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## Prophylactic plasma transfusion for patients undergoing non-cardiac surgery (Protocol)

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# Prophylactic plasma transfusion for patients undergoing non-cardiac surgery

Jonathan Huber<sup>1</sup>, Simon J Stanworth<sup>2</sup>, Carolyn Doree<sup>3</sup>, Marialena Trivella<sup>4</sup>, Susan J Brunskill<sup>3</sup>, Sally Hopewell<sup>5</sup>, Kirstin L Wilkinson<sup>6</sup>, Lise J Estcourt<sup>7</sup>

<sup>1</sup>Shackleton Department of Anaesthesia, University Hospital Southampton, Southampton, UK. <sup>2</sup>National Institute for Health Research (NIHR) Oxford Biomedical Research Centre, Oxford University Hospitals NHS Foundation Trust and University of Oxford, Oxford, UK. <sup>3</sup>Systematic Review Initiative, NHS Blood and Transplant, Oxford, UK. <sup>4</sup>Centre for Statistics in Medicine, University of Oxford, Oxford, UK. <sup>5</sup>Oxford Clinical Trials Research Unit, University of Oxford, Oxford, UK. <sup>6</sup>Paediatric and Adult Cardiothoracic Anaesthesia, Southampton University NHS Hospital, Southampton, UK. <sup>7</sup>Haematology/Transfusion Medicine, NHS Blood and Transplant, Oxford, UK

Contact address: Lise J Estcourt, Haematology/Transfusion Medicine, NHS Blood and Transplant, Level 2, John Radcliffe Hospital, Headington, Oxford, OX3 9BQ, UK. [lise.estcourt@nhsbt.nhs.uk](mailto:lise.estcourt@nhsbt.nhs.uk), [lise.estcourt@ndcls.ox.ac.uk](mailto:lise.estcourt@ndcls.ox.ac.uk).

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## ABSTRACT

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

To determine the clinical effectiveness and safety of prophylactic plasma transfusion for people with confirmed or presumed coagulopathy requiring non-cardiac surgery.

## BACKGROUND

### Description of the condition

A coagulopathy has been defined as a condition leading to impairment of the blood's clotting ability (Hunt 2014). People undergoing surgical procedures may have a coagulopathy for a myriad of reasons: including co-existing medical conditions; nutritional or absorptive abnormalities leading to vitamin K deficiency (which results in a reduction in vitamin K-dependent clotting factors); abnormal physiological states such as hypothermia or acidosis; coagulant factor dilution due to intravenous fluids or red cell trans-

fusion; use of antiplatelet or anticoagulant medication; or clotting factor consumption due to bleeding (McGilvray 2001).

There are also people requiring surgery in whom both prothrombotic (pro- or hyper-coagulant) and coagulopathic (anti-coagulant) states may coexist, such as those with liver disease, disseminated intravascular coagulation, renal failure, and systemic inflammatory response syndrome or sepsis (Martlew 2000). People with perioperative critical illness and sepsis are associated with a net pro-coagulant state, despite laboratory measurements of coagulopathy (McGilvray 2001).

Preoperative screening for people with coagulopathy historically involved measurements of activated partial thromboplastin time

(aPTT) and prothrombin time (PT) (van Veen 2011), both of which measure the time for blood to clot, and are affected by the function of different clotting factors. The PT is often presented as the international normalised ratio (INR), which controls for variations in PT measurements due to sensitivity differences of the commercial reagents (Rand 2005).

Clinicians have used abnormal laboratory coagulation results as a marker of coagulopathy, and these abnormalities have formed the rationale for replacing coagulation factors through the transfusion of human plasma prophylactically (in the absence of bleeding) prior to invasive procedures or surgery (Stanworth 2007).

## Description of the intervention

Human plasma is the non-cellular component of blood, containing: proteins that help the blood to clot (procoagulants) such as fibrinogen and factors II, V, VII, VIII, IX, X, XI; anticoagulant proteins C, S and antithrombin; as well as immunoglobulins, water, albumin, and acute phase proteins (Desborough 2015). It is collected either from a single whole blood donation following separation from red cell and platelet components, or from plasmapheresis.

One unit contains a variable volume of plasma (Desborough 2012), typically 200 mL to 300 mL (Benjamin 2012), and different preparations are available. Fresh frozen plasma (FFP) is frozen within eight hours of collection, and contains greater concentrations of temperature-labile factors V and VIII than frozen plasma (FP), which is frozen within 24 hours (Benjamin 2012). It is stored typically at -30 °C (Stanworth 2007) for up to 36 months (Norfolk 2013). Once thawed to 1 °C to 6 °C, it retains overall coagulation factor content for up to five days, although factors V and VIII undergo the greatest degradation during this time (Stanworth 2007). There is also variability of factor concentrations in pathogen-inactivated preparations, such as solvent-detergent treated FFP - which contains reduced fibrinogen, factor VIII and protein S (Norfolk 2013), or methylene blue-treated FFP - which contains reduced fibrinogen and factor VIII (Pamphilon 2000).

Given the variability of clotting factor levels in healthy donors, together with processing, storage and preparation differences (Stanworth 2007), the potency of coagulation factors in plasma can vary between pooled units from 50% to 150% of pooled standardised controls (Benjamin 2012), and even more between units of single donors. Indeed, mean factor VIII concentration has been the only quality-controlled measure for the specification of plasma in the European Union (Stanworth 2007).

## Risks associated with the intervention

Plasma transfusion has the potential to cause life-threatening complications and carries the highest risk of harm of all blood components (Khan 2007). These include transfusion-related acute

lung injury (TRALI) (Eder 2007; Holness 2004), transfusion-related circulatory overload (TACO) (Narick 2012), anaphylaxis or acute allergic reactions - common in 1 % to 3% of transfusions (Desborough 2015), ABO incompatibility-induced haemolysis (Norfolk 2013), multi-organ failure (Watson 2009), and transfusion-transmitted infection. It is also independently associated with nosocomial infections (Karam 2013) and sepsis (Sarani 2008).

Globally, a significant difference exists in the risk of transfusion-transmitted infections between high-income and low-income countries (Dhingra 2013). World Health Organization (WHO) data from 2006 showed the incomplete ability by 31 of 132 countries to screen for HIV, Hepatitis B, Hepatitis C or syphilis, with limited access to test kits representing one such barrier to screening (WHO 2008). Almost half of donations in low-income countries were tested in laboratories without quality assurance (WHO 2011). Blood shortages and an unreliable donor base have encouraged the use of paid donors or transfusion without prior testing (WHO 2008). Evidence for increased prevalence and transmission of infections such as HIV in the commercial plasma-donor population has been demonstrated (Volkow 2005; Wu 2001), and more recently remains a concern (Abolghasemi 2010).

## How the intervention might work

Given plasma contains a source of procoagulant factors, a current practice exists to transfuse plasma prophylactically (in the absence of bleeding), based on a rationale that replacing clotting factors through plasma transfusion will correct a coagulopathy and reduce perioperative bleeding risk (Desborough 2012; Rutherford 2008; Stanworth 2007). Reducing this risk has clinical importance, given perioperative bleeding and blood transfusion have been associated with increased morbidity and mortality (Glance 2011; Shander 2007).

While further research into exact mechanisms is needed, more recent research has demonstrated that plasma transfusion is associated with a protective and restorative effect on the integrity of the lining of blood vessel walls (vascular endothelial glycocalyx layer) (Kozar 2011; Peng 2013; Potter 2015; Rahbar 2015). The lining of blood vessels plays a fundamental role in the initiation and regulation of coagulation, and is easily damaged by haemorrhagic shock, hypovolaemia or trauma (Schott 2016).

The prophylactic administration of plasma is often based on mildly deranged laboratory tests (Luk 2002; Palo 2006; Stanworth 2011a; Triulzi 2015), despite evidence that coagulation factors at an INR less than two remain at concentrations adequate to support haemostasis (Deitcher 2002). Furthermore, the degree to which plasma transfusion corrects mildly abnormal coagulation tests is poor (Abdel-Wahab 2006; Holland 2006; Stanworth 2011a; Williamson 1999).

Secondly, the underlying premise that abnormal coagulation tests are associated with an increased bleeding risk should be treated with caution (Desborough 2012). Studies suggest no difference

in bleeding risk between people with normal or abnormal PT or aPTT undergoing a range of interventions, including spinal surgery (Schramm 2001), angiography (Darcy 1996), liver biopsy (McGill 1990; McVay 1990), thoracocentesis (Puchalski 2013) and abdominocentesis (McVay 1991). These laboratory tests may be prolonged for a variety of reasons (Stanworth 2007), and are not validated in non-bleeding individuals (Dzik 2004). Their poor predictive value for bleeding risk (Chee 2008; Segal 2005) and poor marker for haemostasis is not surprising given the complexity of haemostatic mechanisms in vivo involving the interplay of the endothelium, inflammatory mediators, pro- and anti-coagulant factors, platelets, and fibrinolysis (Desborough 2012; Stanworth 2007).

An alternative approach to transfusing plasma based on an INR or PT threshold (which only detects low coagulation factor levels) is to use a test such as rotational thromboelastometry (ROTEM) or thromboelastography (TEG) that assesses how well a blood clot forms in whole blood (haemostasis) (Kinard 2013). ROTEM and TEG not only assess coagulation factor function, but also platelet function, strength of the clot and whether the clot is rapidly broken down (Whiting 2014). TEG has demonstrated utility in reducing prophylactic transfusions without increasing bleeding complications in people with liver disease undergoing invasive procedures (De Pietri 2016).

These issues may place people with presumed or confirmed coagulopathy undergoing prophylactic FFP transfusion prior to surgery at risk of potentially life-threatening transfusion-related complications (Khan 2007; MacLennan 2006), without clear evidence that the intervention has benefit.

There are alternatives to prophylactic plasma transfusion. These include the following.

- No treatment or placebo.
- Intravenous fluids, including:
  - crystalloids, such as saline, dextrose or balanced electrolyte solutions; or
  - colloids, which contain a suspension of macromolecules such as starches, gelatins or dextrans (Lira 2014).
- Other prohaemostatic agents such as:
  - prothrombin complex concentrate, which is produced from plasma and contains a rich source of the vitamin K-dependent factors II, VII, IX and X in a more concentrated volume compared with plasma;
  - cryoprecipitate, which is produced from plasma and contains a rich source of fibrinogen, factor VIII and von Willebrand factor in a concentrated volume, and can increase fibrinogen levels with lower transfusion volumes compared with plasma (Norfolk 2013);
  - cryosupernatant, which is cryoprecipitate-depleted plasma, and is used as an alternative to plasma for individuals with Thrombotic Thrombocytopenia Purpura (O'Shaughnessy 2004);
  - fibrinogen concentrate, which contains the substrate

converted to fibrin during the final step in the coagulation cascade and formation of a fibrin clot, and may reduce surgical bleeding when administered pre-operatively;

- antifibrinolytics, which increase clot strength by inhibiting the body's mechanism for lysis of formed clots; or
- recombinant factor VIIa (rFVIIa), which is licensed for congenital factor VII deficiency, haemophilia and inhibitory allo-antibodies, but is also used off-licence in the setting of uncontrolled haemorrhage refractory to other treatments (Desborough 2016).

## Why it is important to do this review

There is significant variation in plasma transfusion (Toumi 2015; Whitaker 2016) and prescribing practice, together with evidence of inappropriate use (Ejaz 2015; Luk 2002; Moylan 2008; Pahuja 2012; Palo 2006; Prathiba 2001; Stanworth 2011a; Stanworth 2011b; Tinmouth 2013; Triulzi 2015). Furthermore, there is evidence of variation in dosing (Stanworth 2011a; Tinmouth 2013; Triulzi 2015) and coagulopathy thresholds for transfusion (Stanworth 2011b), with evidence of significant transfusions occurring for mild INR/PT derangement (Ejaz 2015; Triulzi 2015). These variations highlight inconsistencies in management strategies between clinicians.

Although numerous guidelines for plasma usage exist, there is significant variation in the guidance or quality of the evidence base. Some guidelines specifically highlight the absence of high-quality evidence (O'Shaughnessy 2004; Roback 2010; Szczepiorkowski 2013; Yaddanapudi 2014). Another (NICE 2015) recommends considering plasma transfusion (for people undergoing surgery with coagulopathy and a risk of significant bleeding) based on very low-quality randomised controlled trial (RCT) evidence and the opinion of the Guideline Development Group (Padhi 2015). One guideline recommends that prophylactic transfusion should be avoided (Liumbruno 2009). Another recommends prophylactic transfusion dependent on the severity of coagulation test derangement (Wong 2007), while another recommends seeking specialist advice for consideration of transfusion for people with coagulopathy undergoing intra-cranial, intra-ocular or neuraxial procedures (National Blood Authority 2012). Others make no mention of prophylactic use in non-cardiac surgery (American Society of Anesthesiologists 2006; American Society of Anesthesiologists 2015).

These variations in FFP usage, dosing and thresholds, together with variations in guidance, highlight the need to review high-quality RCT evidence for the role of plasma. A systematic review first published in 2004 (Stanworth 2004) and updated in 2012 (Yang 2012) demonstrated a lack of consistent evidence for prophylactic use across a range of clinical settings. While a Cochrane review has been performed to examine the role of FFP in cardiovascular surgery (Desborough 2015), there is as yet no Cochrane review targeting non-cardiovascular surgery. In the cardiovascular

review 14 trials compared prophylactic use versus no FFP associated with cardiac surgery. Overall, the trials were small and were not powered to determine changes in mortality as a primary outcome. It recommended that large studies are required to assess the therapeutic effect of FFP on clinical outcomes following bleeding. This Cochrane review is needed to update previous reviews ([Stanworth 2004](#); [Yang 2012](#)) with recent RCT evidence, specifically targeting the prophylactic use of plasma in non-cardiac surgery, given its role is currently uncertain whereas transfusions carry a risk of harm. This review will examine the evidence for FFP compared with no plasma or alternative pro-haemostatic agents. It will also examine coagulopathy thresholds for transfusion and will include studies that utilise classical laboratory measurements (PT, INR, aPTT)

## OBJECTIVES

To determine the clinical effectiveness and safety of prophylactic plasma transfusion for people with confirmed or presumed coagulopathy requiring non-cardiac surgery.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We will include RCTs, with no restriction on language or publication status.

#### Types of participants

We will include people of all ages with laboratory confirmed or presumed abnormal coagulation (as defined by the study) undergoing non-cardiac surgery.

We will exclude:

- people in whom there is clinical evidence of bleeding prior to enrolment (as they would likely have received blood products); or
- people with inherited bleeding disorders or use of anticoagulants (e.g. warfarin, rivaroxaban, apixaban).

#### Types of interventions

We will include RCTs comparing three types of plasma transfusion regimens:

- prophylactic plasma transfusion prior to surgery versus no prophylactic plasma transfusion prior to surgery (colloid, crystalloid, placebo or no treatment);
- plasma transfusion prior to surgery compared to alternative pro-haemostatic agents (prothrombin complex concentrate, cryosupernatant, fibrinogen concentrate; antifibrinolytics, and rFVIIa); and
- different haemostatic thresholds for administering a prophylactic plasma transfusion prior to surgery (INR, PT, thromboelastography variables).

If sufficient data are available, we will perform separate meta-analyses for these three comparisons, and will assess age, type and dose of plasma components, and procedure type in subgroup analyses for each of these.

### Types of outcome measures

#### Primary outcomes

- All-cause mortality (up to 24 hours, and up to 30 days).
- Major bleeding within 24 hours and within seven days as defined by the study, or by the following (based on [Schulman 2010](#)):
  - fatal bleeding;
  - intra-cranial/intra-spinal/pericardial/intra-ocular/retro-peritoneal, into a non-operated joint, or intra-muscular causing compartment syndrome;
  - surgical site bleeding requiring a second intervention or reoperation;
  - surgical site bleeding that causes a haematoma or haemarthrosis of sufficient size to delay mobilisation or wound healing;
  - surgical site bleeding that is unexpected and prolonged or causes haemodynamic instability (as defined by the study) that is associated with a 20 g/L drop in haemoglobin (Hb), or requires two or more units of whole blood/red cells within 24 hours of the bleeding; or
  - extra-surgical site bleeding associated with a 20 g/L drop in Hb, or requiring two or more units of whole blood/red cells within 48 hours of the bleeding.

#### Secondary outcomes

- Transfusion requirements (within seven days of surgery):
  - number of individuals requiring a transfusion;
  - mean number of transfusions per participant.
- Use of haemostatic agents (within seven days of surgery).
- Volume of blood loss (within seven days of surgery).
- Serious adverse events (as defined in [Appendix 1](#)) due to:

- plasma transfusion (e.g. TRALI, TACO, transfusion-related infection, transfusion-related dyspnoea, acute transfusion reaction) within 24 hours; or
- surgery (e.g. delayed wound healing, infection) within 30 days after the operation.
  - Resource use: hospital/ITU length of stay, operating time, return to theatre for management of bleeding.
  - Venous and arterial thromboembolism (including deep vein thrombosis; pulmonary embolism; stroke; myocardial infarction) (within 30 days of surgery, and within 90 days of surgery).
  - Coagulation test abnormalities PT, INR, aPTT, or as defined by the study (within 24 hours of surgery).
  - Quality of life, as defined by individual studies.

## Search methods for identification of studies

The Systematic Review Initiative's information specialist working in collaboration with the Cochrane Haematological Malignancies Group, will devise the search strategy. These are listed in the protocol appendices.

## Electronic searches

We will search the following databases with no limitation on dates, language or publication status. Immediately prior to the review submission, the search will be rerun and if additional studies are identified, these will be incorporated into the review and findings updated as required. This strategy serves to avoid missing new studies completed during the review process.

Databases to search:

- Cochrane Central Register of Controlled Trials (CENTRAL, Cochrane Library) ([www.cochranelibrary.com/](http://www.cochranelibrary.com/)) ([Appendix 2](#));
- MEDLINE (OvidSP, 1946 to present) ([Appendix 3](#));
- Embase (OvidSP, 1974 to present) ([Appendix 4](#));
- CINAHL (EBSCOHost) (1937 to present) ([Appendix 5](#));
- PubMed (e-publications and in-process citations ahead of print only) ([www.ncbi.nlm.nih.gov/pubmed](http://www.ncbi.nlm.nih.gov/pubmed)) ([Appendix 6](#));
- Transfusion Evidence Library (1950 to present) ([www.transfusionevidencelibrary.com](http://www.transfusionevidencelibrary.com)) ([Appendix 7](#));
- LILACS (1982 to present) ([lilacs.bvsalud.org/en/](http://lilacs.bvsalud.org/en/)) ([Appendix 8](#)); and
- Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (Thomson Reuters, 1990 to present) ([Appendix 9](#)).

Ongoing trial databases:

- ClinicalTrials.gov ([clinicaltrials.gov](http://clinicaltrials.gov)) ([Appendix 10](#)); and
- WHO International Clinical Trials Registry Search Platform (ICTRP) ([apps.who.int/trialsearch/](http://apps.who.int/trialsearch/)) ([Appendix 11](#)).

## Searching other resources

We will conduct handsearches of the reference lists of included studies and any relevant systematic reviews to identify further relevant studies. We will make contact with lead authors of relevant studies to identify any unpublished material, missing data or information regarding ongoing studies.

## Data collection and analysis

### Selection of studies

Study selection will be managed with reference to chapter seven of the *Cochrane Handbook of Systematic Reviews of Interventions* ([Higgins 2011a](#)). Two review authors (JH, KW) will independently screen titles and abstracts identified by the search of databases for relevance against the eligibility criteria and immediately exclude clearly irrelevant studies. Full-text papers will be retrieved for all references for which a decision on eligibility cannot be made from title and abstract alone.

Two review authors (JH, KW) will then independently assess the references for relevance from their full text. They will not be blinded to individual study meta-data such as author, institution, or publication journal. Additional information will be requested from study authors as necessary to assess the eligibility for inclusion of individual studies.

We will use Covidence software ([Covidence 2016](#)) to perform simultaneous independent screening, and to assist with discrepancy resolution. Disagreement between the authors of a study's eligibility will be resolved through discussion and consensus, and with a third review author (LJE) as necessary.

We will report the search results, screening and selection process using a PRISMA flow diagram ([Liberati 2009](#)). We will record the reasons for excluding studies based on full-text assessment and will add those to the 'Characteristics of excluded studies' table.

Multiple reports of one study will be collated so that the study, and not the report, is the unit of analysis.

### Data extraction and management

As recommended in chapter seven of the *Cochrane Handbook of Systematic Reviews of Interventions* ([Higgins 2011a](#)), two review authors (JH, KW) will independently extract data onto standardised pre-piloted forms, and perform a cross-check using Covidence. The review authors will not be blinded to names of authors, institutions, journals or the study outcomes. We will report the characteristics of the included studies in the 'Characteristics of included studies' table.

Two review authors (JH and KW) will independently extract data using Covidence using a purposefully created, standardised form



and any differences will be reviewed and agreed. Data will be exported from Covidence into Cochrane's systematic review software Review Manager 5 (RevMan 2014).

Data collected will include:

- source: study ID, report ID, study author ID, citation and contact details, date of extraction;
- general study details and eligibility: eligibility for inclusion confirmed, reason for exclusion, funding source, conflict of interest declared, references to other relevant studies;
- study methods: location and country, clinical setting, number of centres, study design/type, recruitment dates and study duration, length of follow-up, power calculation, stopping rules, method of sequence generation, method of allocation sequence concealment, method of blinding, bias concerns;
- participant characteristics: age, gender, study population, primary diagnosis and/or operation, baseline laboratory measures of coagulopathy (PT, INR, aPTT, thromboelastography variables, platelet count, Hb) or evidence of presumed coagulopathy, total number screened, number included, number excluded, arm sample size, number analysed, number who received treatment, dropout rate, protocol violations, missing data;
- intervention characteristics: number of study arms, description of arms, type of plasma, control product e.g. crystalloid, colloid, placebo, alternative pro-haemostatic agent, no treatment, haemostatic threshold for administering transfusion, dose of intervention/control; and
- outcomes and results: all-cause mortality within 24 hours and 30 days, major bleeding within 24 hours and seven days, transfusion requirements or number of patients requiring transfusion, use of haemostatic agents, blood loss volume, serious adverse events due to transfusion within 24 hours, or surgery within 30 days, operating time, return to theatre for haemostatic control, hospital/critical care length of stay, venous and arterial thromboembolism, change in laboratory measures of coagulation (PT, INR, aPTT, thromboelastography variables) within 24 hours of plasma transfusion, estimate of effects with confidence intervals, key conclusions from the authors, miscellaneous comments from the review authors, correspondence with the authors required.

### Assessment of risk of bias in included studies

We will assess the risk of bias for all included RCTs using the Cochrane 'Risk of bias' tool according to chapter eight of the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011b). Two review authors (JH, KH) will work independently to assess each element of potential bias listed below as 'high', 'low' or 'unclear' risk of bias. We will report a brief description of the judgement statements upon which the authors have assessed potential bias in the 'Characteristics of included studies' table. We will ensure that a consensus on the degree of risk of bias is met

through comparison of the review authors' statements and where necessary, through consultation with a third review author (LJE). We will use the Cochrane's tool for assessing risk of bias, which will include the following domains:

- selection bias;
- performance bias;
- detection bias;
- attrition bias;
- reporting bias; and
- other bias.

### Measures of treatment effect

For continuous outcomes, we will record the mean, standard deviation, and total number of participants in both treatment and control groups. We will perform analyses using the mean difference (MD) with 95% confidence intervals (CIs) for continuous outcomes using the same scale, and standardised mean difference (SMD) where the scales are different. If available, we will extract and report hazard ratios (HRs) for mortality data. If HRs are not available, we will make every effort to estimate as accurately as possible the HR using the available data and a purpose-built method based on the Parmar and Tierney approach (Parmar 1998; Tierney 2007). If sufficient studies provide HRs, we will use HRs in favour of risk ratios (RRs) in a meta-analysis, but for completeness we will also perform a separate meta-analysis of data from studies providing only RRs for the same outcome.

For dichotomous data, we will record the number of events and the total number of participants in both treatment and control groups, and will report the pooled RR with 95% CI. Where the number of observed events is small (< 5% of sample per group), and where trials have balanced treatment groups, we will report the Peto's Odds Ratio (OR) with 95% CI (Deeks 2011).

We will report the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH), as well as perform quantitative measurements, or provide a narrative report, as appropriate. If data allow, we will undertake quantitative assessments using Review Manager 5.

### Unit of analysis issues

Although it is unlikely that clustered or cross-over trials will be included, we anticipate unit of analysis issues may arise with recurring events or multiple treatment events. We will follow guidance from chapter 16 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Higgins 2011c). We will report adverse event outcomes as groups of transfusion-related and surgery-related adverse events, as well as venous or arterial events. However often this is not possible due to duplicate counting of the same participant who may have experienced more than one adverse event of the same category (e.g. more than one transfusion-related adverse event).



In this case, we will report subgroup categories of adverse events separately and report the 99% CI of the pooled RR to allow for multiple statistical testing. If this is not possible, we will report as a narrative.

### Dealing with missing data

We will record participants lost to follow-up for each study. We will contact the individual study authors where data are missing. We aim to analyse the data using an intention-to-treat (ITT) analysis.

### Assessment of heterogeneity

If the clinical and methodological characteristics of individual studies are sufficiently homogeneous, we will combine the data to perform a meta-analysis.

We will evaluate the extent of heterogeneity by visual inspection of forest plots as well as by utilising statistical methods.

We will assess statistical heterogeneity of treatment effects between studies using a  $\chi^2$  test (with  $P < 0.1$ ). We will quantify the heterogeneity using the  $I^2$  statistic and classify it as low ( $I^2 \leq 50\%$ ), moderate (50% to 80%) or considerable ( $> 80\%$ ) (Deeks 2011). We will use a random-effects model for low to moderate statistical heterogeneity given we anticipate different but related effects across studies. If statistical heterogeneity is considerable, the overall summary statistic will not be reported. We will explore potential causes of heterogeneity by performing sensitivity and subgroup analyses as appropriate (Deeks 2011).

### Assessment of reporting biases

Where at least 10 studies are incorporated into a meta-analysis, we will explore potential publication bias (small-trial bias) by generating a funnel plot and performing an appropriate test for asymmetry as recommended in chapter 10 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Sterne 2011).

### Data synthesis

If studies are sufficiently homogenous in their study design, we will conduct separate meta-analyses (and subgroup analyses) for the three intervention comparisons based on the recommendations from chapter nine of the *Cochrane Handbook of Systematic Reviews of Interventions* (Deeks 2011). In the event of limited quantitative data for statistical analysis and synthesis, we will report findings through qualitative narrative summaries and tables. If sufficient data are available for meta-analysis, this will be performed using Review Manager 5. One review author (JH) will enter the data into the software program, which will be independently checked for errors by a second review author (KW). Given the likely variation in intervention practice, a random-effects model will be used in the first instance. We will use the Mantel-Haenszel method for

dichotomous data and the inverse variance method for continuous data. We will use the Peto method where event numbers are small. If heterogeneity is found to be above 80%, and we identify a cause for the heterogeneity, we will explore this with subgroup analyses. If we cannot find a cause for the heterogeneity then we will not perform a meta-analysis, but comment on the results as a narrative with the results from all studies presented in tables.

### Subgroup analysis and investigation of heterogeneity

If sufficient data are available we will carry out separate subgroup analyses for the three intervention comparisons to assess heterogeneity for the following:

- age of individual (neonate, infant, child, adult);
- type of procedure;
- plasma type; and
- plasma dose.

The control interventions will be categorised into three groups:

- no prophylactic plasma transfusion prior to surgery (colloid, crystalloid, placebo or no treatment);
- alternative pro-haemostatic agents (prothrombin complex concentrate, cryosupernatant, fibrinogen concentrate; antifibrinolytics, and rFVIIa);
- different haemostatic thresholds for administering a prophylactic plasma transfusion prior to surgery (INR, PT, thromboelastography variables).

### Sensitivity analysis

If possible, we will perform sensitivity analyses to examine the robustness of our findings, by considering only:

- studies with low risk of bias; or
- studies with low dropout rate ( $< 20\%$ ).

### 'Summary of findings' table

We will use GRADEpro (GRADEpro 2015) and the guidance in chapters 11 and 12 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Schünemann 2011a; Schünemann 2011b) to produce a 'Summary of findings' table for each of the three intervention comparisons. This will utilise the GRADE approach, which defines the quality of the body of evidence as 'high', 'moderate', 'low' or 'very low', based on the following five considerations: design and implementation limitations causing risk of bias, indirectness of evidence, inconsistency or imprecision of results, and risk of publication bias. This table will include the following outcomes:

- mortality within 30 days;
- major bleeding within 24 hours;
- transfusion requirements measured by mean number of transfusions per participant;

- transfusion requirements measured by number of individuals requiring a transfusion;
- serious adverse events measured by plasma transfusion-related complications within 24 hours;
- serious adverse events measured by surgery-related complications within seven days; and
- quality of life, as defined by individual studies.

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- \* Indicates the major publication for the study

## APPENDICES

### Appendix 1. Definition of Serious Adverse Event

We used a definition of 'Serious Adverse Event' based on guidance from Chou ([Chou 2010](#)), the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use ([ICH 1994](#)), the International Society of Blood Transfusion (ISBT) ([ISBT 2011](#)), and United States of America Government ([U.S. Government 2016](#)).

Any undesirable medical occurrence in an individual administered a pharmaceutical, medical, or biological product, or undergoing an intervention, that:

- results in death;
- is life-threatening;
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability/incapacity;
- is a congenital anomaly/birth defect; or
- is an important medical event that may not fulfil the criteria above, but may jeopardise the individual and may require medical or surgical intervention to prevent the criteria above.

### Appendix 2. CENTRAL search strategy

#1 MeSH descriptor: [Plasma] this term only

#2 MeSH descriptor: [Blood Component Transfusion] this term only

#3 plasma

#4 #2 and #3

#5 plasma:ti,ab near/5 (transfus\*:ti,ab or prophyla\*:ti,ab or fresh\*:ti,ab or frozen:ti,ab or freez\*:ti,ab or prefrozen:ti,ab or prefreez\*:ti,ab or thaw\*:ti,ab or prethaw\*:ti,ab or liquid:ti,ab or infus\*:ti,ab or treatment\*:ti,ab or therap\*:ti,ab or administ\*:ti,ab or donor\*:ti,ab or donat\*:ti,ab or pasteurized:ti,ab or pasteurised:ti,ab or methylene:ti,ab or solvent:ti,ab or detergent:ti,ab or cryoprecipitate:ti,ab or supernatant:ti,ab or cryosupernatant:ti,ab)

#6 (homolog\* or allogene\* or allo-gen\* or universal or clinical or human or pooled or versus) next plasma

#7 (FFP or SDFFP or MBFFP or F24 or FP24 or PF24 or MB-FFP or SD-FFP or uniplas\* or octaplas\* or lyoplas\* or frischplasma or "plasma versus")

#8 (plasma near/3 (pathogen\* or unit\* or ratio\*))

9 #1 or #4 or #5 or #6 or #7 or #8

#10 MeSH descriptor: [Specialties, Surgical] explode all trees

#11 MeSH descriptor: [Surgical Procedures, Operative] explode all trees

#12 surg\* or presurg\* or postsurg\* or operat\* or preoperat\* or perioperat\* or postoperat\* or transplant\*

#13 #10 or #11 or #12

#14 #9 and #13

### Appendix 3. MEDLINE search strategy

1. \*Plasma/

2. Plasma/ and transfus\*.mp.

3. Blood Component Transfusion/ and plasma.mp.

4. (plasma adj5 (transfus\* or prophyla\* or fresh\* or frozen or freez\* or prefrozen or prefreez\* or thaw\* or prethaw\* or liquid or infus\* or treatment\* or therap\* or administ\* or donor\* or donat\* or pasteurized or pasteurised or methylene or solvent or detergent or cryoprecipitate or supernatant or cryosupernatant)).tw,kf.

5. ((homolog\* or allogene\* or allo-gen\* or universal or clinical or human or pooled or versus) adj plasma).tw,kf.

6. (FFP or SDFFP or MBFFP or F24 or FP24 or PF24 or MB-FFP or SD-FFP or uniplas\* or octaplas\* or lyoplas\* or frischplasma or plasma versus).tw,kf.

7. (plasma adj3 (pathogen\* or unit\* or ratio\*)).tw,kf.

8. or/1-7



9. exp Specialties, Surgical/
10. exp Surgical Procedures, Operative/
11. (surg\* or presurg\* or postsurg\* or operat\* or preoperat\* or perioperat\* or postoperat\* or transplant\*).mp.
12. 9 or 10 or 11
13. Meta-Analysis.pt.
14. ((meta analy\* or metaanaly\*) and (trials or studies)).ab.
15. (meta analy\* or metaanaly\* or evidence-based).ti.
16. ((systematic\* or evidence-based) adj2 (review\* or overview\*)).tw.
17. (cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or science citation index or scopus or search terms or literature search or electronic search\* or comprehensive search\* or systematic search\* or published articles or search strateg\*).ab.
18. Cochrane Database of systematic reviews.jn.
19. (additional adj (papers or articles or sources)).ab.
20. ((electronic\* or online) adj (sources or resources or databases)).ab.
21. (relevant adj (journals or articles)).ab.
22. (reference list\* or bibliograph\* or handsearch\* or hand search\* or manual\* search\*).ab.
23. or/13-22
24. Review.pt.
25. RANDOMIZED CONTROLLED TRIALS AS TOPIC/
26. selection criteria.ab. or critical appraisal.ti.
27. (data adj (extraction or analys\*)).ab.
28. RANDOMIZED CONTROLLED TRIALS/
29. or/25-28
30. 24 and 29
31. 23 or 30
32. randomized controlled trial.pt.
33. controlled clinical trial.pt.
34. randomi\*.tw.
35. (placebo or randomly or groups).ab.
37. trial.tw.
38. or/32-37
39. 31 or 38
40. (ANIMALS/ or exp ANIMAL EXPERIMENTATION/ or exp MODELS, ANIMAL/) not HUMANS/
41. Editorial.pt.
42. 40 or 41
43. 39 not 42
44. 8 and 12 and 43

#### Appendix 4. Embase search strategy

1. Plasma Transfusion/
2. Fresh Frozen Plasma/
3. Octaplas/
4. (plasma adj5 (transfus\* or prophyla\* or fresh\* or frozen or freez\* or prefrozen or prefreez\* or thaw\* or prethaw\* or liquid or infus\* or treatment\* or therap\* or administ\* or donor\* or donat\* or pasteurized or pasteurised or methylene or solvent or detergent or cryoprecipitate or supernatant or cryosupernatant)).tw.
5. ((homolog\* or allogene\* or allo-gen\* or universal or human or pooled or clinical or versus) adj plasma).tw.
6. (FFP or SDFFP or MBFFP or F24 or FP24 or PF24 or MB-FFP or SD-FFP or uniplas\* or octaplas\* or lyoplas\* or frischplasma or plasma versus).tw.
7. (plasma adj3 (pathogen\* or unit\* or ratio\*)).tw.
8. or/1-7
9. exp Surgery/

10. (surg\* or presurg\* or postsurg\* or operat\* or preoperat\* or perioperat\* or postoperat\* or transplant\*).mp.
11. or/9-10
12. 8 and 11
13. Meta Analysis/
14. (meta analy\* or metaanaly\* or evidence-based).ti.
15. ((meta analy\* or metaanaly\*) and (trials or studies)).ab.
16. Systematic Review/
17. ((systematic\* or evidence-based) adj2 (review\* or overview\*)).tw.
18. (cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or science citation index or scopus or search terms or literature search or electronic search\* or comprehensive search\* or systematic search\* or published articles or search strateg\* or reference list\* or bibliograph\* or handsearch\* or hand search\* or manual\* search\*).ab.
19. ((electronic\* or online) adj (sources or resources or databases)).ab.
20. ((additional adj (papers or articles or sources)) or (relevant adj (journals or articles))).ab.
21. Review.pt. and (data extraction or selection criteria).ab.
22. or/13-21
23. Editorial.pt.
24. 22 not 23
25. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/
26. (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.
27. or/24-26
28. 12 and 27
29. limit 28 to embase

## Appendix 5. CINAHL search strategy

- S1 (MM "Plasma")
- S2 (MH "Plasma")
- S3 TX transfus\*
- S4 S2 AND S3
- S5 (MH "Blood Component Transfusion")
- S6 TX plasma
- S7 S5 AND S6
- S8 TI ( plasma N5 (transfus\* or prophyla\* or fresh\* or frozen or freez\* or prefrozen or prefreez\* or thaw\* or prethaw\* or liquid or infus\* or treatment\* or therap\* or administ\* or donor\* or donat\* or pasteurized or pasteurised or methylene or solvent or detergent or cryoprecipitate or supernatant or cryosupernatant ) OR AB ( plasma N5 (transfus\* or prophyla\* or fresh\* or frozen or freez\* or prefrozen or prefreez\* or thaw\* or prethaw\* or infus\* or treatment\* or therap\* or administ\* or donor\* or donat\* or pasteurized or pasteurised or methylene or solvent or detergent or cryoprecipitate or supernatant or cryosupernatant ) )
- S9 TI ( (homolog\* or allogene\* or allo-gen\* or universal or clinical or human or pooled or versus or unit\*) N1 plasma ) OR AB ( (homolog\* or allogene\* or allo-gen\* or universal or clinical or human or pooled or versus) N1 plasma )
- S10 TX (FFP or SDFFP or MBFFP or F24 or FP24 or PF24 or MB-FFP or SD-FFP or uniplas\* or octoplas\* or lyoplas\* or frischplasma or "plasma versus")
- S11 TI ( plasma N3 (pathogen or unit\* or ratio\*) ) OR AB ( plasma N3 (pathogen inactivated or pathogen reduced or unit\* or ratio\*) )
- S12 S1 OR S4 OR S7 OR S8 OR S9 OR S10 OR S11
- S13 (MH "Specialties, Surgical+")
- S14 (MH "Surgery, Operative+")
- S15 TX (surg\* or presurg\* or postsurg\* or operat\* or preoperat\* or perioperat\* or postoperat\* or transplant\*)
- S16 S13 OR S14 OR S15
- S17 S12 AND S16
- S18 (MH Clinical Trials+)
- S19 PT Clinical Trial
- S20 TI ((controlled trial\*) or (clinical trial\*)) OR AB ((controlled trial\*) or (clinical trial\*))

S21 TI ((singl\* blind\*) OR (doubl\* blind\*) OR (trebl\* blind\*) OR (tripl\* blind\*) OR (singl\* mask\*) OR (doubl\* mask\*) OR (tripl\* mask\*)) OR AB ((singl\* blind\*) OR (doubl\* blind\*) OR (trebl\* blind\*) OR (tripl\* blind\*) OR (singl\* mask\*) OR (doubl\* mask\*) OR (tripl\* mask\*))

S22 TI randomi\* OR AB randomi\*

S23 MH RANDOM ASSIGNMENT

S24 TI ((phase three) or (phase III) or (phase three)) or AB ((phase three) or (phase III) or (phase three))

S25 ( TI (random\* N2 (assign\* or allocat\*)) ) OR ( AB (random\* N2 (assign\* or allocat\*)) ) )

S26 MH PLACEBOS

S27 MH META ANALYSIS

S28 MH SYSTEMATIC REVIEW

S29 TI ("meta analys\*" OR metaanalys\* OR "systematic review" OR "systematic overview" OR "systematic search\*") OR AB ("meta analys\*" OR metaanalys\* OR "systematic review" OR "systematic overview" OR "systematic search\*")

S30 TI ("literature review" OR "literature overview" OR "literature search\*") OR AB ("literature review" OR "literature overview" OR "literature search\*")

S31 TI (cochrane OR embase OR cinahl OR cinhal OR lilacs OR BIDS OR science AND citation AND index OR cancerlit) OR AB (cochrane OR embase OR cinahl OR cinhal OR lilacs OR BIDS OR science AND citation AND index OR cancerlit)

S32 TI placebo\* OR AB placebo\*

S33 MH QUANTITATIVE STUDIES

S34 S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33

S35 S17 AND S34

## Appendix 6. PubMed search strategy

#1 (plasma[TIAB] AND (transfus\*[TIAB] OR prophyla\*[TIAB]))

#2 "plasma therapy"[TIAB] OR "plasma treatment"[TIAB] OR "plasma administration"[TIAB] OR "fresh plasma"[TIAB] OR "frozen plasma"[TIAB] OR "prefrozen plasma"[TIAB] OR "thawed plasma"[TIAB] OR "prethawed plasma"[TIAB] OR "liquid plasma"[TIAB] OR "infused plasma"[TIAB] OR "plasma infused"[TIAB] OR "donated plasma"[TIAB] OR "donor plasma"[TIAB] OR "pasteurised plasma"[TIAB] OR "pasteurized plasma"[TIAB] OR "freeze-dried plasma"[TIAB] OR "methylene blue plasma"[TIAB] OR "solvent-detergent plasma"[TIAB] OR "supernatant plasma"[TIAB] OR "cryosupernatant plasma"[TIAB] OR "homologous plasma"[TIAB] OR "allogeneic plasma"[TIAB] OR "allogenic plasma"[TIAB] OR "allo-genic plasma"[TIAB] OR "universal plasma"[TIAB] OR "clinical plasma"[TIAB] OR "human plasma"[TIAB] OR "pooled plasma"[TIAB] OR "versus plasma"[TIAB] OR FFP[TIAB] OR SDFFP[TIAB] OR F24[TIAB] OR FP24[TIAB] OR PF24[TIAB] OR MBFFP[TIAB] OR MB-FFP[TIAB] OR SD-FFP[TIAB] OR uniplas\*[TIAB] OR octaplas\*[TIAB] OR lyoplas\*[TIAB] OR frischplasma[TIAB] OR "plasma versus"[TIAB] OR "pathogen-inactivated plasma"[TIAB] OR "pathogen-reduced plasma"[TIAB] OR "plasma units"[TIAB] OR "units of plasma"[TIAB] OR "plasma ratio"[TIAB]

#3 #1 OR #2

#4 surgery[TIAB] OR surgical\*[TIAB] OR presurg\*[TIAB] OR postsurg\*[TIAB] OR operate\*[TIAB] OR operation[TIAB] OR operations[TIAB] OR operating[TIAB] OR preoperat\*[TIAB] OR perioperat\*[TIAB] OR postoperat\*[TIAB] OR transplant[TIAB] OR transplants[TIAB] OR transplanted[TIAB] OR transplanting[TIAB] OR transplantation\*[TIAB]

#5 #3 AND #4

#6 (random\* OR blind\* OR "control group" OR placebo\* OR controlled OR groups OR trial OR systematic[sb]) AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb])

#7 #5 AND #6

## Appendix 7. Transfusion Evidence Library search strategy

Subject Area: Plasma/FFP

## Appendix 8. LILACS search strategy

tw:((plasma OR FFP OR SDFFP OR MBFFP OR F24 OR FP24 OR PF24 OR MB-FFP OR SD-FFP OR octaplas OR uniplas OR lyoplas) AND (surgery OR surgical OR surgically OR presurgery OR presurgical OR postsurgery OR operated OR operation OR operations OR operating OR preoperation OR preoperating OR perioperation OR perioperated OR postoperated OR postoperating OR transplant OR transplants OR transplanted OR transplanting OR transplantation OR transplantations)) AND (instance: "regional") AND (db:("LILACS") AND type\_of\_study:("clinical\_trials" OR "systematic\_reviews"))

## Appendix 9. Web of Science: CPCI-S search strategy

#1 TS=(plasma NEAR/5 (transfus\* OR prophyla\* OR fresh\* OR frozen OR freez\* OR prefrozen OR prefreez\* OR thaw\* OR prethaw\* OR liquid OR infus\* OR treatment\* OR therap\* OR administ\* OR donor\* OR donat\* OR pasteurized OR pasteurised OR methylene OR solvent OR detergent OR cryoprecipitate OR supernatant OR cryosupernatant OR pathogen\*))  
#2 TS=((homolog\* OR allogene\* OR allo-gen\* OR universal OR clinical OR human OR pooled OR versus OR unit\* OR ratio\*) NEAR/1 plasma)  
#3 TS=(FFP OR SDFFP OR MBFFP OR F24 OR FP24 OR PF24 OR MB-FFP OR SD-FFP OR uniplas\* OR octaplas\* OR lyoplas\* OR frischplasma OR plasma versus)  
#4 #1 OR #2 OR #3  
#5 TS=(surg\* OR presurg\* OR postsurg\* OR operat\* OR preoperat\* OR perioperat\* OR postoperat\* OR transplant\*)  
#6 #4 AND #5  
#7 TS=(systematic\* OR random\* OR blind\* OR trial\* OR controlled OR control group\* OR groups)  
#8 #6 AND #7

## Appendix 10. ClinicalTrials.gov search strategy

Search Terms: randomized OR randomised OR randomly

Interventions: Biological: Plasma OR FFP OR SDFFP OR MBFFP OR F24 OR FP24 OR PF24 OR MB-FFP OR SD-FFP OR uniplas OR octaplas OR lyoplas OR plasma transfusion OR prophylactic plasma OR fresh plasma OR frozen plasma OR liquid plasma OR

Search Terms: randomized OR randomised OR randomly

Interventions: universal plasma OR human plasma OR units plasma OR plasma units OR pathogen-reduced plasma

## Appendix 11. WHO ICTRP search strategy

Recruitment: ALL

Intervention: FFP OR SDFFP OR MBFFP OR F24 OR FP24 OR PF24 OR MB-FFP OR SD-FFP OR plasma transfusion OR prophylactic plasma OR fresh plasma OR frozen plasma OR uniplas OR octaplas OR lyoplas OR universal plasma OR human plasma OR plasma units OR thawed plasma OR liquid plasma OR pathogen-reduced plasma OR pathogen-inactivated plasma OR

randomized AND plasma transfusion OR randomized AND FFP OR randomized AND fresh plasma OR randomized AND frozen plasma OR randomized AND freeze dried plasma OR randomized AND prophylactic AND plasma OR randomized AND prophylaxis AND plasma OR randomized AND octaplas OR randomized AND uniplas OR randomized AND lyoplas OR randomized AND clinical plasma OR randomized AND universal plasma OR randomized AND human plasma OR randomized AND plasma units OR randomized AND units plasma OR randomized AND biological plasma OR randomized AND thawed plasma OR randomized AND liquid plasma OR randomized AND pathogen-reduced plasma OR randomized AND pathogen-inactivated plasma OR

randomised AND plasma transfusion OR randomised AND FFP OR randomised AND fresh plasma OR randomised AND frozen plasma OR randomised AND freeze dried plasma OR randomised AND prophylactic AND plasma OR randomised AND prophylaxis

AND plasma OR randomised AND octaplas OR randomised AND uniplas OR randomised AND lyoplas OR randomised AND clinical plasma OR randomised AND universal plasma OR randomised AND human plasma OR randomised AND plasma units OR randomised AND units plasma OR randomised AND biological plasma OR randomised AND thawed plasma OR randomised AND liquid plasma OR randomised AND pathogen-reduced plasma OR randomised AND pathogen-inactivated plasma  
OR

randomly AND plasma transfusion OR randomly AND FFP OR randomly AND fresh plasma OR randomly AND frozen plasma OR randomly AND freeze dried plasma OR randomly AND prophylactic AND plasma OR randomly AND prophylaxis AND plasma OR randomly AND octaplas OR randomly AND uniplas OR randomly AND lyoplas OR randomly AND clinical plasma OR randomly AND universal plasma OR randomly AND human plasma OR randomly AND plasma units OR randomly AND units plasma OR randomly AND biological plasma OR randomly AND thawed plasma OR randomly AND liquid plasma OR randomly AND pathogen-reduced plasma OR randomised AND pathogen-inactivated plasma

## **CONTRIBUTIONS OF AUTHORS**

- Jonathan Huber: protocol development, content expert.
- Lise Estcourt: protocol development, content expert.
- Simon Stanworth: protocol development, content expert.
- Carolyn Doree: protocol development and search specialist.
- Sally Hopewell: protocol development and methodological expert.
- Marialena Trivella: protocol development and statistical expert.
- Kirstin Wilkinson: protocol development, content expert.
- Susan Brunskill: protocol development, methodologist.

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