activated factor VII (2/42, 4.8%) compared with those who did not (0/42, 0%). The difference was not significant (RR 5.00; 95% CI 0.25, 101.11.00; P = 0.29), noting the study was not large enough to detect any important differences.

**Transfusion volumes**

The volume of red blood cells transfused was not reported in the RCT conducted in women with severe PPH with persistent bleeding after sulprostone treatment.

Outcome Timeframe	Study results and measurements	Comparator standard best practice without recombinant activated factor VII	Intervention recombinant activated factor VII	Certainty of the Evidence (Quality of evidence)	Summary
Mortality, all cause latest reported timepoint	0 (CI 95% 0 — 0) Based on data from 84 participants in 1 studies. <sup>1</sup> (Randomized controlled)	0 per 1000	CI 95%	Very low Due to serious risk of bias, Due to very serious imprecision <sup>2</sup>	The effect of recombinant activated factor VII on mortality in patients with critical bleeding in the obstetrics and maternity setting is unknown.
Morbidity, thromboemboli c events  9 Critical	Relative risk 5 (CI 95% 0.25 — 101.11) Based on data from 84 participants in 1 studies. <sup>3</sup> (Randomized controlled)	0 per 1000  Difference:	0 per 1000  <b>0 fewer per 1000</b> ( CI 95% 0 fewer — 0 fewer )	Very low Due to serious risk of bias, Due to very serious imprecision <sup>4</sup>	The evidence suggests recombinant activated factor VII may result in a slight increase in thromboembolic events in women with severe PPH that persists after sulprostone infusion but the evidence is very uncertain.
Morbidity, need for second-line intervention	Relative risk 0.56 (CI 95% 0.42 — 0.76) Based on data from 84 participants in 1 studies. <sup>5</sup> (Randomized controlled)	929 per 1000  Difference:	520 per 1000  <b>409 fewer per 1000</b> ( CI 95% 539 fewer — 223 fewer )	Very low Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision <sup>6</sup>	Recombinant activated factor VII may reduce the need for second- line interventions in women with severe PPH that persists after sulprostone infusion, but the evidence is very uncertain.
RBC transfusion volume		No studies reported this outcome			The effect of recombinant activated factor VII on red blood cell transfusion volume in women with severe PPH that persists after sulprostone infusion is

Outcome Timeframe	Study results and measurements	Comparator standard best practice without recombinant activated factor VII	Intervention recombinant activated factor VII	Certainty of the Evidence (Quality of evidence)	Summary
					unknown.

1. Systematic review [3] with included studies: Lavigne-Lissalde 2015 (PPH). **Baseline/comparator:** Systematic review. **Supporting references:** [135],
2. **Risk of Bias: serious.** One study with unclear to high risk of bias that was considered to seriously affect the confidence in the observed effect. Certainty of evidence downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: no serious.** Evidence is generalisable to women with severe postpartum haemorrhage after vaginal or Caesarean delivery. The evidence is probably applicable to the Australian healthcare context with some caveats relating to maternity care and to access to second line interventions. Certainty of evidence not downgraded. **Imprecision: very serious.** Wide confidence intervals. Only one study contributing data. Low event rate, with optimal information size to detect the outcome of interest not reached. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**
3. Systematic review [3] with included studies: Lavigne-Lissalde 2015 (PPH). **Baseline/comparator:** Primary study.
4. **Risk of Bias: serious. Inconsistency: no serious. Indirectness: no serious.** Evidence is generalisable to women with severe postpartum haemorrhage after vaginal or Caesarean delivery. The evidence is probably applicable to the Australian healthcare context with some caveats relating to maternity care and to access to second line interventions. Certainty of evidence not downgraded. **Imprecision: very serious.** Wide confidence intervals. Only one study contributing data. Low event rate, with optimal information size to detect the outcome of interest not reached. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**
5. Systematic review [3] with included studies: Lavigne-Lissalde 2015 (PPH). **Baseline/comparator:** Primary study.
6. **Risk of Bias: serious.** One study with unclear to high risk of bias that was considered to seriously affect the confidence in the observed effect. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: serious.** Evidence is generalisable to women with severe postpartum haemorrhage after vaginal or Caesarean delivery. The evidence is probably applicable to the Australian healthcare context with some caveats relating to maternity care and to access to second line interventions. Certainty of evidence downgraded. **Imprecision: serious.** Only one study contributing data. Low event rate, with optimal information size to detect the outcome of interest not reached. Certainty of evidence downgraded. **Publication bias: no serious.**

## References

3. HTANALYSTS, Jorgensen M. rFVIIa for critical bleeding. RevMan 5.4 2019.

135. Lavigne-Lissalde G., Aya AG, Mercier FJ, Roger-Christoph S., Chauleur C., Morau E., et al. Recombinant human FVIIa for reducing the need for invasive second-line therapies in severe refractory postpartum hemorrhage: a multicenter, randomized, open controlled trial. *J Thromb Haemost* 2015;13(4):520-9 [Journal](#)

## 7.2.2 Antifibrinolytics

### Research question

**In patients with critical bleeding, what is the effect of antifibrinolytics on blood loss, red blood cell transfusion and patient outcomes?**

Latest search date: 29 September 2021

Antifibrinolytics include tranexamic acid, aprotinin\*, and 6-aminocaproic acid (also known as 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. For more information about tranexamic acid refer to the Australian Medicines Handbook.

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

^6-aminocaproic acid is not available or registered for use in Australia.

Weak recommendation , Very low certainty evidence

**R6:** In trauma patients with critical bleeding, the reference group suggests 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 1 g 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 [151] 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.

The results of the PATCH-Trauma Study [137] 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

Refer to the technical reports for further information on individual studies.

### What did we find?

Eight systematic reviews (Al-Jeabory 2021 [140], Almuwallad 2021 [142], El-Menyar 2018 [143], Nishida 2017 [144], Huebner 2017 [145], Cannon 2017 [52], Ker 2015 [150], Ausset 2015 [149]) were found that included evidence from 3 RCTs (Guyette 2020, Kakaei 2017, Shakur 2010) that examined the effect of tranexamic acid in civilian trauma patients with critical bleeding. There were also 16 cohort studies identified by the included systematic reviews that examined the effect of tranexamic acid in patients with critical bleeding after trauma (mixed combat and civilian trauma), including one in paediatric trauma.

### Study characteristics

Guyette 2020 [152] was a multicentre RCT conducted in the United States that assessed prehospital administration of tranexamic acid in injured patients with hypotension (SBP  $\leq$  90 mmHg or lower) or tachycardia (heart rate  $\geq$  110 bpm) before arrival at a Level 1 trauma centre. Kakaei 2017 [154] was a small study conducted in a single centre in Iran that enrolled civilian trauma patients with potentially life-threatening injuries or evidence of critical illness (which could include respiratory and cardiac arrest).

Shakur 2010 (CRASH-2 [151]) 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.

There were some concerns of bias relating to the CRASH-2 study (contributes more than 97% of the RCT data) including 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.

Among the cohort studies, the systematic reviews all had concerns of bias relating to confounding (related to the co-administration of other products) and patient selection bias. There were also concerns of reporting bias with a lack of detail regarding injury severity, and protocols for adverse event reporting.

In all studies, participants were typically administered a loading dose of 1 g tranexamic acid as soon possible, followed by a maintenance dose of 1 g tranexamic acid over 8 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 tranexamic acid (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 tranexamic acid 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 thromboembolic events in trauma patients who received tranexamic acid (168/10 060, 1.67%) compared with those who did not receive tranexamic acid (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 thromboembolic events was higher among those who received tranexamic acid (106/1801, 5.89%) compared with those who did not receive tranexamic acid (122/3157, 3.86%) (RR 1.63; 95% CI 1.17, 2.29;  $P = 0.00423$ ,  $I^2 = 23\%$ ) (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 red blood cells transfused in patients who received tranexamic acid (mean 6.06 units) compared with

those who did not receive tranexamic acid (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 red blood cells transfused was higher among patients who received tranexamic acid (range 4.42 units to 22 units) compared with those who did not receive tranexamic acid (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 tranexamic acid had higher incidence of shock, blood loss, and transfusion needs).

Outcome Timeframe	Study results and measurements	Comparator Placebo or no antifibrinolytic s	Intervention Antifibrinolytic s	Certainty of the Evidence (Quality of evidence)	Summary
Mortality, all cause (RCTs) <sup>1</sup> 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. <sup>2</sup> (Randomized controlled)	157 per 1000  Difference:	143 per 1000  <b>14 fewer per 1000</b> ( CI 95% 24 fewer — 5 fewer )	Low Due to very serious indirectness <sup>3</sup>	The evidence suggests antifibrinolytics may slightly reduce mortality in trauma patients with critical bleeding.
Mortality, all cause (Coh) <sup>4</sup> 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. <sup>5</sup> (Observational (non- randomized))	144 per 1000  Difference:	140 per 1000  <b>4 fewer per 1000</b> ( CI 95% 36 fewer — 36 more )	Very low Due to very serious risk of bias, Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision <sup>6</sup>	We are very uncertain about the association of antifibrinolytics on all- cause mortality in trauma patients with critical bleeding.
Morbidity, thromboemboli c event (RCTs)  6 Important	Relative risk 0.84 (CI 95% 0.68 — 1.02) Based on data from 20,127 participants in 1 studies. <sup>7</sup> (Randomized controlled)	20 per 1000  Difference:	17 per 1000  <b>3 fewer per 1000</b> ( CI 95% 6 fewer — 0 fewer )	Very low Due to very serious indirectness, Due to serious imprecision <sup>8</sup>	Antifibrinolytics appear to have little to no effect on vascular thromboembolic events, but we are very uncertain about the evidence.
Morbidity, thromboemboli c events (Coh)  6 Important	Relative risk 1.63 (CI 95% 1.17 — 2.29) Based on data from 4,958 participants in 10 studies. <sup>9</sup> (Observational (non- randomized))	39 per 1000  Difference:	64 per 1000  <b>25 more per 1000</b> ( 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 <sup>10</sup>	We are very uncertain about the association of antifibrinolytics on thromboembolic events in trauma patients with critical bleeding.

Outcome Timeframe	Study results and measurements	Comparator Placebo or no antifibrinolytic s	Intervention Antifibrinolytic s	Certainty of the Evidence (Quality of evidence)	Summary
Red blood cell transfusion volume (RCTs)	Measured by: Number of Units Lower better Based on data from 10,227 participants in 1 studies. <sup>11</sup> (Randomized controlled)	6.29 Units (Mean)  Difference:	6.06 Units (Mean)  <b>SMD 0.02 fewer</b> ( CI 95% 0.06 fewer — 0.02 more )	Low Due to very serious indirectness <sup>12</sup>	The evidence suggests that antifibrinolytics may have little or no difference on the volume of red blood cells transfused in trauma patients with critical bleeding.
Red blood cell transfusion volume (Coh)	Measured by: Number of Units Lower better Based on data from 2,095 participants in 4 studies. <sup>13</sup> (Observational (non- randomized))	2 - 20.1 Units  Difference:	4.43 - 22 Units  <b>SMD 0.53 more</b> ( 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 <sup>14</sup>	We are very uncertain about the association of antifibrinolytics with the volume of red blood cells transfused in trauma patients with critical bleeding.

1. Follow-up range: in-hospital to 30 days
2. Systematic review [5] with included studies: Guyette 2020 (STAAMP) (Civilian), CRASH-2 2010 (Civilian), Kakaei 2017 (Civilian). **Baseline/comparator:** Systematic review.
3. **Risk of Bias: no serious.** RCTs with some concerns of bias not sufficient to raise serious doubts about the results. Certainty of evidence not downgraded. **Inconsistency: no serious.** No statistical heterogeneity ( $I^2 = 0\%$ ). Certainty of evidence not downgraded. **Indirectness: very serious.** The evidence may not be directly generalisable to people with critical bleeding that is life-threatening and likely to result in the need for massive transfusion. Participants included in the CRASH-2 study were classified as being at risk of significant bleeding, in addition to being diagnosed with major haemorrhage. Around 50% of enrolled patients did not receive a blood product. Also, a large number of participants in CRASH-2 came from emerging economies (over 40 countries) with different healthcare systems. It is therefore difficult to comment on the direct applicability of the results in the context of Australian healthcare. Certainty of evidence downgraded 2 levels. **Imprecision: no serious.** **Publication bias: no serious.**
4. Follow-up range: in-hospital to 30 days
5. Systematic review [5] with included studies: Cole 2015 (Civilian, ISS 15), Wafaisade 2016 (prehospital, civilian), Morrison 2012 (MATTERS), Eckert 2014 (paediatric trauma), Valle 2014 (adult trauma), Neeki 2018 (Civilian), Swendsen 2013 (adult trauma), Myers 2019 (Civilian), Howard 2017 (Coh, combat), Harvin 2014 (adult trauma), Lipsky 2014 (Coh, trauma), Morrison 2013 (MATTERS II), Rivas 2021 (Civilian), El-Menyar 2020 (Civilian), Neeki 2017 (prehospital). **Baseline/comparator:** Control arm of reference used for intervention.
6. **Risk of Bias: very serious.** Several cohort studies with some important problems relating to patient selection and incomplete data that seriously weaken the results. Several retrospective studies with variable confounding factors that are not accounted for in the results (e.g., injury severity, coagulopathy, vitals). Certainty of evidence downgraded 2 levels. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high ( $I^2 = 90\%$ ). The direction of the effect is not consistent between the included studies. Certainty of evidence downgraded. **Indirectness: serious.** Several of the included cohort studies include patients who have been treated for penetrating or blast



injuries (gunshot or explosion), which may not be directly relevant to the injuries (blunt) more often encountered in Australia. A test for subgroup differences ( $\text{Chi}^2 = 0.26$ ,  $P = 0.61$ ,  $I^2 = 0\%$ ) suggest any difference is not statistically significant. Certainty of evidence downgraded. **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.** Asymmetrical funnel plot but publication bias judged unlikely to be the underlying cause. Certainty of evidence not downgraded.

7. Systematic review [5] with included studies: CRASH-2 2010 (Civilian). **Baseline/comparator:** Control arm of reference used for intervention.

8. **Risk of Bias: no serious.** RCT with some concerns of bias not sufficient to raise serious doubts about the results. Certainty of evidence not downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: very serious.** The evidence may not be directly generalisable to people with critical bleeding that is life-threatening and likely to result in the need for massive transfusion. Participants included in the CRASH-2 study were classified as being at risk of significant bleeding, in addition to being diagnosed with major haemorrhage. Around 50% of enrolled patients did not receive a blood product. Also, a large number of participants in CRASH-2 came from emerging economies (over 40 countries) with different healthcare systems. It is therefore difficult to comment on the direct applicability of the results in the context of Australian healthcare. Certainty of evidence downgraded 2 levels. **Imprecision: serious.** Only data from one study. Confidence in reporting of vascular events (e.g., deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke) is weak due to uncertainty surrounding their definition and classification. Certainty of evidence downgraded. **Publication bias: no serious.**

9. Systematic review [5] with included studies: Harvin 2014 (adult trauma), [155], Cole 2015 (Civilian, ISS 15), Morrison 2012 (MATTERS), Guyette 2020 (STAAMP) (Civilian), Wafaisade 2016 (prehospital, civilian), Haren 2014 (adult trauma), [153], Myers 2019 (Civilian), Swendsen 2013 (adult trauma).

**Baseline/comparator:** Systematic review.

10. **Risk of Bias: serious.** Several cohort studies with some important problems relating to patient selection and incomplete data that seriously weaken the results. Several retrospective studies with variable confounding factors that are not accounted for in the results (e.g., injury severity, coagulopathy, vitals). Certainty of evidence downgraded. **Inconsistency: serious.** Point estimates vary widely. Certainty of evidence downgraded. **Indirectness: serious.** Several of the included cohort studies include patients who have been treated for penetrating or blast injuries (gunshot or explosion), which may not be directly relevant to the injuries (blunt) more often encountered in Australia. Certainty of evidence downgraded. **Imprecision: very serious.** Wide confidence intervals. Low event rate in the included studies with likely missing data. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

11. Systematic review [5] with included studies: CRASH-2 2010 (Civilian). **Baseline/comparator:** Systematic review.

12. **Risk of Bias: no serious.** RCTs with some concerns of bias not sufficient to raise serious doubts about the results. Certainty of evidence not downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: very serious.** The evidence may not be directly generalisable to people with critical bleeding that is life-threatening and likely to result in the need for massive transfusion. Participants included in the CRASH-2 study were classified as being at risk of significant bleeding, in addition to being diagnosed with major haemorrhage. Around 50% of enrolled patients did not receive a blood product. Also, a large number of participants in CRASH-2 came from emerging economies (over 40 countries) with different healthcare systems. It is therefore difficult to comment on the direct applicability of the results in the context of Australian healthcare. Certainty of evidence downgraded 2 levels. **Imprecision: no serious. Publication bias: no serious.**

13. Systematic review [5] with included studies: Cole 2015 (Civilian, ISS 15), Morrison 2013 (MATTERS



II) (with cryo), Morrison 2013 (MATTERS II) (without cryo), Myers 2019 (Civilian). **Baseline/comparator:** Systematic review.

14. **Risk of Bias: serious.** Several cohort studies with some important problems relating to patient selection and incomplete data that seriously weaken the results. Variable confounding factors may not be accounted for in the results (e.g., injury severity, coagulopathy, vitals). Certainty of evidence downgraded. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high ( $I^2 = 90\%$ ). Point estimates vary widely. Certainty of evidence downgraded. **Indirectness: serious.** Included cohort studies include patients who have been treated for penetrating or blast injuries (gunshot or explosion), which may not be directly relevant to the injuries (blunt) more often encountered in Australia. Certainty of evidence downgraded. **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.**

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#### Good practice statement

**GPS9:** The reference group agreed that there is insufficient evidence to provide a recommendation on the use of tranexamic acid in patients with critical gastrointestinal bleeding.

### Rationale

The development of a good practice statement for critical gastrointestinal bleeding is based on the results of the HALT-IT RCT (HALT-IT Trial Collaborators [156]). The HALT-IT study demonstrated tranexamic acid had no effect on the primary outcome of death due to bleeding within 5 days of randomisation, however, reported higher venous thromboembolic events in the tranexamic acid arm compared to placebo [156].

The reference group noted that the clinical diagnosis of critical bleeding required for HALT-IT differed from the definition of critical bleeding requiring MHP used in this guideline. The reference group agreed the overall benefit of tranexamic acid on critical gastrointestinal bleeding is uncertain based on current evidence [156].

### Clinical question/ PICO

- Population:** People with critical bleeding (medical emergency)
- Intervention:** Antifibrinolytics
- Comparator:** Placebo or no antifibrinolytics

### Summary

Refer to the technical reports for further information on individual studies.

**What did we find?**

The literature search found one RCT (HALT-IT Trial Collaborators [156]) that examined the effect of tranexamic acid in patients with acute upper or lower gastrointestinal bleeding.

**Study characteristics**

The HALT-IT trial [156] included 12 009 participants from 15 countries who were randomised to receive either 1 g tranexamic acid (IV infusion loading dose) followed by 3 g tranexamic acid maintenance dose (infused over 24 hours) (total 4 g tranexamic acid) or matching placebo (0.9% sodium chloride). The primary outcome was death due to bleeding within 5 days of randomisation, and diagnosis of thromboembolic events was made using strict definitions and diagnostic criteria. Approximately 45% of patients had suspected variceal bleeding due to liver disease, which accounted for almost 75% of deaths. Around 12% of patients did not have suspected active bleeding at enrolment and around 30% of patients did not receive a blood product.

**What are the main results?****Mortality**

The RCT evidence (HALT-IT) suggested the mortality rate among patients who received tranexamic acid (564/5956, 9.5%) was comparable to the mortality rate among patients who did not receive tranexamic acid (548/5981, 9.2%) (RR 1.03; 95% CI 0.92, 1.16; P = 0.56; random effect) (GRADE: low).

**Morbidity**

The RCT evidence (HALT-IT) suggested that the risk of any thromboembolic event was similar among those who received tranexamic acid (86/5952, 1.4%) compared with those who did not receive tranexamic acid (72/5977, 1.2%) (RR 1.2; 95% CI 0.88, 1.64; P = 0.25, random effect). Noting that the risk for venous thromboembolic events (DVT, PE) appeared to be higher among those who received tranexamic acid P = 0.25 (48/5952, 0.8%) compared with those who did not receive tranexamic acid (26/5977, 0.4%) (RR 1.85; 95% CI 1.15, 2.98; P = 0.01, random effect) (GRADE: low). The authors noted a similar risk was observed when patients who did not receive the maintenance dose of tranexamic acid were excluded from the analysis (42 vs 20 events; RR 2.11; 95% CI 1.24, 3.59).

The risk of arterial thromboembolic events (myocardial infarction, stroke) was similar across groups (0.7% vs 0.8%; RR 0.92, 95% CI 0.60, 1.39; (GRADE: low).

**Transfusion volumes**

The RCT evidence (HALT-IT) suggested there was little to no difference on the volume of red blood cells transfused in patients who received tranexamic acid (mean 2.8 units) compared with those who did not receive tranexamic acid (mean 2.9 units transfused) (MD -0.10, 95% CI -0.21, 0.01; P = 0.08; random effect) (GRADE: low).

Similar results were observed for the volume of FFP (MD -0.10, 95% CI -0.21, 0.01; P = 0.07; random effect) (GRADE: low) and for the volume of platelets transfused (MD 0.00, 95% CI -0.04, 0.04; P = 1.00; random effect) (GRADE: low).

Outcome Timeframe	Study results and measurements	Comparator Placebo or no antifibrinolytic s	Intervention Antifibrinolytic s	Certainty of the Evidence (Quality of evidence)	Summary
Mortality, all cause latest reported timepoint	Relative risk 1.03 (CI 95% 0.92 — 1.16) Based on data from 11,937 participants in 1 studies. <sup>1</sup> (Randomized controlled) Follow up: discharge up to 28-days.	<b>92</b> per 1000  Difference:	<b>95</b> per 1000  <b>3 more per 1000</b> ( CI 95% 7 fewer — 15 more )	Low Due to very serious indirectness <sup>2</sup>	The evidence suggests that antifibrinolytics may have no difference on all-cause mortality in patients with severe gastrointestinal bleeding.
Morbidity, thromboemboli c events (venous) <sup>3</sup>  6 Important	Relative risk 1.85 (CI 95% 1.15 — 2.98) Based on data from 11,929 participants in 1 studies. <sup>4</sup> (Randomized controlled) Follow up: discharge up to 28-days.	<b>4</b> per 1000  Difference:	<b>7</b> per 1000  <b>3 more per 1000</b> ( CI 95% 1 more — 8 more )	Low Due to very serious indirectness <sup>5</sup>	The evidence suggests that antifibrinolytics may increase the risk of thromboembolic events (venous) in patients with severe gastrointestinal bleeding.
Morbidity, thromboemboli c events (arterial)  6 Important	Relative risk 0.92 (CI 95% 0.6 — 1.39) Based on data from 11,929 participants in 1 studies. <sup>6</sup> (Randomized controlled) Follow up: discharge up to 28-days.	<b>8</b> per 1000  Difference:	<b>7</b> per 1000  <b>1 fewer per 1000</b> ( CI 95% 3 fewer — 3 more )	Low Due to very serious indirectness <sup>7</sup>	The evidence suggests that antifibrinolytics may have little to no difference on the risk of thromboembolic events (arterial) in patients with severe gastrointestinal bleeding.
Red blood cell transfusion volume	Measured by: Number of units Lower better Based on data from 8,205 participants in 1 studies. <sup>8</sup> (Randomized controlled) Follow up: discharge up to 28-days.	<b>2.9</b> Units (Mean)  Difference:	<b>2.8</b> Units (Mean)  <b>MD 0.06 fewer</b> ( CI 95% 0.05 more — 0.18 fewer )	Low Due to very serious indirectness <sup>9</sup>	The evidence suggests that antifibrinolytics may have little or no difference on the volume of red blood cells transfused in patients with severe gastrointestinal bleeding.
FFP transfusion volume	Measured by: Number of units Lower better Based on data from 8,205 participants in 1 studies. <sup>10</sup> (Randomized controlled) Follow up: discharge up to 28-days.	<b>1</b> Units (Mean)  Difference:	<b>0.9</b> Units (Mean)  <b>MD 0.05 fewer</b> ( CI 95% 0.01 fewer — 0.23 fewer )	Low Due to very serious indirectness <sup>11</sup>	The evidence suggests that antifibrinolytics may have little or no difference on the volume of FFP transfused in patients with severe gastrointestinal bleeding.

1. Primary study[156]. **Baseline/comparator:** Control arm of reference used for intervention.
2. **Risk of Bias: no serious.** One RCT with some concerns of bias not sufficient to raise serious doubts about the results. Certainty of evidence not downgraded. **Inconsistency: no serious.** Only one study

contributing data. Certainty of evidence not downgraded. **Indirectness: very serious.** The evidence may not be directly generalisable to patients with gastrointestinal bleeding that is life-threatening and likely to result in the need for massive transfusion. The HALT-IT trial included participants with acute gastrointestinal bleeding, with around 45% having suspected variceal bleeding due to liver disease. Around 12% of patients did not have suspected active bleeding at enrolment and around 30% of patients did not receive a blood product. Also, a large number of participants in the HALT-IT study came from emerging economies (15 countries) with different healthcare systems. It is therefore difficult to comment on the direct applicability of the results in the context of Australian healthcare. Certainty of evidence downgraded 2 levels. **Imprecision: no serious. Publication bias: no serious. Upgrade: all plausible confounding would have reduced the effect.**

3. Venous events (deep vein thrombosis, pulmonary embolism)

4. Primary study[156]. **Baseline/comparator:** Control arm of reference used for intervention.

5. **Risk of Bias: no serious.** One RCT with some concerns of bias not sufficient to raise serious doubts about the results. Certainty of evidence not downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: very serious.** The evidence may not be directly generalisable to patients with gastrointestinal bleeding that is life-threatening and likely to result in the need for massive transfusion. The HALT-IT trial included participants with acute gastrointestinal bleeding, with around 45% having suspected variceal bleeding due to liver disease. Around 12% of patients did not have suspected active bleeding at enrolment and around 30% of patients did not receive a blood product. Also, a large number of participants in the HALT-IT study came from emerging economies (15 countries) with different healthcare systems. It is therefore difficult to comment on the direct applicability of the results in the context of Australian healthcare. Certainty of evidence downgraded 2 levels. **Imprecision: no serious.** Only one study contributing data. A similar risk was observed when patients who did not receive the maintenance dose were excluded from the analysis. Certainty of evidence not downgraded. **Publication bias: no serious.**

6. Systematic review with included studies: [156]. **Baseline/comparator:** Control arm of reference used for intervention.

7. **Risk of Bias: no serious.** One RCT with some concerns of bias not sufficient to raise serious doubts about the results. Certainty of evidence not downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: very serious.** The evidence may not be directly generalisable to patients with gastrointestinal bleeding that is life-threatening and likely to result in the need for massive transfusion. The HALT-IT trial included participants with acute gastrointestinal bleeding, with around 45% having suspected variceal bleeding due to liver disease. Around 12% of patients did not have suspected active bleeding at enrolment and around 30% of patients did not receive a blood product. Also, a large number of participants in the HALT-IT study came from emerging economies (15 countries) with different healthcare systems. It is therefore difficult to comment on the direct applicability of the results in the context of Australian healthcare. Certainty of evidence downgraded 2 levels. **Imprecision: no serious. Publication bias: no serious.**

8. Systematic review with included studies: [156]. **Baseline/comparator:** Control arm of reference used for intervention.

9. **Risk of Bias: no serious.** One RCT with some concerns of bias not sufficient to raise serious doubts about the results. Certainty of evidence not downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: very serious.** The evidence may not be directly generalisable to patients with gastrointestinal bleeding that is life-threatening and likely to result in the need for massive transfusion. The HALT-IT trial included participants with acute gastrointestinal bleeding, with around 45% having suspected variceal bleeding due to liver disease. Around 12% of patients did not have suspected active bleeding at enrolment and around 30% of patients did not receive a blood product. Also, a large number of participants in the HALT-IT study came from emerging economies (15 countries) with different healthcare systems. It is therefore

difficult to comment on the direct applicability of the results in the context of Australian healthcare. Certainty of evidence downgraded 2 levels. **Imprecision: no serious. Publication bias: no serious.**

10. Systematic review with included studies: [156]. **Baseline/comparator:** Control arm of reference used for intervention.

11. **Risk of Bias: no serious.** One RCT with some concerns of bias not sufficient to raise serious doubts about the results. Certainty of evidence not downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: very serious.** The evidence may not be directly generalisable to patients with gastrointestinal bleeding that is life-threatening and likely to result in the need for massive transfusion. The HALT-IT trial included participants with acute gastrointestinal bleeding, with around 45% having suspected variceal bleeding due to liver disease. Around 12% of patients did not have suspected active bleeding at enrolment and around 30% of patients did not receive a blood product. Also, a large number of participants in the HALT-IT study came from emerging economies (15 countries) with different healthcare systems. It is therefore difficult to comment on the direct applicability of the results in the context of Australian healthcare. Certainty of evidence downgraded 2 levels. **Imprecision: no serious. Publication bias: no serious.**

## References

11. National Blood Authority. Update of the 2011 Patient Blood Management Guidelines for people with critical bleeding: Technical report Volume 1. Canberra: The Commonwealth of Australia as represented by the NBA 2022.

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Weak recommendation , Very low certainty evidence

**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 1 g tranexamic bolus over 10 minutes and a second 1 g dose after 30 minutes if bleeding continues.

## 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 of harms are uncertain given the low PPH mortality rate in Australia and New Zealand. In 2018, there were 15 maternal deaths in Australia. Only one was attributable to bleeding [232].

**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 Collaborators 2017 supported the use of tranexamic acid in critically bleeding obstetric patients, but no difference was observed for the primary outcome of hospital mortality [158].

**Clinical question/ PICO**

**Population:** People with critical bleeding (obstetrics and maternity)

**Intervention:** Antifibrinolytics

**Comparator:** Placebo or no antifibrinolytics

**Summary**

Refer to the technical reports for further information on individual studies.

**What did we find?**

Two systematic reviews (Della-Corte 2020 [147], Shakur 2018 [146]) were found that focused on the evidence from 2 RCTs (WOMAN Trial Collaborators 2017 [158], Ducloy-Bouthors 2011 [157]) that assessed the safety and effectiveness of tranexamic acid given to women with primary PPH.



### Study characteristics

The largest study (WOMAN 2017 [158]) enrolled 20,060 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 tranexamic acid 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.

Ducloy-Bouthors 2011 [157] was conducted at a single centre in France and enrolled 151 women with PPH (estimated blood loss after vaginal birth of more than 800 mL). The study was judged by Shakur 2018 [146] to be at high risk of performance bias relating to staff being aware of treatment allocation (no placebo).

### What are the main results?

#### Mortality

The RCT evidence (WOMAN) suggested mortality among women who received tranexamic acid (227/10 111, 2.2%) was comparable to mortality among women who did not receive tranexamic acid (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 tranexamic acid (31/10 034, 0.31%) compared with those who did not receive tranexamic acid (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 tranexamic acid compared with those who did not for the outcomes of MOF (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 antifibrinolytic s	Intervention Antifibrinolytic s	Certainty of the Evidence (Quality of evidence)	Summary
Mortality, all cause latest reported timepoint	Relative risk 0.89 (CI 95% 0.74 — 1.06) Based on data from 20,011 participants in 2	25 per 1000  Difference:	22 per 1000  3 fewer per	Low Due to very serious indirectness <sup>2</sup>	The evidence suggests that antifibrinolytics may have no difference on all-cause mortality in women with major



Outcome Timeframe	Study results and measurements	Comparator Placebo or no antifibrinolytic s	Intervention Antifibrinolytic s	Certainty of the Evidence (Quality of evidence)	Summary
9 Critical	studies. <sup>1</sup> (Randomized controlled)		<b>1000</b> ( CI 95% 6 fewer — 2 more )		obstetric haemorrhage
Morbidity, thromboemboli c events  6 Important	Relative risk 0.91 (CI 95% 0.56 — 1.47) Based on data from 20,011 participants in 1 studies. <sup>3</sup> (Randomized controlled)	<b>3</b> per 1000  Difference:	<b>3</b> per 1000  <b>0 fewer per 1000</b> ( CI 95% 1 fewer — 1 more )	Very low Due to very serious indirectness, Due to serious imprecision <sup>4</sup>	Antifibrinolytics may have little or no effect on thromboembolic events in women with major obstetric haemorrhage, but the evidence is very uncertain.
Morbidity, MOF  6 Important	Relative risk 0.94 (CI 95% 0.71 — 1.23) Based on data from 20,168 participants in 2 studies. <sup>5</sup> (Randomized controlled)	<b>10</b> per 1000  Difference:	<b>9</b> per 1000  <b>1 fewer per 1000</b> ( CI 95% 3 fewer — 2 more )	Very low Due to very serious indirectness, Due to serious imprecision <sup>6</sup>	Antifibrinolytics may have little or no effect on MOF in women with major obstetric haemorrhage, but the evidence is very uncertain.
Morbidity, respiratory failure  6 Important	Relative risk 0.87 (CI 95% 0.67 — 1.12) Based on data from 20,018 participants in 1 studies. <sup>7</sup> (Randomized controlled)	<b>12</b> per 1000  Difference:	<b>10</b> per 1000  <b>2 fewer per 1000</b> ( CI 95% 4 fewer — 1 more )	Very low Due to very serious indirectness, Due to serious imprecision <sup>8</sup>	Antifibrinolytics may have little or no effect on respiratory failure in women with major obstetric haemorrhage, but the evidence is very uncertain.
Morbidity, renal failure  6 Important	Relative risk 1.09 (CI 95% 0.85 — 1.39) Based on data from 20,169 participants in 2 studies. <sup>9</sup> (Randomized controlled)	<b>12</b> per 1000  Difference:	<b>13</b> per 1000  <b>1 more per 1000</b> ( CI 95% 2 fewer — 5 more )	Very low Due to very serious indirectness, Due to serious imprecision <sup>10</sup>	Antifibrinolytics may have little or no effect on renal failure in women with major obstetric haemorrhage, but the evidence is very uncertain.
Red blood cell 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 <sup>11</sup>	Antifibrinolytics may have little or no effect on the volume of red blood cells transfused in women with major obstetric haemorrhage, but the evidence is very uncertain.

1. Systematic review [5] with included studies: Ducloy-Bouthers 2011, WOMAN 2017 (PPH). **Baseline/comparator:** Systematic review.
2. **Risk of Bias: no serious.** RCTs with some concerns of bias not sufficient to raise serious doubts about the results. Certainty of evidence not downgraded. **Inconsistency: no serious.** Only one study

contributing data. Certainty of evidence not downgraded. **Indirectness: very serious.** Differences between the population of interest and those studied. The evidence may not be directly generalisable to women with major obstetric haemorrhage that is life-threatening and likely to result in the need for massive transfusion. Participants in the WOMAN study were enrolled based on estimated blood loss of 500 mL after vaginal birth, or 1000 mL after caesarean section. Approximately 50% of participants had an estimated volume of blood loss <1000 mL and 41% had no clinical signs of haemodynamic instability. Around 54% of women received a blood product. Also, a large number of participants in the WOMAN study came from emerging economies (over 21 countries) with different healthcare systems. It is therefore difficult to comment on the direct applicability of the results in the context of Australian healthcare. Certainty of evidence downgraded 2 levels. **Imprecision: no serious. Publication bias: no serious.**

3. Systematic review [5] with included studies: WOMAN 2017 (PPH). **Baseline/comparator:** Systematic review.

4. **Risk of Bias: no serious.** RCTs with some concerns of bias not sufficient to raise serious doubts about the results. Certainty of evidence not downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: very serious.** Differences between the population of interest and those studied. The evidence may not be directly generalisable to women with major obstetric haemorrhage that is life-threatening and likely to result in the need for massive transfusion. Participants in the WOMAN study were enrolled based on estimated blood loss of 500 mL after vaginal birth, or 1000 mL after caesarean section. Approximately 50% of participants had an estimated volume of blood loss <1000 mL and 41% had no clinical signs of haemodynamic instability. Around 54% of women received a blood product. Also, a large number of participants in the WOMAN study came from emerging economies (over 21 countries) with different healthcare systems. It is therefore difficult to comment on the direct applicability of the results in the context of Australian healthcare. Certainty of evidence downgraded 2 levels. **Imprecision: serious.** Only one study contributing data. Confidence in reporting of vascular events (e.g., deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke) is weak due to uncertainty surrounding their definition and classification. Certainty of evidence downgraded. **Publication bias: no serious.**

5. Systematic review [5] with included studies: Ducloy-Bouthers 2011, WOMAN 2017 (PPH). **Baseline/comparator:** Systematic review.

6. **Risk of Bias: no serious.** RCTs with some concerns of bias not sufficient to raise serious doubts about the results. Certainty of evidence not downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: very serious.** Differences between the population of interest and those studied. The evidence may not be directly generalisable to women with major obstetric haemorrhage that is life-threatening and likely to result in the need for massive transfusion. Participants in the WOMAN study were enrolled based on estimated blood loss of 500 mL after vaginal birth, or 1000 mL after caesarean section. Approximately 50% of participants had an estimated volume of blood loss <1000 mL and 41% had no clinical signs of haemodynamic instability. Around 54% of women received a blood product. Also, a large number of participants in the WOMAN study came from emerging economies (over 21 countries) with different healthcare systems. It is therefore difficult to comment on the direct applicability of the results in the context of Australian healthcare. Certainty of evidence downgraded 2 levels. **Imprecision: serious.** Low event rate. Certainty of evidence downgraded. **Publication bias: no serious.**

7. Systematic review [5] with included studies: WOMAN 2017 (PPH). **Baseline/comparator:** Systematic review.

8. **Risk of Bias: no serious.** RCTs with some concerns of bias not sufficient to raise serious doubts about the results. Certainty of evidence not downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: very serious.** Differences between the population of interest and those studied. The evidence may not be directly generalisable

to women with major obstetric haemorrhage that is life-threatening and likely to result in the need for massive transfusion. Participants in the WOMAN study were enrolled based on estimated blood loss of 500 mL after vaginal birth, or 1000 mL after caesarean section. Approximately 50% of participants had an estimated volume of blood loss <1000 mL and 41% had no clinical signs of haemodynamic instability. Around 54% of women received a blood product. Also, a large number of participants in the WOMAN study came from emerging economies (over 21 countries) with different healthcare systems. It is therefore difficult to comment on the direct applicability of the results in the context of Australian healthcare. Certainty of evidence downgraded 2 levels. **Imprecision: serious.** Low event rate. Certainty of evidence downgraded. **Publication bias: no serious.**

9. Systematic review [5] with included studies: WOMAN 2017 (PPH), Ducloy-Bouthors 2011. **Baseline/comparator:** Systematic review.

10. **Risk of Bias: no serious.** RCTs with some concerns of bias not sufficient to raise serious doubts about the results. Certainty of evidence not downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: very serious.** Differences between the population of interest and those studied. The evidence may not be directly generalisable to women with major obstetric haemorrhage that is life-threatening and likely to result in the need for massive transfusion. Participants in the WOMAN study were enrolled based on estimated blood loss of 500 mL after vaginal birth, or 1000 mL after caesarean section. Approximately 50% of participants had an estimated volume of blood loss <1000 mL and 41% had no clinical signs of haemodynamic instability. Around 54% of women received a blood product. Also, a large number of participants in the WOMAN study came from emerging economies (over 21 countries) with different healthcare systems. It is therefore difficult to comment on the direct applicability of the results in the context of Australian healthcare. Certainty of evidence downgraded 2 levels. **Imprecision: serious.** Low event rate. Certainty of evidence downgraded. **Publication bias: no serious.**

11. **Inconsistency: no serious. Indirectness: very serious.** Differences between the population of interest and those studied. Certainty of evidence downgraded 2 levels. **Imprecision: serious.** Data not provided. Certainty of evidence downgraded. **Publication bias: no serious.**

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2017;389(10084):2105-2116 [Pubmed Journal](#)

### 7.2.3 Viscoelastic haemostatic assays (VHA)

#### Research question

**In patients with critical bleeding, does the use of viscoelastic haemostatic assays change patient outcomes?**

Latest search date: 29 September 2021

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/product and antifibrinolytic therapy as part of an MHP.

Good practice statement , Very low certainty evidence

**GPS10:** 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 RCTs and observational cohort studies comparing transfusion algorithms/haemorrhage protocols guided by VHAs or standard laboratory tests (or clinical judgement) a reduction in mortality was suggested. However, confidence in the results was very low because the studies were susceptible to multiple sources of bias and serious imprecision related to small studies with low event rates. Based on the available evidence, the true benefits of VHAs to guide blood component/product and antifibrinolytic therapy as part of an MHP are 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 VHAs as part of an MHP as recommended in this guideline.

## Resources

Important negative issues

The reference group acknowledged that significant resources and expertise are required to implement, operate and interpret the results of VHAs as part of an MHP compared to standard laboratory testing.

## 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 VHAs as part of an MHP.

## 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 VHAs as part of an MHP.

## Feasibility

Important issues, or potential issues not investigated

The reference group acknowledged that there may be jurisdictional, geographical and/or institutional variability in implementing VHAs as part of an MHP, including training, expertise and access to blood components.

## Rationale

VHAs may be used as part of an MHP in patients who are critically bleeding. 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.

## Clinical question/ PICO

**Population:** People with critical bleeding (any setting)

**Intervention:** Viscoelastic haemostatic assays

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

## Summary

Refer to the technical reports for further information on individual studies.

### What did we find?

Twelve systematic reviews (Amgalan 2020 [173], Bugaev 2020 [168], Li 2019 [171], Roullet 2018 [161], Serraino 2017 [169], Wikkelsø 2017 [164], Fahrendorff 2017 [162], Deppe 2016 [172], Saner 2016 [170], Corredor 2015 [165], Haas 2014 [166], Da Luz 2014 [167]) were found that included evidence from 6 RCTs that examined the effects of TEG (thromboelastography) or ROTEM (rotational thromboelastometry) in patients with critical bleeding. One additional RCT (Baksaas-Aasen 2021 [181]) was identified in the systematic review and handsearching process.

There were also 15 non-randomised cohort studies identified by the included systematic reviews that examined the effects of TEG or ROTEM in guiding coagulopathic management of patients with critical bleeding and were considered relevant to this review.

### Study characteristics

Among the 7 RCTs, 2 used a TEG-guided transfusion algorithm/haemorrhage protocol (Gonzalez 2016 [174], Nuttall 2001 [175]), 4 used a ROTEM-guided transfusion algorithm/haemorrhage protocol (Weber 2012 [177], Kempfert 2011 [176], Paniagua 2011 [178], NCT00772239 [180]), and one multicentre RCT (Baksaas-Aasen 2021 (iTACTIC) [181]) examined the effect of either TEG or ROTEM. Three of the RCTs identified by the included systematic reviews were stopped early. One (Paniagua 2011 [178]) was terminated early due to slow recruitment and included 8 of 52 patients that did not meet the inclusion criteria. One (Weber 2012 [177]) was stopped at an interim analysis due to clear benefits, and another study (NCT00772239 [180]) was stopped early due to futility (no data available).

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 and platelet transfusion due to incomplete reporting of outcome data, with no explanations given for missing data.

Among the 15 cohort studies, 6 used a TEG-guided transfusion algorithm/haemorrhage protocol (Guth 2019 [179], Unruh 2019 [183], Wang 2017 [184], Barinov 2015 [182], Tapia 2013 [185], Kashuk 2012 [186]), and 9 used a ROTEM-guided transfusion algorithm/haemorrhage protocol (McNamara 2019 [187], Snegovskikh 2018 [188], Prat 2017 [189], Nardi 2015 [190], Fassl 2013 [191], Görlinger 2012 [192], Hanke 2012 [193], Nienaber 2011 [194], Schöchl 2011 [195]).

Many of the included observational cohort studies were judged to be 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 issues with changes in clinical practices that occur over time. The studies also had issues with incomplete reporting of outcome data, short follow-up and small sample size.

### What are the main results?

#### Mortality

The use of viscoelastic tests as part of an MHP may provide a 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, product and antifibrinolytic therapy was guided by TEG or ROTEM compared with haemostatic management guided by an MHP, standard laboratory tests or clinical judgement with or without 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 an MHP or transfusion algorithm/haemorrhage protocol not guided by a VHA (28.1%) (RR 0.61; 95% CI 0.37, 1.02;  $P = 0.06$ ; random effect,  $I^2 = 44\%$ ). The difference was considered clinically important.

Data from the included cohort studies, suggested that TEG or ROTEM-guided transfusion algorithms/haemorrhage 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 available data from 4 RCTs, the rate of thromboembolic events in patients with critical bleeding who received a TEG or ROTEM-guided transfusion algorithm/haemorrhage protocol was 7.2% (24/333) compared with 9.4% (30/318) among patients in the comparator group. The difference between treatment groups was not significant (RR 0.83; 95% CI 0.41, 1.66;  $P = 0.60$ ,  $I^2 = 26\%$ ).

### **Red blood cell transfusion volumes**

Available data from 2 RCTs included in this review suggested that the volume of red blood cells transfused was not different between patients who received a TEG or ROTEM-guided MHP ( $n=81$ ) compared with those who received an MHP guided by standard laboratory tests ( $n=72$ ) (SMD  $-0.06$ ; 95% CI  $-0.38$ ,  $0.26$ ;  $P = 0.73$ ,  $I^2 = 0\%$ ). Data from 2 other RCTs 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 red blood cells transfused was observed between patients who received a TEG or ROTEM-guided transfusion algorithm/haemorrhage protocol ( $n=588$ ) compared with those who received haemostatic management guided by a transfusion algorithm/haemorrhage protocol 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 components/products**

Available data from 2 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 2 studies (both 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 among patients who received a TEG or ROTEM-guided transfusion algorithm/haemorrhage protocol ( $n=513$ ) compared with those who received haemostatic management guided by a transfusion algorithm/haemorrhage protocol or standard laboratory tests ( $n=500$ ) (SMD  $-0.82$ ; 95% CI  $-1.51$ ,  $-0.12$ ;  $P = 0.02$ ;  $I^2 = 96\%$ ).

Available data from 2 RCTs suggested that the volume of platelets 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 2 studies (both suggested an effect favouring TEG or ROTEM). Among the observational cohort studies, the available data suggested there was a non-significant reduction in the volume of platelets transfused (around 1 unit saved) among patients who received a TEG or ROTEM-guided transfusion algorithm/haemorrhage protocol ( $n=284$ ) compared with those who received haemostatic management guided by a transfusion algorithm/haemorrhage protocol 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 VHA	Certainty of the Evidence (Quality of evidence)	Summary
Mortality, all cause (RCTs) <sup>1</sup> latest reported timepoint  9 Critical	Relative risk 0.61 (CI 95% 0.37 — 1.02) Based on data from 650 participants in 4 studies. <sup>2</sup> (Randomized controlled)	<b>281</b> per 1000  Difference:	<b>171</b> per 1000  <b>110 fewer per 1000</b> ( CI 95% 177 fewer — 6 more )	Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision <sup>3</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients with critical bleeding (any 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 2,175 participants in 9 studies. <sup>4</sup> (Observational (non- randomized))	<b>166</b> per 1000  Difference:	<b>125</b> per 1000  <b>41 fewer per 1000</b> ( CI 95% 63 fewer — 13 fewer )	Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision <sup>5</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients with critical bleeding (any setting) may be associated with reduced mortality but the evidence is very uncertain.
Morbidity, thromboemboli c events  6 Important	Relative risk 0.83 (CI 95% 0.41 — 1.66) Based on data from 651 participants in 4 studies. <sup>6</sup> (Randomized controlled)	<b>91</b> per 1000  Difference:	<b>76</b> per 1000  <b>15 fewer per 1000</b> ( CI 95% 54 fewer — 60 more )	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias <sup>7</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients with critical bleeding (any setting) may have little or no difference on thromboembolic events but the evidence is very uncertain.
Red blood cell transfusion volume (RCTs)	Measured by: Number of Units Lower better Based on data from 153 participants in 2 studies. <sup>8</sup> (Randomized controlled)	<b>6.42 - 15.65</b> Units  Difference:	<b>7.1 - 13.96</b> Units  <b>SMD 0.06 fewer</b> ( 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 <sup>9</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients with critical bleeding (any setting) may have little or no difference in the volume of red blood cells transfused, but the evidence is very uncertain.



Outcome Timeframe	Study results and measurements	Comparator standard best practice care	Intervention VHA	Certainty of the Evidence (Quality of evidence)	Summary
Red blood cell transfusion volume (Coh)	Measured by: Number of Units Lower better Based on data from 1,605 participants in 7 studies. <sup>10</sup> (Observational (non- randomized))	2 - 11 Units  Difference:	2 - 6.5 Units  <b>SMD 0.46 fewer</b> ( CI 95% 0.72 fewer — 0.2 fewer )	Very low Due to serious risk of bias, Due to serious inconsistency <sup>11</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients with critical bleeding (any setting) may be associated with a slight reduction in the volume of red blood cells transfused, but the evidence is very uncertain.
Transfusion volume, other blood components/ products (RCTs)	<sup>12</sup> (Randomized controlled)	The use of TEG or ROTEM did not demonstrate a statistically significant reduction the volume of FFP or platelets 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 <sup>13</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients with critical bleeding (any setting) may be associated with little or no difference in the volume of FFP or platelets transfused, but the evidence is very uncertain.

1. range: 6 hours to 28 days

2. Systematic review [6] with included studies: Weber 2012 (Cardiac), Baksaas-Aasen 2020 (Trauma), Gonzalez 2016 (Trauma), Paniagua 2011 (Cardiac). **Baseline/comparator:** Systematic review [6] .

3. **Risk of Bias: serious.** High risk of bias due to inadequate or poor reporting of blinding, incomplete reporting of outcome data and short follow-up. Certainty of evidence downgraded.

**Inconsistency: serious.** Results were inconsistent across studies. Moderate statistical heterogeneity detected ( $I^2$  between 25% to 50%). Certainty of evidence downgraded. **Indirectness: no serious.** The evidence is in people with coagulopathy or severe bleeding at inclusion and is considered directly generalisable to the Australian population/healthcare setting with few caveats. Certainty of evidence not downgraded. **Imprecision: serious.** Low event rate in included studies that did not reach the optimal information size to detect the outcome of interest. Certainty of evidence downgraded.

**Publication bias: no serious.**

4. Systematic review with included studies: Guth 2019 (Coh, trauma), Wang 2017 (Coh, trauma), Prat 2017 (Coh, trauma), Schochl 2011 (Coh, trauma), Tapia 2013 (Coh, trauma), Unruh 2019 (Coh, trauma), Kashuk 2012 (Coh, trauma). **Baseline/comparator:** Systematic review.

5. **Risk of Bias: serious.** High risk of bias for included studies. The main concern was the use of historical controls (before and after the implementation of viscoelastic testing protocols) along with high procedural bias associated with nonblinding that is likely to favour the intervention. Certainty of evidence downgraded. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. The magnitude of statistical heterogeneity was low to moderate ( $I^2 = 26\%$ ).

- Certainty of evidence downgraded. **Indirectness: no serious.** The evidence is in people with coagulopathy or severe bleeding at inclusion and is considered directly generalisable to the Australian population/healthcare setting with few caveats. Certainty of evidence not downgraded. **Imprecision: serious.** Low number of patients. Certainty of evidence downgraded. **Publication bias: no serious.**
6. Systematic review [6] with included studies: Weber 2012 (Cardiac), Paniagua 2011 (Cardiac), [174], Baksaas-Aasen 2020 (Trauma). **Baseline/comparator:** Systematic review.
7. **Risk of Bias: serious.** High risk of bias due to inadequate or poor reporting of blinding, incomplete reporting of outcome data, and short follow-up. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** The evidence is in people with coagulopathy or severe bleeding at inclusion and is considered directly generalisable to the Australian population/healthcare setting with few caveats. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Low event rate in included studies with the optimal information size to detect the outcome of interest not reached. Certainty of evidence downgraded. **Publication bias: serious.** Early termination of studies suggests non-reporting bias. Certainty of evidence downgraded.
8. Systematic review [6] with included studies: Paniagua 2011 (Cardiac), Gonzalez 2016 (Trauma). **Baseline/comparator:** Systematic review.
9. **Risk of Bias: serious.** High risk of bias due to inadequate or poor reporting of blinding, incomplete reporting of outcome data, and short follow-up. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** The evidence is in people with coagulopathy or severe bleeding at inclusion and is considered directly generalisable to the Australian population/healthcare setting with few caveats. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals (upper bounds overlaps with no important difference). Certainty of evidence downgraded. **Publication bias: serious.** Two studies not included as they do not report usable data. Certainty of evidence downgraded.
10. Systematic review [6] with included studies: Unruh 2019 (Coh, trauma), Barinov 2015 (Coh, PPH), Wang 2017 (Coh, trauma), Guth 2019 (Coh, trauma), [190], [195], Prat 2017 (Coh, trauma). **Baseline/comparator:** Systematic review.
11. **Risk of Bias: serious.** The main concern was the use of appropriate historical controls before and after the implementation of viscoelastic testing protocols along with high procedural bias associated with nonblinding that is likely to favour the intervention. Certainty of evidence downgraded. **Inconsistency: serious.** Statistical heterogeneity is high ( $I^2 = 78\%$ ). Point estimates vary widely. Certainty of evidence downgraded. **Indirectness: no serious.** The evidence is in people with coagulopathy or severe bleeding at inclusion and is considered directly generalisable to the Australian population/healthcare setting with few caveats. Certainty of evidence not downgraded. **Imprecision: no serious. Publication bias: no serious.**
12. Systematic review [6].
13. **Risk of Bias: serious.** Concerns with the use of appropriate historical controls before and after the implementation of viscoelastic testing protocols along with high procedural bias associated with nonblinding that is likely to favour the intervention. Certainty of evidence downgraded. **Inconsistency: serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies., The direction of the effect is not consistent between the included studies. Certainty of evidence downgraded. **Indirectness: no serious. Imprecision: serious.** Wide confidence intervals (upper bounds overlaps with no important difference). Certainty of evidence downgraded. **Publication bias: no serious.**

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## Clinical question/ PICO

**Population:** People with critical bleeding (trauma setting)

**Intervention:** Viscoelastic haemostatic assays

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

## Summary

Refer to the technical reports for further information on individual studies.

**What did we find?**

Six systematic reviews (Bugaev 2020 [168], Roullet 2018 [161], Wikkelsø 2017 [164], Fahrendorff 2017 [162], Da Luz 2014 [167], Haas 2014 [166]) were found that included evidence from one RCT (Gonzalez 2016) conducted in the trauma setting that examined the effects of TEG or ROTEM in patients with critical bleeding. One additional RCT (Baksaas-Aasen 2020 [181]) was identified in the systematic review and handsearching process. One RCT used a TEG-guided transfusion algorithm/haemorrhage protocol (Gonzalez 2016) and one multicentre RCT (Baksaas-Aasen 2020) examined the effect of an MHP that included either TEG or ROTEM.

There were also 10 non-randomised cohort studies identified by the included systematic reviews that examined the effects of TEG or ROTEM in guiding haemostatic management in trauma patients with critical bleeding and were considered relevant to this review. Five studies used a TEG-guided transfusion algorithm/haemorrhage protocol (Guth 2019, Unruh 2019, Wang 2017, Tapia 2013, Kashuk 2012) and 5 used a ROTEM-guided transfusion algorithm/haemorrhage protocol (Prat 2017, Nardi 2015, Görlinger 2012, Nienaber 2011, Schöchl 2011)

**Study characteristics**

Baksaas-Aasen 2020 (iTACTIC [181]) was a multicentre RCT conducted in trauma centres located in Denmark, The Netherlands, Norway, Germany and the United Kingdom. The study focused on trauma-induced coagulopathy comparing outcomes in 396 patients in whom a local MHP had been initiated, with red blood cell transfusion guided by VHAs or conventional coagulation tests. The MHPs included empiric delivery of tranexamic acid, blood components delivered in a high transfusion ratio of red blood cells, FFP and platelet transfusions (1:1:1) and limited infusion of crystalloid fluids.

Gonzalez 2016 [174] was a single-centre RCT conducted in the United States that enrolled adult patients (aged >18 yrs) with blunt or penetrating trauma sustained less than 6 hours before admission. Patients had to have an ISS greater than 15 and were likely to require transfusion of red blood cells within 6 hours from admission as indicated by clinical assessment. Patients were predominantly male (70.3% 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, 5 were conducted at single centres (Guth 2019 [179], Wang 2017 [184], Tapia 2013 [185], Görlinger 2012 [192], Kashuk 2012 [186]) 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 [183], Prat 2017 [189], Nardi 2015 [190], Nienaber 2011 [194], Schöchl 2011 [195]) involved the collection of data from trauma registries (civilian and/or combat), with patients being selected based on injury severity (e.g. ISS  $\geq$  16, base deficit  $\geq$  2.0 mmol/L) or the need for blood components (e.g. receiving at least 3 units of red blood cells 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 a TEG or ROTEM-guided MHP was used (23.7%) compared with an MHP guided by 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 a TEG or ROTEM-guided transfusion algorithm/haemorrhage protocol is associated with a significantly lower mortality rate than a transfusion algorithm/haemorrhage protocol guided by 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 showed that the rate of thromboembolic events in patients who received a TEG or ROTEM-guided MHP was 9.3% (24/257), which was comparable with the group whose MHP was guided by 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 MOF (4.3%, 11/257) among trauma patients who received a TEG or ROTEM-guided MHP compared with those whose MHP was guided by standard laboratory tests (3.2%, 8/250) (RR 1.33; 95% CI 0.53, 3.34;  $P = 0.54$ ,  $I^2=0\%$ ).

### Red blood cell transfusion volumes

Data from one RCT suggested that the use of a TEG-guided MHP does not reduce the volume of red blood cells transfused when compared to an MHP guided by standard laboratory tests (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 components/products

Data from one RCT suggested that the use of a TEG-guided MHP does not reduce the volume of FFP transfused when compared to an MHP guided by standard laboratory tests (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 suggested that the use of a TEG or ROTEM-guided transfusion algorithm/haemorrhage protocol does not reduce the volume of FFP transfused when compared to a transfusion algorithm/haemorrhage protocol 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 a TEG or ROTEM-guided transfusion algorithm/haemorrhage protocol does not reduce the volume of platelets transfused when compared to a transfusion algorithm/haemorrhage protocol 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 VHA	Certainty of the Evidence (Quality of evidence)	Summary
Mortality, all cause (RCTs)	Relative risk 0.75 (CI 95% 0.48 — 1.17)	301 per 1000	226 per 1000	Very low Due to serious	The use of a TEG or ROTEM-guided

Outcome Timeframe	Study results and measurements	Comparator standard best practice care	Intervention VHA	Certainty of the Evidence (Quality of evidence)	Summary
latest reported timepoint  9 Critical	Based on data from 506 participants in 2 studies. <sup>1</sup> (Randomized controlled)	Difference:	<b>75 fewer per 1000</b> ( CI 95% 157 fewer — 51 more )	risk of bias, Due to serious inconsistency, Due to serious imprecision <sup>2</sup>	transfusion algorithm/ haemorrhage protocol to manage coagulopathy 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. <sup>3</sup> (Observational (non- randomized))	<b>173</b> per 1000  Difference:	<b>130</b> per 1000  <b>43 fewer per 1000</b> ( CI 95% 66 fewer — 14 fewer )	Very low Due to serious risk of bias, Due to serious imprecision <sup>4</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients with critical bleeding in the trauma setting may be associated with reduced mortality but the evidence is very uncertain.
Morbidity, thromboemboli c events  6 Important	Relative risk 0.9 (CI 95% 0.42 — 1.95) Based on data from 507 participants in 2 studies. <sup>5</sup> (Randomized controlled)	<b>113</b> per 1000  Difference:	<b>102</b> per 1000  <b>11 fewer per 1000</b> ( 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 <sup>6</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients with critical bleeding in the trauma setting may have little or no difference on thromboembolic events but the evidence is very uncertain.
Morbidity, MOF  6 Important	Relative risk 1.75 (CI 95% 0.6 — 5.12) Based on data from 396 participants in 1 studies. <sup>7</sup> (Randomized controlled)	<b>26</b> per 1000  Difference:	<b>46</b> per 1000  <b>20 more per 1000</b> ( CI 95% 10 fewer — 107 more )	Very low Due to serious risk of bias, Due to very serious imprecision <sup>8</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients with critical bleeding in the trauma setting may have no difference on MOF but the evidence is very uncertain.
Red blood cells transfusion	Measured by: Number of Units	<b>15.65</b> Units (Mean)	<b>13.96</b> Units (Mean)	Very low Due to serious	The use of a TEG or ROTEM-guided



Outcome Timeframe	Study results and measurements	Comparator standard best practice care	Intervention VHA	Certainty of the Evidence (Quality of evidence)	Summary
volume (RCTs)	Lower better Based on data from 109 participants in 1 studies. <sup>9</sup> (Randomized controlled)	Difference:	<b>SMD 0.13 fewer</b> ( CI 95% 0.5 fewer — 0.25 more )	risk of bias, Due to very serious imprecision <sup>10</sup>	transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients with critical bleeding in the trauma setting may have little to no difference in the volume of red blood cells transfused.
Red blood cell transfusion volume (Coh)	Measured by: Number of Units Lower better Based on data from 1,484 participants in 7 studies. <sup>11</sup> (Observational (non- randomized))	2 - 11 Units  Difference:	2 - 6.5 Units  <b>SMD 0.41 fewer</b> ( CI 95% 0.68 fewer — 0.14 fewer )	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency <sup>12</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients with critical bleeding in the trauma setting may be associated with a slight reduction in the volume of red blood cells 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. <sup>13</sup> (Observational (non- randomized))	1 - 7.57 Units  Difference:	1 - 7.49 Units  <b>SMD 0.32 fewer</b> ( 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 <sup>14</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients 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.
Platelet transfusion volume	Measured by: Number of Units Lower better Based on data from 580 participants in 4 studies. <sup>15</sup> (Observational (non- randomized))	0.95 - 4.2 Units  Difference:	0.4 - 2.7 Units  <b>SMD 0.91 fewer</b> ( CI 95% 1.83 fewer — 0.11 more )	Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision <sup>16</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients with critical bleeding in the trauma setting may be associated with little or no difference in the volume of platelets transfused but the

Outcome Timeframe	Study results and measurements	Comparator standard best practice care	Intervention VHA	Certainty of the Evidence (Quality of evidence)	Summary
					evidence is very uncertain.

1. Systematic review [6] with included studies: Gonzalez 2016 (Trauma), Baksaas-Aasen 2020 (Trauma). **Baseline/comparator:** Systematic review.
2. **Risk of Bias: serious.** High risk of bias due to inadequate or poor reporting of blinding, incomplete reporting of outcome data, and short follow-up. Certainty of evidence downgraded. **Inconsistency: serious.** Results were inconsistent across studies. Moderate heterogeneity detected ( $I^2$  between 25% to 50%). Certainty of evidence downgraded. **Indirectness: no serious.** The evidence is in people with coagulopathy or severe bleeding at inclusion and is considered directly generalisable to the Australian population/healthcare setting with some caveats. Certainty of evidence not downgraded. **Imprecision: serious.** Low event rate in included studies that were not the optimal information size to detect the outcome of interest. Certainty of evidence downgraded. **Publication bias: no serious.**
3. Systematic review [6] with included studies: Guth 2019 (Coh, trauma), Prat 2017 (Coh, trauma), Kashuk 2012 (Coh, trauma), Unruh 2019 (Coh, trauma), Tapia 2013 (Coh, trauma), Schochl 2011 (Coh, trauma), [190], Wang 2017 (Coh, trauma). **Baseline/comparator:** Systematic review.
4. **Risk of Bias: serious.** Moderate to high risk of bias in included studies. The main concern was the use of appropriate historical controls before and after the implementation of viscoelastic testing protocols along with high procedural bias associated with nonblinding that is likely to favour the intervention. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** The evidence is in people with coagulopathy or severe bleeding at inclusion and is considered directly generalisable to the Australian population/healthcare setting with some caveats. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.**
5. Systematic review [6] with included studies: Baksaas-Aasen 2020 (Trauma), [174]. **Baseline/comparator:** Systematic review.
6. **Risk of Bias: serious.** High risk of bias due to inadequate or poor reporting of blinding, incomplete reporting of outcome data, and short follow-up. Certainty of evidence downgraded. **Inconsistency: serious.** The direction of the effect is not consistent between the included studies. Certainty of evidence downgraded. **Indirectness: no serious. Imprecision: serious.** Low event rate in included studies that were not the optimal information size to detect the outcome of interest. Certainty of evidence downgraded. **Publication bias: serious.** Suspected under-reporting of the outcome. Certainty of evidence downgraded.
7. Systematic review [6] with included studies: Baksaas-Aasen 2020 (Trauma). **Baseline/comparator:** Primary study.
8. **Risk of Bias: serious.** High risk of bias due to inadequate or poor reporting of blinding, incomplete reporting of outcome data, and short follow-up. Certainty of evidence downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: no serious.** The evidence is applicable to the Australian healthcare context with few caveats. Certainty of evidence not downgraded. **Imprecision: very serious.** Only data from one study. Wide confidence intervals. Low event rate in included studies that were not the optimal information size to detect the outcome of interest. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

9. Systematic review [6] with included studies: Gonzalez 2016 (Trauma). **Baseline/comparator:** Primary study.
10. **Risk of Bias: serious.** High risk of bias due to inadequate or poor reporting of blinding, incomplete outcome data, and short follow-up. Certainty of evidence downgraded. **Inconsistency: no serious.** Inconsistency not able to be assessed. One study. Certainty of evidence not downgraded. **Indirectness: no serious.** **Imprecision: very serious.** Wide confidence intervals. Only data from one study. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**
11. Systematic review [6] with included studies: Guth 2019 (Coh, trauma), [195], Wang 2017 (Coh, trauma), Prat 2017 (Coh, trauma), Unruh 2019 (Coh, trauma), [190]. **Baseline/comparator:** Systematic review.
12. **Risk of Bias: serious.** Concern with the use of appropriate historical controls before and after the implementation of viscoelastic testing protocols along with high procedural bias associated with nonblinding that is likely to favour the intervention. Certainty of evidence downgraded. **Inconsistency: serious.** Point estimates vary widely. Substantial statistical heterogeneity observed ( $I^2 = 78\%$ ). Certainty of evidence downgraded. **Indirectness: no serious.** The evidence is probably applicable to the Australian healthcare context with few caveats. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.**
13. Systematic review [6] with included studies: [190], Gonzalez 2016 (Trauma), Guth 2019 (Coh, trauma), Wang 2017 (Coh, trauma), Prat 2017 (Coh, trauma), Unruh 2019 (Coh, trauma). Includes data from 1 RCT (Gonzalez 2016). **Baseline/comparator:** Control arm of reference used for intervention.
14. **Risk of Bias: serious.** Concerns with the use of appropriate historical controls before and after the implementation of viscoelastic testing protocols along with high procedural bias associated with nonblinding that is likely to favour the intervention. Certainty of evidence downgraded. **Inconsistency: very serious.** Result were inconsistent across studies. Substantial heterogeneity observed ( $I^2 > 90\%$ ). Certainty of evidence downgraded 2 levels. **Indirectness: no serious.** The evidence is applicable to the Australian healthcare context with few caveats. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.**
15. Systematic review [6] with included studies: Wang 2017 (Coh, trauma), Gonzalez 2016 (Trauma), Unruh 2019 (Coh, trauma), [190]. Evidence includes one RCT (Gonzalez 2016). **Baseline/comparator:** Systematic review.
16. **Risk of Bias: serious.** **Inconsistency: serious.** The magnitude of statistical heterogeneity was high, ( $I^2 = 89\%$ ). Point estimates vary widely. The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies. Certainty of evidence downgraded. **Indirectness: no serious.** **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded.

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## Clinical question/ PICO

**Population:** People with critical bleeding (surgical setting)

**Intervention:** Viscoelastic haemostatic assays

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

## Summary

Refer to the technical reports for further information on individual studies.

### What did we find?

Nine systematic reviews (Li 2019 [171], Roullet 2018 [161], Serraino 2017 [169], Wikkelsø 2017 [164], Fahrendorff 2017 [162], Saner 2016 [170], Deppe 2016 [172], Corredor 2015 [165], Haas 2014 [166]) were found that included evidence from 5 RCTs (Weber 2012, Paniagua 2011, Kempfert 2011, NCT00772239, Nuttall 2001) and 2 cohort studies (Fassl 2013 [191], Hanke 2012 [193]) conducted in the cardiac setting that examined the effects of a TEG or ROTEM-guided transfusion algorithm/haemorrhage protocol in patients with critical bleeding.

### Study characteristics

All 5 RCTs (Weber 2012 [177], Paniagua 2011 [178], Kempfert 2011 [176], NCT00772239 [180], Nuttall 2001 [175]) 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 8 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 single centres and included adult patients undergoing urgent proximal aortic surgery with hypothermic circulatory arrest with major bleeding (Fassl 2013 [191]) or adult patients with acute type A aortic dissection and aortic valve replacement (Hanke 2012 [193]).

All but one study (Nuttall 2001) used a ROTEM-guided transfusion algorithm/haemorrhage protocol.

### **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 2 RCTs suggested those who received a ROTEM-guided transfusion algorithm/haemorrhage protocol 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 ROTEM (RR 0.33; 95% CI 0.12, 0.91;  $P = 0.03$ ;  $I^2 = 0\%$ ). This outcome was not reported in 3 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 a ROTEM-guided transfusion algorithm/haemorrhage protocol 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.

### **Red blood cell transfusion volumes**

Data from one small RCT suggested that there was no difference in volume of red blood cells transfused comparing a ROTEM-guided MHP 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 2 studies and 2 other studies suggested an effect favouring TEG or ROTEM but did not provide suitable data for analysis.

### **Transfusion volumes, other blood components/products**

Data from one small RCT and one small cohort study suggested that there was no difference in volume of FFP transfused comparing a ROTEM-guided transfusion algorithm/haemorrhage protocol 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 platelets transfused (SMD -0.33; 95% CI -0.94, 0.27;  $P = 0.28$ ). Data were not reported in 2 studies and 2 other 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 VHA	Certainty of the Evidence (Quality of evidence)	Summary
Mortality, all cause (RCTs) <sup>1</sup> latest reported timepoint  9 Critical	Relative risk 0.33 (CI 95% 0.12 — 0.91) Based on data from 144 participants in 2 studies. <sup>2</sup> (Randomized controlled)	206 per 1000  Difference:	68 per 1000  <b>138 fewer per 1000</b> ( CI 95% 181 fewer — 19 fewer )	Low Due to serious risk of bias, Due to serious imprecision <sup>3</sup>	The evidence suggests the use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients with critical bleeding in the surgical setting (cardiothoracic) may reduce mortality.
Morbidity, thromboemboli c events  6 Important	Relative risk 0.2 (CI 95% 0.01 — 4.06) Based on data from 144 participants in 2 studies. <sup>4</sup> (Randomized controlled)	29 per 1000  Difference:	6 per 1000  <b>23 fewer per 1000</b> ( CI 95% 29 fewer — 89 more )	Very low Due to serious risk of bias, Due to very serious imprecision <sup>5</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy 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 uncertain.
Red blood cell transfusion volume (RCTs)	Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies. <sup>6</sup> (Randomized controlled)	6.42 Units (Mean)  Difference:	7.1 Units (Mean)  <b>SMD 0.12 more</b> ( 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 <sup>7</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients with critical bleeding in the surgical setting (cardiothoracic) may have little or no difference on the volume of red blood cells 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. <sup>8</sup> (Randomized controlled)	2.8 - 9.2 Units  Difference:	1.6 - 3.2 Units  <b>SMD 0.5 fewer</b> ( 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 serious publication bias <sup>9</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients with critical bleeding in the surgical setting (cardiothoracic) may have little or no



Outcome Timeframe	Study results and measurements	Comparator standard best practice care	Intervention VHA	Certainty of the Evidence (Quality of evidence)	Summary
					difference on the volume of FFP transfused but the evidence is very uncertain.
Platelet transfusion volume	Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies. <sup>10</sup> (Randomized controlled)	1.34 Units (Mean)  Difference:	0.85 Units (Mean)  <b>SMD 0.33 fewer</b> ( 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 <sup>11</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in patients with critical bleeding in the surgical setting (cardiothoracic) may have little or no difference on the volume of platelets transfused but the evidence is very uncertain.

1. range 6 months to 28 days

2. Systematic review [6] with included studies: Paniagua 2011 (Cardiac), Weber 2012 (Cardiac).

**Baseline/comparator:** Systematic review [6] with included studies: Paniagua 2011 (Cardiac), Weber 2012 (Cardiac).

3. **Risk of Bias: serious.** RCTs with high risk of bias due to inadequate or poor reporting of blinding, incomplete reporting of outcome data, and short follow-up. Certainty of evidence downgraded.

**Inconsistency: no serious. Indirectness: no serious.** The evidence is in people with coagulopathy or severe bleeding at inclusion and is considered directly generalisable to the Australian population/ healthcare setting with some caveats. Certainty of evidence not downgraded. **Imprecision: serious.** Low event rate in included studies that were not the optimal information size to detect the outcome of interest. Certainty of evidence downgraded. **Publication bias: no serious. Upgrade: clear dose-response gradient.**

4. Systematic review [6] with included studies: Weber 2012 (Cardiac), Paniagua 2011 (Cardiac).

**Baseline/comparator:** Systematic review.

5. **Risk of Bias: serious.** High risk of bias due to inadequate or poor reporting of blinding, incomplete reporting of outcome data, and short follow-up. Certainty of evidence downgraded.

**Inconsistency: no serious. Indirectness: no serious.** The evidence is applicable to the Australian healthcare context with few caveats. Certainty of evidence not downgraded. **Imprecision: very serious.** Only data from one study. Wide confidence intervals. Low event rate in included studies that were not the optimal information size to detect the outcome of interest. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

6. Systematic review [6] with included studies: Paniagua 2011 (Cardiac). **Baseline/comparator:** Control arm of reference used for intervention. **Supporting references:** [162],

7. **Risk of Bias: serious.** High risk of bias due to inadequate or poor reporting of blinding, incomplete reporting of outcome data, and short follow-up. Certainty of evidence downgraded.

**Inconsistency: no serious. Indirectness: no serious.** The evidence is applicable to the Australian

healthcare context with few caveats, Certainty of evidence not downgraded. **Imprecision: serious.** Only data from one study. Low number of patients. Certainty of evidence downgraded. **Publication bias: serious.** Early termination of studies suggests publication bias likely. Certainty of evidence downgraded.

8. Systematic review [6] with included studies: Paniagua 2011 (Cardiac), Hanke 2012 (RCoh, Cardiac). includes one RCT (Paniagua 2011). **Baseline/comparator:** Control arm of reference used for intervention.

9. **Risk of Bias: serious.** High risk of bias in both studies. Certainty of evidence downgraded. **Inconsistency: serious.** The magnitude of statistical heterogeneity was high ( $I^2 = 70\%$ ). Certainty of evidence downgraded. **Indirectness: no serious.** **Imprecision: serious.** Wide confidence intervals. Low number of patients. Certainty of evidence downgraded. **Publication bias: serious.** Early termination of RCT suggests publication bias likely. Certainty of evidence downgraded.

10. Systematic review [6] with included studies: Paniagua 2011 (Cardiac). **Baseline/comparator:** Primary study.

11. **Risk of Bias: serious.** High risk of bias due to inadequate or poor reporting of blinding, incomplete reporting of outcome data, and short follow-up. Certainty of evidence downgraded. **Inconsistency: no serious.** **Indirectness: no serious.** **Imprecision: serious.** Only data from one study. Wide confidence intervals. Low number of patients. Certainty of evidence downgraded. **Publication bias: serious.** Early termination of studies suggests publication bias likely. Certainty of evidence downgraded.

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## Clinical question/ PICO

- Population:** People with critical bleeding (obstetrics and maternity)
- Intervention:** Viscoelastic haemostatic assays
- Comparator:** Standard best practice care (blood component therapy guided by MHP protocol or standard laboratory tests)

## Summary

Refer to the technical reports for further information on individual studies.

**What did we find?**

Five systematic reviews (Amgalan 2020 [173], Roulet 2018 [161], Wikkelsø 2017 [164], Fahrendorff 2017 [162], Haas 2014 [166]) were found that included evidence from 3 nonrandomised cohort studies (McNamara 2019, Snegovskikh 2018, Barinov 2015) conducted in the obstetrics setting that evaluated the effect of a VHA-guided algorithm for treatment of coagulopathy to improve outcomes for women with severe PPH.

**Study characteristics**

Two studies were conducted at single centres in either the United States (Snegovskikh 2018 [188]) or the United Kingdom (McNamara 2019 [187]) and reported data covering a 4 to 4.5 year period. The studies included women with severe PPH (defined as an estimated blood volume loss of  $\geq 1500$  mLs) who had received care either before or after the introduction of an MHP that included a point-of-care viscoelastic test.

One study (Barinov 2015 [182]) was conducted in Russia and prospectively included women with PPH managed using a combined strategy involving TEG assessment of coagulation, *early* surgical haemostasis (estimated blood volume loss of  $\geq 1000$  mLs) and mechanical compression of the uterine wall combined with uterine cavity draining, via intrauterine balloon tamponade. The comparator group received uterine massage, manual examination of the uterus, and transfusion of FFP, red blood cells, platelets and protease inhibitors, with *late* surgical haemostasis (blood loss volume  $\geq 2000$  mL). In cases of severe obstetric haemorrhage, autologous red blood cell reinfusion was carried out (cell salvage).

**What are the main results?**

Viscoelastic tests may be used in clinically guiding transfusion therapy in women with severe haemorrhage but its potential in managing coagulopathies is relatively under studied.

**Mortality**

No deaths were observed in the observational studies that assessed the effects of a TEG or ROTEM-guided transfusion algorithm/haemorrhage protocol among women with major obstetric haemorrhage. The studies are small and not the optimal information size to detect the outcome of interest.

**Morbidity**

Among women with severe PPH, the use of a TEG or ROTEM-guided transfusion algorithm/haemorrhage protocol was reported to reduce the incidence of postpartum hysterectomy compared with management of coagulopathy guided by standard laboratory tests (8.4% vs 33.8%; RR 0.37; 95% CI 0.18, 0.77;  $P = 0.008$ ;  $I^2 = 54\%$ ).

**RBC transfusion volumes**

Data from one cohort study (Barinov 2015) suggested that the use of TEG is associated with a statistically significant reduction in the volume of red blood cells transfused (around 1 unit saved) compared with management of coagulopathy guided by standard laboratory tests (SMD of  $-0.82$ ; 95% CI  $-1.25$ ,  $-0.39$ ;  $P = 0.0002$ ). One study suggested there were no reduction in the median volume of red blood cells transfused (McNamara 2019). One study did not report this outcome (Snegovskikh 2018).

**Transfusion volumes, other blood components/products**

Data from one cohort study (Barinov 2015) suggested that the use of TEG is associated with a large reduction in the volume of FFP transfused (around 4.4 units saved) compared with management of coagulopathy guided by standard laboratory tests (SMD of -2.73; 95% CI -3.28, -2.19;  $P < 0.0001$ ) but not a reduction in the volume of platelets transfused (SMD of 0.06; 95% CI -0.32, 0.43;  $P = 0.76$ ). The other two studies did not report these outcomes.

Outcome Timeframe	Study results and measurements	Comparator Standard best practice care	Intervention Viscoelastic haemostatic assays	Certainty of the Evidence (Quality of evidence)	Summary
Mortality, all cause latest reported timepoint  9 Critical	Relative risk 0 (CI 95% 0 — 0) Based on data from 460 participants in 3 studies. <sup>1</sup> (Observational (non- randomized))	0 per 1000  Difference:	0 per 1000  <b>0 fewer per 1000</b> ( CI 95% 0 fewer — 0 fewer )	Very low Due to serious risk of bias, Due to serious imprecision <sup>2</sup>	There were too few who experienced the outcome to determine whether the use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in women with major obstetric haemorrhage made a difference.
Morbidity, need for hysterectomy  6 Important	Relative risk 0.37 (CI 95% 0.18 — 0.77) Based on data from 460 participants in 3 studies. <sup>3</sup> (Observational (non- randomized))	346 per 1000  Difference:	128 per 1000  <b>218 fewer per 1000</b> ( CI 95% 284 fewer — 80 fewer )	Very low Due to serious risk of bias <sup>4</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in women with major obstetric haemorrhage may be associated with a reduction in the need for hysterectomy but the evidence is very uncertain.
Red blood cell transfusion volume	Measured by: Number of Units Lower better Based on data from 121 participants in 1 studies. <sup>5</sup> (Observational (non- randomized))	6.1 Units (Mean)  Difference:	4.81 Units (Mean)  <b>SMD 0.82 fewer</b> ( CI 95% 1.25 fewer — 0.39 fewer )	Very low Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias <sup>6</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in women with major obstetric haemorrhage may be associated with a slight reduction in the volume of RBCs transfused but the evidence is very uncertain.
FFP transfusion	Measured by: Number of	9.25	4.8	Very low	The use of a TEG or

Outcome Timeframe	Study results and measurements	Comparator Standard best practice care	Intervention Viscoelastic haemostatic assays	Certainty of the Evidence (Quality of evidence)	Summary
volume	Units Lower better Based on data from 121 participants in 1 studies. <sup>7</sup> (Observational (non- randomized))	Units (Mean)  Difference:	Units (Mean)  <b>SMD 2.73 fewer</b> ( CI 95% 3.28 fewer — 2.19 fewer )	Due to serious risk of bias, Due to very serious indirectness, Due to serious imprecision <sup>8</sup>	ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in women with major obstetric haemorrhage may be associated with a reduction in 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 109 participants in 1 studies. <sup>9</sup> (Observational (non- randomized))	1.52 Units (Mean)  Difference:	1.64 Units (Mean)  <b>SMD 0.06 more</b> ( CI 95% 0.32 fewer — 0.43 more )	Very low Due to serious risk of bias, Due to serious imprecision <sup>10</sup>	The use of a TEG or ROTEM-guided transfusion algorithm/ haemorrhage protocol to manage coagulopathy in women with major obstetric haemorrhage may be associated with little or no difference in the volume of PLTs transfused but the evidence is very uncertain.

1. Systematic review [6] with included studies: [187], [188], [182]. **Baseline/comparator:** Primary study. **Supporting references:** [173],
2. **Risk of Bias: serious.** Concerns with the use of appropriate historical controls before and after the implementation of viscoelastic testing protocols along with high procedural bias associated with nonblinding that is likely to favour the intervention. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Low number of patients. Low event rate in included studies that were not the optimal information size for the outcome of interest. Certainty of evidence downgraded. **Publication bias: no serious.**
3. Systematic review [6] with included studies: Snegovskikh 2018 (Coh, PPH), [187], [182]. **Baseline/comparator:** Systematic review.
4. **Risk of Bias: serious.** Concerns with the use of appropriate historical controls before and after the implementation of viscoelastic testing protocols along with high procedural bias associated with nonblinding that is likely to favour the intervention. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious. Imprecision: no serious. Publication bias: no serious.**
5. Systematic review [6] with included studies: Barinov 2015 (Coh, PPH). **Baseline/comparator:** Primary study.
6. **Risk of Bias: serious.** Concerns with the use of appropriate historical controls before and after the implementation of viscoelastic testing protocols along with high procedural bias associated with nonblinding that is likely to favour the intervention. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious.** The evidence is directly generalisable to the Australian population with few caveats. Certainty of evidence not downgraded. **Imprecision: serious.** Only data from one study. Low number of patients. Certainty of evidence downgraded. **Publication bias:**



**serious.** Suspected nonreporting of data. Certainty of evidence downgraded.

7. Systematic review [6] with included studies: Barinov 2015 (Coh, PPH). **Baseline/comparator:** Primary study.

8. **Risk of Bias: serious.** Concern with the use of appropriate historical controls before and after the implementation of viscoelastic testing protocols along with high procedural bias associated with nonblinding that is likely to favour the intervention. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: very serious. Imprecision: serious.** Only data from one study. Low number of patients. Wide confidence intervals. Certainty of evidence downgraded. **Publication bias: no serious.**

9. Systematic review [6] with included studies: Barinov 2015 (Coh, PPH). **Baseline/comparator:** Systematic review.

10. **Risk of Bias: serious.** Concern with the use of appropriate historical controls before and after the implementation of viscoelastic testing protocols along with high procedural bias associated with nonblinding that is likely to favour the intervention. Certainty of evidence downgraded. **Inconsistency: no serious. Indirectness: no serious. Imprecision: serious.** Only data from one study. Low number of patients. Certainty of evidence downgraded. **Publication bias: no serious.**

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Clin Anesth 2018;44:50-56 [Journal](#)

## 7.2.4 Cell salvage

### Research question

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

Latest search date: 29 September 2021

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 blood component transfusion.

Good practice statement , Very low certainty evidence

**GPS11:** 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 an MHP 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 an MHP. 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 an MHP.

**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 an MHP in patients who are critically bleeding. 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 patients who are critically bleeding 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**

Refer to the technical reports for further information on individual studies.

**What did we find?**

One systematic review (Meybohm 2016 [196]) was found that included evidence from one small RCT (Bowley 2006) examining the effect of cell salvage in patients with critical bleeding. No additional RCTs were identified through the systematic review and hand-searching process. The literature search found one prospective cohort study (Bhangu 2013 [199]) that was not included in the evidence summary as it was judged not applicable to the Australian healthcare context. The study was conducted in Afghanistan among patients admitted to a combat support hospital with blast injuries.

**Study characteristics**

Bowley 2006 [198] enrolled adult patients (aged > 18 years) presenting to emergency with penetrating torso injuries requiring laparotomy and had exhibited hypotension (< 90 mmHg) either prehospital or on arrival and in whom there was significant blood loss. All but 4 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 red blood cells 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 platelets 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)	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. <sup>1</sup> (Randomized controlled)	652 per 1000  Difference:	665 per 1000  <b>13 more per 1000</b> ( CI 95% 215 fewer — 365 more )	Very low Due to serious indirectness, Due to very serious imprecision <sup>2</sup>	Cell salvage may have little or no difference on mortality in trauma patients with critical bleeding, but the evidence is very uncertain.
Morbidity, post- operative complications sepsis  9 Critical	Relative risk 0.78 (CI 95% 0.29 — 2.09) Based on data from 44 participants in 1 studies. <sup>3</sup> (Randomized controlled)	304 per 1000  Difference:	237 per 1000  <b>67 fewer per 1000</b> ( CI 95% 216 fewer — 331 more )	Very low Due to serious indirectness, Due to very serious imprecision <sup>4</sup>	Cell salvage may have little or no difference in morbidity (sepsis) in trauma patients with critical bleeding, 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)	Summary
Red blood cell transfusion volume	Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies. <sup>5</sup> (Randomized controlled)	<b>11.17</b> Units (Mean)  Difference:	<b>6.47</b> Units (Mean)  <b>SMD 0.82 fewer</b> ( CI 95% 1.44 fewer — 0.2 fewer )	Very low Due to serious indirectness, Due to very serious imprecision <sup>6</sup>	Cell salvage may reduce the volume of allogenic red blood cells 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. <sup>7</sup> (Randomized controlled)	<b>4.04</b> Units (Mean)  Difference:	<b>4.76</b> Units (Mean)  <b>SMD 0.16 more</b> ( CI 95% 0.44 fewer — 0.75 more )	Very low Due to serious indirectness, Due to very serious imprecision <sup>8</sup>	Cell salvage may have no difference on the volume of FFP transfused in trauma patients with critical bleeding, but evidence is very uncertain.
Platelet transfusion volume	Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies. <sup>9</sup> (Randomized controlled)	<b>0.56</b> Units (Mean)  Difference:	<b>1</b> Units (Mean)  <b>SMD 0.26 more</b> ( CI 95% 0.33 fewer — 0.85 more )	Very low Due to serious indirectness, Due to very serious imprecision <sup>10</sup>	Cell salvage may have no difference on the volume of platelets transfused in trauma patients with critical bleeding, but the evidence is very uncertain.

1. Systematic review [7] with included studies: Bowley 2006 (RCT, penetrating trauma). Only the Bowley 2006 (RCT, penetrating trauma) included in the effect estimates. Bhangu 2012 (coh, combat trauma) was in patients with sustained combat-related injury requiring more than 10 units of RBCs in the first 12 hours after injury.. **Baseline/comparator:** Systematic review. **Supporting references:** [196],
2. **Risk of Bias: no serious.** The RCT was considered to have a low risk of bias for patient selection. Other domains assessed as unclear, due to poor reporting. Certainty of evidence not downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded. **Indirectness: serious.** The available evidence is in predominantly males with penetrating abdominal trauma, which was considered homogeneous and not broadly representative of trauma patients with critical bleeding commonly seen in Australia. Certainty of evidence downgraded. **Imprecision: very serious.** The available evidence is in one RCT with fewer than 50 patients. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**
3. Systematic review [7] with included studies: Bowley 2006 (RCT, penetrating trauma). **Baseline/comparator:** Primary study.
4. **Risk of Bias: no serious.** The RCT was considered to have a low risk of bias for patient selection. Other domains assessed as unclear, due to poor reporting. Certainty of evidence not downgraded. **Inconsistency: no serious. Indirectness: serious.** Available evidence is in predominantly males with penetrating abdominal trauma, which was considered homogeneous and not broadly representative of trauma patients with critical bleeding commonly seen in Australia. Certainty of evidence downgraded. **Imprecision: very serious.** The available evidence is in one RCT with fewer than 50 patients. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

5. Systematic review [7] with included studies: Bowley 2006 (RCT, penetrating trauma). **Baseline/comparator:** Control arm of reference used for intervention.
6. **Inconsistency: no serious. Indirectness: serious.** The available evidence is in predominantly males with penetrating abdominal trauma, which was considered homogeneous and not broadly representative of trauma patients with critical bleeding commonly seen in Australia. Certainty of evidence downgraded. **Imprecision: very serious.** Low number of patients. Only data from one study. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**
7. Systematic review [7] with included studies: Bowley 2006 (RCT, penetrating trauma). **Baseline/comparator:** Primary study.
8. **Inconsistency: no serious. Indirectness: serious.** The available evidence is in predominantly males with penetrating abdominal trauma, which was considered homogeneous and not broadly representative of trauma patients with critical bleeding commonly seen in Australia. Certainty of evidence downgraded. **Imprecision: very serious.** Low number of patients. Only data from one study. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**
9. Systematic review [7] with included studies: Bowley 2006 (RCT, penetrating trauma). **Baseline/comparator:** Control arm of reference used for intervention.
10. **Inconsistency: no serious. Indirectness: serious.** The available evidence is in predominantly males with penetrating abdominal trauma, which was considered homogeneous and not broadly representative of trauma patients with critical bleeding commonly seen in Australia. Certainty of evidence downgraded. **Imprecision: very serious.** Low number of patients. Only data from one study. Certainty of evidence downgraded 2 levels. **Publication bias: no serious.**

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## Clinical question/ PICO

**Population:** People with critical bleeding (medical emergency)

**Intervention:** Cell salvage

**Comparator:** No cell salvage

## Summary

Refer to the technical reports for further information on individual studies.

## What did we find?

One systematic review (Shantikumar 2011 [197]) was found that included evidence from 5 non-randomised studies

(Markovic 2009, Tawfick 2008, Serricino-Inglott 2005, Shuhaiber 2003, Posacioglu 2002) involving urgent abdominal aortic aneurysm (AAA) repair that were considered relevant to this review. Due to the unpredictability and urgency of admissions and difficulties with ethical approval, none of the above studies were randomised. All studies had important problems relating to patient selection bias, outcome assessment and reporting bias.

### Study characteristics

Markovic 2009 [200] 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, elective AAA repair or rAAA repair. Because the focus of the review was urgent, symptomatic or rAAA repair that would be presenting as a life-threatening and time critical medical emergency (not scheduled surgery), only the subpopulation with rAAA repair was considered.

Tawfick 2008 [204] retrospectively reviewed rAAA 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 [202] was a prospective cohort study that examined 154 rAAA repairs reported to a regional vascular audit database in the United Kingdom over a 4-year period (January 2000 to June 2004). The 2 groups were matched for age, cardiac and respiratory symptoms, cardiac medication, incidence of myocardial infarction and diabetes.

Shuhaiber 2003 [203] was a small retrospective cohort study conducted at a single centre in the United Kingdom 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 [201] retrospectively reviewed mortality, post-operative morbidity and blood loss in 56 patients with suprarenal and infrarenal rAAA repairs by a single surgeon in Turkey. There were no differences in baseline characteristics (98% [55/56] were male), with the mean age being  $68 \pm 8$  years.

### What are the main results?

#### Mortality

Among patients requiring urgent AAA 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

### Post-operative complications

Among patients requiring urgent AAA repair\*, the risk of post-operative 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 was not statistically significant (RR 3.20, 95% CI 0.83, 12.35; P = 0.09). Similar data were observed for post-operative renal complications (12% vs 1.3%; RR 2.00, 95% CI 0.49, 8.14; P = 0.33) and post-operative 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 red blood cells 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 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 platelets 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.

\*Studies that reported combined data for elective and urgent abdominal aortic aneurysm repair were not included.

Outcome Timeframe	Study results and measurements	Comparator No cell salvage	Intervention Cell salvage	Certainty of the Evidence (Quality of evidence)	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. <sup>1</sup> (Observational (non- randomized))	416 per 1000  Difference:	308 per 1000  <b>108 fewer per 1000</b> ( CI 95% 187 fewer — 4 more )	Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision <sup>2</sup>	Cell salvage may be associated with little or no difference in mortality in patients undergoing urgent AAA repair, but the evidence is very uncertain.
Morbidity, respiratory complications  9 Critical	Relative risk 3.2 (CI 95% 0.83 — 12.35) Based on data from 235 participants in 3 studies. <sup>3</sup> (Observational (non- randomized))	13 per 1000  Difference:	42 per 1000  <b>29 more per 1000</b> ( CI 95% 2 fewer — 148 more )	Very low Due to serious risk of bias, Due to serious imprecision <sup>4</sup>	The evidence is very uncertain about the association of cell salvage with post- operative respiratory complications in patients undergoing urgent AAA repair.
Morbidity, renal complications	Relative risk 2 (CI 95% 0.49 — 8.14) Based on data from 235 participants in 3 studies.	13 per 1000  Difference:	26 per 1000  <b>13 more per</b>	Very low Due to serious risk of bias, Due to serious	The evidence is very uncertain about the association of cell salvage with post- operative renal



Outcome Timeframe	Study results and measurements	Comparator No cell salvage	Intervention Cell salvage	Certainty of the Evidence (Quality of evidence)	Summary
9 Critical	<sup>5</sup> (Observational (non-randomized))		<b>1000</b> ( CI 95% 7 fewer — 93 more )	imprecision, Due to serious risk of bias <sup>6</sup>	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. <sup>7</sup> (Observational (non-randomized))	<b>6</b> per 1000  Difference:	<b>10</b> per 1000  <b>4 more per 1000</b> ( CI 95% 5 fewer — 73 more )	Very low Due to serious risk of bias, Due to serious imprecision <sup>8</sup>	The evidence is very uncertain about the association of cell salvage with post- operative gastrointestinal complications in patients undergoing urgent AAA repair.
Red blood cell transfusion volume	Measured by: Number of Units Lower better Based on data from 350 participants in 5 studies. <sup>9</sup> (Observational (non-randomized))	<b>3.63 - 12.6</b> Units  Difference:	<b>4 - 11.2</b> Units  <b>SMD 0.36 fewer</b> ( CI 95% 0.87 fewer — 0.14 more )	Very low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision <sup>10</sup>	Cell salvage may be associated with little or no difference on the volume of allogenic red blood cells transfused in patients undergoing urgent AAA repair, but the evidence is very uncertain.

1. Systematic review [7] with included studies: Markovic 2009 (Coh, ruptured AAA), Tawfick 2008 (Coh, urgent AAA), Posacioglu 2002 (Coh, urgent AAA), Shuhaiber 2003 (Coh, urgent AAA), Serracino-Inglott 2005 (Coh, urgent AAA). **Baseline/comparator:** Systematic review. **Supporting references:** [197],
2. **Risk of Bias: serious.** Comparative observational studies with concerns of bias that weaken the confidence in the results. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. Certainty of evidence downgraded. **Inconsistency: serious.** The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies. Certainty of evidence downgraded. **Indirectness: no serious.** The available evidence is specific to urgent and/or elective AAA. The evidence is not directly generalisable to all patients with critical bleeding but could be sensibly applied. Certainty of evidence not downgraded. **Imprecision: serious.** Low event rate. Wide confidence intervals (upper bound overlaps with no effect). Certainty of evidence downgraded. **Publication bias: no serious.**
3. Systematic review [7] with included studies: Shuhaiber 2003 (Coh, urgent AAA), Posacioglu 2002 (Coh, urgent AAA), Serracino-Inglott 2005 (Coh, urgent AAA). Data from published studies that combine elective and emergency AAA repair not included in the analysis.. **Baseline/comparator:** Systematic review.
4. **Risk of Bias: serious.** Comparative observational studies with concerns of bias relating to patient selection and censoring of patients with early in-hospital mortality. Certainty of evidence downgraded. **Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded.. **Indirectness: no serious.** The available evidence is specific to urgent AAA repair and may not be directly generalisable to all medical emergency patients with critical bleeding but could be sensibly applied. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Low event rate. Only data from one study. Certainty of evidence downgraded. **Publication bias: no**

**serious.**

5. Systematic review [7] with included studies: Serracino-Inglott 2005 (Coh, urgent AAA), Posacioglu 2002 (Coh, urgent AAA), Shuhaiber 2003 (Coh, urgent AAA). Data from published studies that combine elective and emergency AAA repair not included in the analysis.. **Baseline/comparator:** Systematic review.

6. **Risk of Bias: serious.** Comparative observational studies with concerns of bias relating to patient selection and censoring of patients with early in-hospital mortality. Certainty of evidence downgraded.

**Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded.

**Indirectness: no serious.** The available evidence is specific to urgent AAA repair and may not be directly generalisable to all medical emergency patients with critical bleeding but could be sensibly applied. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Low event rate. Certainty of evidence downgraded. **Publication bias: no serious.**

7. Systematic review [7] with included studies: Shuhaiber 2003 (Coh, urgent AAA), Serracino-Inglott 2005 (Coh, urgent AAA), Posacioglu 2002 (Coh, urgent AAA). **Baseline/comparator:** Systematic review.

8. **Risk of Bias: serious.** Comparative observational studies with concerns of bias relating to patient selection and censoring of patients with early in-hospital mortality. Certainty of evidence downgraded.

**Inconsistency: no serious.** Only one study contributing data. Certainty of evidence not downgraded.

**Indirectness: no serious.** The available evidence is specific to urgent AAA repair and may not be directly generalisable to all medical emergency patients with critical bleeding but could be sensibly applied. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Low number of patients. Certainty of evidence downgraded.

9. Systematic review [7] with included studies: Markovic 2009 (Coh, ruptured AAA), Posacioglu 2002 (Coh, urgent AAA), Tawfick 2008 (Coh, urgent AAA), Serracino-Inglott 2005 (Coh, urgent AAA), Shuhaiber 2003 (Coh, urgent AAA). Markovic 2009 and Shuhaiber 2003 data reported as mLs.

**Baseline/comparator:** Systematic review.

10. **Risk of Bias: serious.** Comparative observational studies with concerns of bias relating to patient selection and censoring of patients with early in-hospital mortality. Certainty of evidence downgraded.

**Inconsistency: serious.** The magnitude of statistical heterogeneity was high ( $I^2 = 75\%$ ). Point estimates vary widely. Certainty of evidence downgraded. **Indirectness: no serious.** The available evidence is specific to urgent AAA repair and may not be directly generalisable to all medical emergency patients with critical bleeding but could be sensibly applied. Certainty of evidence not downgraded. **Imprecision: serious.** Wide confidence intervals. Certainty of evidence downgraded.

**Publication bias: no serious.**

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## 8. 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 salvage 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 transfusion ratios, members considered whether the existing guidance to implement an MHP with blood component ratio of 2:1:1 (RBC:FFP:PLT) was still appropriate or whether a higher blood component ratio of 1:1:1 should be considered. While the reference group acknowledged that the implementation of an MHP with a higher 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 blood component ratio of at least 2:1:1 where a critically bleeding patient should receive at least 8 units of red blood cells, 4 units of FFP and 1 adult unit of platelets.

However, if the MHP template is modified by health service organisations to include a 1:1:1 ratio whereby a critically bleeding patient would receive 4 units of red blood cells, 4 units of FFP and 1 adult unit of platelets, 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.

## 9. Supply considerations

In Australia, the supply of blood components and blood products are managed by the NBA under the *National Blood Authority Act 2003* [90] 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.

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.

Blood components produced in Australia by Lifeblood are described in the Blood Component Information book. In 2023, CSL Behring manufactures and imports blood products such as prothrombin complex concentrate and fibrinogen concentrate. The Australian Product Information can be found on the CSL Behring Product List. All 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.

The NBA works closely with all Australian governments, Lifeblood, commercial suppliers of blood products, health professionals, patient groups and many other stakeholders to ensure the continuity of national blood supply 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.

## 10. Adverse events

### Transfusion risks in the context of PBM

The benefit of transfusion must always be balanced against the risk of a potential adverse event. Adverse events can be immediate or delayed and may be related to the patient, the blood component or the procedure [99].

For detailed information on adverse event management and reporting visit the NBA Adverse Events webpage (Recognising, Managing and Reporting Adverse Events for Blood Products | National Blood Authority). The Australian Haemovigilance Report outlines the most up to date rates of adverse events reported to the national haemovigilance program.

Despite improvements in systems management, each step in the transfusion process is susceptible to errors and could contribute to a near miss or an adverse event such as an acute haemolytic reaction from ABO incompatibility [217][223]. Clear written procedures and adequate staff training are essential to ensure the right patient receives the right blood component or product [107][224].

The decision to transfuse should:

- consider the full range of available treatments
- balance the evidence for efficacy and improved clinical outcome against the risks
- consider patient values and choices

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

### **Adverse event and haemovigilance reporting**

Compliance with the National Safety and Quality Health Service (NSQHS) Blood Management Standard requires health service organisations to meet several actions related to reporting adverse events and haemovigilance. Refer to Australian Commission on Safety and Quality in Health Care (ACSQHC).

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 [95][96].

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 will inform the risk assessment and recommended 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.

For more information about where to report adverse events visit the Where do I Report Adverse Events webpage on the NBA website.

## **11. Patient consent**

The ACSQHC define informed consent as “a person’s decision, given voluntarily, to agree to a healthcare treatment, procedure or other intervention that is made:

- following the provision of accurate and relevant information about the healthcare intervention and alternative options available; and
- with adequate knowledge and understanding of the benefits and material risks of the proposed intervention relevant to the person who would be having the treatment, procedure or other intervention” [226].

The administration of blood components or blood products requires informed consent consistent with the NSQHS Standards and applicable national, state or territory legislation.

One exception, where obtaining consent may not be required, is emergency treatment for a person without capacity [227]. The description of an emergency differs between applicable legislation in some states and territories. Each state and territory has different guardianship and/or medical treatment legislation about capacity and consent [226]. It is the responsibility of all health professionals to know and understand their legal obligations in whichever state or territory they are practicing [226]. If a health professional is aware of valid refusal (that complies with local state/territory legislation), blood components or products may not be given as emergency treatment.

If blood products or components are administered in an emergency, without informed consent, this should be documented in the patient’s clinical record and the patient (or their substitute decision maker) should be advised as soon as practical. The patient should be provided with information about the care they received, product/s administered, the intended benefits and potential risks. 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 [228].

A health professional should take all practical steps to meet a patient’s language, cultural and/or communication needs [227]. When

necessary, if a patient or substitute decision maker is unable to speak or understand English, accredited language interpreters should be used [229].

For further information on informed consent see the ACSQHC Fact sheet for clinicians Informed consent in health care.

## 12. 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 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 (e.g., 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.

There is widespread geographical and institutional variability in composition and delivery of MHPs throughout Australia [252]. There are many contributing factors to this including variations in access to blood components and timely access to results from standard coagulation tests, point of care tests and/or viscoelastic haemostatic assays to guide an MHP.

The number of facilities that can appropriately store and supply blood products is limited by requirements for storage conditions, financial costs, educational and staff training and wastage implications [253]. Maintaining platelet supplies in remote settings presents a particular challenge due to the short shelf life of platelets and increased wastage due to expiry [254][255].

Implementation of this guideline requires adaptation of the recommendations and good practice statements to the local context. Health service organisations should have local policies and procedures outlining the structure, composition and delivery of an MHP which is appropriate for their local inventory, supply logistics, resources requirements, local practice and system limitations.

The use of blood components in an MHP differs across the country and the impact of implementing this guideline is unclear. Changes in blood component ratios for MHPs may increase or decrease red blood cell use, wastage and use of other components.

### Donors and supply issues

Lifeblood collects blood from non-remunerated donors to ensure that the Australian demand for blood components and blood products 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 RhD negative red blood cell inventory and use, including its use in emergency transfusion, provides significant benefit, minimising pressure on group O RhD negative donors.

Group O RhD negative red blood cells 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 [97], group O RhD negative red blood cells have represented as high as 17% of total red blood cells issued to Australian health providers [98].

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 red blood cells in an MHP 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 components and blood products. Good inventory management is necessary to ensure appropriate use of a precious resource. Maintaining inappropriate inventory may adversely impact patients or disrupt routine services.

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 an MHP.

### **Implementing recommendations into clinical practice**

Guideline implementation is a complex and challenging process [221], with different issues impacting the implementation of interventions discussed in this guideline. The reference group considered potential implementation issues for the recommendations and good practice statements included in this guideline during the evidence to decision process. For example, significant resources and expertise are required to implement, operate and interpret the results of VHAs. While there are also implementation issues associated with ratio-based blood component therapy, particularly in regional and remote areas, their impact is not as significant at this time. These factors were considered along with the evidence base when crafting and grading recommendations and good practice statements.

Health care organisation wide initiatives are one strategy that can assist with implementing recommendations into practice. Organisation wide strategies can be used to set clinical practice expectations, manage therapeutic goods/services and influence specific clinical decisions/practices, including those recommended in the PBM Guidelines. Clinical decisions may also be influenced by health system regulation, accreditation, and funding.

Health care organisations should ensure that guideline recommendations are incorporated into local policies, procedures and protocols [220]. Local adoption/adaption of clinical guidelines supports evidence-based practice and reduces unwanted variation in care [222]. Practice should be monitored and evaluated against guidelines or locally adapted policies, procedures or protocols. Further suggestions are available in the Blood Management Standard.

### **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
- Make it simple 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

### 13. Evidence gaps and potential research priorities

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

- indications for initiation and cessation of a major haemorrhage protocol
- patient specific physiological and biochemical endpoints to guide cessation of an MHP
- the optimal strategy for storage, transport and use of blood components and products including, but not limited to:
  - whole blood
  - plasma
  - platelets
  - fibrinogen
  - coagulation 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

### 14. 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 Advisory 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.

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 [93] 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. [94]

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](mailto: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.

## 15. Abbreviations and acronyms

Abbreviation	Definition
AAA	abdominal aortic aneurysm
ANZSBT	Australia & New Zealand Society of Blood Transfusion
APTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
BP	blood pressure
bpm	beats per minute
Ca <sup>2+</sup>	ionised calcium
CI	confidence interval
DIC	disseminated intravascular coagulation
DVT	deep vein thrombosis
EVAR	endovascular aortic repair
FFP	fresh frozen plasma
GPS	good practice statement
GRADE	Grading of Recommendations Assessment, Development and Evaluation

Abbreviation	Definition
HSCT	hematopoietic stem cell transplantation
ICU	intensive care unit
INR	international normalised ratio
IQR	interquartile range
ISS	injury severity score
IU	international unit
JBC	Jurisdictional Blood Committee
Lifeblood	Australian Red Cross Lifeblood
LOS	length of stay
MD	mean difference
MHP	major haemorrhage protocol
µg/kg	micrograms per kilogram
mmHg	millimetre(s) of mercury
mmol/L	millimole(s) per litre
MOF	multiple organ failure
MTP	massive transfusion protocol
NBA	National Blood Authority
NHMRC	National Health and Medical Research Council
NSQHS	National Safety and Quality Health Service Standards
OR	odds ratio
PBM	patient blood management
PE	pulmonary embolus
PICO	population, intervention, comparator, outcome
PLT	platelets
PPH	postpartum haemorrhage
PT	prothrombin time
R	recommendation
rAAA	ruptured abdominal aortic aneurysm
RBC	red blood cells
RBC:FFP:PLT	red blood cells: fresh frozen plasma: platelets
RCT	randomised controlled trial

Abbreviation	Definition
reference group	Clinical/Consumer Reference Group
ROTEM	rotational thromboelastometry
RR	relative risk
SBP	systolic blood pressure
SMD	standardised mean difference
TACO	transfusion-associated circulatory overload
TEG	thromboelastography
TRALI	transfusion-related acute lung injury
UGIB	upper gastrointestinal bleeding
VHA	viscoelastic haemostatic assay

## 16. 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 6 state governments and 2 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*. 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* 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

### **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.

Member	Declarations
Dr Don Campbell	Dr Campbell receives income from Queensland Health.
A/Prof Shannon Farmer	<p>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.</p> <p>A/Prof Farmer has received:</p> <ul style="list-style-type: none"> <li>• PBM lectures and consultancy fees through involvement with the International Foundation for PBM</li> <li>• PBM lecture honoraria Ethicon Biosurgery</li> <li>• PBM webinar honorarium Pfizer Australia</li> <li>• PBM in a pandemic webinar honorarium Baxter Australia</li> </ul> <p>A/Prof Farmer has memberships or affiliations with:</p> <ul style="list-style-type: none"> <li>• Executive Committee, Western Australia Patient Blood Management Group, The University of Western Australia</li> <li>• Scientific Associate, International Foundation of PBM</li> <li>• 2021 World Health Organization (WHO) External Working Group to develop a PBM Policy Brief</li> <li>• 2022 WHO External Steering Committee for development of the WHO Guidance for implementation of PBM</li> </ul> <p>A/Prof Farmer has almost 50 peer-reviewed publications, 32 abstracts, 8 book chapters and 2 books on PBM and transfusion appropriateness, thresholds and outcomes.</p>
A/Prof Craig French	<p>A/Prof French received NHMRC funding for transfuse study blood care.</p> <p>A/Prof French is a member of the Lifeblood Advisory Committee, is recognised as clinical leader in PBM in critical care and has given numerous presentations.</p>
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.
A/Prof Anthony Holley	<p>A/Prof Holley receives income from Queensland Health and the Australian Defence Force.</p> <p>A/Prof Holley is a member of the Australian and New Zealand Intensive Care Society (ANZICS) Board. He has also served as the Treasurer and President of the ANZICS Board.</p>
Dr Anastazia Keegan	<p>Dr Keegan is employed at PathWest Laboratory Medicine, King Edward Memorial Hospital and the Australian Red Cross Lifeblood, Transfusion Policy and Education.</p> <p>Dr Keegan has memberships or affiliations with ANZSBT, International Society of Blood Transfusion (ISBT), The Royal College of Pathologists of Australia (RCPA), Royal Australasian College of Physicians (RACP).</p> <p>Dr Keegan was awarded an ANZSBT Research Grant in 2019 and an NBA grant for the RATIONAL study in 2016.</p>



Member	Declarations
Prof Biswadev Mitra (Chair)	<p>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.</p> <p>Prof Mitra's spouse owns shares in CSL Ltd through a managed fund.</p> <p>Prof Mitra is a member of the Australian Red Cross Lifeblood advisory committee.</p>
Prof Michael Parr	<p>Prof Parr has received benefits from the:</p> <ul style="list-style-type: none"> <li>• CONTROL study (Efficacy and safety of recombinant activated Factor VII in the management of refractory traumatic haemorrhage) Steering Committee (funded by NovoNordisk).</li> <li>• Chinese Critical Care Society (funded by CSL).</li> </ul> <p>Prof Parr was an advisory committee member to NovoNordisk from 2004-2009.</p> <p>Prof Parr was a lecturer/advisor to CSL on albumin use in ICU in 2019.</p> <p>Prof Parr lectures on haemorrhage, coagulopathy, MTPs, albumin use in ICU and trauma management guidelines.</p>
Prof Michael Reade	<p>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).</p> <p>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.</p> <p>Prof Reade has written and spoken several times in the general area of blood transfusion.</p>
Ms Cindy Schultz-Ferguson	<p>Ms Schultz-Ferguson is a Board member of Dhelkaya Health.</p>
Dr Richard Seigne	<p>Dr Seigne receives income from the Canterbury District Health Board.</p> <p>Dr Seigne prescribes blood and blood components as part of his role as Anaesthetist.</p> <p>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.</p> <p>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.</p> <p>Dr Seigne is a member of ANZSBT and the Canterbury District Health Board Transfusion Committee.</p>
Dr James Winearls	<p>Dr Winearls receives income from Queensland Health.</p> <p>Dr Winearls received a CSL Travel Grant in 2015.</p>

### **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.

Twenty-five 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.

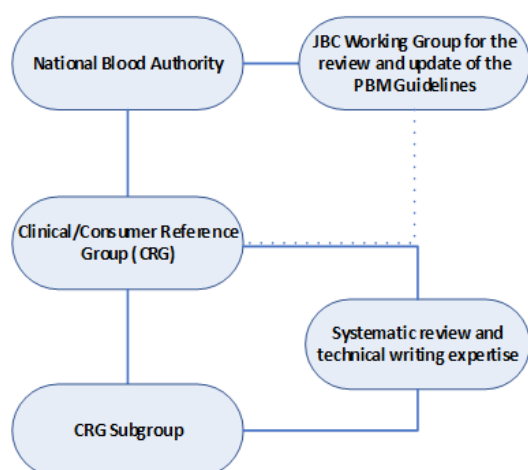
### **Appraisal of the guideline**

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 assessors recommended the guideline for use and gave a rating of 7/7 for its overall quality (with 7 being the highest possible rating).

### **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.



The **JBC** is a committee of senior government officials with representation from the Australian Government, the 6 state governments and 2 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 (i.e. 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**

Member	Clinical College/Society
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
A/Prof 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 Winearls	College of Intensive Care Medicine

#### **Systematic review team (HTAnalysts)**

Member	Role
Dr Margaret Jorgensen	Project lead and methodological oversight
Ms Alison Miles	Senior Project Manager 2021-2022

Member	Role
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)**

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

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