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Plasma transfusions prior to lumbar punctures and epidural catheters for people with abnormal coagulation (Protocol)

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Cochrane Database of Systematic Reviews 2017, Issue 1. Art. No.: CD012497.

DOI: 10.1002/14651858.CD012497.

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Plasma transfusions prior to lumbar punctures and epidural catheters for people with abnormal coagulation

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Editorial group: Cochrane Haematological Malignancies Group.

Publication status and date: New, published in Issue 1, 2017.

Citation: Estcourt LJ, Desborough M, Doree C, Hopewell S, Trivella M, Stanworth SJ. Plasma transfusions prior to lumbar punctures and epidural catheters for people with abnormal coagulation. *Cochrane Database of Systematic Reviews* 2017, Issue 1. Art. No.: CD012497. DOI: 10.1002/14651858.CD012497.

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ABSTRACT

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

To assess the effect of different prophylactic plasma transfusion regimens prior to insertion of a lumbar puncture needle or epidural catheter in people with abnormal coagulation.

BACKGROUND

Description of the condition

Abnormal coagulation refers to the condition in which the blood's ability to clot is impaired (Hunt 2014). People requiring insertion of a lumbar puncture (LP) needle or an epidural catheter often develop abnormal coagulation as a consequence of their underlying illness, co-morbidities or the effects of treatment.

People requiring LPs and epidurals can have a variety of conditions and include people with liver failure, people who are critically ill and people requiring chemotherapy (Doherty 2014).

An LP is usually performed by inserting a needle into the lower back (underneath the spinal L4 bony process) (Williams 2008). A diagnostic LP is an invasive procedure to obtain samples of

cerebrospinal fluid (CSF) (Doherty 2014). CSF is the fluid that bathes and protects the brain and spinal cord. The CSF obtained can then be used for the investigation of haematological malignancies (Vavricka 2003), subarachnoid haemorrhages, meningitis (Riordan 2002), or neurological disorders. LPs are performed by doctors or specially trained nurses. Therapeutic LPs administer drugs into the CSF. This can be for the administration of therapeutics such as chemotherapy or antibiotics, or administration of local anaesthetic to the nerves of the lower spine (spinal anaesthetic) (Doherty 2014). This usually involves inserting a fine needle into the lower back, administration of the therapeutic agent and then removal of the needle (Ng 2004).

An epidural catheter is inserted to administer anaesthetic. Epidural anaesthesia typically involves inserting a larger diameter needle than a spinal needle. The epidural needle passes through the same

tissues as a spinal needle but stops short of penetrating the dura (tissue sac that contains CSF). An epidural catheter is often passed through the needle and left in position so that additional local anaesthetic medications can be administered (Ng 2004). The most common indication for epidural anaesthesia is in pregnant women to aid in pain relief during labour (Venn 2015). However, epidural anaesthesia can also be used in postoperative pain management especially for people with lower limb ischaemia (narrowing or blockage of the arteries, which markedly reduces blood flow to the legs and feet) (Venn 2015), and people undergoing thoracic surgery (Mendola 2009), as alternatives to general anaesthesia.

In the general population, the risk of a spinal haematoma is very low 0.85 per 100,000 (95% confidence interval (CI) 0 to 1.8 per 100,000) (Cook 2009). The risk varies depending upon the type of person undergoing the procedure (1 in 200,000 epidural anaesthetic procedures during labour to 1 in 3600 epidural anaesthetic procedures in older women having knee surgery) (Li 2010; Moen 2004; Ruppen 2006; Vandermeulen 1994). Risk factors for major bleeding are multifactorial and include: increasing age (the procedure is more difficult in older people due to changes to the spine that occur with age), low platelet count, abnormal coagulation (including anticoagulant medication) and traumatic needle or catheter insertion (Erbay 2014; Li 2010; Moen 2004; Vandermeulen 1994). Performing an LP or administration of epidural anaesthesia is a relative contraindication in people with abnormal coagulation due to this perceived higher risk of complications (AAGBI 2013). However, overall, there are no current reliable estimates of the risks of adverse effects such as spinal haematomas in people with abnormal coagulation (AAGBI 2013; Cook 2009).

A large national study of fresh frozen plasma (FFP) use in critical illness reported that 30% of people admitted to the intensive care unit (ICU) developed an abnormality of coagulation (Walsh 2010). The aetiology of coagulopathy in critical illness is complex and multi-factorial; sepsis, haemodilution, haemorrhage, disseminated intravascular coagulation, hepatic and renal disease and anticoagulant medication are all implicated (Hunt 2014). The causes of abnormal coagulation in people who are not critically ill are similarly broad.

Description of the intervention

Current practice in many countries is to correct abnormal coagulation tests ((prolonged prothrombin time (PT) or elevated international normalised ratio (INR)) with transfusion of plasma prior to insertion of an LP needle or epidural catheter, in order to mitigate the risk of serious peri- or post-procedural bleeding (Moiz 2006; NICE 2015; Vlaar 2009; Yaddanapudi 2014).

Plasma is the liquid component of blood (Benjamin 2012). FFP refers to plasma that is frozen within eight hours of removal to -30°C, whereas frozen plasma (F24) is that which is frozen within 24 hours. Both contain concentrations of clotting factors equivalent

to those found in *in vivo* blood, although the levels of factor V and VIII fall rapidly on thawing (Stanworth 2007). Current recommendations regarding the correction of coagulopathy prior to invasive procedures reflect expert opinion rather than high-quality evidence from randomised controlled trials (RCTs) (AAGBI 2013; NICE 2015). An INR greater than or equal to 1.5 is frequently advocated as the threshold above which patients should undergo correction of coagulopathy prior to insertion of an LP needle or epidural catheter (Hunt 2014; NICE 2015). Whilst the use of standard laboratory tests of coagulation to assess bleeding has been criticised, an INR over 1.5 demarcates the level above which the activity of some coagulation factors falls to less than 50% (Hall 2014). An alternative approach to transfusing based on an INR 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) (Kinnaird 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).

Recent studies report that 15% to 26% of non-bleeding critically ill patients receive prophylactic FFP transfusions prior to an invasive procedure (Dara 2005; Stanworth 2010; Stanworth 2011). However, there remains substantial heterogeneity in clinicians' views about the effectiveness of this intervention, with doubts over its effectiveness and the balance of the risk-benefit ratio (Watson 2011).

How the intervention might work

Plasma transfusion is administered to people with abnormal coagulation in order to correct multiple clotting factor deficiencies and therefore reduce the incidence of bleeding. A dose of at least 10 mL to 15 mL/kg is required to significantly improve the INR (O'Shaughnessy 2004). However, clinical studies indicate that the INR is often minimally reduced following administration of FFP, especially when only modestly increased pre-transfusion (Abdel-Wahab 2006; Stanworth 2011). It remains unclear whether plasma transfusion in people with abnormal coagulation, despite improving standard laboratory tests of coagulation, reduces the incidence of clinically important bleeding or improves other meaningful patient-oriented outcomes such as mortality.

Risks associated with the intervention

If plasma transfusions are ineffective, it is exposing people to the risks associated with plasma transfusion unnecessarily. These include transfusion-associated lung injury (Khan 2007; Rana 2006), transfusion-associated circulatory overload (Narick 2011), multi-organ failure (Watson 2009), and sepsis (Sarani 2008).

The requirement to administer plasma to correct coagulopathy prior to insertion of an LP needle or epidural catheter may additionally delay the start of a treatment. This could lead to unnecessary delays and cancellations of procedures, which may be time-critical in an emergency situation. Delays in initiating treatment may lead to poorer patient outcomes (increased morbidity and mortality). It also may mean that a person does not receive regional anaesthesia, but instead receives a general anaesthetic that may place them at greater risk of complications (Amini 2015; Sanford 2015).

Why it is important to do this review

It is uncertain whether plasma transfusions are effective at preventing bleeding in patients with abnormal coagulation undergoing an invasive procedure (Desborough 2012; Hunt 2014; Segal 2005; Stanworth 2007). If effective, the INR threshold above which plasma transfusions are clinically effective is also uncertain. Wide variation in the use of FFP prior to invasive procedures exists, indicating significant clinician uncertainty and potentially exposing patients to varying risks (Watson 2011).

Previous systematic reviews have either only assessed the evidence from RCTs (Stanworth 2004; Yang 2012); only assessed the evidence associated with one or two outcomes (all-cause mortality and multi-organ failure) (Murad 2010); or were performed more than 10 years ago (Segal 2005; Stanworth 2004). In these previous systematic reviews, there was no RCT evidence for the use of plasma transfusions prior to insertion of an LP needle or epidural catheter (Murad 2010; Segal 2005; Stanworth 2004; Yang 2012). This review addresses an important question for clinicians and the best available evidence needs to be summarised. This review will therefore summarise the evidence from a broad range of studies and include a broad range of outcomes.

OBJECTIVES

To assess the effect of different prophylactic plasma transfusion regimens prior to insertion of a lumbar puncture needle or epidural catheter in people with abnormal coagulation.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs), non-randomised controlled trials (non-RCTs) and controlled before-after studies (CBAs), irrespective of language or publication status. We will exclude uncontrolled studies, cross-sectional studies and case-control studies.

We will only include cluster-RCTs, non-randomised cluster trials, and CBAs with at least two intervention sites and two control sites. In studies with only one intervention or control site, the intervention (or comparison) is completely confounded by study site making it difficult to attribute any observed differences to the intervention rather than to other site-specific variables.

Types of participants

People, of any age, with abnormal coagulation (as defined by the included studies) requiring insertion of a lumbar puncture needle or epidural catheter.

We will not include people with haemophilia as they should be treated with the appropriate factor concentrate (WFH 2012). We will not include people on warfarin as guidelines recommend the use of prothrombin complex concentrate for emergency reversal of warfarin (Keeling 2011; Tran 2013).

Types of interventions

Comparison 1: Plasma transfusion (for example, when an INR is 1.5 or above; INR 2 or above; INR 3 or above; or other study-specified INR or prothrombin time (PT) ratio threshold; or thromboelastography guided) versus no plasma transfusion

Comparison 2: plasma transfusion when an INR is at a higher threshold (for example, INR 2 or above or INR > 3 or thromboelastography guided) versus plasma transfusion when INR is at a lower threshold (for example INR 1.5 or above)

Types of outcome measures

Primary outcomes

- Major procedure-related bleeding within 24 hours of the procedure (as defined by 24 hours after removal of lumbar puncture needle or catheter in the case of epidural anaesthesia). For example: spinal haematoma; intraventricular, intracerebral or subarachnoid haemorrhage; or major bleeding (not further defined) as reported by individual studies.
- Serious adverse events:
 - transfusion-related complications within 24 hours of the procedure (including transfusion-related acute lung injury (TRALI), transfusion-transmitted infection, transfusion-associated circulatory overload (TACO), transfusion-associated dyspnoea (TAD), acute transfusion reactions);

- venous and arterial thromboembolism (including deep vein thrombosis; pulmonary embolism; stroke; myocardial infarction) (up to 30 days);
- LP-related or epidural anaesthetic-related complications within seven days of the procedure (infection, headache, cerebral herniation, neurological symptoms such as radicular pain or numbness, back pain).

Secondary outcomes

- All-cause mortality (up to 24 hours and up to 30 days)
- Minor LP-related or epidural anaesthetic-related bleeding within 24 hours of the procedure (defined as prolonged bleeding at the insertion site that only required treatment with a pressure bandage) or minor bleeding (not further defined) as reported by individual studies.
 - Total number of days in hospital.
 - Proportion of patients receiving plasma transfusions within 24 hours of the procedure.
 - Change in baseline coagulation test abnormalities PT ratio, INR or as defined by the study within 24 hours after the plasma transfusion.
 - Quality of life, as defined by the individual studies.

Search methods for identification of studies

The Systematic Review Initiative's Information Specialist (CD) formulated the search strategies in collaboration with the Cochrane Haematological Malignancies Group.

Electronic searches

We will search the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL, the Cochrane Library, current issue) (<http://www.cochranelibrary.com/>) ([Appendix 1](#)).
- MEDLINE (OvidSP, Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE 1946 to present) ([Appendix 2](#)).
- Embase (OvidSP, 1974 to present) ([Appendix 3](#)).
- CINAHL (EBSCOHost, 1937 to present) ([Appendix 4](#)).
- PubMed (e-publications ahead of print only) (<http://www.ncbi.nlm.nih.gov/pubmed>) ([Appendix 5](#)).
- Transfusion Evidence Library (1950 to present) (www.transfusionevidencelibrary.com), this includes a search of grey literature ([Appendix 6](#)).
- LILACS (1980 to present) (<http://lilacs.bvsalud.org/en/>) ([Appendix 7](#)).
- IndMed (1986 to present) (<http://indmed.nic.in/indmed.html>) ([Appendix 8](#)).
- KoreaMed (1958 to present) (<http://koreamed.org/>) ([Appendix 9](#)).

- PakMediNet (1995 to present) (<http://www.pakmedinet.com/>) ([Appendix 10](#)).
- Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (Thomson Reuters, 1990 to present) ([Appendix 11](#)).

We will search for ongoing trials in the following clinical trial registers.

- ClinicalTrials.gov (<https://www.clinicaltrials.gov/>) ([Appendix 12](#)).
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (<http://apps.who.int/trialsearch/>) ([Appendix 13](#)).

We will combine searches in MEDLINE and Embase with the recommended Cochrane RCT search filters ([Lefebvre 2011](#)) and with systematic review and observational studies filters based on those of the Scottish Intercollegiate Guidelines Network (SIGN) (www.sign.ac.uk/methodology/filters.html). Searches in CINAHL will be combined with SIGN systematic review, observational studies and RCT filters. We will not limit searches by language, year of publication or publication type. Once we identify studies for inclusion we will search MEDLINE (Ovid) for errata or retraction statements for the reports of these studies.

Searching other resources

We will conduct handsearching 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

We will summarise data in accordance with standard Cochrane methodologies.

Selection of studies

We will select studies with reference to the methods outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). The Systematic Review Initiative's Information Specialist (CD) will initially screen all search hits for relevance against the eligibility criteria and discard all those that are clearly irrelevant. Thereafter, two review authors (LE, MD) will independently screen all the remaining references for relevance against the full eligibility criteria.

Full-text papers will be retrieved for all references for which a decision on eligibility cannot be made from title and abstract alone. We will request additional information from study authors as necessary to assess the eligibility for inclusion of individual studies.

The two review authors will discuss the results of study selection and try to resolve any discrepancies between themselves. In the event that this is not possible, the decision of eligibility will be referred to a third review author (SS).

The results of study selection will be reported using a PRISMA flow diagram (Moher 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 the *Cochrane Handbook for Systematic Reviews of Interventions*, two review authors (LE, MD) will independently extract data onto standardised forms and perform a cross-check (Higgins 2011a). The data extraction form will be piloted on two included studies. The review authors will come to a consensus on the required changes. If an agreement cannot be reached, a third author (SS) will be consulted. 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.

The following information will be extracted for each study.

- Source: Study ID; report ID; review author ID; date of extraction; ID of author checking extracted data; citation of paper; contact authors details.
- General study information: Publication type; study objectives; funding source; conflict of interest declared; other relevant study publication reviewed.
- Study details & methods: Location; country; setting; number of centres; total study duration; recruitment dates; length of follow-up; power calculation; primary analysis (and definition); stopping rules; method of sequence generation; allocation concealment; blinding (of clinicians, participants and outcome assessors); any other concerns regarding bias; inclusion and exclusion criteria.
- Characteristics of interventions: Number of study arms; description of experimental arm; description of control arm; and other relevant information.
- Characteristics of participants: Age; gender; primary diagnosis; subgroup classification of primary disease type where appropriate, severity of primary disease, where appropriate, prognostic classification of primary disease where appropriate; additional therapy received; risk of alloimmunisation; baseline haematology laboratory parameters; confounders reported.
- Participant flow: Total number screened for inclusion; total number recruited; total number excluded; total number allocated to each study arm; total number analysed (for review outcomes); number of allocated patients who received planned treatment; number of dropouts with reasons (percentage in each arm); protocol violations; missing data.

- Outcomes: Major procedure-related bleeding within 24 hours of the procedure; serious adverse events (transfusion-related complications within 24 hours of the procedure; venous and arterial thromboembolism; LP-related or epidural anaesthetic-related complications within seven days of the procedure); all-cause mortality (up to 24 hours and up to 30 days); minor LP-related or epidural anaesthetic-related bleeding within 24 hours of the procedure; total number of days in hospital; proportion of patients receiving plasma transfusions within 24 hours of the procedure; venous and arterial thromboembolism; change in baseline coagulation test abnormalities; quality of life, as defined by the individual studies.

- For interventional cohort and pre-post single arm or multiple arms studies, we will also collect data if available on: confounding factors, the comparability of groups on confounding factors; methods used to control for confounding and on multiple effect estimates (both unadjusted and adjusted estimates) as recommended in chapter 13 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2011).

Assessment of risk of bias in included studies

Randomised Controlled Trials (RCTs)

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 for Systematic Reviews of Interventions* (Higgins 2011b). Two review authors (LE, MD) 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 (SS). We will use Cochrane's tool for assessing risk of bias, that will include the following domains.

Selection bias

We will describe for each included study if and how the allocation sequence was generated and if allocation was adequately concealed prior to assignment. We will also describe the method used to conceal the allocation sequence in detail and determine if intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

Performance bias

We will describe for each included study, where possible, if the study participants and personnel were adequately blinded from knowledge of which intervention a participant received. We will

judge studies as low risk of bias if they were blinded, or if we judge that lack of blinding could not have affected the results.

Detection bias:

Was blinding of the outcome assessors effective in preventing systematic differences in the way in which the outcomes were determined?

Attrition bias

We will describe for each included study the attrition bias due to amount, nature or handling of incomplete outcome data. We will also try to evaluate whether intention-to-treat analysis has been performed or could be performed from published information.

Reporting bias

We will describe for each included study the possibility of selective outcome reporting bias.

Other issues

Was the study apparently free of other problems that could put it at risk of bias?

We will summarise the risk of bias for each key outcome for each included study. We will judge studies with at least one domain of high risk at high risk of bias overall etc.

Non-randomised studies

We will use ROBINS-I tool (formerly known as ACROBAT-NRSI) to rate the quality of non-randomised controlled trials (non-RCTs) and controlled before-after studies (CBAs) studies (Sterne 2014). This tool is based on the Cochrane 'Risk of bias' tool for rating the quality of RCTs (Higgins 2011c). The tool covers seven domains and the quality of evidence is rated as low, moderate, serious, critical or no information (see Appendix 14 for a copy of the tool), and uses signalling questions for the assessment of:

- bias due to confounding;
- bias in the selection of participants;
- bias in measurement of interventions;
- bias due to departure from intended interventions;
- bias due to missing data;
- bias in measurement of outcomes;
- bias in the selection of the reported result.

We will resolve disagreements on the assessment of quality of an included trial by discussion until we reach consensus or failing that by consulting a third review author (SS).

We have pre-specified the following main potential confounding factors.

- Primary diagnosis of patient (e.g. liver disease; critical illness; pregnancy)
- Age: variability in the age of patients included, e.g. paediatric (less than 16 years) versus adult (> 16 years) versus older adult (> 60 years)
- Gender: male to female ratio
- Previous severe bleeding (e.g. World Health Organization (WHO) grade 3 or 4 or equivalent)

Measures of treatment effect

Randomised controlled trials (RCTs)

For continuous outcomes, we will record the mean, standard deviation and total number of participants in both the treatment and control groups. For dichotomous outcomes, we will record the number of events and the total number of participants in both the treatment and control groups.

For continuous outcomes using the same scale, we will perform analyses using the mean difference (MD) with 95% confidence intervals (CIs). If continuous outcomes are reported using different scales we will use standardised mean difference (SMD).

If available, we will extract and report hazard ratios (HRs) for time-to-event data (mortality or time in hospital) 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 RRs or MDs in a meta-analysis, but for completeness, we will also perform a separate meta-analysis of data from studies providing only RRs or MDs for the same outcome.

For dichotomous outcomes, we will report the pooled risk ratio (RR) with a 95% CI (Deeks 2011). 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).

For cluster-randomised trials, we will extract and report direct estimates of the effect measure (e.g. RR with a 95% CI) from an analysis that accounts for the clustered design. We will obtain statistical advice (MT) to ensure the analysis is appropriate. If appropriate analyses are not available, we will make every effort to approximate the analysis following the recommendations in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011d).

If data allow, we will undertake quantitative assessments using Review Manager 5 (RevMan 2014).

Non-randomised studies

For dichotomous outcomes, if available we will extract and report the RR with a 95% CI from statistical analyses adjusting for baseline differences (such as Poisson regressions or logistic regressions)

or the ratio of risk ratios (i.e. the risk ratio post intervention/risk ratio pre intervention). For continuous variables, if available we will extract and report the absolute change from a statistical analysis adjusting for baseline differences (such as regression models, mixed models or hierarchical models), or the relative change adjusted for baseline differences in the outcome measures (i.e. the absolute post-intervention difference between the intervention and control groups, as well as the absolute pre-intervention difference between the intervention and control groups/the post-intervention level in the control group) (EPOC 2015).

If data allow, we will undertake quantitative assessments using Review Manager 5 (RevMan 2014).

All studies

Where appropriate, we will report the number needed to treat to benefit (NNTB) and the number needed to treat to harm (NNTH) with 95% CIs.

If we cannot report the available data in any of the formats described above, we will perform a narrative report, and if appropriate, we will present the data in tables.

Unit of analysis issues

We do not expect to encounter unit of analysis issues as cluster-randomised trials, cross-over studies, and multiple observations for the same outcome are unlikely to be included in this review. Should any studies of these designs arise, we will treat these in accordance with the advice given in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c).

Dealing with missing data

Where we identify data to be missing or unclear in published literature, we will contact study authors directly. If unsuccessful, our analysis will be based on the number reaching follow-up and we will perform analysis for worse- and best-case scenarios. We will record the number of patients lost to follow-up for each study. Where possible, we will analyse data by intention-to-treat (ITT), but if insufficient data are available, we will present per protocol (PP) analyses (Higgins 2011c).

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 analyse the data in RCTs, non-RCTs, and CBA studies separately.

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 χ^2 test with a significance level at $P < 0.1$. We

will use the I^2 statistic to quantify the degree of potential heterogeneity and classify it as low if the I^2 is $\leq 50\%$, moderate if the I^2 is 50% to 80% or considerable if the I^2 is $> 80\%$. We will use the random-effects model for low to moderate heterogeneity. If statistical heterogeneity is considerable, and we cannot identify a cause for the heterogeneity, the overall summary statistic will not be reported. Potential causes of heterogeneity will be assessed by sensitivity and subgroup analyses (Deeks 2011).

Assessment of reporting biases

Where at least 10 studies are identified for inclusion in a meta-analysis, we will explore potential publication bias (small trial bias) by generating a funnel plot and using a linear regression test. We will consider a P value of less than 0.1 as significant for this test (Lau 2006, Sterne 2011).

Data synthesis

If studies are sufficiently homogenous in their study design, we will conduct meta-analyses according to Cochrane recommendations (Deeks 2011). We will not conduct meta-analyses that include both RCTs and non-RCTs. We will conduct separate meta-analyses for each comparison. Different thresholds within the comparisons will only be grouped together if they are considered to be clinically similar.

Randomised controlled trials (RCTs)

For RCTs where meta-analysis is feasible, we will use the random-effects model for pooling the data. For binary outcomes, we will base the estimation of the between-study variance on the Mantel-Haenszel estimator. We will use the inverse-variance method for continuous outcomes, outcomes that include data from cluster-RCTs, or outcomes where HRs are available. 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.

Non-randomised studies

If meta-analysis is feasible for non-RCTs or CBA studies, we will analyse non-RCTs and CBA studies separately. We will only analyse outcomes with adjusted effect estimates if these are adjusted for the same factors using the inverse-variance method as recommended in chapter 13 of the *Cochrane Handbook of Systematic Reviews of Interventions* (Reeves 2011).

All studies

We will use the random-effects model for all analyses as we anticipate that true effects will be related but will not be the same for included studies. If we cannot perform a meta-analysis, we will comment on the results as a narrative with the results from all studies presented in tables.

Summary of Findings

We will use the GRADE tool (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of evidence for each outcome. We will present a 'Summary of findings' table as suggested in Chapters 11 and 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schunemann 2011a; Schunemann 2011b). The outcomes we will include are listed below in order of most relevant endpoints for patients.

- Major procedure-related bleeding
- Serious adverse events - transfusion-related
- Serious adverse events - venous and arterial thromboembolism
- Serious adverse events - LP or epidural-related
- All-cause mortality
- Total number of days in hospital
- Quality of life, as defined by the individual studies.

Subgroup analysis and investigation of heterogeneity

If adequate data are available, we will perform subgroup analyses for each of the following outcomes in order to assess the effect on heterogeneity.

- Type of participant (such as obstetric, intensive care, liver disease, etc.)
- Age of participants grouped as infant (0 to 1 year); paediatric (1 to 16 years) adult (17 years to 60 years) elderly adult (greater than 60 years)

- Underlying bleeding tendencies (e.g. associated thrombocytopenia, platelet dysfunction)
- Type of procedure (diagnostic LP; therapeutic LP; epidural catheter)
- Type of plasma component
- Dose of plasma component

Sensitivity analysis

We will assess the robustness of our findings by performing the following sensitivity analyses where appropriate:

- including only those studies with a 'low risk of bias' (e.g. RCTs with methods assessed as low risk for random sequence generation and concealment of treatment allocation);
- including only those studies with less than a 20% dropout rate.

ACKNOWLEDGEMENTS

We thank the editorial base of the Cochrane Haematological Malignancies Review Group.

We thank the peer and consumer reviewers of this protocol (Guido Schwarzer, Liat Vidal, and Therese Dowswell).

We thank NHS Blood and Transplant.

We thank the National Institute of Health Research (NIHR). This review is part of a series of reviews that have been funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components. This research was also supported by the NIHR Oxford Biomedical Research Centre Programme. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

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- * Indicates the major publication for the study

APPENDICES

Appendix 1. CENTRAL (the Cochrane Library) 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 near/5 (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*))
- #6 ((autologous or homolog* or allogene* or allo-gen*) next plasma)
- #7 (FFP or SDFFP or MBFFP or uniplas* or octaplas* or FP24 or frischplasma or "clinical plasma")
- #8 (plasma near/3 (pathogen inactivated or pathogen reduced or universal or donor*))
- #9 ((pasteurized or pasteurised or methylene or solvent or detergent or cryoprecipitate or supernatant or cryosupernatant or thawed) near/5 plasma)
- #10 #1 or #4 or #5 or #6 or #7 or #8 or #9
- #11 MeSH descriptor: [Spinal Puncture] this term only
- #12 MeSH descriptor: [Anesthesia, Epidural] explode all trees
- #13 MeSH descriptor: [Anesthesia, Spinal] this term only
- #14 MeSH descriptor: [Injections, Spinal] explode all trees
- #15 MeSH descriptor: [Myelography] this term only
- #16 MeSH descriptor: [Nerve Block] explode all trees
- #17 ((spine or spinal or intraspinal* or dura* or intradural* or extradural* or lumbar* or intralumbar* or theca* or intrathecal or subarachnoid* or peridural* or caudal*) near/6 (punctur* or inject* or infus* or anesth* or anaesth* or needle* or tap* or catheter* or block* or drug* or administ*))
- #18 ((intrathecal or theca*) near/6 (treatment* or chemotherapy or antibiotic* or therapy or inject*))
- #19 (epidural or nerve block* or chemical neurolys* or chemoneurolys* or chemodenervation* or myelogra*)
- #20 #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
- #21 #10 and #20

Appendix 2. MEDLINE (OvidSP) search strategy

- 1. Plasma/
- 2. Blood Component Transfusion/ and plasma.tw,kf.
- 3. (plasma adj5 (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*).tw,kf.
- 4. ((autologous or homolog* or allogene* or allo-gen*) adj plasma).tw,kf.
- 5. (FFP or SDFFP or MBFFP or uniplas* or octaplas* or FP24 or frischplasma or clinical plasma).tw,kf.
- 6. (plasma adj3 (pathogen inactivated or pathogen reduced or universal or donor*).tw,kf.
- 7. ((pasteurized or pasteurised or methylene or solvent or detergent or cryoprecipitate or supernatant or cryosupernatant or thawed) adj5 plasma).tw,kf.
- 8. or/1-7
- 9. Spinal Puncture/
- 10. exp Anesthesia, Epidural/
- 11. Anesthesia Spinal/
- 12. exp Injections, Spinal/
- 13. Myelography/
- 14. exp Nerve Block/
- 15. ((spine or spinal or intraspinal* or dura* or intradural* or extradural* or lumbar* or intralumbar* or theca* or intrathecal or subarachnoid* or peridural* or caudal*) adj6 (punctur* or inject* or infus* or anesth* or anaesth* or needle* or tap* or catheter* or block* or drug* or administ*).tw,kf.
- 16. ((intrathecal or theca*) adj6 (treatment* or chemotherapy or antibiotic* or therapy or inject*).tw,kf.

17. (epidural or nerve block* or chemical neurolysis* or chemoneurolysis* or chemodenervation* or myelogra*).tw,kf.
18. or/9-17
19. 8 and 18
20. RANDOMIZED CONTROLLED TRIAL.pt.
21. CONTROLLED CLINICAL TRIAL.pt.
22. (randomi* or trial*).tw,kf.
23. (placebo* or randomly or groups).ab.
24. CLINICAL TRIALS AS TOPIC.sh.
25. or/20-24
26. exp COHORT STUDIES/
27. (cohort* or controlled trial* or controlled stud* or comparative trial* or comparative stud* or comparison group* or comparator group* or control group*).tw,kf.
28. ((follow up or observational) adj (study or studies)).tw,kf.
29. (longitudinal* or retrospective* or prospective* or cross sectional*).mp.
30. CROSS-SECTIONAL STUDIES/
31. CONTROLLED BEFORE-AFTER STUDIES/
32. OBSERVATIONAL STUDY/
33. HISTORICALLY CONTROLLED STUDY/
34. INTERRUPTED TIME SERIES ANALYSIS/
35. (nonrandom* or non random*).tw,kf.
36. ((before adj15 (after or during)) or "before-after" or time series or time point* or repeated measur*).tw,kf.
37. (pre-post or pre-test* or pretest* or posttest* or post-test* or (pre adj5 post)).tw,kf.
38. or/26-37
39. Meta-Analysis.pt.
40. (meta analy* or metaanaly*).ab.
41. META-ANALYSIS/
42. or/39-41
43. (studies or trials).ab.
44. 42 and 43
45. (meta analy\$ or metaanaly\$).ti.
46. (systematic* adj2 (review* or overview*)).tw,kf.
47. (cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or science citation index or search terms or published articles or search strateg* or reference list* or bibliograph* or handsearch* or hand search* or manual* search*).ab.
48. (additional adj (papers or articles or sources)).ab.
49. (electronic adj (sources or resources or databases)).ab.
50. (relevant adj (journals or articles)).ab.
51. "REVIEW LITERATURE AS TOPIC"/
52. META-ANALYSIS AS TOPIC/
53. or/44-52
54. Review.pt.
55. exp CLINICAL TRIALS AS TOPIC/
56. selection criteria.ab. or critical appraisal.ti.
57. (data adj (extraction or analys*)).ab.
58. RANDOMIZED CONTROLLED TRIALS/
59. OBSERVATIONAL STUDY/
60. ((cohort* or observational or retrospective*) adj1 (trial* or stud*)).tw,kf.
61. or/55-59
62. 54 and 61
63. 53 or 62
64. (Comment or Letter or Editorial).pt.
65. 63 not 64
66. 25 or 38 or 65
67. exp animals/ not humans/

68. 66 not 67
69. 19 and 68

Appendix 3. Embase (OvidSP) search strategy

1. Fresh Frozen Plasma/
2. Plasma Transfusion/
3. (plasma adj5 (transfus* or prophyla* or fresh* or frozen or freez* or prefrozen or prefroz* or thaw* or prethaw* or infus* or treatment* or therap* or administ* or donor* or donat*)).tw.
4. ((autologous or homolog* or allogene* or allo-gen*) adj plasma).tw.
5. (FFP or SDFFP or MBFFP or uniplas* or octaplas* or FP24 or frischplasma or clinical plasma).tw.
6. (plasma adj3 (pathogen inactivated or pathogen reduced or universal)).tw.
7. ((pasteurized or pasteurised or methylene or solvent or detergent or cryoprecipitate or supernatant or cryosupernatant or thawed) adj5 plasma).tw.
8. or/1-7
9. Lumbar Puncture/
10. Puncture/
11. exp Intraspinal Drug Administration/
12. exp Epidural Anesthesia/
13. Spinal Anesthesia/
14. Myelography/
15. exp Nerve Block/
16. ((spine or spinal or intraspinal* or dura* or intradural* or extradural* or lumbar* or intralumbar* or theca* or intrathecal or subarachnoid* or peridural* or caudal*) adj6 (punctur* or inject* or infus* or anesth* or anaesth* or needle* or tap* or catheter* or block* or drug* or administ*)).tw.
17. ((intrathecal or theca*) adj6 (treatment* or chemotherapy or antibiotic* or therapy or inject*)).tw.
18. (epidural or nerve block* or chemical neurolys* or chemoneurolys* or chemodenervation* or myelogra*).tw.
19. or/9-18
20. 8 and 19
21. MAJOR CLINICAL STUDY/
22. LONGITUDINAL STUDY/
23. RETROSPECTIVE STUDY/
24. OBSERVATIONAL STUDY/
25. INTERVENTION STUDY/
26. PROSPECTIVE STUDY/ not RANDOMIZED CONTROLLED TRIAL/
27. COHORT ANALYSIS/
28. COMPARATIVE STUDY/
29. (cohort* or controlled trial* or controlled stud* or comparative trial* or comparative stud* or comparison group* or comparator group* or control group*).tw.
30. ((follow up or observational) adj (study or studies)).tw.
31. (longitudinal* or retrospective* or prospective* or cross sectional*).mp.
32. (nonrandom* or non random*).tw.
33. ((before adj15 (after or during)) or "before-after" or time series or time point* or repeated measur*).tw.
34. (pre-post or pre-test* or pretest* or posttest* or post-test* or (pre adj5 post)).tw.
35. or/21-34
36. Meta Analysis/
37. Systematic Review/
38. (meta analy* or metaanalys*).tw.
39. (systematic adj2 (review* or overview* or search*)).tw.
40. (literature adj2 (review* or overview* or search*)).ti,ab.
41. (cochrane or embase or cinahl or cinhal or lilacs or BIDS or science citation index or psyclit or psychlit or psycinfo or psychinfo or cancerlit).ti,ab.

42. (electronic* adj (sources or resources or databases)).ab.
43. reference lists.ab.
44. (bibliograph* or handsearch* or hand search* or manual* search*).ab.
45. (hand-search* or handsearch*).ab.
46. (additional adj (papers or articles or sources)).ab.
47. (relevant adj (journals or articles)).ab.
48. (search term* or published articles or search strateg*).ab.
49. 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50. data extraction.ab.
51. selection criteria.ab.
52. 50 or 51
53. review.pt.
54. 52 and 53
55. editorial.pt.
56. 49 or 54
57. 56 not 55
58. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/
59. (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.
60. 58 or 59
61. 35 or 57 or 60
62. 20 and 61

Appendix 4. CINAHL (EBSCOHost) search strategy

- S1 (MH "Plasma")
- S2 (MH "Blood Component Transfusion")
- S3 TX plasma
- S4 S2 AND S3
- S5 TX (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*))
- S6 TX ((autologous or allogene* or allo-gen* or homolog*) next plasma)
- S7 TX (FFP or SDFFP or MBFFP or uniplas* or octaplas* or FP24 or frischplasma or clinical plasma)
- S8 TX (plasma N3 (pathogen inactivated or pathogen reduced or universal or donor*))
- S9 TX ((pasteurized or pasteurised or methylene or solvent or detergent or cryoprecipitate or supernatant or cryosupernatant or thawed) N5 plasma)
- S10 S1 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9
- S11 (MH "Spinal Puncture")
- S12 (MH "Anesthesia, Epidural") OR (MH "Anesthesia, Spinal") OR (MH "Nerve Block+")
- S13 (MH "Injections, Intraspinal+")
- S14 (MH "Myelography")
- S15 TX ((spine or spinal or intraspinal* or dura* or intradural* or extradural* or lumbar* or intralumbar* or theca* or intrathecal or subarachnoid* or peridural* or caudal*) N6 (punctur* or inject* or infus* or anesth* or anaesth* or needle* or tap* or catheter* or block* or drug* or administ*))
- S16 TX ((intrathecal or theca*) N6 (treatment* or chemotherapy or antibiotic* or therapy or inject*))
- S17 TX (epidural or nerve block* or chemical neurolys* or chemoneurolys* or chemodenervation* or myelogra*)
- S18 S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17
- S19 S10 AND S18
- S20 (MH "Prospective Studies+")
- S21 (MH "Case Control Studies+")
- S22 (MH "Correlational Studies") OR (MH "Cross Sectional Studies")
- S23 TI ((cohort study or cohort studies)) OR AB ((cohort study or cohort studies))

S24 TI ((observational stud* or retrospective stud*)) OR AB ((observational stud* or retrospective stud*))
 S25 S20 OR S21 OR S22 OR S23 OR S24
 S26 (MH Clinical Trials+)
 S27 PT Clinical Trial
 S28 TI ((controlled trial*) or (clinical trial*)) OR AB ((controlled trial*) or (clinical trial*))
 S29 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*))
 S30 TI randomi* OR AB randomi*
 S31 MH RANDOM ASSIGNMENT
 S32 TI ((phase three) or (phase III) or (phase three)) or AB ((phase three) or (phase III) or (phase three))
 S33 (TI (random* N2 (assign* or allocat*))) OR (AB (random* N2 (assign* or allocat*))))
 S34 MH PLACEBOS
 S35 MH META ANALYSIS
 S36 MH SYSTEMATIC REVIEW
 S37 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*")
 S38 TI ("literature review" OR "literature overview" OR "literature search*") OR AB ("literature review" OR "literature overview" OR "literature search*")
 S39 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)
 S40 TI placebo* OR AB placebo*
 S41 MH QUANTITATIVE STUDIES
 S42 S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41
 S43 S25 OR S42
 S44 S19 AND S43

Appendix 5. PubMed (for epublications ahead of print only)

#1 (plasma AND (transfus* OR prophyla* OR fresh* OR frozen OR freez* OR prefrozen OR prefrez* OR thaw* OR prethaw* OR infus* OR treatment* OR therapy OR therapeutic* OR therapies OR administ* OR donor* OR donat* OR autologous OR allogene* OR allo-gen* OR homolog* OR pathogen inactivated OR pathogen reduced OR universal OR donor* OR pasteurized OR pasteurised OR methylene OR solvent OR detergent OR cryoprecipitate OR supernatant OR cryosupernatant OR thawed))
 #2 (FFP OR SDFFP OR MBFFP OR uniplas* OR octaplas* OR FP24 OR frischplasma OR "clinical plasma")
 #3 #1 OR #2
 #4 ((spine OR spines OR spinal OR intraspinal* OR dura OR dural OR intradural OR extradural OR lumbar* OR intralumbar* OR theca* OR intrathecal OR subarachnoid* OR peridural* OR caudal*) AND (punctur* OR inject* OR infus* OR anesth* OR anaesth* OR needle* OR tap OR taps OR catheter* OR block* OR drug* OR administ*))
 #5 ((intrathecal OR theca*) AND (treatment* OR chemotherapy OR antibiotic* OR therapy OR therapeutic* OR inject*))
 #6 (epidural OR nerve block* OR chemical neurolysis* OR chemoneurolysis* OR chemodenervation* OR myelogra*)
 #7 #4 OR #5 OR #6
 #8 #3 AND #7
 #9 ((random* OR blind* OR "control group" OR placebo OR "controlled trial" OR "controlled study" OR groups OR trials OR "systematic review" OR "systematic overview" OR "meta-analysis" OR metaanalysis OR "literature search" OR medline OR cochrane OR embase OR cohort* OR observational* OR retrospective* OR non-random* OR "before and after")
 #10 (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]))
 #11 #8 AND #9 AND #10

Appendix 6. Transfusion Evidence Library search strategy

Subject Area: Plasma/FFP

Search Box: spine OR spines OR spinal OR intraspinal OR dura OR dural OR intradural OR extradural OR epidural OR lumbar OR intralumbar OR theca OR intrathecal OR subarachnoid OR peridural OR caudal OR myelograph OR myelography

Appendix 7. LILACS search strategy

tw:(((spine OR spines OR spinal OR intraspinal OR dura OR dural OR intradural OR extradural OR lumbar* OR intralumbar* OR theca* OR intrathecal OR subarachnoid* OR peridural* OR caudal*) AND (punctur* OR inject* OR infus* OR anesth* OR anaesth* OR needle* OR tap OR taps OR catheter* OR block* OR drug* OR administ*)) OR ((intrathecal OR theca*) AND (treatment* OR chemotherapy OR antibiotic* OR therapy OR therapeutic* OR inject*)) OR epidural OR myelogra*) AND ((plasma AND (transfus* OR prophyla* OR fresh* OR frozen OR freez* OR prefrozen OR prefrez* OR thaw* OR prethaw* OR infus* OR treatment* OR therapy OR therapeutic* OR therapies OR administ* OR donor* OR donat* OR autologous OR allogene* OR allo-gen* OR homolog* OR pathogen inactivated OR pathogen reduced OR universal OR donor* OR pasteurized OR pasteurised OR methylene OR solvent OR detergent OR cryoprecipitate OR supernatant OR cryosupernatant OR thawed)) OR (FFP OR SDFFP OR MBFFP OR uniplas* OR octaplas* OR FP24 OR frischplasma OR "clinical plasma")) AND (instance:"regional") AND (db:"LILACS") AND type_of_study:(clinical_trials))

Appendix 8. IndMed search strategy

(spine OR spines OR spinal OR intraspinal OR dura OR dural OR intradural OR extradural OR epidural OR lumbar OR intralumbar OR thecal OR intrathecal OR subarachnoid OR peridural OR caudal OR myelograph OR myelography) AND (FFP OR SDFFP OR MBFFP OR uniplas OR octaplas OR FP24 OR frischplasma OR plasma) AND (randomized OR randomised OR randomly OR blind OR blinded OR trial OR control group OR cohort OR cohorts OR groups OR observational OR retrospective OR retrospectively)

Appendix 9. KoreaMed search strategy

plasma [ALL] AND "Randomized Controlled Trial" [PT]
plasma [ALL] AND "Clinical Trial"[PT]
plasma [ALL] AND "Comparative Study"[PT]
plasma [ALL] AND transfus*[ALL] AND retrospective* [ALL]
plasma [ALL] AND transfus*[ALL] AND observational [ALL]
plasma [ALL] AND transfus*[ALL] AND cohort* [ALL]
plasma [ALL] AND transfus*[ALL] AND randomi* [ALL]

Appendix 10. PakMediNet search strategy

(plasma OR FFP) AND (randomised OR randomized OR observational OR retrospective OR cohort OR cohorts)

Appendix 11. Web of Science CPCI-S search strategy

#1 TS=((spine OR spines OR spinal OR intraspinal OR dura OR dural OR intradural OR extradural OR lumbar* OR intralumbar* OR theca* OR intrathecal OR subarachnoid* OR peridural* OR caudal*) AND (punctur* OR inject* OR infus* OR anesth* OR anaesth* OR needle* OR tap OR taps OR catheter* OR block* OR drug* OR administ*)) OR ((intrathecal OR theca*) AND (treatment* OR chemotherapy OR antibiotic* OR therapy OR therapeutic* OR inject*)) OR epidural OR myelogra*)

#2 TS=((plasma AND (transfus* OR prophyla* OR fresh* OR frozen OR freez* OR prefrozen OR prefreez* OR thaw* OR prethaw* OR infus* OR treatment* OR therapy OR therapeutic* OR therapies OR administ* OR donor* OR donat* OR autologous OR allogene* OR allo-gen* OR homolog* OR pathogen inactivated OR pathogen reduced OR universal OR donor* OR pasteurized OR pasteurised OR methylene OR solvent OR detergent OR cryoprecipitate OR supernatant OR cryosupernatant OR thawed)) OR (FFP OR SDFFP OR MBFFP OR uniplas* OR octaplas* OR FP24 OR frischplasma OR "clinical plasma"))

#3 TS= (systematic* OR random* OR blind* OR trial* OR control* OR groups OR cohort* OR observational* OR retrospective* OR cross-sectional* OR "before and after")

#4 #1 AND #2 AND #3

Appendix 12. ClinicalTrials.gov search strategy

Search Terms: spine OR spines OR spinal OR intraspinal OR dura OR dural OR intradural OR extradural OR epidural OR lumbar OR intralumbar OR thecal OR intrathecal OR subarachnoid OR peridural OR caudal OR myelography

Intervention: plasma OR FFP OR SDFFP OR MBFFP OR uniplas OR octaplas OR FP24

Study Type: All studies

Appendix 13. WHO ICTRP search strategy

Title/Intervention: spine OR spines OR spinal OR intraspinal OR dura OR dural OR intradural OR extradural OR epidural OR lumbar OR intralumbar OR thecal OR intrathecal OR subarachnoid OR peridural OR caudal OR myelograph OR myelography

Title/Intervention: plasma OR FFP OR SDFFP OR MBFFP OR uniplas OR octaplas OR FP24

Recruitment Status: All

Appendix 14. ROBINS-I (A Cochrane Risk Of Bias Assessment Tool: for Non-Randomized Studies of Interventions)

ROBINS-I tool (Stage I)

Specify the review question

Participants	People with abnormal coagulation (as defined by the included studies) requiring insertion of a lumbar puncture needle or epidural catheter We will not include people with haemophilia as they should be treated with the appropriate factor concentrate. We will not include people on warfarin as guidelines recommend the use of prothrombin complex concentrate for emergency reversal of warfarin
Experimental intervention 1	Plasma transfusion when: INR 1.5 or above; INR 2 or above; INR 3 or above; or other study specified threshold; or thromboelastography guided

(Continued)

Control intervention 1	No plasma transfusion
Experimental intervention 2	Plasma transfusion when INR is at a higher threshold (for example INR 2 or above or INR 3 or above) or thromboelastography guided
Control intervention 2	Plasma transfusion when INR 1.5 or above
Outcomes	Primary outcomes • The number of participants with at least one bleeding episode. • The total number of days on which bleeding occurred or the total number of bleeding episodes per participant. • The number of participants with at least one episode of severe or life-threatening bleeding. • Time to first bleeding episode from the start of the study. Secondary outcomes • Mortality (all-causes, secondary to bleeding, and secondary to infection). • Number of platelet transfusions per participant and number of platelet components per participant. • Number of red cell transfusions per participant and number of red cell components per participant. • Platelet transfusion interval. • Proportion of participants requiring additional interventions to stop bleeding (surgical, medical e.g. tranexamic acid, other blood products e.g. fresh frozen plasma (FFP), cryoprecipitate, fibrinogen) within x days from the start of the study. • Quality of life assessment using validated tools. • Transfusion-related adverse events (transfusion reactions, transfusion-associated infections, development of platelet antibodies, or platelet refractoriness, thromboembolic events).

List the confounding areas relevant to all or most studies

We have pre-specified the main potential confounding factors.

1. Primary diagnosis of patient (e.g. liver disease; critical illness; pregnancy)
2. Age: variability in the age of patients included, e.g. paediatric (less than 16 years) versus adult (> 16 years) versus older adult (> 60 years)
3. Gender: male to female ratio
4. Previous severe bleeding (e.g. WHO grade 3 or 4 or equivalent)

List the possible co-interventions that could be different between intervention groups and could have an impact on outcomes

We have pre-specified the possible co-interventions that could be different between intervention groups and could have an impact on outcomes.

1. Use of antifibrinolytics or other procoagulant drugs
2. Use of anticoagulants or antiplatelet agents

The ROBINS-I tool (Stage II): For each study

Specify a target trial specific to the study.

Design	Individually randomised/cluster-randomised/matched
Participants	
Experimental intervention	
Control intervention	

Is your aim for this study...?

- ☐ To assess the effect of initiating intervention (as in an intention-to-treat analysis)
- ☐ To assess the effect of initiating and adhering to intervention (as in a per-protocol analysis)

Specify the outcome

Specify which outcome is being assessed for risk of bias (typically from among those earmarked for the 'Summary of findings' table). Specify whether this is a proposed benefit or harm of intervention.

Specify the numerical result being assessed

In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.

Preliminary consideration of confounders

Complete a row for each important confounding area

(i) listed in the review protocol; and

(ii) relevant to the setting of this particular study, or which the study authors identified as potentially important. "Important" confounding areas are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention. "Validity" refers to whether the confounding variable or variables fully measure the area, while "reliability" refers to the precision of the measurement (more measurement error means less reliability).

(i) Confounding areas listed in the review protocol				
Confounding area	Measured Variable (s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding area measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is adjusting for this variable (alone) expected to favour the experimental or the control group?
			Yes / No / No information	Favour intervention / Favour control / No information

(Continued)

(ii) Additional confounding areas relevant to the setting of this particular study, or which the study authors identified as important

Confounding area	Measured Variable (s)	Is there evidence that controlling for this variable was unnecessary?*	Is the confounding area measured validly and reliably by this variable (or these variables)?	OPTIONAL: Is adjusting for this variable (alone) expected to favour the experimental or the control group?
			Yes / No / No information	Favour intervention / Favour control / No information

* In the context of a particular study, variables can be demonstrated not to be confounders and so not included in the analysis: (a) if they are not predictive of the outcome; (b) if they are not predictive of intervention; or (c) because adjustment makes no or minimal difference to the estimated effect of the primary parameter. Note that “no statistically significant association” is not the same as “not predictive”.

Preliminary consideration of co-interventions

Complete a row for each important co-intervention (i) listed in the review protocol; and (ii) relevant to the setting of this particular study, or which the study authors identified as important.

“Important” co-interventions are those for which, in the context of this study, adjustment is expected to lead to a clinically important change in the estimated effect of the intervention.

(i) Co-interventions listed in the review protocol

Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental or the control group
		Favour experimental / Favour comparator / No information

(Continued)

		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

(ii) Additional co-interventions relevant to the setting of this particular study, or which the study authors identified as important

Co-intervention	Is there evidence that controlling for this co-intervention was unnecessary (e.g. because it was not administered)?	Is presence of this co-intervention likely to favour outcomes in the experimental or the control group
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information
		Favour experimental / Favour comparator / No information

'Risk of bias' assessment (cohort-type studies)

Bias domain	Signalling questions	Elaboration	Response options
Bias due to confounding	1.1 Is there potential for confounding of the effect of intervention in this study? If N or PN to 1.1: the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered	In rare situations, such as when studying harms that are very unlikely to be related to factors that influence treatment decisions, no confounding is expected and the study can be considered to be at low risk of bias due to confounding, equivalent to a fully randomised trial There is no NI (No information) option for this signalling question	Y / PY / PN / N
	If Y or PY to 1.1: determine whether there is a need to assess time-varying confounding:		

(Continued)

	1.2. Was the analysis based on splitting participants' follow-up time according to intervention received? If N or PN, answer questions relating to baseline confounding (1.4 to 1.6) If Y or PY, proceed to question 1.3.	If participants could switch between intervention groups then associations between intervention and outcome may be biased by time-varying confounding. This occurs when prognostic factors influence switches between intended interventions	NA / Y / PY / PN / N / NI
	1.3. Were intervention discontinuations or switches likely to be related to factors that are prognostic for the outcome? If N or PN, answer questions relating to baseline confounding (1.4 to 1.6) If Y or PY, answer questions relating to both baseline and time-varying confounding (1.7 and 1.8)	If intervention switches are unrelated to the outcome, for example when the outcome is an unexpected harm, then time-varying confounding will not be present and only control for baseline confounding is required	NA / Y / PY / PN / N / NI
Questions relating to baseline confounding only			
	1.4. Did the authors use an appropriate analysis method that controlled for all the important confounding areas?	Appropriate methods to control for measured confounders include stratification, regression, matching, standardization, and inverse probability weighting. They may control for individual variables or for the estimated propensity score. Inverse probability weighting is based on a function of the propensity score. Each method depends on the assumption that there is no unmeasured or residual confounding	NA / Y / PY / PN / N / NI
	1.5. If Y or PY to 1.4: Were confounding areas that were controlled for measured validly and reliably by the variables available in this study?	Appropriate control of confounding requires that the variables adjusted for are valid and reliable measures of the confounding domains. For some topics, a list of valid and reliable measures of confounding domains will be specified in the review protocol but for others such a list may not be avail-	NA / Y / PY / PN / N / NI

(Continued)

		able. Study authors may cite references to support the use of a particular measure. If authors control for confounding variables with no indication of their validity or reliability pay attention to the subjectivity of the measure. Subjective measures (e.g. based on self-report) may have lower validity and reliability than objective measures such as lab findings	
	1.6. Did the authors control for any post-intervention variables?	Controlling for post-intervention variables is not appropriate. Controlling for mediating variables estimates the direct effect of intervention and may introduce confounding. Controlling for common effects of intervention and outcome causes bias	NA / Y / PY / PN / N / NI
Questions relating to baseline and time-varying confounding			
	1.7. Did the authors use an appropriate analysis method that adjusted for all the important confounding areas and for time-varying confounding?	Adjustment for time-varying confounding is necessary to estimate per-protocol effects in both randomised trials and NRSI. Appropriate methods include those based on inverse-probability weighting. Standard regression models that include time-updated confounders may be problematic if time-varying confounding is present	NA / Y / PY / PN / N / NI
	1.8. If Y or PY to 1.7: Were confounding areas that were adjusted for measured validly and reliably by the variables available in this study?	See 1.5 above.	NA / Y / PY / PN / N / NI
	'Risk of bias' judgement	Low - No confounding expected. Moderate - Confounding expected, all known important confounding domains appro-	Low / Moderate / Serious / Critical / NI

(Continued)

		appropriately measured and controlled for; and Reliability and validity of measurement of important domains were sufficient, such that we do not expect serious residual confounding	
		Serious - At least one known important domain was not appropriately measured, or not controlled for; or Reliability or validity of measurement of a important domain was low enough that we expect serious residual confounding	
		Critical - Confounding inherently not controllable, or the use of negative controls strongly suggests unmeasured confounding	
	Optional: What is the predicted direction of bias due to confounding?	Can the true effect estimate be predicted to be greater or less than the estimated effect in the study because one or more of the important confounding domains was not controlled for? Answering this question will be based on expert knowledge and results in other studies and therefore can only be completed after all of the studies in the body of evidence have been reviewed. Consider the potential effect of each of the unmeasured domains and whether all important confounding domains not controlled for in the analysis would be likely to change the estimate in the same direction, or if one important confounding domain that was not controlled for in the analysis is	Favours experimental / Favours comparator / Unpredictable

(Continued)

		likely to have a dominant impact	
Bias in selection of participants into the study	2.1. Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention?	This domain is concerned only with selection into the study based on participant characteristics observed after the start of intervention. Selection based on characteristics observed before the start of intervention can be addressed by controlling for imbalances between intervention and control groups in baseline characteristics that are prognostic for the outcome (baseline confounding)	Y / PY / PN / N / NI
	If N or PN to 2.1: go to 2.4		
	2.2. If Y or PY to 2.1: Were the post-intervention variables that influenced selection likely to be associated with intervention	Selection bias occurs when selection is related to an effect of either intervention or a cause of the outcome. Therefore, the result is at risk of selection bias if selection into the study is related to both the intervention and the outcome	NA / Y / PY / PN / N / NI
	2.3 If Y or PY to 2.2: Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?		NA / Y / PY / PN / N / NI
	2.4. Do start of follow-up and start of intervention coincide for most participants?	If participants are not followed from the start of the intervention then a period of follow-up has been excluded, and individuals who experienced the outcome soon after intervention will be missing from analyses. This problem may occur when prevalent, rather than new (incident), users of the intervention are included in analyses	Y / PY / PN / N / NI

(Continued)

	2.5.If Y or PY to 2.2 and 2.3, or N or PN to 2.4: Were adjustment techniques used that are likely to correct for the presence of selection biases?	It is in principle possible to correct for selection biases, for example by using inverse probability weights to create a pseudo-population in which the selection bias has been removed, or by modelling the distributions of the missing participants or follow-up times and outcome events and including them using missing data methodology. However such methods are rarely used and the answer to this question will usually be “No”	NA / Y / PY / PN / N / NI
	'Risk of bias' judgement	Low - All participants who would have been eligible for the target trial were included in the study and start of follow-up and start of intervention coincide for all participants Moderate - Selection into the study may have been related to intervention and outcome, but the authors used appropriate methods to adjust for the selection bias; or Start of follow-up and start of intervention do not coincide for all participants, but (a) the proportion of participants for which this was the case was too low to induce important bias; (b) the authors used appropriate methods to adjust for the selection bias; or (c) the review authors are confident that the rate (hazard) ratio for the effect of intervention remains constant over time Serious - Selection into the study was related to intervention and outcome; or Start of follow-up and start of intervention do not coincide, and a potentially impor-	Low / Moderate / Serious / Critical / NI

(Continued)

		tant amount of follow-up time is missing from analyses, and the rate ratio is not constant over time Critical - Selection into the study was strongly related to intervention and outcome; or A substantial amount of follow-up time is likely to be missing from analyses, and the rate ratio is not constant over time	
	Optional: What is the predicted direction of bias due to selection of participants into the study?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias in classification of interventions	3.1 Were intervention groups clearly defined?	A pre-requisite for an appropriate comparison of interventions is that the interventions are well defined. Ambiguity in the definition may lead to bias in the classification of participants. For individual-level interventions, criteria for considering individuals to have received each intervention should be clear and explicit, covering issues such as type, setting, dose, frequency, intensity and/or timing of intervention. For population-level interventions (e.g. measures to control air pollution), the question relates to whether the population is clearly defined, and the answer is likely to be 'Yes'	Y / PY / PN / N / NI
	3.2 Was the information used to define intervention groups recorded at the start of the intervention?	In general, if information about interventions received is available from sources that could not have been affected by subsequent outcomes, then differential misclassification of intervention status is unlikely. Col-	Y / PY / PN / N / NI

(Continued)

		lection of the information at the time of the intervention makes it easier to avoid such misclassification. For population-level interventions (e.g. measures to control air pollution), the answer to this question is likely to be 'Yes'	
	3.3 Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Collection of the information at the time of the intervention may not be sufficient to avoid bias. The way in which the data are collected for the purposes of the NRSI should also avoid misclassification	Y / PY / PN / N / NI
	'Risk of bias' judgement	Low - Intervention status is well defined and based solely on information collected at the time of intervention	Low / Moderate / Serious / Critical / NI
		Moderate - Intervention status is well defined but some aspects of the assignments of intervention status were determined retrospectively	
		Serious - Intervention status is not well defined, or major aspects of the assignments of intervention status were determined in a way that could have been affected by knowledge of the outcome	
		Critical - (Unusual) An extremely high amount of misclassification of intervention status, e.g. because of unusually strong recall biases	
	Optional: What is the predicted direction of bias due to measurement of outcomes or interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

(Continued)

Bias due to departures from intended interventions	4.1. Was the intervention implemented successfully for most participants?	Consider the success of implementation of the intervention in the context of its complexity. Was recommended practice followed by those administering the intervention?	Y / PY / PN / N / NI
	If your aim for this study is to assess the effect of initiating and adhering to intervention (as in a per-protocol analysis), answer questions 4.2 to 4.4		
	4.2. Did study participants adhere to the assigned intervention regimen?	Lack of adherence to assigned intervention includes cessation of intervention, crossovers to the comparator intervention and switches to another active intervention. We distinguish between analyses where: (1) intervention switches led to follow-up time being assigned to the new intervention, and (2) intervention switches (including cessation of intervention) where follow-up time remained allocated to the original intervention (1) is addressed under time-varying confounding, and should not be considered further here Consider available information on the proportion of study participants who continued with their assigned intervention throughout follow-up. Was lack of adherence sufficient to impact the intervention effect estimate?	NA/ Y / PY / PN / N / NI
	4.3. Were important co-interventions balanced across intervention groups?	Consider the co-interventions that are likely to affect the outcome and to have been administered in the context of this study, based on the preliminary consideration of co-interventions and available literature. Consider whether these co-interventions are balanced between intervention groups	NA/ Y / PY / PN / N / NI

(Continued)

	4.4. If N or PN to 4.1, 4.2 or 4.3: Were adjustment techniques used that are likely to correct for these issues?	Such adjustment techniques include inverse-probability weighting to adjust for censoring at deviation from intended intervention, or inverse probability weighting of marginal structural models to adjust for time-varying confounding. Specialist advice may be needed to assess studies that used these approaches	NA / Y / PY / PN / N / NI
	'Risk of bias' judgement	Low - No bias due to deviation from the intended intervention is expected, for example if both the intervention and comparator are implemented over a short time period, and subsequent interventions are part of routine medical care, or if the specified comparison relates to initiation of intervention regardless of whether it is continued Moderate - Bias due to deviation from the intended intervention is expected, and switches, co-interventions, and some problems with intervention fidelity are appropriately measured and adjusted for in the analyses. Alternatively, most (but not all) deviations from intended intervention reflect the natural course of events after initiation of intervention Serious - Switches in treatment, co-interventions, or problems with implementation fidelity are apparent and are not adjusted for in the analyses Critical - Substantial deviations from the intended intervention are present and are not adjusted for in the analysis	Low / Moderate / Serious / Critical / NI

(Continued)

	Optional: What is the predicted direction of bias due to departures from the intended interventions?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias due to missing data	5.1 Were there missing outcome data?	This aims to elicit whether the proportion of missing observations is likely to result in missing information that could substantially impact our ability to answer the question being addressed. Guidance will be needed on what is meant by 'reasonably complete'. One aspect of this is that review authors would ideally try and locate an analysis plan for the study	Y / PY / PN / N / NI
	5.2 Were participants excluded due to missing data on intervention status?	Missing intervention status may be a problem. This requires that the intended study sample is clear, which it may not be in practice	Y / PY / PN / N / NI
	5.3 Were participants excluded due to missing data on other variables needed for the analysis?	This question relates particularly to participants excluded from the analysis because of missing information on confounders that were controlled for in the analysis	Y / PY / PN / N / NI
	5.4 If Y or PY to 5.1, 5.2 or 5.3: Are the proportion of participants and reasons for missing data similar across interventions?	This aims to elicit whether either (i) differential proportion of missing observations or (ii) differences in reasons for missing observations could substantially impact on our ability to answer the question being addressed	NA / Y / PY / PN / N / NI
	5.5 If Y or PY to 5.1, 5.2 or 5.3: Were appropriate statistical methods used to account for missing data?	It is important to assess whether assumptions employed in analyses are clear and plausible. Both content knowledge and statistical expertise will often be	NA / Y / PY / PN / N / NI

(Continued)

		required for this. For instance, use of a statistical method such as multiple imputation does not guarantee an appropriate answer. Review authors should seek naïve (complete-case) analyses for comparison, and clear differences between complete-case and multiple imputation-based findings should lead to careful assessment of the validity of the methods used	
	'Risk of bias' judgement	Low - Data were reasonably complete; or Proportions of and reasons for missing participants were similar across intervention groups; or Analyses that addressed missing data are likely to have removed any risk of bias Moderate - Proportions of missing participants differ across interventions; or Reasons for missingness differ minimally across interventions; and Missing data were not addressed in the analysis Serious - Proportions of missing participants differ substantially across interventions; or Reasons for missingness differ substantially across interventions; and Missing data were addressed inappropriately in the analysis; or The nature of the missing data means that the risk of bias cannot be removed through appropriate analysis Critical - (Unusual) There were critical differences between interventions in participants with missing data that were not, or could not, be addressed through appropriate analysis	Low / Moderate / Serious / Critical / NI

(Continued)

	Optional: What is the predicted direction of bias due to missing data?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias in measurement of outcomes	6.1 Could the outcome measure have been influenced by knowledge of the intervention received?	Some outcome measures involve negligible assessor judgment, e.g. all-cause mortality or non-repeatable automated laboratory assessments. Risk of bias due to measurement of these outcomes would be expected to be low	Y / PY / PN / N / NI
	6.2 Were outcome assessors aware of the intervention received by study participants?	If outcome assessors were blinded to intervention status, the answer to this question would be 'No'. In other situations, outcome assessors may be unaware of the interventions being received by participants despite there being no active blinding by the study investigators; the answer to this question would then also be 'No'. In studies where participants report their outcomes themselves, for example in a questionnaire, the outcome assessor is the study participant. In an observational study, the answer to this question will usually be 'Yes' when the participants report their outcomes themselves	Y / PY / PN / N / NI
	6.3 Were the methods of outcome assessment comparable across intervention groups?	Comparable assessment methods (i.e. data collection) would involve the same outcome detection methods and thresholds, same time point, same definition, and same measurements	Y / PY / PN / N / NI

(Continued)

	6.4 Were any systematic errors in measurement of the outcome related to intervention received?	This question refers to differential misclassification of outcomes. Systematic errors in measuring the outcome, if present, could cause bias if they are related to intervention or to a confounder of the intervention-outcome relationship. This will usually be due either to outcome assessors being aware of the intervention received or to non-comparability of outcome assessment methods, but there are examples of differential misclassification arising despite these controls being in place	Y / PY / PN / N / NI
	'Risk of bias' judgement	Low - The methods of outcome assessment were comparable across intervention groups; and The outcome measure was unlikely to be influenced by knowledge of the intervention received by study participants (i.e. is objective) or the outcome assessors were unaware of the intervention received by study participants; and Any error in measuring the outcome is unrelated to intervention status Moderate - The methods of outcome assessment were comparable across intervention groups; and The outcome measure is only minimally influenced by knowledge of the intervention received by study participants; and Any error in measuring the outcome is only minimally related to intervention status	Low / Moderate / Serious / Critical / NI

(Continued)

		Serious - The methods of outcome assessment were not comparable across intervention groups; or The outcome measure was subjective (i.e. likely to be influenced by knowledge of the intervention received by study participants) and was assessed by outcome assessors aware of the intervention received by study participants; or Error in measuring the outcome was related to intervention status	
		Critical - The methods of outcome assessment were so different that they cannot reasonably be compared across intervention groups	
	Optional: What is the predicted direction of bias due to measurement of outcomes?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Bias in selection of the reported result	Is the reported effect estimate unlikely to be selected, on the basis of the results, from..		
	7.1. ... multiple outcome <i>measurements</i> within the outcome domain?	For a specified outcome domain, it is possible to generate multiple effect estimates for different measurements. If multiple measurements were made, but only one or a subset is reported, there is a risk of selective reporting on the basis of results	Y / PY / PN / N / NI
	7.2 ... multiple <i>analyses</i> of the intervention-outcome relationship?	Because of the limitations of using data from non-randomised studies for analyses of effectiveness (need to control confounding, substantial missing data,	Y / PY / PN / N / NI

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		etc), analysts may implement different analytic methods to address these limitations. Examples include unadjusted and adjusted models; use of final value vs change from baseline vs analysis of covariance; different transformations of variables; a continuously scaled outcome converted to categorical data with different cut-points; different sets of co-variables used for adjustment; and different analytic strategies for dealing with missing data. Application of such methods generates multiple effect estimates for a specific outcome metric. If the analyst does not pre-specify the methods to be applied, and multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results	
	7.3 ... different <i>subgroups</i> ?	Particularly with large cohorts often available from routine data sources, it is possible to generate multiple effect estimates for different subgroups or simply to omit varying proportions of the original cohort. If multiple estimates are generated but only one or a subset is reported, there is a risk of selective reporting on the basis of results	Y / PY / PN / N / NI
	'Risk of bias' judgement	Low - There is clear evidence (usually through examination of a pre-registered protocol or statistical analysis plan) that all reported results correspond to all intended outcomes, analyses and sub-cohorts Moderate - The outcome measurements and analyses are consistent with an a priori plan; or	Low / Moderate / Serious / Critical / NI

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		are clearly defined and both internally and externally consistent; and There is no indication of selection of the reported analysis from among multiple analyses; and There is no indication of selection of the cohort or subgroups for analysis and reporting on the basis of the results	
		Serious - Outcome measurements or analyses are internally or externally inconsistent; or There is a high risk of selective reporting from among multiple analyses; or The cohort or subgroup is selected from a larger study for analysis and appears to be reported on the basis of the results	
		Critical - There is evidence or strong suspicion of selective reporting of results, and the unreported results are likely to be substantially different from the reported results	
	Optional: What is the predicted direction of bias due to selection of the reported result?	If the likely direction of bias can be predicted, it is helpful to state this. The direction might be characterized either as being towards (or away from) the null, or as being in favour of one of the interventions	Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable
Overall bias	'Risk of bias' judgement	Low - The study is judged to be at low risk of bias for all domains	Low / Moderate / Serious / Critical / NI
		Moderate - The study is judged to be at low or moderate risk of bias for all domains	
		Serious - The study is judged to be at serious risk of bias in at least one domain, but not at	

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		critical risk of bias in any domain	
		Critical - The study is judged to be at critical risk of bias in at least one domain	
		No information - There is no clear indication that the study is at serious or critical risk of bias and there is a lack of information in one or more key domains of bias (a judgement is required for this)	
	Optional: What is the overall predicted direction of bias for this outcome?		Favours experimental / Favours comparator / Towards null / Away from null / Unpredictable

CONTRIBUTIONS OF AUTHORS

- Lise Estcourt: conceiving the review, protocol development, content expert.
- Michael Desborough: protocol development, content expert
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- Sally Hopewell: protocol development and methodological expert.
- Marialena Trivella: protocol development and statistical expert.
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DECLARATIONS OF INTEREST

Lise Estcourt: partly funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components.

Michael Desborough: none to declare.

Carolyn Doree: none to declare.

Sally Hopewell: partly funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components.

Marialena Trivella: partly funded by the NIHR Cochrane Programme Grant - Safe and Appropriate Use of Blood Components.

Simon Stanworth: none to declare.

SOURCES OF SUPPORT

Internal sources

- NHS Blood and Transplant, Research and Development, UK.

To fund the work of the Systematic Review Initiative (SRI)

External sources

- National Institute for Health Research (NIHR) Cochrane Programme Grant, UK.

To provide funding for systematic reviewers and methodological support from the Centre for Statistics in Medicine, Oxford