Supporting Information 1

Supplementary material

This appendix was part of the submitted manuscript and has been peer reviewed.
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Supplementary Material

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

Literature search date: 29 September 2021

Strong recommendation	

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

Evidence to decision

Benefits and harms	Substantial net benefits of the recommended alternative

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

Certainty of the Evidence	Very low

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

Values and preferences	No substantial variability expected

There is no plausible reason to suspect that patients who are critically bleeding would not accept treatment via an MHP 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 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

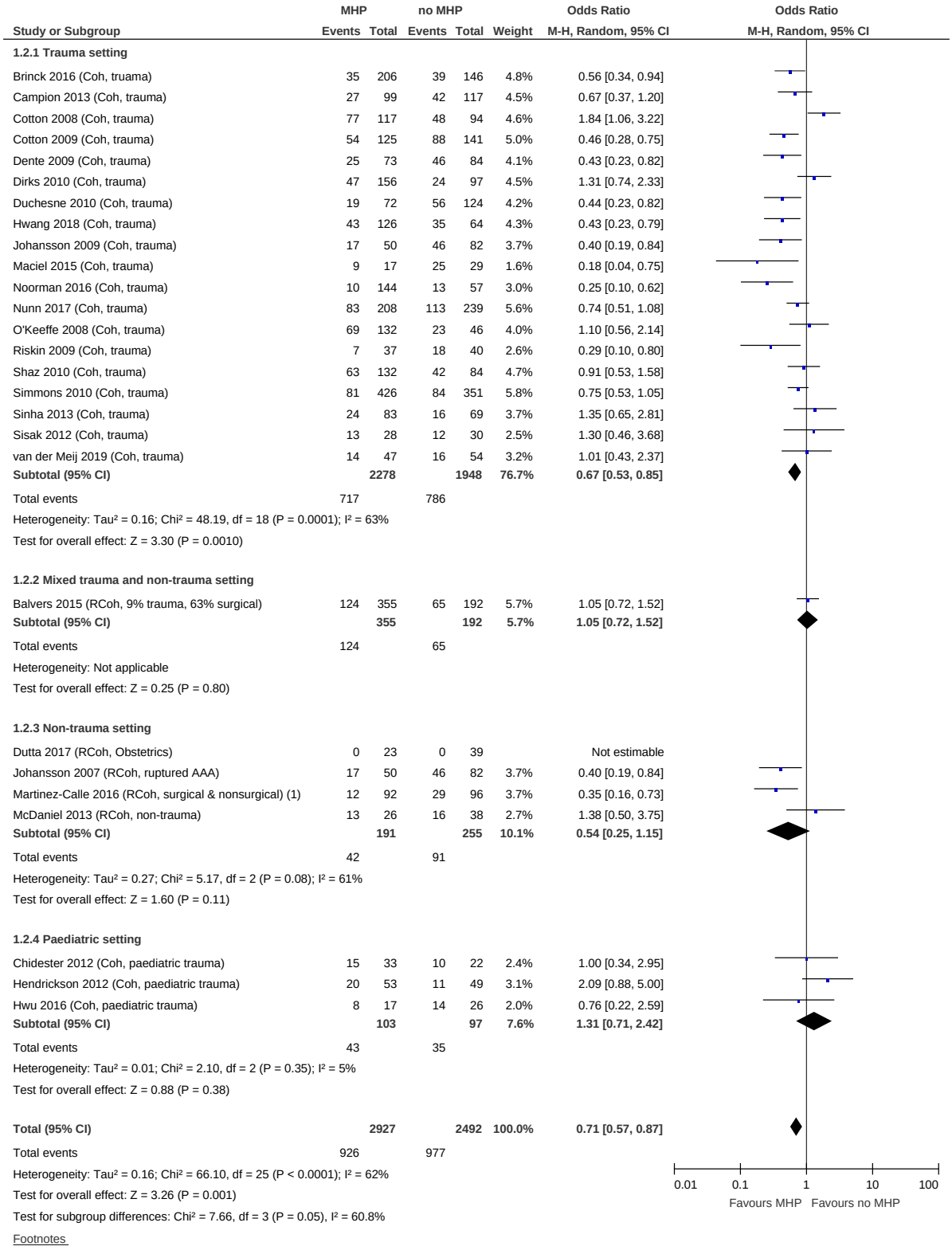
The reference group acknowledged the logistical challenges associated with implementing an MHP to treat patients who are critically bleeding. Adaptation of this guidance at a local level is required upon consideration of the resources available.

Rationale

Practical benefits of an MHP include:

- allowing blood bank to anticipate needs and provide blood components and products quickly.
- optimising timing of delivery of blood components and products
- optimising administration of blood components and products

Figure S1: Forest plot of comparison: MHPs vs no MHPs, outcome: Mortality, latest timepoint



Footnotes

(1) Data reported from most recent protocol updates (i.e. Group 2B) used for the MHP group.

MHP in Trauma: PICO

Population: People with critical bleeding (trauma setting)

Intervention: Defined MHP

Comparator: No defined MHP

Table S1: MHP vs no MHP in trauma setting

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No defined MHP	**Absolute effect estimates** Defined MHP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 24 hours	Odds ratio: 0.79 (CI 95% 0.56 - 1.11) Based on data from 1030 participants in 6 studies	**296** per 1000	**249** per 1000 Difference: **47 fewer per 1000** (CI 95% 105 fewer – 160 fewer)	**Very low** Due to serious risk of bias, Due to serious imprecision	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 latest reported timepoint	Odds ratio: 0.67 (CI 95% 0.53 - 0.85) Based on data from 4226 participants in 19 studies	**403** per 1000	**311** per 1000 Difference: **92 fewer per 1000** (CI 95% 140 fewer - 38 fewer)	**Very low** Due to serious risk of bias, Due to serious inconsistency	There is a large association between a defined MHP and lower 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 2493 participants in 10 studies	**12-25**	**11.8-24** Difference: **SMD 0.13 fewer** (CI 95% 0.33 fewer - 0.07 more)	**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision	A defined MHP may reduce volume of red blood cells transfused but the evidence is very uncertain and MHPs can be overactivated leading to wastage.

MHP in non-trauma: PICO

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

Table S2: MHP vs no MHP in non-trauma setting

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No defined MHP	**Absolute effect estimates** Defined MHP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality 24 hours	Odds ratio: 1.05 (CI 95% 0.35 - 3.12) Based on data from 861 participants in 4 studies	**99** per 1000	**103** per 1000 Difference: **4 more per 1000** (CI 95% 62 fewer - 156 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency	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.
Mortality, all cause	Odds ratio: 0.67 (CI 95% 0.35 - 1.29)	**349** per 1000	**264** per 1000	**Very low**	There is little to no association between a defined MHP and lower mortality in

latest reported timepoint	Based on data from 993 participants in 5 studies	Difference: **85 fewer per 1000** (CI 95% 191 fewer - 60 more)	Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision	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	**12.2** Units (Mean) **12.6** Units (Mean) Difference: **SMD 0.04 more** (CI 95% 0.46 fewer - 0.54 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency	An MHP has little or no effect on volume of red blood cels transfused in patients with critical bleeding in the non-trauma setting, but the evidence is very uncertain.

MHP in critical bleeding (any setting: PICO)

Population: People with critical bleeding (any setting)

Intervention: Defined MHP

Comparator: No defined MHP

Table S3: MHP vs no MHP in any setting

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No defined MHP	Defined MHP	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint	Odds ratio: 0.71 (CI 95% 0.57 - 0.87) Based on data from 5419 participants in 27 studies	**392** per 1000	**314** per 1000 Difference: **78 fewer per 1000** (CI 95% 123 fewer - 33 fewer)	**Very low** Due to serious risk of bias, Due to serious inconsistency	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 2459 participants in 9 studies	**8-15**	**8-14** Difference: **SMD 0.09 fewer** (CI 95% 0.41 fewer - 0.23 more)	**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision	A defined MHP may reduce volume of FFP transfused but the evidence is very uncertain and MHPs can be overactivated leading to wastage.
Platelet transfusion volume	Measured by: Number of Units Lower better Based on data from 3715 participants in 15 studies	**1.7 -15**	**1.1-31** Difference: **SMD 0.54 more** (CI 95% 0.26 fewer - 1.33 more)	**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision	A defined MHP may increase the volume of platelets transfused but the evidence is very uncertain and MHPs can be overactivated leading to wastage.

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

Literature search date: 29 September 2021

Strong recommendation

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

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

*in addition to standard continuous physiological monitoring.

Evidence to decision

Benefits and harms

Identified cohort studies suggest there is an association between prognostic factors and higher 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 prognostic factors as recommended.

Resources No important issues with the recommended alternative

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

Equity No important issues with the recommended alternative

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

Acceptability No important issues with the recommended alternative

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

Feasibility No important issues with the recommended alternative

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

Rationale

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

Temperature and critical bleeding in any setting: PICO

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

Table S4: Temperature and outcomes

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** N/A Temperature	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint	Based on data from 707803 participants in 4 studies	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 2.82).	**Very low** Due to serious risk of bias	Hypothermia (< 35°C) is associated with higher mortality.

Transfusion volume	Based on data from 756 participants in 2 studies	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	Hypothermia (<35°C) is associated with higher volume of red blood cells transfused.

Acid-base status and critical bleeding in any setting: PICO

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

Table S5: Acid-base status and outcomes

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** N/A — Acid-base status	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint	Based on data from 41328 participants in 14 studies	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[1]	Higher lactate levels are associated with higher mortality.
Transfusion volume	Based on data from 1193 participants in 6 studies	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	Higher lactate levels are associated with higher volume of red blood cells transfused.

Calcium levels and critical bleeding in any setting: PICO

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

Table S6: Calcium and outcomes

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** N/A — Ionised calcium	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint	Based on data from 1373 participants in 4 studies	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, I2= 0%)	**Very low** Due to serious risk of bias, Due to serious imprecision	Hypocalcaemia (<1mmol/L ionised calcium) is associated with higher mortality.
Red blood cell transfusion volume	Based on data from 977 participants in 3 studies	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 (>	**Very low** Due to serious risk of bias, Due to serious imprecision	Hypocalcaemia (<1 mmol/L ionised calcium) is associated with higher volume of red blood cells transfused.

		5 or >10 units of red blood cells transfused).		
Transfusion volume, other blood products	Based on data from 160 participants in 1 studies	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	Hypocalcaemia (<1mmol/L ionised calcium) is associated with higher volume of blood products (red blood cells, plasma and cryoprecipitate) transfused.

Haemoglobin levels and critical bleeding in any setting: PICO

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

Table S7: Haemoglobin levels and outcomes

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** N/A Haemoglobin	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint		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 2349 participants in 5 studies	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	Lower haemoglobin levels are associated with increased volume of red blood cells transfused.

Platelet counts and critical bleeding in any setting: PICO

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

Table S8: Platelet count and outcomes

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** N/A Platelet count	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint	Based on data from 6762 participants in 5 studies	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	The association between platelet count and mortality is uncertain.

Transfusion volume	Based on data from 30735 participants in 7 studies	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	Lower platelet counts are associated with higher volume of red blood cells transfused.

INR/PT and critical bleeding in any setting: PICO

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

Table S9: INR/PT and outcomes

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** N/A PT/INR	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint	Based on data from 50466 participants in 7 studies	Seven studies reported an association between high PT/INR levels 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	Abnormal PT/INR (INR >1.2) is associated with higher mortality.
Transfusion volume	Based on data from participants in 3 studies	Studies found an association between high PT/INR levels 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	Abnormal PT/INR (>1.2) is associated with higher volume of red blood cells transfused.

APTT and critical bleeding in any setting: PICO

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

Table S10: aPTT and outcomes

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** N/A APTT	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint	Based on data from 9516 participants in 6 studies	Five studies reported an association between high APTT levels and mortality (4 studies reported OR range 1.01 and 4.26, one study reported no risk data).	**Very low** Due to serious risk of bias, Due to serious imprecision	Higher APTT levels are associated with higher mortality.
Transfusion volume	Based on data from participants in 2 studies	Studies reported an association between high APTT levels and the need for increased transfusion volume. No risk data reported.	**Very low** Due to serious risk of bias, Due to serious imprecision	Higher APTT levels are associated with higher volume of red blood cells transfused.

Fibrinogen count and critical bleeding in any setting: PICO

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

Table S11: Fibrinogen count and outcomes

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** N/A Fibrinogen levels	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint	Based on data from 9714 participants in 6 studies	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	Lower fibrinogen levels are associated with higher mortality.
Transfusion volume	Based on data from 625 participants in 5 studies	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	Lower fibrinogen levels are associated with higher volume of red blood cells transfused.

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 platelets.

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?

Literature search date: 29 September 2021

Weak recommendation

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

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

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

Evidence to decision

Benefits and harms	Small net benefit, or little difference between alternatives

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

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

Certainty of the Evidence	Very low

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

Values and preferences	No substantial variability expected

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

Resources	Important issues, or potential issues not investigated

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

Equity	Important issues, or potential issues not investigated

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

Acceptability	No important issues with the recommended alternative

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

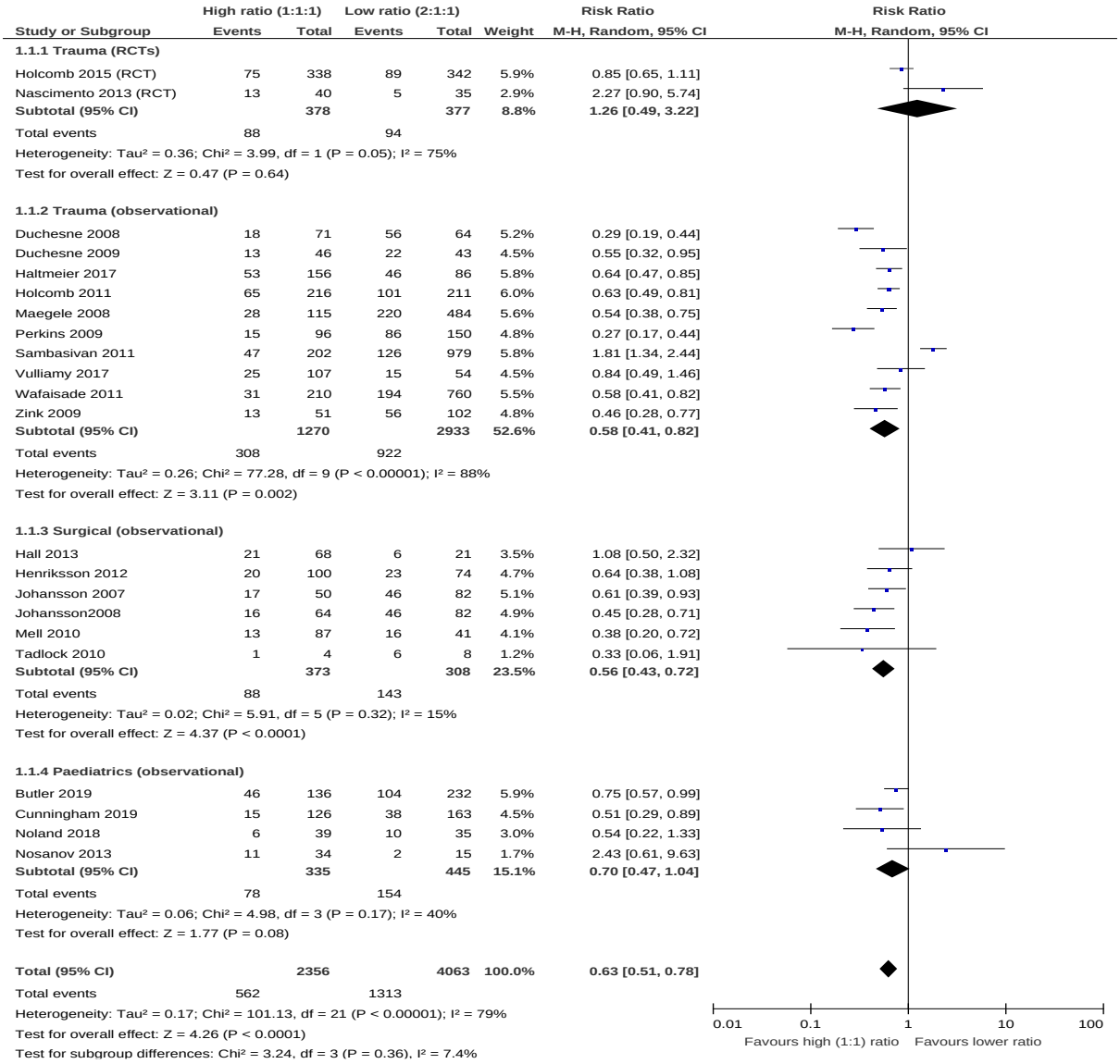
Feasibility	Important issues, or potential issues not investigated

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

Rationale

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

Figure S2: Forest plot of comparison: high ratio vs low ratio blood components on mortality at latest timepoint



Ratio of blood components in trauma: PICO

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

Table S12: Ratio of blood components and outcomes in trauma setting

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Lower ratios of blood components	High ratio (1:1:1) of blood components		
Mortality, all cause (RCTs) latest reported timepoint	Relative risk: 1.26 (CI 95% 0.49 - 3.22) Based on data from 755 participants in 2 studies	**249** per 1000	**314** per 1000 Difference: **65 more per 1000** (CI 95% 127 fewer - 553 more)	**Very low** Due to very serious inconsistency, Due to very serious imprecision	High (1:1:1) RBC:FFP:PLT ratio may result in little or no difference in mortality in trauma patients with critical bleeding but we are very uncertain about the evidence.
Mortality, all cause (Coh) latest reported timepoint	Odds ratio: 0.38 (CI 95% 0.22 - 0.69) Based on data from 4203 participants in 10 studies	**314** per 1000	**148** per 1000 Difference: **166 fewer per 1000** (CI 95% 223 fewer - 74 fewer)	**Very low** Due to serious risk of bias, Due to very serious inconsistency	High (1:1:1) RBC:FFP:PLT ratio may reduce mortality in trauma patients with critical bleeding but we are very uncertain about the evidence.
Morbidity, thromboembolic events	Relative risk: 1.07 (CI 95% 0.7 - 1.63) Based on data from 680 participants in 1 studies	**108** per 1000	**116** per 1000 Difference: **8 more per 1000** (CI 95% 32 fewer - 68 more)	**Low** Due to very serious imprecision	High (1:1:1) RBC:FFP:PLT ratio may have little or no difference on thromboembolic events in trauma patients with critical bleeding.
Morbidity, MOF	Relative risk: 1.39 (CI 95% 0.74 - 2.64) Based on data from 749 participants in 2 studies	**40** per 1000	**56** per 1000 Difference: **16 more per 1000** (CI 95% 10 fewer - 66 more)	**Low** Due to very serious imprecision	High (1:1:1) RBC:FFP:PLT ratio 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	9-10.3	7.7-9.7 Difference: **SMD 0.1 lower** (CI 95% 0.24 lower - 0.05 higher)	**Low** Due to serious imprecision	High (1:1:1) RBC:FFP:PLT ratio may slightly reduce red blood cell transfusion volume in trauma patients with critical bleeding.
Transfusion volume, other blood products	Measured by: Number of Units of FFP transfused Lower better Based on data from 749 participants in 2 studies	5-5.7	6-7.7 Difference: **SMD 0.3 higher** (CI 95% 0.15 higher - 0.44 higher)	**Low** Due to serious imprecision	High (1:1:1) RBC:FFP:PLT ratio may slightly increase the volume of FFP transfused in trauma patients with critical bleeding. The effect on other blood products is unclear.

Ratio of blood components in surgical setting: PICO

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

Table S13: Ratio of blood components and outcomes in surgical setting

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

Red cell transfusion volumes and outcomes: PICO

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

Table S14: Blood volumes and outcomes

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Normal RBC transfusion volumes	Increased RBC transfusion volumes		
Mortality, all cause (Coh) latest reported timepoint	Based on data from 18009 participants in 9 studies[1]	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	Each additional red blood cell unit transfused is associated with higher mortality.
Morbidity, MOF (Coh) Any timepoint	Based on data from 3050 participants in 3 studies	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	Each additional red blood cell unit transfused is associated with higher risk of MOF.
Morbidity, ARDS (Coh) Any timepoint	Based on data from 14136 participants in 2 studies	The odds of ARDS or acute lung injury 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	Each additional red blood cell unit transfused is associated with higher risk of ARDS or acute lung injury.

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

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

- FFP: a minimum 1 unit for every 2 units of red blood cells
- Platelets * *: a minimum of 1 adult unit for 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, 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 for patients who are critically bleeding.

Certainty of the Evidence	Very low

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

Values and preferences	No substantial variability expected

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

Resources	Important issues, or potential issues not investigated

In the absence of high certainty evidence, the effect of blood components on resources (transfusion volume, 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.

Acceptability	Important issues, or potential issues not investigated

Feasibility	Important issues, or potential issues not investigated

The reference group acknowledged the logistical challenges associated with providing blood components to treat 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.

Figure S3: Forest plot of comparison: FFP vs no FFP on mortality at latest reported timepoint

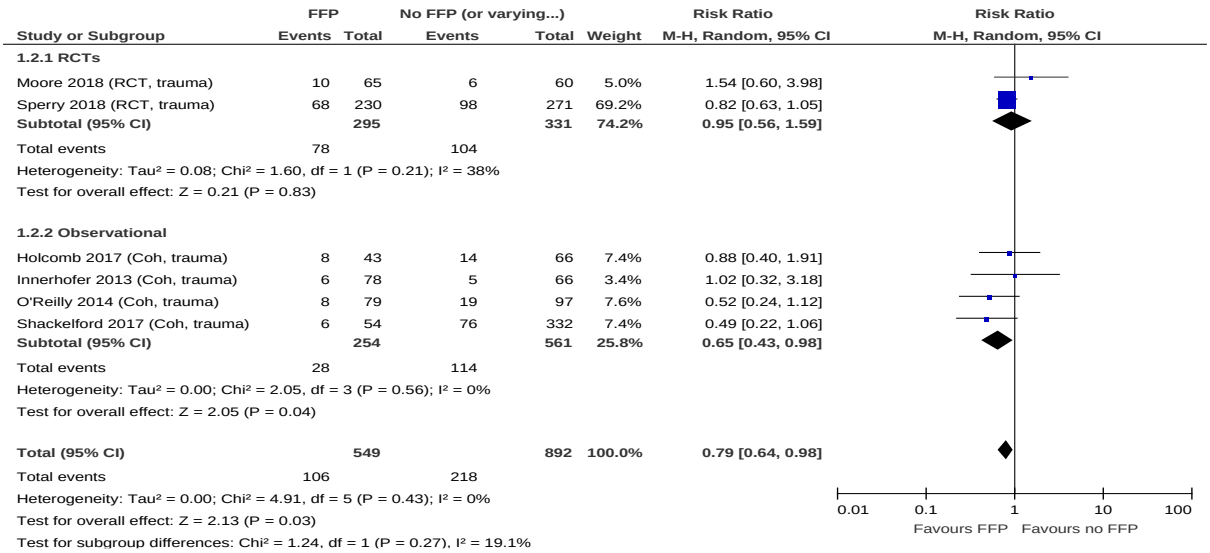
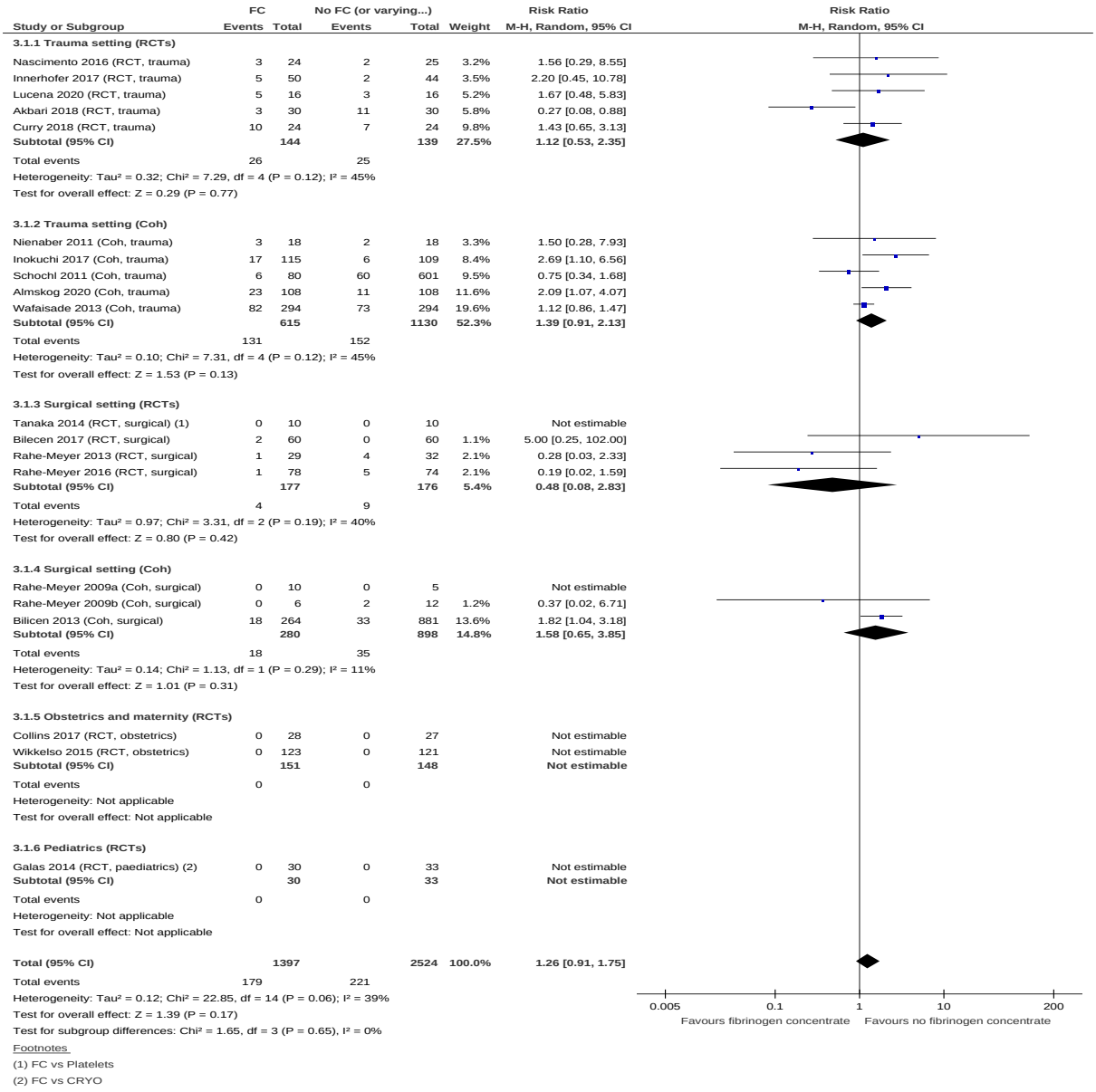


Figure S4: Forest plot of comparison: Fibrinogen concentrate vs no fibrinogen concentrate (or varying administration of) on mortality at latest reported timepoint)



FFP and outcomes: PICO

Population: People with critical bleeding (trauma setting)

Intervention: FFP

Comparator: No FFP (or varying administration of)

Table S15: FFP and outcomes

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		No FFP (or varying administration of)	FFP (or varying administration of)		

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	**314** per 1000 **298** per 1000 Difference: **16 fewer per 1000** (CI 95% 138 fewer - 185 more)	**Low** Due to serious inconsistency, Due to serious imprecision	The evidence suggests FFP may have little or no effect on 30-day mortality in trauma patients with critical bleeding.
Mortality, all cause (Coh) latest reported timepoint	Relative risk: 0.65 (CI 95% 0.43 - 0.98) Based on data from 815 participants in 4 studies	**203** per 1000 **132** per 1000 Difference: **71 fewer per 1000** (CI 95% 116 fewer - 4 fewer)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision	FFP appears to reduce 30-day mortality in trauma patients with critical bleeding, but the evidence is very uncertain.
Morbidity, thromboembolic events	Relative risk: 0.85 (CI 95% 0.29 - 2.5) Based on data from 144 participants in 1 studies	**91** per 1000 **77** per 1000 Difference: **14 fewer per 1000** (CI 95% 65 fewer - 137 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision	The evidence is very uncertain about the effect of FFP on thromboembolic events in trauma patients with critical bleeding.
Morbidity, MOF	Relative risk: 1.76 (CI 95% 0.4 - 7.68) Based on data from 626 participants in 2 studies	**476** per 1000 **838** per 1000 Difference: **362 more per 1000** (CI 95% 286 fewer - 3180 more)	**Low** Due to serious inconsistency, Due to serious imprecision	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	The median (IQR) volume of red blood cells transfused (units to 24 hours) among patients who received FFP was 7 (4, 11) compared with a median volume of 2 (0, 6) among those who did not receive FFP (P = 0.001).	**Very low** Due to serious risk of bias, Due to serious imprecision	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 products	Based on data from 144 participants in 1 studies	The median (IQR) volume of platelets transfused (units to 24 hours) was higher among patients who received FFP compared with those who did not receive FFP (P = 0.003). There was no significant difference between treatment groups for the volume of fibrinogen concentrate or prothrombin complex transfused (units to 24 hours).	**Very low** Due to serious risk of bias, Due to very serious imprecision	The evidence is very uncertain about the effect of FFP on the volume of platelets, fibrinogen concentrate or prothrombin complex transfused in trauma patients with critical bleeding.
LOS, hospital or ICU Days	Based on data from 144 participants in 1 studies	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	The evidence is very uncertain about the effect of FFP on hospital or ICU LOS in trauma patients with critical bleeding.

Cryoprecipitate and outcomes: PICO

Population: People with critical bleeding (trauma setting)

Intervention: Cryoprecipitate

Comparator: No cryoprecipitate (or varying administration of)

Figure S5: Forest plot of comparison: CRYO vs no CRYO on mortality at latest timepoint.

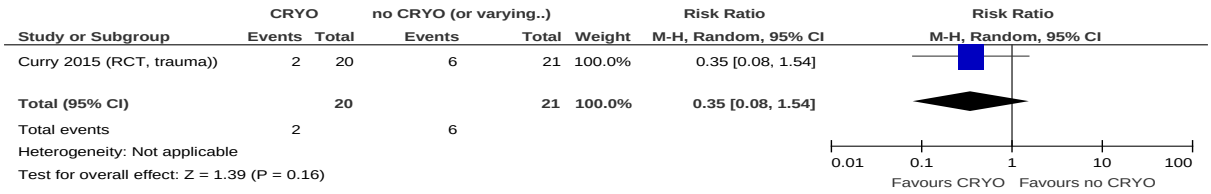


Table S16: Cryoprecipitate and outcomes

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** No cryoprecipitate (or varying administration of)	**Absolute effect estimates** Cryoprecipitate	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (RCTs) latest reported timepoint	Relative risk: 0.35 (CI 95% 0.08 - 1.54) Based on data from 41 participants in 1 studies	**286** per 1000	**100** per 1000 Difference: **186 fewer per 1000** (CI 95% 263 fewer - 154 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision	Cryoprecipitate may have little or no effect on mortality in trauma patients with critical bleeding, but the evidence is very uncertain.
Morbidity, thromboembolic events	Relative risk: 0.35 (CI 95% 0.02 - 8.1) Based on data from 41 participants in 1 studies	**95** per 1000	**33** per 1000 Difference: **62 fewer per 1000** (CI 95% 93 fewer - 675 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision	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	Relative risk: 3.14 (CI 95% 0.14 - 72.92) Based on data from 41 participants in 1 studies	**0** per 1000	**0** per 1000 Difference: **0 fewer per 1000** (CI 95% 0 fewer - 0 fewer)	**Very low** Due to serious risk of bias, Due to very serious imprecision	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	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	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 products	Based on data from 41 participants in 1 studies	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	We are very uncertain about the effect of cryoprecipitate on the volume of FFP, platelets or cryoprecipitate transfused in trauma patients with critical bleeding.
LOS, hospital or ICU	Based on data from 41 participants in 1 studies	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	We are very uncertain about the effect of cryoprecipitate on hospital or ICU LOS in trauma patients with critical bleeding.

Fibrinogen concentrate and outcomes in trauma setting: PICO

Population: People with critical bleeding (trauma setting)

Intervention: Fibrinogen concentrate

Comparator: No Fibrinogen concentrate (or varying administration of)

Table S17: Fibrinogen concentrate and outcomes in trauma setting

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		No fibrinogen concentrate (or varying administration of)	Fibrinogen concentrate		
Mortality, all cause (RCTs) latest reported timepoint	Relative risk: 1.12 (CI 95% 0.53 - 2.35) Based on data from 283 participants in 5 studies	**180** per 1000	**202** per 1000 Difference: **22 more per 1000** (CI 95% 85 fewer - 243 more)	**Very low** Due to serious indirectness, Due to very serious imprecision	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	Relative risk: 1.39 (CI 95% 0.91 - 2.13) Based on data from 1745 participants in 5 studies	**135** per 1000	**188** per 1000 Difference: **53 more per 1000** (CI 95% 12 fewer - 153 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision	The evidence is very uncertain about the effect of fibrinogen concentrate on mortality in trauma patients with critical bleeding.
Morbidity, thromboembolic events (RCTs)	Relative risk: 0.9 (CI 95% 0.42 - 1.91) Based on data from 210 participants in 4 studies	**117** per 1000	**105** per 1000 Difference: **12 fewer per 1000** (CI 95% 68 fewer - 106 more)	**Low** Due to very serious imprecision	The evidence suggests that fibrinogen concentrate may have little or no difference on thromboembolic events in trauma patients with critical bleeding.
Morbidity, MOF (RCTs)	Relative risk: 0.74 (CI 95% 0.53 - 1.03) Based on data from 195 participants in 3 studies	**388** per 1000	**287** per 1000 Difference: **101 fewer per 1000**	**Low** Due to very serious imprecision	The evidence suggests that fibrinogen concentrate may have little or no

		(CI 95% 182 fewer - 12 more)		difference on MOF in trauma patients with critical bleeding.
Red blood cell transfusion volume Units	Based on data from 1574 participants in 5 studies	No significant difference observed for volume of red blood cells transfused among 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).	**Very low** Due to serious risk of bias, Due to serious imprecision	The evidence is very uncertain about the association of fibrinogen concentrate on the volume of red blood cells transfused in trauma patients with critical bleeding.
Transfusion volume, other blood products Units	Based on data from 1574 participants in 5 studies	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 (fibrinogen concentrate).	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision, Due to serious publication bias	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 1491 participants in 7 studies	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	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 1647 participants in 6 studies	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	Fibrinogen concentrate may have little or no difference on ICU LOS in the trauma setting but the evidence is very uncertain.

Fibrinogen concentrate and outcomes in surgical setting: PICO

Population: People with critical bleeding (surgical setting)

Intervention: Fibrinogen concentrate

Comparator: Fibrinogen concentrate (or varying administration of)

Table S18: Fibrinogen concentrate and outcomes in surgical setting

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		No Fibrinogen concentrate (or varying administration of)	Fibrinogen concentrate		
Mortality, all cause (RCTs) latest reported timepoint	Relative risk: 0.48 (CI 95% 0.08 - 2.83) Based on data from 353 participants in 4 studies	**51** per 1000	**24** per 1000	**Low** Due to very serious imprecision	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.
		Difference: **27 fewer per 1000** (CI 95% 47 fewer - 93 more)			

Mortality, all cause (Coh) latest reported timepoint	Relative risk: 1.58 (CI 95% 0.65 - 3.85) Based on data from 1178 participants in 3 studies	**39** per 1000 **62** per 1000 Difference: **23 more per 1000** (CI 95% 14 fewer - 111 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision	The evidence is very uncertain about the effect of fibrinogen concentrate on mortality in patients with critical bleeding in the surgical setting.
Morbidity, thromboembolic events (RCTs)	Relative risk: 2.03 (CI 95% 0.63 - 6.58) Based on data from 201 participants in 3 studies	**39** per 1000 **79** per 1000 Difference: **40 more per 1000** (CI 95% 14 fewer - 218 more)	**Low** Due to very serious imprecision	There were too few who experienced the outcome to determine whether fibrinogen concentrate made a difference on thromboembolic events in patients with critical bleeding in the surgical setting.
Transfusion volume, other blood products Units	Based on data from 33 participants in 2 studies	Two studies found a significant reduction in the volume of FFP transfused among patients who received 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	There were too few who experienced the outcome to determine whether fibrinogen concentrate made a difference on the volume of FFP transfused in patients with critical bleeding in the surgical setting.
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	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.
LOS, ICU	Based on data from 18 participants in 1 studies	One small cohort study suggested fibrinogen concentrate is associated with a reduction in the LOS 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	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.

Prothrombin complex concentrates and outcomes in trauma: PICO

Population: People with critical bleeding (trauma setting)

Intervention: Prothrombin complex

Comparator: No Prothrombin complex (or varying administration of)

Figure S6: Forest plot of comparison: PCC vs no PCC on mortality (trauma setting)

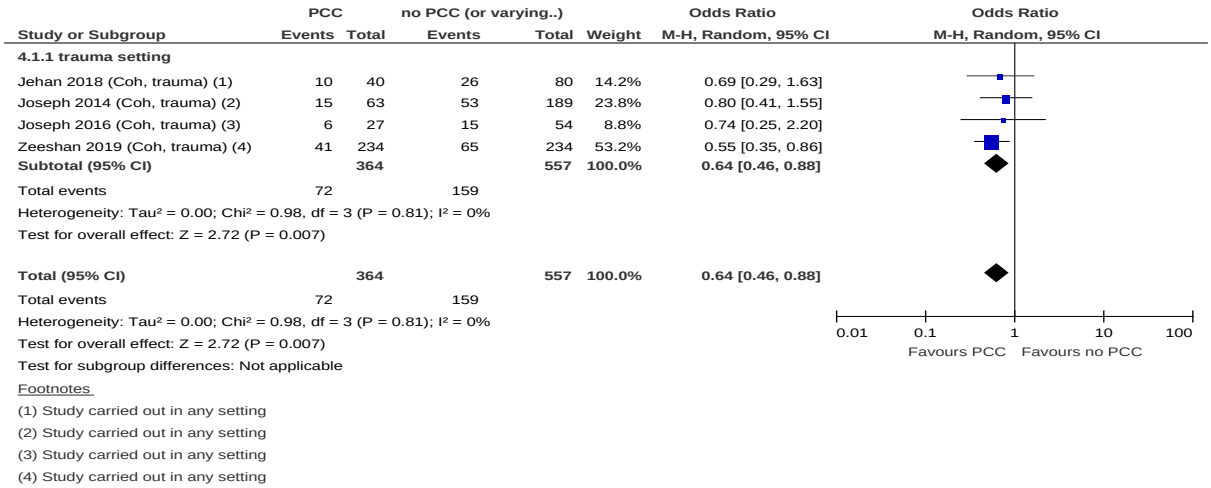


Table S19: Fibrinogen concentrate and outcomes in trauma setting

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

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.

Weak recommendation against

R5: The reference group suggest against the routine use of recombinant activated factor VII in patients with critical bleeding*.

* Recombinant activated factor VII is approved in Australia and New Zealand for the control of bleeding and prophylaxis for surgery in patients with specific bleeding disorders. 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 placebo-controlled trials 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.

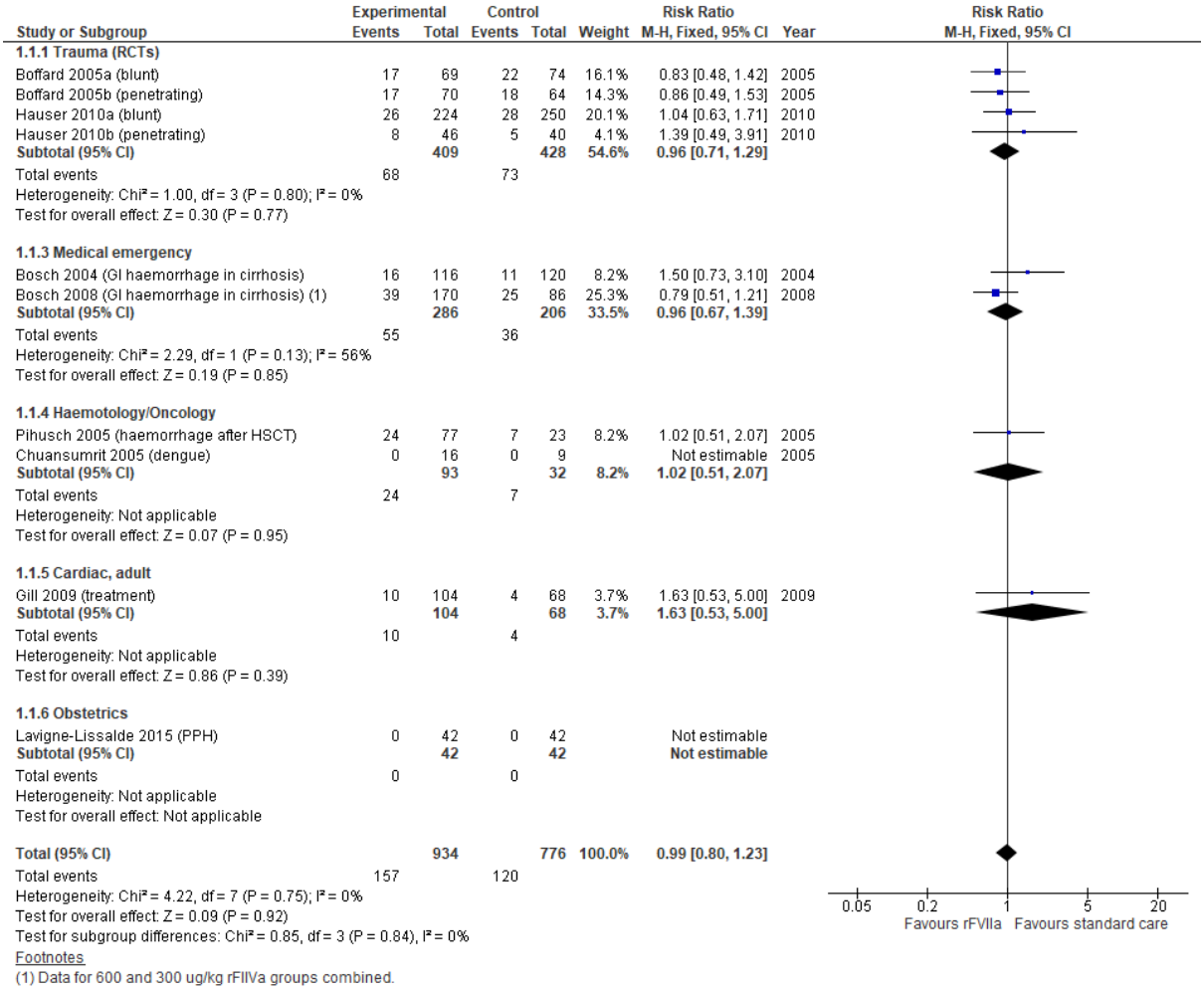
Feasibility	No important issues with the recommended alternative

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.

Figure S7: Forest plot of comparison: rFVIIa vs placebo, outcome: Mortality, latest timepoint



Recombinant activated factor VII and outcomes in trauma: 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

Table S20: Activated factor VIIa and outcomes in trauma setting

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		standard best practice without recombinant activated factor VII	recombinant activated factor VII		
Mortality, all cause latest reported timepoint	Relative risk: 0.96 (CI 95% 0.71 - 1.29) Based on data from 837 participants in 3 studies	**171** per 1000	**164** per 1000 Difference: **7 fewer per 1000** (CI 95% 50 fewer - 50 more)	**Low** Due to serious risk of bias, Due to serious imprecision	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, thromboembolic events	Relative risk: 1.1 (CI 95% 0.74 - 1.63) Based on data from 837 participants in 3 studies	**100** per 1000 **110** per 1000 Difference: **10 more per 1000** (CI 95% 26 fewer - 63 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to serious imprecision	The use of recombinant activated factor VII in patients with critical bleeding due to blunt or penetrating trauma may have little or no difference on thromboembolic events compared with placebo but we are very uncertain about the evidence.
Morbidity, ARDS	Relative risk: 0.39 (CI 95% 0.22 - 0.71) Based on data from 837 participants in 3 studies	**89** per 1000 **35** per 1000 Difference: **54 fewer per 1000** (CI 95% 69 fewer - 26 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision	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	Relative risk: 0.56 (CI 95% 0.32 - 0.97) Based on data from 837 participants in 3 studies	**79** per 1000 **44** per 1000 Difference: **35 fewer per 1000** (CI 95% 54 fewer - 2 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision	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, units up to 48 hours	Measured by: Number of Units Lower better Based on data from 713 participants in 3 studies	**6.8-10.9** **4.5-7.8** Difference: **MD 2.35 fewer** (CI 95% 3.70 fewer - 1.0 fewer)	**Very low** Due to very serious risk of bias, Due to serious imprecision	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 products	Based on data from 410 participants in 1 studies	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	Recombinant activated factor VII may slightly reduce the volume of FFP transfused, but not platelets, fibrinogen concentrate or cryoprecipitate, in patients with critical bleeding due to blunt or penetrating trauma, but we are very uncertain about the evidence.

Recombinant activated factor VII and outcomes in medical emergencies: 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

Table S21: Activated factor VIIa and outcomes in medical emergency setting

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		standard best practice without recombinant activated factor VII	recombinant activated factor VII		
Mortality, all cause latest reported timepoint	Relative risk: 1.02 (CI 95% 0.55 - 1.9) Based on data from 492 participants in 2 studies	**175** per 1000	**179** per 1000 Difference: **4 more per 1000** (CI 95% 79 fewer - 158 more)	**Very low** Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision	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, thromboembolic events	Relative risk: 0.8 (CI 95% 0.4 - 1.6) Based on data from 507 participants in 2 studies	**67** per 1000	**54** per 1000 Difference: **13 fewer per 1000** (CI 95% 40 fewer - 40 more)	**Low** Due to serious indirectness, Due to serious imprecision	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	**1.3-3.3**	**1.5-2.55** Difference: **MD 0.24 fewer** (CI 95% 1.17 fewer - 0.69 more)	**Very low** Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision	Recombinant activated factor VII may have little to no effect on the volume of red blood cells transfused in patients with severe gastrointestinal bleeding, but we are very uncertain about the evidence.

Recombinant activated factor VII and outcomes in haematology oncology emergencies: 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

Table S22: Activated factor VIIa and outcomes in haematology/oncology setting

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		standard best practice without recombinant activated factor VII	recombinant activated factor VII		
Mortality, all cause latest reported timepoint	Relative risk: 1.02 (CI 95% 0.51 - 2.07) Based on data from 125 participants in 2 studies	**219** per 1000	**223** per 1000 Difference: **4 more per 1000** (CI 95% 107 fewer - 234 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious indirectness	The use of recombinant activated factor VII in patients with critical bleeding after HSCT may result in little or no difference in mortality but we are very uncertain about the evidence.
Morbidity, thromboembolic events	Relative risk: 5.23 (CI 95% 0.31 - 87.34) Based on data from 125 participants in 2 studies	**0** per 1000	**0** per 1000 Difference: **0 fewer per 1000** (CI 95% 0 fewer - 0 fewer)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision	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.

Recombinant activated factor VII and outcomes in cardiac emergencies: 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

Table S23: Activated factor VIIa and outcomes in cardiac surgery setting

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		standard best practice without recombinant activated factor VII	recombinant activated factor VII		
Mortality, all cause	Relative risk: 1.63 (CI 95% 0.53 - 5.0)	**59** per 1000	**96** per 1000	**Low** Due to very serious imprecision	The evidence suggests that the use

latest reported timepoint	Based on data from 172 participants in 1 studies	Difference: **37 more per 1000** (CI 95% 28 fewer - 236 more)		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, thromboembolic 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 Difference: **54 more per 1000** (CI 95% 6 fewer - 531 more)	**Low** Due to very serious imprecision	The evidence suggests recombinant activated factor VII results in a slight increase in 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.

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

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*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

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

Evidence to decision

Benefits and harms	Small net benefit, or little difference between alternatives

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

Certainty of the Evidence	Very low

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

Values and preferences	No substantial variability expected

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

Resources	No important issues with the recommended alternative

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

Equity	No important issues with the recommended alternative

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

Acceptability	No important issues with the recommended alternative

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

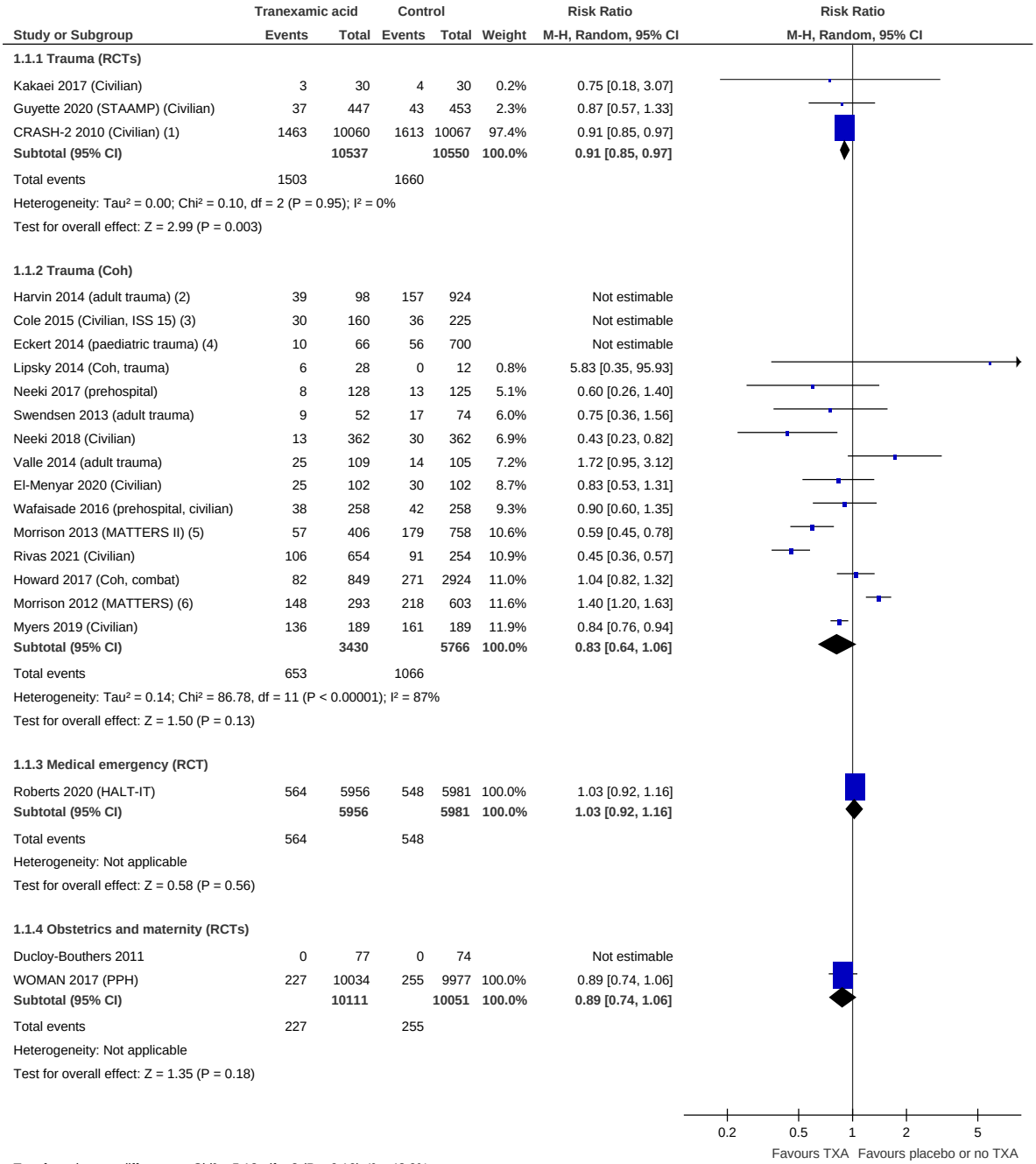
Feasibility	No important issues with the recommended alternative

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

Rationale

The CRASH-2 trial supported the use of tranexamic acid in trauma patients, however the evidence is not directly generalisable to the Australian and New Zealand settings where there are advanced trauma centres. The results of the PATCH-Trauma Study were not included in the evidence base as it was completed after the literature search cut-off date.

Figure S8: Forest plot of comparison: TXA vs no TXA, outcome: Mortality, latest timepoint



Test for subgroup differences: Chi² = 5.18, df = 3 (P = 0.16), I² = 42.0%

Footnotes

(1) within 4 weeks of injury

(2) in-hospital; non significant effect after adjustment for confounders (OR 0.74, 95% CI 0.380, 1.403; p=0.801).

(3) not adjusted for confounders

(4) Effect favouring TXA observed after adjusting for confounders (OR 0.27; 95% CI 0.85, 0.89; p=0.03)

(5) within 48 hours of injury

(6) within 48 hours of injury

Antifibrinolytics and outcomes in trauma setting: PICO

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

Table S24: Antifibrinolytics in trauma setting

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Placebo or no antifibrinolytics	Antifibrinolytics		
Mortality, all cause (RCTs) latest reported timepoint	Relative risk: 0.91 (CI 95% 0.85 - 0.97) Based on data from 21087 participants in 3 studies	**157** per 1000	**143** per 1000 Difference: **14 fewer per 1000** (CI 95% 24 fewer - 5 fewer)	**Low** Due to very serious indirectness	The evidence suggests antifibrinolytics may slightly reduce mortality in trauma patients with critical bleeding.
Mortality, all cause (Coh) latest reported timepoint	Relative risk: 0.97 (CI 95% 0.75 - 1.25) Based on data from 11369 participants in 15 studies	**144** per 1000	**140** per 1000 Difference: **4 fewer per 1000** (CI 95% 36 fewer - 36 more)	**Very low** Due to very serious risk of bias, Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision	We are very uncertain about the association of antifibrinolytics on all-cause mortality in trauma patients with critical bleeding.
Morbidity, thromboembolic event (RCTs)	Relative risk: 0.84 (CI 95% 0.68 - 1.02) Based on data from 20127 participants in 1 studies[7]	**20** per 1000	**17** per 1000 Difference: **3 fewer per 1000** (CI 95% 6 fewer - 0 fewer)	**Very low** Due to very serious indirectness, Due to serious imprecision	Antifibrinolytics appear to have little to no effect on vascular thromboembolic events, but we are very uncertain about the evidence.
Morbidity, thromboembolic events (Coh)	Relative risk: 1.63 (CI 95% 1.17 - 2.29) Based on data from 4958 participants in 10 studies	**39** per 1000	**64** per 1000 Difference: **25 more per 1000** (CI 95% 7 more - 50 more)	**Very low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision, Due to serious inconsistency	We are very uncertain about the association of antifibrinolytics on thromboembolic events in trauma patients with critical bleeding.
Red blood cell transfusion volume (RCTs)	Measured by: Number of Units Lower better Based on data from 10227 participants in 1 studies	**6.29** Units (Mean)	**6.06** Units (Mean) Difference: **SMD 0.02 fewer** (CI 95% 0.06 fewer - 0.02 more)	**Low** Due to very serious indirectness	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 2095 participants in 4 studies	**2-20.1**	**4.43 - 22** Difference: **SMD 0.53 more** (CI 95% 0.22 more - 0.85 more)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious indirectness, Due to serious imprecision	We are very uncertain about the association of antifibrinolytics with the volume of red blood cells transfused in trauma patients with critical bleeding.

Antifibrinolytics and outcomes in medical emergency settings: PICO

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

Table S25: Antifibrinolytics in medical emergency

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Placebo or no antifibrinolytics	**Absolute effect estimates** Antifibrinolytics	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause latest reported timepoint	Relative risk: 1.03 (CI 95% 0.92 - 1.16) Based on data from 11937 participants in 1 studies Follow up discharge up to 28-days	**92** per 1000	**95** per 1000 Difference: **3 more per 1000** (CI 95% 7 fewer - 15 more)	**Low** Due to very serious indirectness	The evidence suggests that antifibrinolytics may have no difference on all-cause mortality in patients with severe gastrointestinal bleeding.
Morbidity, thromboembolic events (venous)	Relative risk: 1.85 (CI 95% 1.15 - 2.98) Based on data from 11929 participants in 1 studies Follow up discharge up to 28-days	**4** per 1000	**7** per 1000 Difference: **3 more per 1000** (CI 95% 1 more - 8 more)	**Low** Due to very serious indirectness	Antifibrinolytics may increase the risk of thromboembolic events (vascular) in patients with severe gastrointestinal bleeding.
Morbidity, thromboembolic events (arterial)	Relative risk: 0.92 (CI 95% 0.6 - 1.39) Based on data from 11929 participants in 1 studies Follow up discharge up to 28-days	**8** per 1000	**7** per 1000 Difference: **1 fewer per 1000** (CI 95% 3 fewer - 3 more)	**Low** Due to very serious indirectness	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 8205 participants in 1 studies Follow up discharge up to 28-days	**2.9** Units (Mean)	**2.8** Units (Mean) Difference: **MD 0.06 fewer** (CI 95% 0.05 more - 0.18 fewer)	**Low** Due to very serious indirectness	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 8205 participants in 1 studies Follow up discharge up to 28-days	**1.0** Units (Mean)	**0.9** Units (Mean) Difference: **MD 0.05 fewer** (CI 95% 0.01 fewer - 0.23 fewer)	**Low** Due to very serious indirectness	Antifibrinolytics may have little or no difference on the volume of FFP transfused in patients with severe gastrointestinal bleeding.

Weak recommendation

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

Evidence to decision

Benefits and harms	Small net benefit, or little difference between alternatives

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

Certainty of the Evidence	Very low

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

Values and preferences	No substantial variability expected

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

Resources	No important issues with the recommended alternative

Equity	No important issues with the recommended alternative

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

Acceptability	No important issues with the recommended alternative

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

Feasibility	No important issues with the recommended alternative

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

Rationale

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

Antifibrinolytics and outcomes in obstetric emergencies: PICO

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

Table S26: Antifibrinolytics obstetric emergency

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		Placebo or no antifibrinolytics	Antifibrinolytics		
Mortality, all cause latest reported timepoint	Relative risk: 0.89 (CI 95% 0.74 - 1.06) Based on data from 20011 participants in 2 studies	**25** per 1000	**22** per 1000 Difference: **3 fewer per 1000** (CI 95% 6 fewer - 2 more)	**Low** Due to very serious indirectness	The evidence suggests that antifibrinolytics may have no difference on all-cause mortality in women with major obstetric haemorrhage
Morbidity, thromboembolic events	Relative risk: 0.91 (CI 95% 0.56 - 1.47) Based on data from 20011 participants in 1 study	**3** per 1000	**3** per 1000 Difference: **0 fewer per 1000** (CI 95% 1 fewer - 1 more)	**Very low** Due to very serious indirectness, Due to serious imprecision	Antifibrinolytics may have little or no effect on thromboembolic events in women with major obstetric haemorrhage, but the evidence is very uncertain.
Morbidity, MOF	Relative risk: 0.94 (CI 95% 0.71 - 1.23) Based on data from 20168 participants in 2 studies	**10** per 1000	**9** per 1000 Difference: **1 fewer per 1000** (CI 95% 3 fewer - 2 more)	**Very low** Due to very serious indirectness, Due to serious imprecision	Antifibrinolytics may have little or no effect on MOF in women with major obstetric haemorrhage, but the evidence is very uncertain.
Morbidity, respiratory failure	Relative risk: 0.87 (CI 95% 0.67 - 1.12) Based on data from 20018 participants in 1 study	**12** per 1000	**10** per 1000 Difference: **2 fewer per 1000** (CI 95% 4 fewer - 1 more)	**Very low** Due to very serious indirectness, Due to serious imprecision	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	Relative risk: 1.09 (CI 95% 0.85 - 1.39) Based on data from 20169 participants in 2 studies	**12** per 1000	**13** per 1000 Difference: **1 more per 1000** (CI 95% 2 fewer - 5 more)	**Very low** Due to very serious indirectness, Due to serious imprecision	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 20060 participants in 1 study	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	Antifibrinolytics may have little or no effect on the volume of RBCs transfused in women with major obstetric haemorrhage, but

				the evidence is very uncertain.

Research question: In patients with critical bleeding, does the use of VHAs change patient outcomes?

Latest search date: 29 September 2021

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 a reduction in mortality was demonstrated. However, the certainty of the evidence for the trials was very low. Based on the available evidence the true benefit is unknown.

Certainty of the Evidence	Very low

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

Values and preferences	No substantial variability expected

There is no plausible reason to suspect that patients who are critically bleeding would not accept VHAs as part of an MHP as recommended in this guideline.

Resources	Important negative issues

The reference group acknowledged there are significant additional resources associated with the implementation and use of VHAs as part of an MHP.

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.

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.

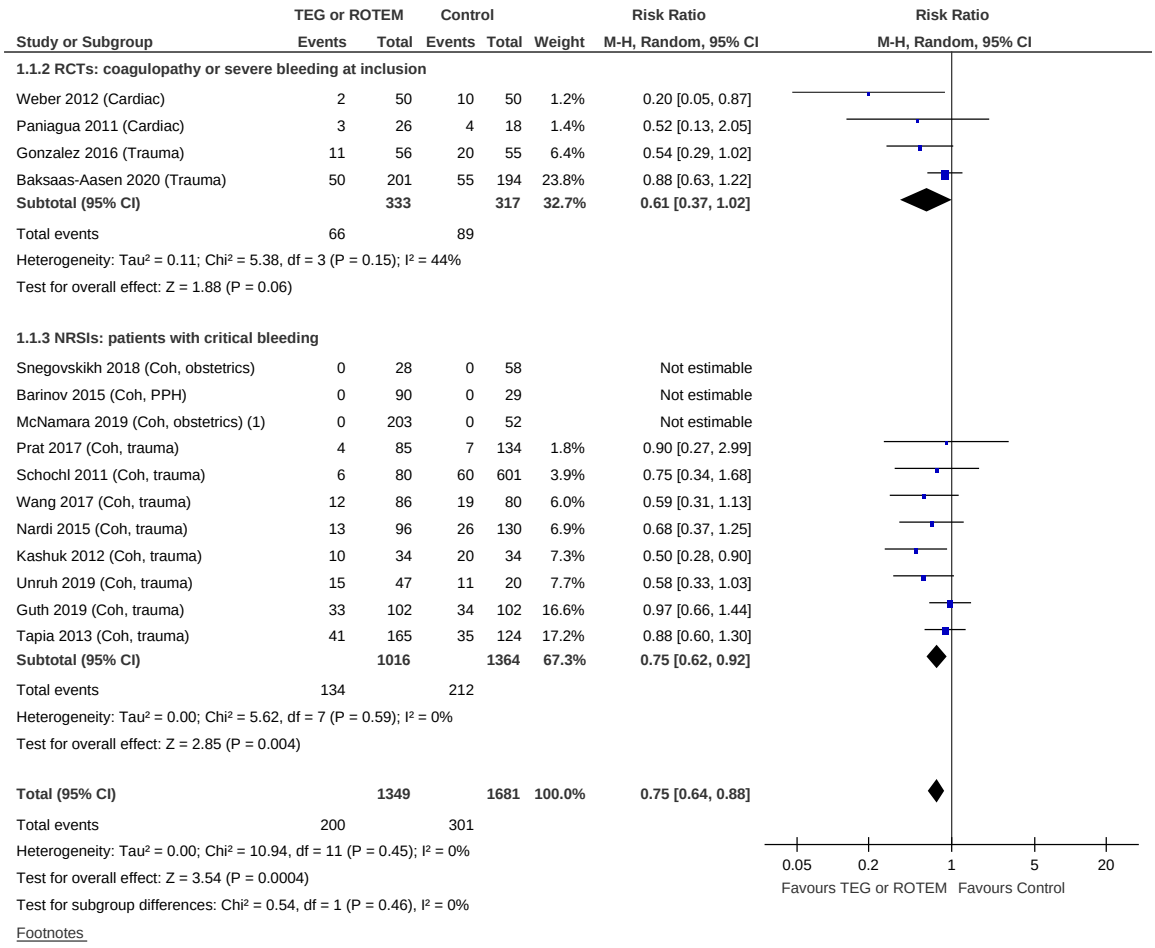
Implementation

Expertise is required to undertake and interpret the test.

Research needs

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

Figure S9: Forest plot of comparison: TEG or ROTEM vs MHP or standard laboratory testson mortality at latest timepoint



Footnotes

(1) women with major obstetric haemorrhage (estimated blood loss > 1500 mL) and coagulopathy

VHA and outcomes in any setting: PICO

Population: People with critical bleeding (any setting)

Intervention: VHA

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

Table S27: VHA guided resuscitation and outcomes

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		standard best practice care	VHA		
Mortality, all cause (RCTs)[1] latest reported timepoint	Relative risk: 0.61 (CI 95% 0.37 - 1.02) Based on data from 650 participants in 4 studies	**281** per 1000	**171** per 1000	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision	The use of TEG or ROTEM to guide blood component therapy may reduce mortality in patients with critical bleeding (any setting) but the evidence is very uncertain.
		Difference: **110 fewer per 1000** (CI 95% 177 fewer - 6 more)			

Mortality, all cause (Coh) latest reported timepoint	Relative risk: 0.75 (CI 95% 0.62 - 0.92) Based on data from 2175 participants in 9 studies	**166** per 1000 **125** per 1000 Difference: **41 fewer per 1000** (CI 95% 63 fewer - 13 fewer)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision	The use of TEG or ROTEM to guide blood component therapy may be associated with reduced mortality in patients with critical bleeding (any setting) but the evidence is very uncertain.
Morbidity, thromboembolic events	Relative risk: 0.83 (CI 95% 0.41 - 1.66) Based on data from 651 participants in 4 studies	**91** per 1000 **76** per 1000 Difference: **15 fewer per 1000** (CI 95% 54 fewer - 60 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias	The use of TEG or ROTEM to guide blood component therapy may have no difference on thromboembolic events in patients with critical bleeding (any setting) but the evidence is very uncertain.
Red blood cell transfusion volume (RCTs)	Measured by: Number of Units Lower better Based on data from 153 participants in 2 studies	**6.42-15.65** **7.1-13.96** Difference: **SMD 0.06 fewer** (CI 95% 0.38 fewer - 0.26 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias	The evidence suggests use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding (any setting) may have little or no difference in the volume of red blood cells transfused.
Red blood cells transfusion volume (Coh)	Measured by: Number of Units Lower better Based on data from 1605 participants in 7 studies	**2-11** **2-6.5** Difference: **SMD 0.46 fewer** (CI 95% 0.72 fewer - 0.20 fewer)	**Very low** Due to serious risk of bias, Due to serious inconsistency	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding (any setting) may be associated with a slight reduction in the volume of red blood cells transfused but the evidence is very uncertain.
Transfusion volume, other blood components		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	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding (any setting) may be associated with little or no difference in the volume of FFP or platelets transfused but the evidence is very uncertain.

VHA and outcomes in trauma setting: PICO

Population: People with critical bleeding (trauma setting)

Intervention: VHA

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

Table S28: VHA guided resuscitation and outcomes in trauma setting

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		standard best practice care	VHA		
Mortality, all cause (RCTs) latest reported timepoint	Relative risk: 0.75 (CI 95% 0.48 - 1.17) Based on data from 506 participants in 2 studies	**301** per 1000	**226** per 1000 Difference: **75 fewer per 1000** (CI 95% 157 fewer - 51 more)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the trauma setting may reduce mortality but the evidence is very uncertain.
Mortality, all cause (Coh) latest reported timepoint	Relative risk: 0.75 (CI 95% 0.62 - 0.92) Based on data from 1920 participants in 8 studies	**173** per 1000	**130** per 1000 Difference: **43 fewer per 1000** (CI 95% 66 fewer - 14 fewer)	**Very low** Due to serious risk of bias, Due to serious imprecision	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the trauma setting may be associated with reduced mortality but the evidence is very uncertain.
Morbidity, thromboembolic events	Relative risk: 0.9 (CI 95% 0.42 - 1.95) Based on data from 507 participants in 2 studies	**113** per 1000	**102** per 1000 Difference: **11 fewer per 1000** (CI 95% 66 fewer - 107 more)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision, Due to serious publication bias	The use of TEG or ROTEM to guide blood component therapy may have little or no difference on thromboembolic events in patients with critical bleeding in the trauma setting but the evidence is very uncertain.
Morbidity, MOF	Relative risk: 1.75 (CI 95% 0.6 - 5.12) Based on data from 396 participants in 1 studies	**26** per 1000	**46** per 1000 Difference: **20 more per 1000** (CI 95% 10 fewer - 107 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision	The use of TEG or ROTEM to guide blood component therapy may have no difference on MOF in patients with critical bleeding in the trauma setting but the evidence is very uncertain.
Red blood cell transfusion volume (RCTs)	Measured by: Number of Units Lower better Based on data from 109 participants in 1 studies	**15.65** Units (Mean)	**13.96** Units (Mean) Difference: **SMD 0.13 fewer** (CI 95% 0.50 fewer - 0.25 more)	**Low** Due to serious risk of bias, Due to serious imprecision	The evidence suggests the use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding (any setting) may have little to no difference in the volume of red blood cells transfused.
Red blood cell transfusion volume (Coh)	Measured by: Number of Units Lower better Based on data from 1484 participants in 7 studies	**2-11**	**2-6.5** Difference: **SMD 0.41 fewer** (CI 95% 0.68 fewer - 0.14 fewer)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious inconsistency	The use of TEG or ROTEM to guide blood component therapy 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	**1-7.57** **1-7.49** Difference: **SMD 0.32 fewer** (CI 95% 0.86 fewer - 0.21 more)	**Very low** Due to serious risk of bias, Due to very serious inconsistency, Due to serious imprecision	The use of TEG or ROTEM to guide blood component therapy in patient with critical bleeding in the trauma setting may be associated with little or no difference on the volume of FFP transfused but the evidence is very uncertain.
Platelet transfusion volume	Measured by: Number of Units Lower better Based on data from 580 participants in 4 studies	**0.95-4.2** **0.4-2.7** Difference: **SMD 0.91 fewer** (CI 95% 1.83 fewer - 0.11 more)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the trauma setting may be associated with little or no difference in the volume of platelets transfused but the evidence is very uncertain.

VHA and outcomes in surgical setting: PICO

Population: People with critical bleeding (surgical setting)
Intervention: VHA
Comparator: Standard best practice care (blood component therapy guided by MHP protocol or standard laboratory tests)

Table S29: VHA guided resuscitation and outcomes in surgical setting

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** standard best practice care	 VHA	**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
Mortality, all cause (RCTs) latest reported timepoint	Relative risk: 0.33 (CI 95% 0.12 - 0.91) Based on data from 144 participants in 2 studies	**206** per 1000	**68** per 1000 Difference: **138 fewer per 1000** (CI 95% 181 fewer - 19 fewer)	**Low** Due to serious risk of bias, Due to serious imprecision	The evidence suggests the use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the surgical setting (cardiothoracic) may reduce mortality.
Morbidity, thromboembolic events	Relative risk: 0.2 (CI 95% 0.01 - 4.06) Based on data from 144 participants in 2 studies	**29** per 1000	**6** per 1000 Difference: **23 fewer per 1000** (CI 95% 29 fewer - 89 more)	**Very low** Due to serious risk of bias, Due to very serious imprecision	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the surgical setting (cardiothoracic) may be associated with

				little or no difference on the incidence of thromboembolic events but the evidence is very uncertain.
Red blood cell transfusion volume (RCTs)	Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies	**6.42** Units (Mean) **7.1** Units (Mean) Difference: **SMD 0.12 more** (CI 95% 0.48 fewer - 0.72 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the surgical setting (cardiothoracic) may have little or no difference on the volume of 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	**2.8-9.2** **1.6-3.2** Difference: **SMD 0.50 fewer** (CI 95% 1.91 fewer - 0.91 more)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision, Due to very serious publication bias	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the surgical setting (cardiothoracic) may have little or no difference on the volume of FFP transfused but the evidence is very uncertain.
Platelet transfusion volume	Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies	**1.34** Units (Mean) **0.85** Units (Mean) Difference: **SMD 0.33 fewer** (CI 95% 0.94 fewer - 0.27 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious publication bias	The use of TEG or ROTEM to guide blood component therapy in patients with critical bleeding in the surgical setting (cardiothoracic) may have little or no difference on the volume of platelets transfused but the evidence is very uncertain.

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

Latest search date: 29 September 2021

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

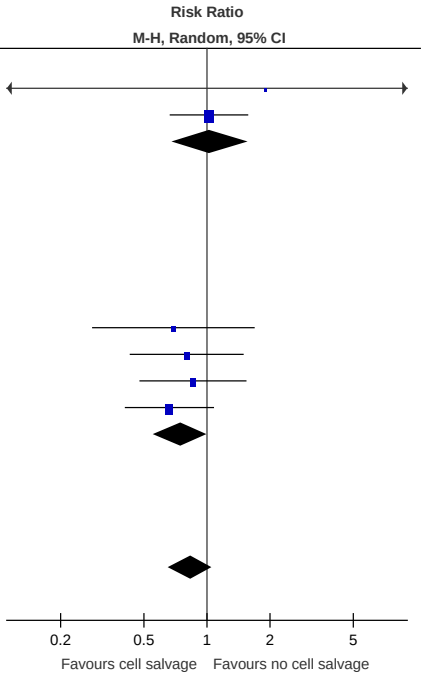
The reference group acknowledged the logistical challenges associated with providing cell salvage as part of an MHP in patients who are critically bleeding. Adaptation of this guidance at a local level is required upon consideration of the resources available.

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.

Figure S10: Forest plot of comparison: cell salvage vs no cell salvage on mortality at any timepoint up to 30 days

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Trauma						
Bhangu 2012 (coh, combat trauma) (1)	1	18	0	11	0.6%	1.89 [0.08, 42.82]
Bowley 2006 (RCT, penetrating trauma) (2)	14	21	15	23	33.1%	1.02 [0.67, 1.56]
Subtotal (95% CI)		**39**		**34**	**33.7%**	**1.03 [0.68, 1.57]**
Total events	15		15			
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.15 (P = 0.88)						
1.1.2 Urgent abdominal aortic aneurysm repair						
Shuhaiber 2003 (Coh, urgent AAA) (3)	0	4	0	21		Not estimable
Tawfick 2008 (Coh, urgent AAA) (4)	6	27	9	28	7.6%	0.69 [0.28, 1.68]
Posacioglu 2002 (Coh, urgent AAA) (5)	16	40	8	16	15.6%	0.80 [0.43, 1.49]
Markovic 2009 (Coh, ruptured AAA) (6)	12	30	14	30	17.7%	0.86 [0.48, 1.53]
Serracino-Inglott 2005 (Coh, urgent AAA) (7)	13	40	56	114	25.5%	0.66 [0.41, 1.07]
Subtotal (95% CI)		**141**		**209**	**66.3%**	**0.74 [0.55, 1.01]**
Total events	47		87			
Heterogeneity: Tau² = 0.00; Chi² = 0.54, df = 3 (P = 0.91); I² = 0%						
Test for overall effect: Z = 1.92 (P = 0.05)						
Total (95% CI)		**180**		**243**	**100.0%**	**0.83 [0.65, 1.06]**
Total events	62		102			
Heterogeneity: Tau² = 0.00; Chi² = 2.35, df = 5 (P = 0.80); I² = 0%						
Test for overall effect: Z = 1.48 (P = 0.14)						
Test for subgroup differences: Chi² = 1.54, df = 1 (P = 0.21), I² = 35.2%						



Footnotes

(1) One patient in the intervention group died before cell salvage could occur.

(2) Cause of death: I = exsanguination (8/14) or MOF related to sepsis (6/14). C = exsanguination (10/15) and MOF related to sepsis (5/15).

(3) Ten out of 25 (40%) patients in the total study cohort died (intra- and post-operative). A further 5 patients in the control group died up to 30-days.

(4) Data retrieved from primary study. 30-day mortality

(5) Date retrieved from primary study. Includes post-opererative deaths only.

(6) Data retrieved from primary study. Includes intro-operative and post-operative deaths among patients with ruptured AAA.

(7) Data retrieved from primary study. Includes intro-operative and post-operative deaths.

Cell Salvage and outcomes in trauma setting: PICO

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

Table S30: Cell salvage in trauma setting

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		No cell salvage	Cell salvage		
Mortality, all cause (RCTs) latest reported timepoint	Relative risk: 1.02 (CI 95% 0.67 - 1.56) Based on data from 44 participants in 1 studies	**652** per 1000	**665** per 1000 Difference: **13 more per 1000** (CI 95% 215 fewer - 365 more)	**Very low** Due to serious indirectness, Due to very serious imprecision	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	Relative risk: 0.78 (CI 95% 0.29 - 2.09) Based on data from 44 participants in 1 studies	**304** per 1000	**237** per 1000 Difference: **67 fewer per 1000** (CI 95% 216 fewer - 331 more)	**Very low** Due to serious indirectness, Due to very serious imprecision	Cell salvage may have little or no difference in morbidity (sepsis) in trauma patients with critical bleeding, but the evidence is very uncertain.
Red blood cell transfusion volume	Measured by: Number of Units Lower better Based on data from 44 participants in 1 studies	**11.17** Units (Mean)	**6.47** Units (Mean) Difference: **SMD 0.82 fewer** (CI 95% 1.44 fewer - 0.20 fewer)	**Very low** Due to serious indirectness, Due to very serious imprecision	Cell salvage may reduce the volume of allogenic red blood cell 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	**4.04** Units (Mean)	**4.76** Units (Mean) Difference: **SMD 0.16 more** (CI 95% 0.44 fewer - 0.75 more)	**Very low** Due to serious indirectness, Due to very serious imprecision	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	**0.56** Units (Mean)	**1** Units (Mean) Difference: **SMD 0.26 more** (CI 95% 0.33 fewer - 0.85 more)	**Very low** Due to very serious indirectness, Due to serious imprecision	Cell salvage may have no difference on the volume of platelets transfused in trauma patients with critical bleeding, but the evidence is very uncertain.

Cell Salvage and outcomes in medical emergencies: PICO

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

Table S31: Cell salvage in medical emergency setting

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty of the Evidence** (Quality of evidence)	**Plain language summary**
		No cell salvage	Cell salvage		

Mortality, all cause latest reported timepoint	Relative risk: 0.74 (CI 95% 0.55 - 1.01) Based on data from 350 participants in 5 studies	**416** per 1000 **308** per 1000 Difference: **108 fewer per 1000** (CI 95% 187 fewer - 4 more)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision	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	Relative risk: 3.2 (CI 95% 0.83 - 12.35) Based on data from 235 participants in 3 studies	**13** per 1000 **42** per 1000 Difference: **29 more per 1000** (CI 95% 2 fewer - 148 more)	**Very low** Due to serious risk of bias, Due to serious imprecision	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: 2.0 (CI 95% 0.49 - 8.14) Based on data from 235 participants in 3 studies	**13** per 1000 **26** per 1000 Difference: **13 more per 1000** (CI 95% 7 fewer - 93 more)	**Very low** Due to serious risk of bias, Due to serious imprecision, Due to serious risk of bias	The evidence is very uncertain about the association of cell salvage with post-operative renal complications in patients undergoing urgent AAA repair.
Morbidity, gastrointestinal complications	Relative risk: 1.6 (CI 95% 0.19 - 13.24) Based on data from 235 participants in 3 studies	**6** per 1000 **10** per 1000 Difference: **4 more per 1000** (CI 95% 5 fewer - 73 more)	**Very low** Due to serious risk of bias, Due to serious imprecision	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	**3.63-12.6** **4-11.2** Difference: **SMD 0.36 fewer** (CI 95% 0.87 fewer - 0.14 more)	**Very low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision	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.