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[Intervention Protocol]

Strategies for use of blood products for major bleeding in trauma

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

The objective of this review is to assess the effects and safety of blood product transfusion strategies started in the first 24 hours after injury for trauma patients of all ages with major bleeding.

BACKGROUND

Description of the condition

Worldwide, trauma is one of the leading causes of death and disability among children and young adults aged 44 and under (Cap 2015). Approximately 40% of deaths from trauma are due to uncontrolled bleeding or its consequences (Frith 2010). Death from exsanguination occurs early, with the majority of patients dying within the first few hours after injury (Cripps 2013). Some patients are hypercoagulable after trauma, some have normal coagulation parameters, and some are hypocoagulable. Approximately one quarter of trauma patients with major bleeding develop a coagulopathy (abnormal clotting) known as acute traumatic coagulopathy or trauma-induced coagulopathy (we will use the term trauma-induced coagulopathy) soon after injury (Brohi 2003). In

patients with this coagulopathy, the ability of their blood to form a clot is impaired. Coagulopathy in trauma is known to be associated with increased transfusion requirements, organ injury, sepsis, critical care stays, and death (Cohen 2012; Frith 2010; MacLeod 2003; Maegele 2007).

Trauma-induced coagulopathy may be diagnosed by elevated laboratory test results, such as prothrombin time (PT), international normalised ratio (INR), or the activated partial thromboplastin time (APTT). There is no consensus on the laboratory definition of trauma-induced coagulopathy. Two different ranges are commonly used within the research and clinical literature: a PT/INR ratio of 1.2 and above (Frith 2010), and a PT/INR ratio of 1.5 and above (Chin 2014). Using a global test of haemostasis, trauma-induced coagulopathy has been defined as a reduction in clot strength (amplitude), measured at five minutes ($A5 \leq 40$ mm) by rotational thromboelastometry (ROTEM (Hagemo 2015)). Al-

though the mechanisms of trauma-induced coagulopathy are incompletely understood, it is clear that it is a complex process that involves clotting pathways, platelet and endothelial dysfunction, and a rapid breakdown of clots (Curry 2012; Dobson 2015; Raza 2013; Rourke 2012).

If not adequately treated, trauma-induced coagulopathy worsens during bleeding (Brohi 2003; Kahn 2014). In traumatic brain injury, coagulopathy is associated with adverse outcomes. It has been suggested that the release of a key protein, known as tissue factor, plays a key role in the development of abnormal clotting. How this compares to the coagulopathy in patients without traumatic brain injury is beginning to be better understood (Maegele 2013).

Description of the intervention

Trauma patients who arrive at the hospital with major haemorrhage are treated with an approach known as damage control resuscitation. This integrated approach has a primary aim of stopping the bleeding. It focuses on: (1) diagnostic and treatment pathways to identify and stop on-going bleeding, e.g. early surgery or interventional radiology, and (2) best supportive care, using a transfusion strategy.

In the trauma setting, different strategies have been used to address shock and deranged coagulation. These include transfusion with different combinations or ratios of blood products, i.e. red blood cells (RBCs), fresh frozen plasma (FFP), platelets, cryoprecipitate, whole blood, lyophilised platelets, lyophilised plasma, or liquid plasma. These strategies have developed from an increased understanding about the role that transfusion resuscitation may play in treating and limiting this clotting abnormality (Borgman 2007).

Current approaches to resuscitation specify early delivery of blood products without waiting for clotting results (empiric transfusion), while avoiding colloid or crystalloid infusions, in an attempt to prevent and immediately correct coagulopathy (Holcomb 2007). To facilitate empiric transfusion, many hospitals use a major haemorrhage protocol, whereby a fixed ratio of blood products is delivered to the bedside in a major haemorrhage pack. Further blood product administration is then guided by conventional hospital laboratory clotting tests or viscoelastic haemostatic assays, such as traditional thromboelastography (TEG) or ROTEM. Tranexamic acid is routinely given to patients with traumatic haemorrhage, the first dose administered within three hours of the injury (CRASH-2 trial 2010). In addition to transfusion strategies that use FFP to red blood cell ratios higher than 1:2, some studies have explored the use of more balanced platelet to red blood cell ratios, with the result that some centres now advocate a 1:1 ratio. Early timing of platelet transfusion may be important, as there is evidence of early platelet dysfunction in major trauma (Wohlauer 2012).

There has also been recent recognition of the critical role of fibrinogen, one of the first clotting factors to decrease in major bleeding from trauma. The main exogenous concentrated sources of

fibrinogen are cryoprecipitate and fibrinogen concentrate. Cryoprecipitate is a pooled plasma product containing high concentrations of FVIII, fibrinogen, vWF, fibronectin and FXIII. Fibrinogen concentrate is a lyophilised product (reconstituted from a powder) from pooled donors that has been subjected to viral inactivation.

Logistical issues, such as blood product storage or shelf-life may hinder timely administration of blood products. This has led to interest in the use of lyophilised plasma and platelet products. Advantages of lyophilised products include a stable shelf-life, ease of use and storage, and a low volume for administration.

How the intervention might work

Traumatic haemorrhage results in decreased circulating volume, loss of oxygen-carrying capacity, and coagulopathy. Restoring circulating volume is key to oxygen delivery. Transfusion of red blood cells improves oxygen carriage and contributes to restoration of adequate circulating volume, but given alone, is also associated with worsening coagulopathy (Brohi 2003). For patients in need of massive transfusion of individual components, some argue that fresh whole blood is the optimum transfusion product, since all blood constituents are administered in physiological quantities.

The addition of FFP decreases further depletion of clotting factors, and provides the coagulation factors needed for clot formation and prevention of clot breakdown. Platelets promote clotting by providing a surface on which the clotting process can occur, and sticking together to form a platelet plug. Cryoprecipitate is administered as a main source of fibrinogen (Rourke 2012). Fresh frozen plasma also appears to stabilise the lining of the blood vessels, to help form a stable clot (Torres 2013).

However, the administration of blood products is not without risk. Red blood cell transfusion is an independent predictor of mortality in victims of trauma, and reducing administration would be ideal, not least because of the high cost of the product and its limited availability. Concerns have also been raised about the adverse effects of administering higher volumes of FFP and platelet products. But at present, the published data do not provide clear answers on the risks of adverse events with high volume transfusion, which include multi-organ failure, sepsis, thrombosis (blood clots), and acute respiratory distress syndrome (Curry 2012).

Why it is important to do this review

The global impact of injury is under appreciated. In 2010, trauma accounted for 5.1 million more deaths than HIV-AIDS, TB, and malaria combined (Norton 2013). Rapid haemorrhage control and improved resuscitation techniques may lead to better outcomes for patients.

Currently, there is no consensus on transfusion strategies for the acute management of bleeding in trauma. Despite recent changes

to the delivery of blood products in trauma and much research effort in the area, there are few completed trials to determine the optimal transfusion strategy of blood products in trauma, and to examine the adverse effects of such strategies.

OBJECTIVES

The objective of this review is to assess the effects and safety of blood product transfusion strategies started in the first 24 hours after injury for trauma patients of all ages with major bleeding.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider randomised controlled trials that relate to the early management of haemorrhage (within the first 24 hours of injury) with blood products (red blood cells, whole blood, fresh frozen plasma, platelets, cryoprecipitate, including lyophilised plasma, lyophilised platelets, and liquid plasma) in injured patients. We will only include trials that were prospectively registered, unless the final report was published before 2010.

Types of participants

We will include adults and children (with no age restriction) with major bleeding caused by trauma.

Patients with major bleeding will be defined as those with active bleeding and shock, those who require activation of the major haemorrhage protocol, or those predicted to bleed, using a scoring system for haemorrhage in trauma, or as otherwise described by the study authors. We will exclude trials that assessed isolated burns injuries, due to the different mechanism of injury.

Types of interventions

A variety of transfusion strategies is currently used in trauma haemorrhage, but consensus is lacking. Interventions will be examining different ways of using blood products (blood transfusion strategies) in acute bleeding due to trauma. We will consider all trials that are comparing two transfusion strategies, including the following examples:

- Goal-directed strategy of laboratory clotting tests versus viscoelastic haemostatic assay
- Different ratios of blood products e.g. a transfusion strategy with fresh frozen plasma (FFP), platelets, and red blood cells in a

1:1:1 unit ratio compared to FFP, platelets, and red blood cells in a 1:1:2 ratio).

- Whole blood versus individual blood components

Each blood transfusion strategy must include at least one of: red blood cells or a blood component (FFP, cryoprecipitate, whole blood, platelets, lyophilised or liquid plasma, or lyophilised platelets), and must not contain only recombinant or plasma derived single factor, or multiple coagulation factor concentrates, such as fibrinogen concentrate, prothrombin complex concentrate, and recombinant FVIIa, since these interventions are covered elsewhere (Fabes 2013). There is no standardised transfusion strategy for major bleeding in trauma. The 2016 guidelines from the National Institute for Health and Clinical Excellence (NICE) recommend initial empirical transfusion of red cells and FFP in a 1:1 ratio (NICE 2016). The 2016 European Trauma Society Guidelines recommend transfusion to keep haemoglobin at 70 to 90 g/L, and FFP or fibrinogen replacement in patients with massive bleeding; if further plasma is administered, an optimal plasma to red blood cell ratio of at least 1:2 is suggested. The European guidelines also suggest a threshold-based approach to platelet transfusion (Rossaint 2016). Both guidelines recommend starting transfusions within 24 hours of injury.

Examples of blood transfusion strategies for trauma patients with major bleeding include:

- blood component transfusion guided by laboratory or global haemostatic tests;
- FFP to platelets to red blood cells in 1:1:1 ratio;
- FFP to platelets to red blood cells in 1:1:2 ratio;
- FFP to red blood cells in 1:2 ratio;
- two pools of early cryoprecipitate, then FFP to red cells in 6:4 ratio;
- modified whole blood;
- individual or combination transfusion of any of the following blood components: red cells, FFP, platelets, cryoprecipitate, lyophilised plasma, lyophilised platelets, and liquid plasma.

We will consider all trials, including placebo-controlled trials, where the comparator is a non-blood component (e.g. fluid resuscitation). An example of placebo-controlled trials might be studies evaluating blood products that are not the current standard, e.g. early cryoprecipitate with empirical transfusion versus saline placebo and empirical transfusion. We recognise that placebo-controlled trials may be challenging for studies of blood components.

Types of outcome measures

Primary outcomes

- All-cause mortality at 24 hours;
- All-cause mortality at 30 days.

Secondary outcomes

- Mortality due to haemorrhage within 24 hours.
- Time-to-anatomical haemostasis, as described in the study.
- Total thromboembolic events (arterial and venous) in the first 30 days after injury.
 - Transfusion requirements (number of units or volume of red cells, FFP, Cryoprecipitate, and Platelets) in the first 24 hours.
 - Degree of coagulopathy (defined as maximal change in prothrombin time (PT) or INR between baseline and post intervention). Post intervention will be defined as up to one hour after the final blood product transfusion.
 - Requirement for surgery or interventional procedure to control bleeding in the first 24 hours after injury.
 - Length of stay in intensive care.

Information size estimate

In a sample size estimate, we calculated we would need to pool 3000 patients to have a 90% chance of detecting a decrease in the primary outcome measure of death at the 5% level of significance (from 26% in the control group to 21% in the experimental group).

Search methods for identification of studies

Electronic searches

We will search the following databases for randomised controlled trials (RCTs):

- Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, current issue; [Appendix 1](#));
- MEDLINE Ovid (1946 to present; [Appendix 2](#));
- Embase Ovid (1974 to present; [Appendix 3](#));
- PubMed (in-process and epublications ahead of print only; [Appendix 4](#));
- [Transfusion Evidence Library](#) (1950 to present; [Appendix 5](#));
- Web of Science Conference Proceedings Citation Index - Science (CPCI-S, 1990 to present; [Appendix 6](#));
- [ClinicalTrials.gov](#);
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP).

The Cochrane Injuries Group will search the two ongoing trial registries. We have listed the search strategies for the other databases in the appendices. We will combine searches in MEDLINE and Embase with adaptations of RCT filters suggested in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Lefebvre 2011](#)). We will not limit searches by language, year of publication, or publication type.

We will report the number of papers retrieved, assessed, included, and excluded in the review. We will seek translators for potential reports published in languages other than English.

Searching other resources

We will handsearch the reference lists of included studies to identify further relevant studies, and contact lead authors of the included studies to identify any unpublished material, missing data, or information about ongoing studies.

Data collection and analysis

Selection of studies

One review author (CD) will initially screen all search results for relevance against the eligibility criteria and discard all titles that are clearly irrelevant. Two review authors (HW, NC) will independently screen the remaining titles and abstracts. We will obtain the full texts of reports that appear to be eligible, or of which we are unsure, to determine their ultimate relevance. We will seek further information from the trial authors when articles contain insufficient data to make a decision about eligibility. We will resolve differences of opinion through discussion and consensus, and consult with a third review author (SS) if necessary.

Data extraction and management

Two review authors (HW, JB) will independently extract data onto study-specific data extraction forms. They will pilot the forms on two relevant RCTs, and adjust the form as necessary after discussion. Throughout the data extraction process, they will resolve any disagreement by discussion with a third review author (NC). If agreement cannot be reached, they will consult with a fourth author (SS).

The review authors will not be blinded to the names of authors, institutions, journals, or outcomes of the trials. If considered relevant, they will request copies of the trial protocols from the trial authors.

Data will include:

1. Trial details: review author's name; year; date of data extraction; first author of study; author's contact address (if available); objectives of the trial; country of origin; clinical setting; number of centres; recruitment dates; method of sequence generation; allocation concealment; blinding (of clinicians, participants, and outcome assessors); inclusion and exclusion criteria; definition of major haemorrhage; definition of coagulopathy; comparability of groups; length of follow-up; use of intention-to-treat analysis; funding source.
2. Participant data: age; gender; mechanism of injury (blunt or penetrating trauma); isolated traumatic brain injury;

percentage of patients on anticoagulant or anti-platelet therapy; Injury Severity Score (ISS); total number of participants recruited; total number randomised; total number analysed for endpoints; losses to follow-up and dropouts.

3. Interventions: nature of experimental and control interventions; timing, dosage and route of intervention; compliance to interventions; additional interventions given including tranexamic acid.

4. Outcomes: primary and secondary outcomes; outcome cutoffs; incomplete outcome data; conclusions reported.

Assessment of risk of bias in included studies

Two review authors will independently assess bias using the Cochrane tool. To assess risk of bias, we will address the following questions in the 'Risk of bias' table for each included study (Higgins 2011).

1. Was the allocation sequence adequately generated?
2. Was allocation adequately concealed?
3. Was knowledge of the allocated intervention adequately prevented (i.e. blinded) throughout the study for participants, study personnel, and outcome assessors?
4. Were incomplete outcome data adequately addressed for the main outcome?
5. Are reports of the study free of selective outcome reporting?

We will report 'Risk of bias' domains 2, 3, 4, and 5 separately for each of the two main outcomes, and where data allow, for the secondary outcomes.

We will categorise individual studies as being at low, high, or unclear overall risk of bias according to the following:

- low risk of bias - all domains were at low risk of bias (plausible bias unlikely to seriously alter the results);
- unclear risk of bias - one or more domains had an unclear risk of bias (plausible bias that raises some doubt about the results); or
- high risk of bias - one or more domains were at high risk of bias (plausible bias that seriously weakens confidence in the results).

We anticipate that knowledge of the allocated intervention will be difficult to blind from clinicians and participants. However, we believe that it would be possible to blind knowledge of the allocated intervention from outcome assessors. We will bear these considerations in mind when assessing risk of bias for domain 3 above. We will record all quotes from studies separately from our judgement in the 'Risk of bias' table.

Measures of treatment effect

We will calculate risk ratios (RR) for dichotomous data outcomes with 95% confidence intervals (CI). Where the number of observed events is small (less than 5% of sample per group), and where trials have balanced treatment groups, we will report the

Peto odds ratio (OR) with 95% CI (Deeks 2011). We will express treatment effects for continuous data outcomes as mean differences (MD) with 95% CI; if the outcomes are measured using different scales, we will use standardised mean differences (SMD) with 95% CI.

Unit of analysis issues

We anticipate that the patient will be the unit of analysis.

We do not expect to encounter any cluster-randomised trials, but if we do identify any, we will treat them in accordance with the advice given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will treat multi-arm trials in accordance with the advice given in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

We will attempt to contact the trial authors to obtain missing data or to clarify unclear data. For each included study, we will record the number of participants lost to follow-up. Where possible, we will analyse data on an intention-to-treat basis, but if there are missing data, we will present per-protocol analyses. Where standard deviations are not reported, we will try to determine these from standard errors, confidence intervals, or exact P values.

Assessment of heterogeneity

We will use the I^2 statistic to quantify the possible degree of heterogeneity of treatment effects between trials. We will assume moderate heterogeneity when the I^2 is higher than 50% and considerable heterogeneity when it is higher than 80%. Due to the nature of the studies, we expect moderate heterogeneity, therefore, in the first instance, we will use a random-effects model. We will explore potential causes of heterogeneity by sensitivity and subgroup analysis (Deeks 2011).

Assessment of reporting biases

Although every effort will be made to identify unpublished studies, we will assess publication bias using funnel plots, provided there are at least 10 studies included in each meta-analysis.

Data synthesis

If studies are considered sufficiently homogeneous, we will conduct a meta-analysis, according to Cochrane recommendations (Deeks 2011). We will enter data into Review Manager 5 (Review Manager 2014) for statistical analysis.

Where meta-analysis is feasible, we will use the random-effects model for pooling the data. For dichotomous outcomes we will use the Mantel-Haenszel method or the Peto method as necessary, and the inverse variance method for continuous outcomes,

according to the recommendations of Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). If heterogeneity is found to be above 80%, we will not perform a meta-analysis, but will perform a qualitative analysis, grouping similar transfusion strategies, and commenting on the results as a narrative.

A network meta-analysis would not be appropriate due to issues with transitivity.

Subgroup analysis and investigation of heterogeneity

If there are sufficient data, we will perform subgroup analyses to see if there are significant differences in treatment effect:

1. Children versus adults for patients treated with the same protocol (since different definitions of coagulopathy apply).
2. Studies of older adults (over 65 years of age) compared with younger adults, since older patients are more likely to have comorbidities, such as cardiovascular disease, and possible differences in efficacy of transfusion interventions.
3. Studies of patients with traumatic brain injury, in view of the effect of a central nervous system injury on coagulopathy, and the possible differences in efficacy of interventions in this group. If we identify any other subgroup effects, we will clearly identify them as hypothesis-generating. We will use the test for subgroup differences provided in Review Manager 5, to establish whether the subgroups are statistically significantly different from one another.

Sensitivity analysis

If data are available, we will perform sensitivity analyses to explore aspects of trial and review methodology. These will include exploring the effects of removing trials at high or unclear risk of the following domains of bias:

1. selection bias (reflecting lack of confirmation of random sequence generation and allocation concealment);
2. detection bias (reflecting lack of assessor blinding);
3. attrition bias, such as from high levels of missing data.

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Brohi 2003

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We will perform trial sequential analysis to explore the robustness of any statistically significant effects found for the review's primary outcomes that did not meet the expected sample size.

'Summary of Findings' table

We will use GRADEpro GDT software and the GRADE approach to create a 'Summary of findings' table, as suggested in Chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (GRADEpro GDT; Schünemann 2011). We will provide rationale for the figure used to calculate the assumed risk in a footnote. We will use the GRADE approach to rate the quality of the evidence as 'high', 'moderate', 'low', or 'very low', using the five GRADE considerations below. We will provide the rationale for downgrading in a footnote.

- Risk of bias: serious or very serious
- Inconsistency: serious or very serious
- Indirectness: serious or very serious
- Imprecision: serious or very serious
- Publication bias: serious or very serious

We will present the following outcomes in a separate 'summary of findings' table for each comparison. The following five outcomes will be included because we consider these to be most clinically important and useful for review users.

- All-cause mortality at 24 hours
- All-cause mortality at 30 days
- Time-to-anatomical haemostasis
- Transfusion requirements - total number of red cell units during first 24 hours
- Total thromboembolic events in the first 30 days

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* Indicates the major publication for the study

APPENDICES

Appendix I. CENTRAL search strategy

#1 MeSH descriptor: [Multiple Trauma] this term only

#2 MeSH descriptor: [Shock, Hemorrhagic] this term only

#3 MeSH descriptor: [Shock, Traumatic] explode all trees

#4 MeSH descriptor: [Trauma Severity Indices] explode all trees

#5 MeSH descriptor: [Trauma Centers] explode all trees

#6 MeSH descriptor: [Accidents] explode all trees

#7 MeSH descriptor: [Traumatology] this term only

#8 (stabb* or shooting or gunshot* or blast* or bomb* or explosi* or disaster* or casualt* or catastroph* or combat* or battlefield*):ti

#9 ((uncontroll* or ongoing or massive* or major or shock* or critical* or serious* or severe* or life-threatening* or trauma* or pelvic or pelvis or abdominal* or arterial* or catastrophic* or control* or manag*) near/3 (haemorrhag* or hemorrhag* or bleed* or bloodloss* or blood loss*))

#10 ((trauma* or injur*) near/3 (penetrating or blunt or multip*))

#11 (trauma* or combat* or gunshot* or blast* or battle*) near/2 surg*

#12 (trauma* or injur* or accident* or wound*) near/3 (critical* or massive* or major or serious* or severe* or life-threatening* or coagulopath* or coagulat*)

#13 (injur* or wound*) near/3 (lacerat* or crush* or stab* or penetrating or blunt)

#14 (polytrauma* or "hypotensive resuscitation" or "hypovolemic shock" or "hypovolaemic shock")

#15 (trauma* or exsanguin* or hypovolemi* or hypovolaemi* or coagulopath* or (abnormal* near/2 coagulation) or hyperfibrinolysis):ti

#16 MeSH descriptor: [Military Medicine] explode all trees
 #17 MeSH descriptor: [Amputation, Traumatic] this term only
 #18 MeSH descriptor: [Blast Injuries] this term only
 #19 MeSH descriptor: [Rupture] explode all trees
 #20 MeSH descriptor: [Wounds, Penetrating] explode all trees
 #21 MeSH descriptor: [Lacerations] explode all trees
 #22 MeSH descriptor: [Resuscitation] this term only
 #23 MeSH descriptor: [Femoral Fractures] explode all trees
 #24 ((hip* or pelvi* or femoral or femur) near/2 fracture*):ti
 #25 MeSH descriptor: [Cranio cerebral Trauma] explode all trees
 #26 ((head or brain or cerebrocranial* or cranial* or craniocerebral* or cerebral or intracranial* or intra-cranial* or intracortical* or intra-cortical* or subcortical* or sub-cortical* or intraventricul* or intra-ventricular* or periventricular* or peri-ventricular* or cerebell* or cerebrum or corpus callosum or posterior fossa or hemisphere*) near/5 (trauma* or injur* or wound*)):ti
 #27 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26
 #28 MeSH descriptor: [Blood Transfusion] this term only
 #29 MeSH descriptor: [Blood Component Transfusion] explode all trees
 #30 (RBC* or "red cell" or "red cells" or "red blood cell" or "red blood cells" or platelet* or FFP or cryoprecipitate or transfus* or pretransfus* or posttransfus* or retransfus* or hypertransfus*):ti
 #31 ((RBC* or "red cell" or "red cells" or "red blood cell" or "red blood cells" or platelet* or plasma or FFP or "whole blood" or cryoprecipitate) near/6 (transfus* or pretransfus* or posttransfus* or retransfus* or hypertransfus*)):ab
 #32 ("liquid plasma" or "fresh plasma" or "frozen plasma" or "cryopreserved plasma" or octaplas or "thawed plasma" or "platelet concentrate*" or "cold-storage platelets" or "rehydrated platelets" or "fresh whole blood")
 #33 ((lyophilized or freeze-dried) near/3 (plasma or platelet*))
 #34 ("blood product*" or "blood component*" or "blood management" or "blood therapy" or "blood replacement therapy")
 #35 (blood near/2 (storage or age or new* or old* or fresh* or stored)):ti
 #36 ((massive* or major) near/3 transfus*):ab
 #37 #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36
 #38 #27 and #37
 #39 MeSH descriptor: [Thrombelastography] explode all trees
 #40 (thrombo-elastogra* or thrombelastogra* or thrombelasto-gra* or thromboelastogra* or TEG or ROTEM or ROTEG or haemoscope* or hemoscope* or haemonetics or hemonectics or EXTEM or INTEM or FIBTEM or HEPTEM or APTEM or thrombo-elastomet* or thrombelastomet* or thromboelastomet* or Sonoclot or sono-clot)
 #41 ((thromb* near/2 (elastogra* or elasto-gra* or elastom*)) or (rotational near/2 (thrombelast* or thromboelast*)))
 #42 (viscoelastic or visco-elastic) and (detect* or coagulation or haemostatic or hemostatic)
 #43 whole blood hemosta* system* or whole blood haemosta* system*
 #44 #39 or #40 or #41 or #42 or #43
 #45 #27 and #44
 #46 #38 or #45

Appendix 2. MEDLINE Ovid search strategy

1. BLOOD TRANSFUSION/
2. exp BLOOD COMPONENT TRANSFUSION/
3. (transfus* or pretransfus* or posttransfus* or retransfus* or hypertransfus* or RBC* or red cell* or red blood cell* or platelet* or FFP or cryoprecipitate).ti.
4. (blood product* or blood component* or blood management or blood therapy or blood replacement therapy).tw,kf.
5. (blood adj2 (storage or age or new* or old* or fresh* or stored)).ti,kf.
6. ((RBC* or red cell* or red blood cell* or platelet* or plasma or FFP or whole blood or cryoprecipitate) adj6 (transfus* or pretransfus* or posttransfus* or retransfus* or hypertransfus*)):ab,kf.
7. (liquid plasma or fresh plasma or frozen plasma or cryopreserved plasma or thawed plasma or octaplas or platelet concentrate* or cold-storage platelets or rehydrated platelets or fresh whole blood).tw,kf.

8. ((lyophilized or freeze-dried) adj3 (plasma or platelet*)).tw,kf.
9. ((massive* or major) adj3 transfus*).ab,kf.
10. or/1-9
11. exp Multiple Trauma/
12. Shock, Hemorrhagic/
13. exp Shock, Traumatic/
14. exp Trauma Severity Indices/
15. Traumatology/
16. Trauma Centers/
17. Military Medicine/
18. Amputation, Traumatic/
19. Blast Injuries/
20. exp Crush Syndrome/
21. exp *Rupture/
22. exp *Wounds, Penetrating/
23. *Lacerations/
24. *Resuscitation/
25. (trauma* or exsanguin* or hypovolemi* or hypovolaemi* or coagulopath* or (abnormal* adj2 coagulation) or hyperfibrinolysis).ti.
26. (polytrauma* or hypotensive resuscitation or hypovolemic shock or hypovolaemic shock).tw,kf.
27. ((uncontroll* or ongoing or massive* or major or shock* or critical* or serious* or severe* or life-threatening* or trauma* or pelvic or pelvis or abdominal* or arterial* or catastrophic* or control* or management) adj3 (haemorrhag* or hemorrhag* or bleed* or bloodloss* or blood loss*)).tw,kf.
28. ((trauma* or injur* or accident* or wound*) adj3 (critical* or massive* or serious* or severe* or life-threatening* or coagulopath* or coagulat*)).tw,kf.
29. ((trauma* or injur*) adj3 (penetrating or blunt or multip*)).tw,kf.
30. ((injur* or wound*) adj3 (lacerat* or stab* or crush* or penetrating or blunt)).tw,kf.
31. (stabb* or shooting or gunshot* or blast* or bomb* or explosi* or disaster* or casual* or catastroph* or combat* or battlefield*).ti,kf.
32. ((trauma* or combat* or gunshot* or blast* or battle*) adj2 surger*).tw,kf.
33. exp *Femoral Fractures/ or ((pelvi* or femoral* or femur* or hip*) adj2 fracture*).ti,kf.
34. exp Craniocerebral Trauma/
35. ((head or brain or cerebrocranial* or cranial* or craniocerebral* or cerebral or intracranial* or intra-cranial* or intracortical* or intra-cortical* or subcortical* or sub-cortical* or intraventricul* or intra-ventricular* or periventricular* or peri-ventricular* or cerebell* or cerebrum or corpus callosum or posterior fossa or hemisphere*) adj5 (trauma* or injur* or wound*)).ti,kf.
36. or/11-35
37. Thrombelastography/
39. (TEG or ROTEM or ROTEG).tw,kf.
40. (thromb* adj2 (elastogra* or elasto-gra*)).tw,kf.
41. (haemoscope* or hemoscope* or haemonetics or hemonectics).tw,kf.
42. whole blood h?emosta* system*.tw,kf.
43. (EXTEM or INTEM or FIBTEM or HEPTEM or APTEM).tw,kf.
44. (thrombo-elastomet* or thrombelastomet* or thromboelastomet*).tw,kf.
45. ((thromb* adj2 elasto?m*) or (rotational adj2 thromb?elast*)).tw,kf.
46. (Sonoclot or sono-clot).tw,kf.
47. ((viscoelastic or visco-elastic) adj5 (detect* or coagulation or haemostatic or hemostatic) adj5 (system* or process or test or tests or analyz* or analys* or assay* or device* or measurement*)).tw,kf.
48. or/37-47
49. (10 or 48) and 36
50. randomized controlled trial.pt.
51. controlled clinical trial.pt.
52. (randomi* or trial).tw,kf.
53. (placebo or randomly or groups).ab.
54. clinical trials as topic.sh.
55. or/50-54

56. (ANIMALS/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/) not HUMANS/
 57. 55 not 56
 58. 49 and 57

Appendix 3. Embase Ovid search strategy

1. exp Blood Component Therapy/
2. Blood Transfusion/
3. ((RBC* or red cell* or red blood cell* or platelet* or plasma or FFP or whole blood or cryoprecipitate) adj6 (transfus* or pretransfus* or posttransfus* or retransfus* or hypertransfus*)).ab.
4. (liquid plasma or fresh plasma or frozen plasma or platelet concentrate* or cold-storage platelets or rehydrated platelets or fresh whole blood).tw.
5. ((lyophilized or freeze-dried) adj3 (plasma or platelet*)).tw.
6. (transfus* or pretransfus* or posttransfus* or retransfus* or hypertransfus* or RBC* or red cell* or red blood cell* or platelet* or plasma or FFP or cryoprecipitate).ti.
7. (blood product* or blood component* or blood management or blood therapy or blood replacement therapy).tw.
8. (blood adj2 (storage or age or new* or old* or fresh* or stored)).ti.
9. ((massive* or major) adj3 transfus*).ab.
10. or/1-9
11. Multiple Trauma/
12. Exsanguination/ or Hemorrhagic Hypotension/ or Hemorrhagic Shock/
13. exp Injury Scale/
14. exp Traumatology/
15. Battle Injury/ or Blast Injury/ or Blunt Trauma/ or Crush Trauma/ or Traumatic Amputation/
16. Military Medicine/ or Gunshot Injury/ or Missile Wound/ or Stab Wound/ or Wound Hemorrhage/
17. ((uncontrol* or ongoing or massive* or major or shock* or critical* or serious* or severe* or life-threatening* or trauma* or pelvic or pelvis or abdominal* or arterial* or catastrophic* or control* or management) adj3 (haemorrhag* or hemorrhag* or bleed* or bloodloss* or blood loss*)).ti.
18. (polytrauma* or hypotensive resuscitation or hypovolemic shock or hypovolaemic shock or ((trauma* or injur*) adj3 (penetrating or blunt or multip*))).tw.
19. (trauma* or exsanguin* or hypovolemi* or hypovolaemi* or coagulopath* or (abnormal* adj2 coagulation) or hyperfibrinolysis).ti.
20. ((trauma* or injur* or accident* or wound*) adj3 (critical* or massive* or serious* or severe* or life-threatening* or coagulopath* or coagulat*)).tw.
21. ((injur* or wound*) adj3 (lacerat* or crush* or penetrating or blunt)).ti.
22. (stabb* or shooting or gunshot* or blast* or bomb* or explosi* or disaster* or casual* or catastroph* or combat* or battlefield*).ti.
23. (trauma surger* or combat surger* or ((gunshot* or blast* or battle*) adj2 surger*)).tw.
24. exp *Hip Fracture/ or ((femoral* or femur* or hip* or pelvi*) adj2 fracture*).ti.
25. exp *"Head and Neck Injury"/
26. ((head or brain or cerebrocranial* or cranial* or craniocerebral* or cerebral or intracranial* or intra-cranial* or intracortical* or intra-cortical* or subcortical* or sub-cortical* or intraventricul* or intra-ventricular* or periventricular* or peri-ventricular* or cerebell* or cerebrum or corpus callosum or posterior fossa or hemisphere*) adj5 (trauma* or injur* or wound*)).ti.
27. blood clotting disorder/ and trauma*.mp.
28. or/11-27
29. 10 and 28
30. Thrombelastography/
31. (thrombo-elastogra* or thrombelastogra* or thrombelasto-gra* or thromboelastogra* or TEG).tw.
32. (thromb* adj2 (elastogra* or elasto-gra*)).tw.
33. (haemoscope* or hemoscope* or haemonetics or hemonectics).tw.
34. whole blood h?emosta* system*.tw.
35. (ROTEM or ROTEG).tw.
36. (thrombo-elastomet* or thrombelastomet* or thromboelastomet*).tw.
37. ((thromb* adj2 elasto?m*) or (rotational adj2 thrombelast*) or "TEM international").tw.

38. (Sonoclot or sono-clot).tw.
 39. ((viscoelastic or visco-elastic) and (detect* or coagulation) and (system* or process or test or tests or analyz* or analys* or assay* or device* or measurement*)).tw.
 40. or/30-39
 41. 28 and 40
 42. 29 or 41
 43. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/
 44. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or doubl* blind* or singl* blind* or assign* or allocat* or volunteer*).mp.
 45. or/43-44
 46. exp animal experiment/ not (exp human experiment/ or human/)
 47. 45 not 46
 48. 42 and 47
 49. limit 48 to embase

Appendix 4. PubMed search strategy (in-process/publications only)

- #1 trauma[TI] OR traumatic*[TI] OR exsanguin*[TI] OR hypovolemi*[TI] OR hypovolaemi*[TI] OR stab[TI] OR stabb*[TI] OR shooting[TI] OR gunshot*[TI] OR blast[TI] OR bomb*[TI] OR explosi*[TI] OR disaster*[TI] OR casual*[TI] OR catastroph*[TI] OR combat*[TI] OR battlefield*[TI] OR coagulopath*[TI]
 #2 ((uncontroll*[TI] OR ongoing[TI] OR massive*[TI] OR major[TI] OR shock*[TI] OR critical*[TI] OR serious*[TI] OR severe*[TI] OR life-threatening*[TI] OR pelvic[TI] OR pelvis[TI] OR abdominal*[TI] OR arterial*[TI] OR catastrophic*[TI] OR control*[TI] OR manag*[TI]) AND (haemorrhag*[TI] OR hemorrhag*[TI] OR bleed*[TI] OR bloodloss*[TI] OR blood loss*[TI]))
 #3 "critical injury"[TIAB] OR "critical injuries"[TIAB] OR "critically injured"[TIAB] OR "serious injury"[TIAB] OR "serious injuries"[TIAB] OR "seriously injured"[TIAB] OR "severe injury"[TIAB] OR "severe injuries"[TIAB] OR "severely injured"[TIAB] OR "life-threatening injuries"[TIAB] OR "life-threateningly injured" OR "penetrating injury"[TIAB] OR "penetrating injuries"[TIAB] OR "blunt injury"[TIAB] OR "multiple injuries"[TIAB] OR "multiply injured"[TIAB]
 #4 ((trauma[TIAB] OR traumatic*[TIAB] OR combat*[TIAB] OR gunshot*[TIAB] OR blast[TIAB] OR battle*[TIAB]) AND (surgery[TIAB] OR surgical*[TIAB] OR coagulopath* OR coagulat*[TIAB]))
 #5 polytrauma*[TIAB] OR "hypotensive resuscitation"[TIAB] OR "hypovolemic shock"[TIAB] OR "hypovolaemic shock"[TIAB]
 #6 (hip*[TI] OR pelvi*[TI] OR femoral[TI] OR femur[TI]) AND fracture*[TI]
 #7 ((head[TI] OR brain[TI] OR cerebrocranial*[TI] OR cranial*[TI] OR craniocerebral*[TI] OR cerebral[TI] OR intracranial*[TI] OR intra-cranial*[TI] OR intracortical*[TI] OR intra-cortical*[TI] OR subcortical*[TI] OR sub-cortical*[TI] OR intraventricular*[TI] OR intra-ventricular*[TI] OR periventricular*[TI] OR peri-ventricular*[TI] OR cerebell*[TI] OR cerebrum[TI] OR corpus callosum[TI] OR posterior fossa[TI] OR hemispher*[TI]) AND (trauma*[TI] OR injur*[TI] OR wound*[TI]))
 #8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
 #9 (thrombo-elastogra* OR thrombelastogra* OR thrombelasto-gra* OR thromboelastogra* OR TEG OR ROTEM OR ROTEG OR haemoscope* OR hemoscope* OR haemonetics OR hemonetics OR EXTEM OR INTEM OR FIBTEM OR HEPTEM OR APTEM OR thrombo-elastomet* OR thrombelastomet* OR thromboelastomet* OR Sonoclot OR sono-clot)
 #10 (thromb* AND elastom*) OR (rotational AND (thromboelast* OR thrombelast*))
 #11 ((viscoelastic OR visco-elastic) AND (detect* OR coagulation OR haemostatic OR hemostatic) AND (system* OR process OR test OR tests OR analyz* OR analys* OR assay* OR device* OR measurement*))
 #12 whole blood hemosta* system* OR whole blood haemostat* system*
 #13 RBC*[TI] OR "red cell"[TI] OR "red cells"[TI] OR "red blood cell"[TI] OR "red blood cells"[TI] OR platelet*[TI] OR FFP[TI] OR cryoprecipitate[TI] OR transfus*[TI] OR pretransfus*[TI] OR posttransfus*[TI] OR retransfus*[TI] OR hypertransfus*[TI]
 #14 ((RBC*[TIAB] OR "red cell"[TIAB] OR "red cells"[TIAB] OR "red blood cell"[TIAB] OR "red blood cells"[TIAB] OR platelet*[TIAB] OR plasma[TIAB] OR FFP[TIAB] OR "whole blood"[TIAB] OR cryoprecipitate[TIAB]) AND (transfus*[TIAB] OR pretransfus*[TIAB] OR posttransfus*[TIAB] OR retransfus*[TIAB] OR hypertransfus*[TIAB]))
 #15 ("liquid plasma" OR "fresh plasma" OR "frozen plasma" OR "cryopreserved plasma" OR octoplas OR "thawed plasma" OR "platelet concentrate*" OR "cold-storage platelets" OR "rehydrated platelets" OR "fresh whole blood")
 #16 ((lyophilized OR lyphilised OR freeze-dried) AND (plasma OR platelet*))

#17 (“blood product” OR “blood products” OR “blood component” OR “blood components” OR “blood management” OR “blood therapy” OR “blood replacement therapy”)
 #18 (blood[TI] AND (storage[TI] OR age[TI] OR new*[TI] OR old*[TI] OR fresh*[TI] OR stored[TI]))
 #19 “massively transfused”[TIAB] OR “massive transfusion”[TIAB] OR “massive transfusions”[TIAB] OR “major transfusion”[TIAB] OR “major transfusions”[TIAB]
 #20 #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
 #21 #8 AND #20
 #22 (random* OR blind* OR “control group” OR placebo* OR controlled OR groups OR trial*) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])
 #23 #21 AND #22

Appendix 5. Transfusion Evidence Library search strategy

Clinical Specialty: Trauma

Appendix 6. Web of Science CPCI-S search strategy

#1 TI=(RBC* OR “red cell” OR “red cells” OR “red blood cell” OR “red blood cells” OR platelet* OR FFP OR cryoprecipitate OR transfus* OR pretransfus* OR posttransfus* OR retransfus* OR hypertransfus*)
 #2 TS=(transfus* OR pretransfus* OR posttransfus* OR retransfus* OR hypertransfus* OR “liquid plasma” OR “fresh plasma” OR “frozen plasma” OR “cryopreserved plasma” OR octoplas OR “thawed plasma” OR “platelet concentrate” OR “platelet concentrates” OR “cold-storage platelets” OR “rehydrated platelets” OR “whole blood” OR “massive transfusion” OR “massively transfused” OR “major transfusion” OR “lyophilized plasma” OR “lyophilised plasma” OR “freeze-dried plasma” OR “lyophilized platelets” OR “lyophilised platelets” OR “freeze-dried platelets” OR “blood product*” OR “blood component*” OR “blood management” OR “blood therapy” OR “blood replacement therapy”)
 #3 TS=((thrombo-elastogra* OR thrombelastogra* OR thrombelasto-gra* OR thromboelastogra* OR TEG OR ROTEM OR ROTEG OR haemoscope* OR hemoscope* OR haemonetics OR hemonectics OR EXTEM OR INTEM OR FIBTEM OR HEPTEM OR APTM OR thrombo-elastomet* OR thrombelastomet* OR thromboelastomet* OR Sonoclot OR sono-clot))
 #4 TS=((thromb* AND elastom*) OR (rotational AND (thromboelast* OR thrombelast*)))
 #5 TS=((viscoelastic OR visco-elastic) AND (detect* OR coagulation OR haemostatic OR hemostatic) AND (system* OR process OR test OR tests OR analyz* OR analys* OR assay* OR device* OR measurement*))
 #6 TS=(whole blood hemosta* system* OR whole blood haemostat* system*)
 #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
 #8 TI=(stabb* OR stab OR shooting OR gunshot* OR blast* OR bomb* OR explosi* OR disaster* OR casual* OR catastroph* OR combat* OR battlefield* OR trauma* OR “haemorrhagic shock” OR “hemorrhagic shock” OR “hip fracture” OR “pelvic fracture”)
 #9 TS=(trauma* OR “haemorrhagic shock” OR “hemorrhagic shock” OR “hip fracture” OR “pelvic fracture” OR “critical injury” OR “critical injuries” OR “critically injured” OR “serious injury” OR “serious injuries” OR “seriously injured” OR “severe injury” OR “severe injuries” OR “severely injured” OR “life-threatening injuries” OR “life-threateningly injured” OR “penetrating injury” OR “penetrating injuries” OR “blunt injury” OR “multiple injuries” OR “multiply injured” OR polytrauma* OR “hypotensive resuscitation” OR “hypovolemic shock” OR “hypovolaemic shock” OR coagulopath*)
 #10 #8 OR #9
 #11 TS=(random* OR “controlled trial” OR “control group” OR “controlled study” OR blind*) OR TI=(randomi* OR trial)
 #12 #7 AND #10 AND #11

CONTRIBUTIONS OF AUTHORS

Henna Wong prepared the protocol.

Jack Pottle contributed to the preparation of the protocol.

Nicola Curry is a content expert for this review (haemostasis in trauma management) and contributed to the preparation of the protocol.

Simon Stanworth is a content expert for this review (transfusion in trauma management) and contributed to the preparation of the protocol.

Ross Davenport is a content expert for this review (traumatic haemorrhage and coagulopathy) and contributed to the preparation of the protocol.

Susan Brunskill is a methodological expert for this review who assisted in the preparation of the protocol.

Carolyn Dorée is the information specialist who developed the search strategies and drafted the text for the search section.

All authors have seen and commented on drafts and the final version of the protocol.

DECLARATIONS OF INTEREST

Henna Wong: None known.

Jack Pottle: None known.

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