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Pharmacological interventions for the prevention of bleeding in people undergoing elective hip or knee surgery: a systematic review and network meta-analysis

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ABSTRACT

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

To determine the relative efficacy of pharmacological interventions for preventing blood loss in elective primary or revision hip or knee replacement, and to identify optimal administration of interventions regarding timing, dose and route.

BACKGROUND

Description of the condition

Musculoskeletal conditions such as osteoarthritis represent a major international public health challenge. Hip and knee osteoarthritis is one of the leading causes of global disability and was reported as being the eleventh highest contributor to global disability in the Global Burden of Disease Study (Cross 2014).

Hip and knee replacement surgery is a well-established means of improving quality of life and offers effective pain relief, as well as restoration of function in people suffering from hip or knee disease. Data from the National Joint Registry in the UK demonstrate that 85.6% of people having hip replacement surgery and 70.8% of

people having knee replacement surgery report being 'much better' following their surgery (NJR 2017a; NJR 2017b).

Internationally the number of total hip replacements is increasing. In a study across 20 OECD (Organisation for Economic Co-operation and Development) countries, the annual growth rate of hip replacement surgery is projected to rise from 1.8 million hip replacements per year in 2015 to 2.8 million per year in 2050. The mean incidence of hip replacement is expected to increase from 184 per 100,000 population to 275 per 100,000 population (Pabinger 2018). In 2015, the incidence of knee replacements was 150 per 100,000 population; it is anticipated that this figure will increase four-fold by the year 2030 (Pabinger 2015).

Despite the benefits, hip and knee replacement surgery is associated with significant risk. In the UK, mortality from primary hip replacement within 90 days of surgery ranges from 0.2% in

younger people, to 3.1% in older people, with even higher risk following revision surgery (NJR 2018). It is estimated that one-third of people undergoing primary joint replacement are anaemic preoperatively (Munoz 2017). Hip and knee surgery can result in more than two litres of blood loss, and up to 90% of patients are anaemic following surgery (Lasocki 2015; Park 2013). For revision surgery, the prevalence of preoperative anaemia and the average blood loss is even greater (Kasivisvanathan 2016). The increased prevalence of preoperative anaemia amongst people undergoing revision surgery is probably because the people who require revision surgery are older, and so more likely to suffer with chronic diseases and to be malnourished, all of which are factors that contribute to anaemia (Clevenger 2015).

As a consequence, people undergoing orthopaedic surgery receive 3.9% of all packed red blood-cell transfusions in the UK and, of those, hip and knee replacement surgery uses 77% (Tingate 2016). Bleeding and the need for allogenic blood transfusions (donated blood from other people) has been shown to increase the risk of surgical site infection and mortality (Kim 2017). In addition, it is associated with an increased duration of hospital stay, and increased costs associated with surgery (Monsef 2014; Stokes 2011).

Prevention of bleeding during surgery offers the opportunity to reduce the risk of allogenic blood transfusion, reduce cost and improve patients' outcomes following surgery. Several interventions are available and are currently employed as part of routine clinical care. These interventions include pharmacological therapies that have been proven to reduce blood loss from surgery (Schulman 2012; Li 2016).

Description of the intervention

There are many pharmacological interventions that can be administered to reduce bleeding during surgery (Schulman 2012). This review will focus on several interventions including antifibrinolytics, desmopressin, factor VIIa and factor XIII, fibrinogen and sealants. Antifibrinolytics include tranexamic acid, aprotinin and epsilon-aminocaproic acid. Tranexamic acid and epsilon-aminocaproic acid are synthetic derivatives of the amino acid lysine and aprotinin is a non-specific serine protease inhibitor derived from bovine lung. Antifibrinolytics are widely used in cardiac surgery to prevent bleeding (Henry 2011). Sealants can be grouped into fibrin containing sealants and non-fibrin containing sealants. Fibrin sealants are composed of blood clotting agents and are applied to the wound to reduce blood loss; they have been found to be most effective when used in orthopaedic surgery (Carless 2003). Non-fibrin sealants tend to function through mechanical expansion and prevent bleeding in a similar way to the application of pressure to a wound (Baird 2015). These interventions provide an advantage over blood transfusion through a reduction in the risk of the infective and compatibility complications associated with blood transfusion. In addition, there is a greater availability of

pharmacological interventions than of blood transfusions. Finally, pharmacological interventions are versatile; they can be administered in a variety of different ways including intravenously, orally, topically and nasally (see Appendix 1).

How the intervention might work

When blood loss from hip or knee surgery results in a haemoglobin level below a certain threshold and the onset of associated symptoms, patients are often transfused with red blood cells, even though this procedure is associated with significant risk. All of the interventions described above aim to reduce bleeding and minimise blood loss. Each intervention and its mode of action, along with any limitations or potential risks is described below.

Antifibrinolytics (tranexamic acid, aprotinin and epsilon-aminocaproic acid)

During surgery the clotting mechanism is activated. Antifibrinolytic drugs block the process of blood clot break down (fibrinolysis), therefore increasing clot strength and stability, which prevents excessive bleeding (Okamoto 1997). The most commonly used antifibrinolytic agents include tranexamic acid, aprotinin and epsilon-aminocaproic acid (Henry 2011). In the UK, tranexamic acid is used in 42% of planned surgical cases (NCABT 2017). These medicines may be given orally, intravenous or topically (BNF 2018). Most have few side-effects, however there is a theoretical increased risk of venous thromboembolism with their use (Levy 2018; Myers 2019).

Desmopressin

Desmopressin functions as a vasopressin analogue that increases the levels of von Willebrand factor and factor VIII (Pearson 2016). Von Willebrand factor and factor VIII enable platelets to adhere to wound sites and form clots to prevent bleeding. Desmopressin may be administered intravenously, subcutaneously or intranasally (BNF 2018). Side effects include facial flushing and possibly low blood sodium levels, especially with repeated doses (Desborough 2017a; Desborough 2017b).

Recombinant factor VIIa and factor XIII

Recombinant factor VIIa (rFVIIa) is an intervention licensed for use in people with haemophilia, congenital factor VII deficiency and inhibitory alloantibodies. However, it has also been used off-license to prevent bleeding in surgery where the potential for blood loss is expected to be high (Simpson 2012). Despite its use, the efficacy of the drug in people without haemophilia remains uncertain. Factor XIII protects a developing clot from fibrinolysis and improves clot strength. Recombinant factor XIII (rFXIII) has

been shown to mediate clot formation in a dose-dependent manner and it has been suggested that maintaining higher levels of rFXIII levels may prevent bleeding (Aleman 2014).

Fibrinogen

Fibrinogen concentrate is a blood component that is administered intravenously. Fibrinogen is converted to fibrin by thrombin and forms the structural basis of a clot. As it is derived from blood, there is a small risk of viral infection with its use, however, due to its manufacturing process this is unlikely to result in infection (Franchini 2012).

Fibrin sealants

Fibrin sealants are derived from plasma and may be applied to actively bleeding bony surfaces or the wound. They usually consist of fibrinogen, thrombin, factor XIII, an antifibrinolytic agent and calcium chloride. However, some sealants do not contain an antifibrinolytic agent (Fischer 2011). Allergy is a rare complication (Aguilera 2013). Although fibrin sealants are derived from blood plasma, they have a lower risk of transmitting infections than allogeneic blood transfusions (Carless 2003).

Non-fibrin sealants

Non-fibrin sealants tend to be low-viscosity liquids that polymerise to form a film that enables platelet activation and aggregation. This allows a clot to form, but relies on the patient's own fibrin to create the clot. Other forms of non-fibrin sealants include dressings, powders or bandages. Non-fibrin sealants may enable clot formation where the use of a tourniquet is impractical. Adverse events that have been reported with their use are either associated with expansion of the sealant, e.g. nerve compression, or are the result of allergy (Baird 2015).

Why it is important to do this review

A key objective for global health agencies such as the World Health Organization (WHO) is to ensure that every country is able to provide universal access to safe and adequate blood supplies to help save lives (WHO Factsheet 2017). Undertaking unnecessary transfusions and using unsafe transfusion practices can expose people to transfusion-transmitted infections and serious adverse transfusion reactions, as well as consuming blood products that could be better used in those who are in need (WHO Factsheet 2017). This review will focus on the question of which pharmacological bleeding prevention treatment is most effective at preventing blood transfusion and blood loss. Bleeding and the need for blood transfusion may lead to costly adverse events such as infections and increased length of hospital stay (Monsef 2014; Stokes 2011). Reducing the number of blood transfusions is important to reduce

these risks and to help preserve an already limited resource. Saving blood by reducing bleeding during surgery through pharmacological interventions may offer a lower risk option and will be cheaper than transfusing blood. For example an ampoule of tranexamic acid or desmopressin costs approximately GBP 1.50 (BNF 2018), whereas one unit of red blood cells costs GBP 128.99 (NHSBT 2018).

To date, audits in orthopaedic hip and knee surgery suggest there is still limited use of alternatives to allogeneic blood transfusion (NCABT 2017). In addition, there is some concern around using pharmacological interventions such as tranexamic acid due to a theoretical risk of unwanted blood clots, such as deep vein thrombosis or pulmonary embolism (blood clots in the lungs which can affect breathing). In other populations, the timing of the dose has been shown to be of importance when considering adverse events. In the CRASH-2 trial (a large multicentre international trial of tranexamic acid versus placebo) patients with significant bleeding from trauma had an increased risk of mortality if tranexamic acid was given after three hours (Roberts 2013). The dose of the intervention is also important from a cost perspective, as well as minimising the side-effect profile of the agent. Safety concerns in people at increased risk of stroke or myocardial infarction have led to limited use of alternative interventions (Danninger 2015). In addition, topical alternatives may aid haemostasis while reducing systemic exposure to the treatment.

It is unlikely there will be any trials that compare timing, dose and route of all these interventions directly, and this can lead to uncertainty for decision makers. Therefore, in order to lessen this uncertainty and provide the highest level of evidence for treatment decisions in those undergoing orthopaedic surgery, we will carry out a network meta-analysis that synthesises direct and indirect evidence to enable the evaluation of different treatment strategies for the prevention of bleeding in hip and knee surgery.

Description of network meta-analysis

Network meta-analysis (NMA) allows the comparison of more than two treatments (Lu 2004). The evidence for each comparison is represented within a network map where each treatment is represented by a node (vertex), with lines connecting treatments to be compared (Jansen 2011). As with any meta-analysis it is crucial to ensure a NMA is conducted with a rigorous systematic approach in mind. Even in a network map with no missing data, there will be a mix of solid and blank lines: solid lines represent 'direct' comparisons where the treatments in question have been compared in clinical trials. However, absent lines represent 'indirect' comparisons, and indicate that there are no clinical trials that made that comparison (Bucher 1997; Jansen 2011).

NMA utilises clinical trial data from the 'direct' comparisons to infer and estimate the effects of the missing comparisons 'indirectly' (Caldwell 2005; Jansen 2011; Jansen 2013; Song 2003). By doing this, NMA can be used to bridge gaps in the evidence

by combining data from direct comparisons in clinical trials with missing comparison information in the network structure, and enables more precise estimates to be obtained by using data from across the network (Krahn 2013; Salanti 2014). The foundation of a NMA is the assumption that all the people and trials included in the network are similar enough in terms of effect modifiers across all direct comparisons to draw robust conclusions (Jansen 2013). Another advantage of NMA is that the results generated from this kind of analysis can be presented in a tabular format specifying treatment and outcome, which is useful for clinical decision making. This helps those making clinical decisions by having all the relevant evidence in one table, but also by displaying both the risks and benefits of a particular treatment (Hoaglin 2011; Jansen 2011; Sutton 2008; van der Valk 2009).

OBJECTIVES

To determine the relative efficacy of pharmacological interventions for preventing blood loss in elective primary or revision hip or knee replacement, and to identify optimal administration of interventions regarding timing, dose and route.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). If a publication states that a trial was randomised but the method of randomisation used was not described, we will explore this further by contacting the trial authors. If this information is unobtainable, then we will include the trial and consider it to be at an unclear risk of bias. This information will be recorded on the data extraction form. Eligible trials must compare at least one of the active interventions of interest versus placebo or versus another active treatment. We will include abstracts and full text publications if they contain sufficient information on study design, participant characteristics, and interventions given. We will only include trials that are registered prospectively, unless the final trial report was published before 2010.

Types of participants

We will include any person who has undergone elective hip and knee replacement or revision surgery. If trials contain mixed populations (e.g. those requiring trauma surgery) then we will only use data from the elective hip and knee subgroups, if available. If

no subgroup data are presented and the corresponding author is not contactable for the information, at least 80% of the sample size must be from our population of interest for the trial to be eligible for inclusion. We will include people who have had total knee replacements, partial or unicondylar knee replacements, hip replacements, and revision hip or knee surgery. We will exclude people with known bleeding disorders such as haemophilia. We will place no restrictions on ethnicity or gender.

Types of interventions

We will include trials that have compared one or more of the following interventions:

- antifibrinolytics:
 - tranexamic acid;
 - aprotinin;
 - epsilon-aminocaproic acid;
- desmopressin;
- factor VIIa and factor XIII;
- fibrinogen;
- fibrin sealants/glue (not including surface dressings);
- non-fibrin sealants (not including surface dressings).

Drugs and treatments that are not listed above will not be combined in the NMA. Acceptable comparators will include placebo or one of the active interventions listed above.

We will consider interventions given at a range of threshold doses, and as single or multiple doses via intravenous, subcutaneous, intranasal, oral or topical routes of administration. We will also consider the timing of the interventions.

There are a large number of possible doses, routes and times at which interventions can be given. The table in Appendix 1, illustrates possible combinations that could be used in the trials. All interventions are categorised according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) system (Bagg 2018). ATC codes are given in Appendix 2. We anticipate that tranexamic acid will be the largest intervention group and, therefore, is likely to be the focus of the network.

Types of outcome measures

We will assess the relative hierarchy ranking of the interventions using the following outcome measures.

Primary outcomes

- Need for allogenic blood transfusion (up to 30 days)
- All-cause mortality (deaths occurring up to 30 days after the operation)

Secondary outcomes

- Mean number of transfusion episodes per person (up to 30 days)
- Re-operation due to bleeding (within seven days)
- Length of hospital stay*
- Adverse events:
 - thromboembolism (deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke): within 30 days
 - transfusion reactions (acute): within 24 hours
 - suspected serious drug reactions: within 30 days

*The 30 day mortality rate of people undergoing hip and knee replacement is considered low at 0.08% (Smith 2015). Therefore we selected length of hospital stay as a secondary outcome, as the data are unlikely to be affected by deaths.

We will also collect and present any cost or resource information reported in the included studies. Although this does not constitute a formal economic evaluation, it will provide useful additional information that may be of value in a decision-making context.

Search methods for identification of studies

The Systematic Review Initiative (SRI) Information Specialist (CD) will formulate the search strategies in collaboration with the Cochrane Injuries Group.

Electronic searches

Bibliographic databases

We will develop thorough and sensitive search strategies to search for RCTs and systematic reviews from database inception to the present, in the following databases:

- CENTRAL (The Cochrane Library; current issue) (www.cochranelibrary.com);
- MEDLINE (OvidSP; 1946 onwards);
- Embase (OvidSP; 1974 onwards);
- CINAHL (EBSCOhost; 1937 onwards);
- Transfusion Evidence Library (1950 onwards) (www.transfusionevidencelibrary.com);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch).

Search strategies developed specifically for this review will consist of index terms, text words and word variations for the concepts of population (hip and knee surgery) and intervention/comparator (pharmacological interventions for the prevention of bleeding). We will combine our searches in MEDLINE, Embase and CINAHL with adaptations of the recommended Cochrane RCT filter (Lefebvre 2011), and of the SIGN systematic review filters (www.sign.ac.uk/search-filters.html). We will not limit searches by

language, year of publication or publication type. Search strategies for all databases are presented in Appendix 3.

Searching other resources

To complement the database searches, we will handsearch reference lists of all included trials, relevant review articles and other current evidence to identify additional trials potentially missed by the electronic searches, but also to ensure we have collected as much of the available evidence as possible. We will identify the most recent systematic reviews on interventions for preventing blood loss in those undergoing elective hip or knee surgery, and contact the corresponding authors to determine whether they are aware of any further trials in this area. In addition, we will contact authors of ongoing trials to obtain any unpublished data. We will also examine any relevant retraction statements and errata for included studies. We will contact authors in the field to help us identify additional published or unpublished studies.

Data collection and analysis

We will perform the review following the methods stated in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We will perform the analyses using Review Manager 5 (RevMan 5) (Review Manager 2014), and Stata 15 (StataCorp 2017).

Selection of studies

Independently, two review authors (VNG, RC) will screen all titles and abstracts identified by the electronic searches for eligibility. They will exclude any citations deemed irrelevant at this stage. Independently, these review authors (VNG, RC) will then screen the full texts of all potentially relevant trials for eligibility against the criteria set out in the protocol. We will resolve disagreements through discussion or, if required, through consultation with a third reviewer (LJE). We will request information from trial authors when we have insufficient information from trial reports to make a decision about eligibility. We will keep records of the selection process, as well as details of our reasons for exclusion at the full text stage. These will be used to populate a PRISMA flowchart to demonstrate the selection of studies (Moher 2009). We will use colleagues or Cochrane resources such as Task Exchange for translation of articles written in languages that the review authors cannot read.

Data extraction and management

Independently, VNG and RC will undertake data extraction of included trials, using standardised, piloted forms designed according to the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). The review authors will

not be blinded to institutions, authors or outcome of the trials. Colleagues who are providing translation of studies written in languages other than English, will also be expected to extract data. Data extraction forms will be piloted on a random sample of 10 included trials (split equally between the review authors) following which, adjustments will be made if necessary. If a trial is identified as relevant by one author but not by the other, the authors will discuss the rationale behind their assessments. If a consensus is not reached between the two authors, LJE will serve as arbitrator. We will contact corresponding authors of included trials up to three times to request additional trial data. If no response is received within four weeks we will deem the data to be unobtainable. If there is conflict over data sources, we will give preference to published data over unpublished, as published will have been through a peer review process.

The combinations of dose, route and timing of each intervention are tabulated in [Appendix 1](#). As there are a large number of possible combinations for each intervention, data synthesis is difficult to determine prior to data extraction. Taxonomy of interventions will take place prior to outcome data extraction, with help from an external expert panel to create clinically meaningful groups ready for data analysis.

We will extract the following information.

- **General information:** name of review author carrying out data extraction; date of when data extraction was done; study ID (and any other unique trial identifiers); surname and contact address of first author of included trial; citation of included trial; language of trial and details of any duplicate publications.
- **Trial information:** trial design - type of RCT; location of trial; setting; sample size; duration of trial; power calculation; treatment arms; randomisation; inclusion and exclusion criteria; comparability of groups and length of follow-up.
- **Characteristics of participants:** age; sex; ethnicity; breakdown of total numbers for those recruited, randomised and analysed; type of surgery; numbers lost to follow-up; dropouts (percentage in each arm) with reasons; protocol violations and co-morbidities.
- **Characteristics of interventions:** number of treatment arms; description of experimental arm(s); description of control arm; timing, dose and route of administration of intervention; and other differences between intervention arms.
- **Outcomes:** need for blood transfusion within 30 days postoperatively; number of units of red blood cells transfused; mortality due to any cause within 30 days postoperatively; proportion of participants requiring each type of transfusion; and adverse effects (transfusion reactions, thromboembolism and drug reactions), re-operation due to bleeding, and length of hospital stay. (We will extract exactly how 'adverse effects' and 'serious adverse effects' are defined in each study.)
- **Quality assessment:** allocation concealment; blinding (participants, personnel, outcome assessors); incomplete outcome data; selective outcome reporting; other sources of bias.

(Blinding will not be possible for some comparisons.)

We will utilise arm-level data rather than study-level data from both abstracts and full text papers. We will obtain maximal data by extracting data from all publications available and will use one data extraction form per trial. We will contact the primary or corresponding author of a trial, study groups or companies for additional data, if insufficient information is provided in the trial reports.

We will also collect and present data on any cost or resource information reported in the included studies. Although this does not constitute a formal economic evaluation, it will provide useful additional information that may be of value in a decision-making context.

Both review authors (VNG, RC) will enter the data into RevMan 5 and will cross check entries for accuracy.

Data on potential risk modifiers

From every included trial we will also extract data on the following characteristics which may act as treatment risk modifiers.

- **Type of surgery (primary hip or knee replacement or hip or knee revision):** surgery may have an impact on allogenic transfusion and mortality, as often revision joint surgery results in more blood loss than primary joint replacement ([Kasivisvanathan 2016](#)). This is probably due to revision surgery generally taking longer and being more complex in nature than primary joint replacement.
- **Reason for surgery:** the indication for surgery may also affect blood loss during surgery, as, although most primary replacements are performed for arthritis, people who have replacements performed for other reasons such as bony cancer, may bleed more due to the tumour being more vascular than normal bone ([Kumar 2014](#)).
- **Duration of surgery:** longer surgery is likely to result in more bleeding.
- **Incidence of preoperative anaemia:** people with anaemia have a higher risk of blood transfusion following surgery ([Kasivisvanathan 2016](#); [Park 2013](#)).
- **Type of anaesthetic used (general or spinal):** general anaesthesia has been associated with increased risk of blood transfusion, which may be due to loss of maintenance of venous pressure when the anaesthetic agents are administered ([Basques 2015](#)).
- **Use of tourniquet (in knee replacement surgery):** tourniquet use may reduce intraoperative blood loss, however, some studies suggest that this may not affect total blood loss ([Zhang 2014](#)).
- **Use of anticoagulation:** participants on anticoagulants are likely to bleed more.

Assessment of risk of bias in included studies

We will perform quality assessment on all the included trials using the methods described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We will use the Cochrane 'Risk of bias' tool (RoB tool) (Higgins 2016). We will test the RoB tool in a small, random sample of trials. The two review authors (VNG, RC) will independently assess risk of bias for each trial to assign each a classification of high, low or unclear risk. We will create a 'Characteristics of included studies' table and will outline the judgement process. We will compare the two review authors' statements and reach a consensus on the classification of risk of bias. If necessary a third author (LJE) will be consulted.

Using this information, we will explore statistical heterogeneity in each study and perform sensitivity analyses. We will follow Cochrane methods for assessing risk of bias and will address the following domains:

- selection bias (random sequence generation and allocation concealment);
- reporting bias (selective reporting);
- attrition bias (incomplete outcome data);
- performance bias (blinding of participants, personnel and outcome assessors);
- detection bias (blinding of outcome assessment);
- other forms of bias.

We will assign each of the domains listed above a classification of risk:

- **low risk** - if the criterion has been adequately fulfilled in the study;
- **high risk** - if the criterion has not been fulfilled in the study;
- **unclear risk** - if the study report does not provide enough information with which to reach a clear decision.

We will assess risk of bias using Grades of Recommendation, Assessment, Development and Evaluation (GRADE) (Salanti 2014). We will resolve any conflicts through discussion between the two review authors (VNG and RC), or by involving a third author (LJE).

Measures of treatment effect

When extracting data for dichotomous outcomes (number of participants with at least one bleeding episode, number of participants with at least one severe or life-threatening bleeding episode, mortality, proportion of participants needing an allogenic blood transfusion, adverse events) we will note the number of events and number of participants in the intervention and control arms.

However, for continuous outcomes (number of units of allogenic blood transfused per participant, mean number of allogenic blood transfusions episodes per participant) we will note the mean, standard deviation and total number of participants in both the intervention and control arms. If only study-level data are available

we will record the reported effect size and the associated standard error. If the data permit we will undertake quantitative evaluations using Stata.

We will use mean difference (MD) with 95% confidence intervals (CI) to analyse continuous outcome data measured using the same scale. It is unlikely that continuous outcomes will not be measured using the same scales.

Unit of analysis issues

In pairwise meta-analyses, we will treat trials with multiple treatment group comparisons as individual, independent two-arm studies. The control group will act as a node in the NMA, which will help with indirect analyses and formation of a hierarchy of interventions. In the NMA, we will include all comparisons where there are sufficient data to do so. These trials will be analysed appropriately to take into account the respective treatment effects. The NMA method accounts correctly for correlations in relative effects from trials with more than two arms. We will perform our analyses using the participant as the unit of analysis.

Dealing with missing data

We will handle missing data according to the methods described in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). We will contact corresponding authors to obtain missing data. We will record the number of participants lost to follow-up in each trial. In trials that also include other populations, such as those undergoing non elective hip or knee replacements, we will only extract data for the elective hip and knee subgroup. If this is not possible, we will attempt to contact the authors up to a maximum of three times to obtain the information. If we are still unable to obtain the information, and where missing data are thought to introduce serious bias, we will perform a sensitivity analysis to evaluate the impact of missing outcome data.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity within treatment comparisons

If we deem the data to be homogenous, we will combine them and perform a meta-analysis. We will assess whether clinical and methodological heterogeneity are present within each comparison by looking at trial and participant characteristics across all included trials. If significant clinical and methodological heterogeneity are found within a particular comparison, this may mean that meta-analysis cannot be performed, or that the summary statistic cannot be reported. Should this happen, we will provide a descriptive summary.

In the NMA we will assume a common estimate for heterogeneity across our comparisons and we will estimate a total I^2 value for the network. We will assess statistical heterogeneity in the entire network based on the magnitude of the heterogeneity variance parameter (τ^2) which will be estimated from the NMA models. We will perform a likelihood ratio test for the null hypothesis of no heterogeneity versus presence of heterogeneity. For pairwise meta-analyses we will estimate different heterogeneity variances for each pairwise comparison. We will calculate the heterogeneity within each pair using the I^2 statistic and 95% CI ($I^2 > 50\%$ will indicate moderate heterogeneity), which describes the variability that cannot be due to random error. If heterogeneity exists, and if possible, we will explore it by performing subgroup meta-regression.

Assessment of reporting biases

If there is an adequate number of studies (at least 10), we will explore the existence of small-study effects in our pairwise meta-analyses by producing funnel plots and using linear regression. We will deem a P value below the threshold of 0.10 to be statistically significant. The association between study effect size and funnel plot asymmetry is affected by several factors. Contour-enhanced funnel plots can help to differentiate between funnel plot asymmetry caused by publication bias and asymmetry that has other causes (Peters 2008). The contour lines in the plot represent levels of statistical significance. We will assume that a lack of studies in areas of non-significance will be indicative of publication bias.

Data synthesis

We will perform a NMA in Stata using the method of multivariate meta-analysis which will treat different comparisons as different outcomes (StataCorp 2017). We will outline the estimated treatment effect for each comparison along with 95% CI. For direct treatment comparisons, we will perform meta-analysis according to the methods outlined in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). We will perform meta-analyses using RevMan 5 software where data sets demonstrate enough similarity to do so (Review Manager 2014). We will present the results using the network forest command along with 95% CI for all analyses. Two review authors (VNG and RC) will enter the data into the software and will cross check for accuracy. Where appropriate, if interventions can be grouped into clinically meaningful groups during the first stage of the data extraction, we will treat each group as a single node of the network analysis. We will perform a sensitivity analysis using different groupings. Any groupings will consist only of one type of pharmacological intervention, e.g. only tranexamic acid, but may contain a narrow range of dosage regimes or similar timings, so as to have a pharmacologically similar predicted effect.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis

If adequate data are available we will perform subgroup analyses and network meta-regression for each of the following variables in order to explain heterogeneity, inconsistency, or both.

- Participants with preoperative anaemia
- Type of surgery (hip or knee primary replacement or hip or knee revision)
- Type of anaesthesia (general or spinal)
- Duration of surgery
- Use of tourniquet in knee replacement surgery
- Reason for surgery
- Use of anticoagulation

Investigation of heterogeneity

In pairwise meta-analyses, we will estimate heterogeneity for each pairwise comparison. We will assess statistical heterogeneity using the I^2 statistic with 95% CI. We will assess statistical heterogeneity in the network using the heterogeneity variance parameter τ^2 , which is estimated from the NMA and perform a likelihood ratio test. We will also estimate a total I^2 for the whole network.

Assessment of statistical inconsistency

We will use the 'loop' inconsistency model of Lu and Ades (Lu 2006), using the `luades` option in STATA to evaluate any inconsistency within each loop of the network (StataCorp 2017). This will provide an assessment of consistency within each loop of the network. We will assess transitivity to determine the presence of inconsistency, if there are no closed loops. Within each loop we will assume a common heterogeneity. The results will be presented in a forest plot through the network graphs package in Stata. If there is evidence of global inconsistency we will explore further using the node-splitting method (Dias 2010).

Sensitivity analysis

We will assess the strength of the overall results by performing sensitivity analyses where appropriate with respect to the trials deemed to be at high risk of bias. We will perform our main analysis using studies at low risk of bias and then perform a sensitivity analysis to include all studies. We will assess the influence of participant dropout and will categorise RCTs into those with less than 20% dropout, those with 20% to 50% dropout, and those with more than 50% dropout, and analyse these groups separately. As part of the exploration of heterogeneity we will use the fixed-effect model for sensitivity.

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* Indicates the major publication for the study

APPENDICES

Appendix I. Table of intervention variables

This table highlights the scope of our question by demonstrating all possible variable combinations

	TXA	Aprotinin	Epsilon-aminocaproic acid	Desmopressin	Factor VIIa	Factor XIII	Fibrinogen	Fibrin sealants/ glue	Non-fibrin sealants
Timing									
Pre-operative	✓	✓	✓	✓	✓	✓	✓	X	X
Intra-operative	✓	✓	✓	✓	✓	✓	✓	✓	✓

(Continued)

Postoperative	✓	X	X	✓	✓	✓	✓	X	X
Route									
IV (injection, infusion)	✓	✓	✓	✓	✓	✓	✓	X	X
Topical	✓	X	X	X	X	X	X	✓	✓
Intranasal	X	X	X	✓	X	X	X	X	X
Subcutaneous injection	X	X	X	✓	X	X	X	X	X
IV + topical	✓	X	X	X	X	X	X	X	X
Oral	✓	X	✓	X	X	X	X	X	X
IV + oral	✓	X	X	X	X	X	X	X	X
Topical + oral	✓	X	X	X	X	X	X	X	X
Dose									
Single	✓	X	✓	✓	✓	✓	✓	✓	✓
Multiple	✓	✓	X	✓	✓	✓	✓	X	X
Variable units/kg	✓	X	✓	X	✓	✓	✓	X	X
Variable trial set dose	✓	✓	X	✓	✓	✓	✓	✓	✓
Abbreviations TXA: tranexamic acid IV: intravenous Notes This table is for illustrative purposes only and is limited to transfusion related indications Ticks indicate which intervention and timing or route or dose combinations are clinically possible Crosses indicate which intervention and timing or route or dose combinations are not clinically possible									

Appendix 2. Interventions of interest by ATC code

Drug name	ATC code	Notes
Epsilon-aminocaproic acid	B02AA01	Code only available for aminocaproic acid
Tranexamic acid	B02AA02	
Aprotinin	B02AB01	
Fibrinogen	B02BB01	
Fibrin sealants or glue	B02BC	Fibrin sealants providing haemostasis at the site of application
Factor XIII	B02BD07	
Factor VIIa	B02BD08	
Desmopressin	H01BA02	

Abbreviation

ATC: anatomical therapeutic chemical

Appendix 3. Search strategies

CENTRAL (The Cochrane Library)

- #1 MeSH descriptor: [Arthroplasty, Replacement, Hip] this term only
- #2 MeSH descriptor: [Hip] this term only and with qualifier(s): [surgery - SU]
- #3 MeSH descriptor: [Osteoarthritis, Hip] explode all trees and with qualifier(s): [surgery - SU]
- #4 MeSH descriptor: [Arthroplasty, Replacement, Knee] this term only
- #5 MeSH descriptor: [Knee Injuries] explode all trees and with qualifier(s): [surgery - SU]
- #6 MeSH descriptor: [Knee] explode all trees and with qualifier(s): [surgery - SU]
- #7 MeSH descriptor: [Osteoarthritis, Knee] explode all trees and with qualifier(s): [surgery - SU]
- #8 ((hip* or knee* or femur or femoral) near/10 (replac* or operat* or surg* or arthroplast* or reconstruct* or repair* or osteotom* or alloplast* or plast* or resurfac* or implant* or prosthes*))
- #9 (acetabuloplast* or acetabulum arthroplast*)
- #10 (THA or THR or TKA or TKR or UKA or UKR)
- #11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10
- #12 MeSH descriptor: [Antifibrinolytic Agents] this term only
- #13 MeSH descriptor: [Tranexamic Acid] this term only
- #14 MeSH descriptor: [Aminocaproic Acid] explode all trees
- #15 antifibrinolytic* or anti-fibrinolytic* or antifibrinolysin* or antiplasmin* or plasmin inhibitor* or tranexamic or tranhexamic or cyclohexanecarboxylic acid* or amcha or t-amcha or amca or transamin or amchafibrin or anvitoff or spotof or cyklokapron or femstrual or ugurol
- #16 AMCHA or amchafibrin or amikapron or amstat or antivoff or caprilon or cl65336 or cyclocapron or cyclokapron or cyklokapron or exacyl or frenolyse or fibrinon or hemostan or hexacapron
- #17 hexakapron or kalnex or lysteda or rikaparin or ronex or theranex or tranexam or tranexanic or tranexic or “trans achma” or transexamic or trenaxin or TXA
- #18 (fibrinolysis near/2 inhibitor*)

#19 (Agretax or Bio-Stat or Capiloc or Capitrax or Clip Inj or Clot-XL or Clotawin-T or Coastat or Cuti or Cymin or Dubatran or Espercil or Examic or Existat or Extam or Fibrin or Gynae-Pil or Hemstate or Kapron or Menogia or Monitex or Nestran or Nexamic or Nexi-500 or Nexmeff or Nicolda or Nixa-500 or Pause or Rheonex or Sylstep TX or Synostat or T-nex or T Stat or T Stat or Tanmic or Temsyl-T or Texakind or Texanis or Texapar or Texid or Thams or Tonopan or Traklot or Tramic or Tramix or Tranarest or Trance Inj or Tranecid or Tranee or Tranemic or Tranex or Tranexa or Tranfib or Tranlok or Transtat or Transys or Transcam or Tranxi or Trapic or Traxage or Traxamic or Traxyl or Trenaxa or Trexamic or Trim Inj or Tx-1000 or Tx 500 or Wistran or X-Tran or Xamic)

#20 ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or epsilonaminocaproinsav or ethaaminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or neocaprol or resplamin or tachostyptan

#21 lederle or acikaprin or afibrin or amicar or caprocid or capracid or capramol or caprogel or caprolest or caprolisin* or caprolysin* or capromol or epsikapron or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid

#22 aminohexanoic or aminocaproic or aminohexanoic or amino caproic or amino-caproic or amino-n-hexanoic

#23 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22

#24 MeSH descriptor: [Aprotinin] this term only

#25 (antagosan or antilysin* or aprotimbin or apronitin* or aprotinin* or bayer a128 or contrical or contrycal or contrykal or dilmintal or frey inhibitor or kontrycal or Kunitz inhibitor or gordox or haemoprot or kallikrein-trypsin inactivator or iniprol or kontrikal or kontrykal or kunitz pancreatic trypsin inhibitor or midran or pulmin or tracylol or trascolan or trasilol or tra?ylol or traskolan or zymofren or pancreas antitrypsin or protinin or riker 52g or Rivilina zymofren)

#26 #24 or #25

#27 MeSH descriptor: [Factor VIIa] this term only

#28 (factor viia or factor 7a or rfviia or fviia or novoseven* or novo seven* or aryoseven or acet or eptacog* or proconvertin)

#29 (activated near/1 (factor seven or factor vii or rfvii or fvii))

#30 (factor seven or factor vii or factor 7):ti

#31 #27 or #28 or #29 or #30

#32 MeSH descriptor: [Fibrinogen] this term only

#33 ("fibrinogen concentrate" or "factor I" or Haemocomplettan* or Riastap* or Fibryga* or Fibryna*)

#34 #32 or #33

#35 MeSH descriptor: [Deamino Arginine Vasopressin] this term only

#36 (desmopressin* or vasopressin deamino or D amino D arginine vasopressin or deamino 8 d arginine vasopressin or vasopressin desamino 8 arginine or desmotabs or DDAVP or desmogalen or adin or adiuretin or concentraid or d void or dav ritter or deamino 8 dextro arginine vasopressin or deamino 8d arginine vasopressin or deamino dextro arginine vasopressin or deaminovasopressin or defirin or defirin melt or desmirin pr desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin or minirinette or minirinmelt or minrin or minurin or miram or nictur or noctisson or nocturin or nocutil or nordurine or novidin or nucotil or octim or octostim or presinex or stimate or wetirin)

#37 #35 or #36

#38 MeSH descriptor: [Factor XIII] explode all trees

#39 (factor xiii or fxiii or fibrin stabili?ing factor* or Tretten* or Catridecacog)

#40 #38 or #39

#41 MeSH descriptor: [Tissue Adhesives] explode all trees

#42 MeSH descriptor: [Collagen] explode all trees and with qualifier(s): [therapeutic use - TU]

#43 MeSH descriptor: [Thrombin] explode all trees and with qualifier(s): [therapeutic use - TU]

#44 MeSH descriptor: [Gelatin] explode all trees and with qualifier(s): [therapeutic use - TU]

#45 MeSH descriptor: [Gelatin Sponge, Absorbable] this term only

#46 ((fibrin* or collagen or cellulose or gelatin or gel or thrombin* or albumin or hemostatic* or haemostatic*) next (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste or powder*))

#47 ((nonfibrin* or non-fibrin* or synthetic* or non-biological* or nonbiological* or biological*) near/3 (glue* or seal* or adhesive*))

#48 (surgical* near/3 (glue* or sealant* or adhesive*))

#49 ((fibrin* or collagen or cellulose or gelatin or thrombin) near/3 (hemosta* or haemosta*))

#50 (8Y or Aaact or Actif-VIII or Advate or Artiss or Biogluce or Biocol or Collaseal or Omrixil or Transglutine or Raplixa or Evarrest or Aleviate or Alphanate or Amofil or Beriate or Beriplast or Biostat or Bolheal or Cluvot or Conco-Eight-HT or Crosseel or Crosseal or Crosseight or Emoclot or Evarrest or Evicel or Factane or Fanhdi or Fibrogammin P or Green VIII or Green VIII Factor or Greengene or Greenmono or Greenplast or Haemate or Haemate P or Haemate P or Haemate P500 or Haemate-P or Haemoctin or Haemoctin

SDH or Haemoctin-SDH or Hemaseel or Hemaseal or Hemofil M or Hemoraas or Humacloot or Humafactor-8 or Humate-P or Immunate or Innovate or Koate or Koate-DVI or Kogenate Bayer or Kogenate FS or Monoclate-P or NovoThirteen or Octafil or Octanate or Octanate or Optivate or Quixil or Talate or Tisseel or Tisseal or Tissel or Tissucol or Tricos or Vivostat or Voncento or Wilate or Wilnativ or Wilstart or Xyntha)

#51 (Glubran or Gluetiss or Ifabond or Indermil or LiquiBand or TissuGlu or Evithrom or Floseal or Hemopatch or Gel-Flow or Gelfoam or Gelfilm or Recothrom or Surgifoam or Surgiflo* or "rh Thrombin" or Thrombi-Gel or Thrombi-Pad or Thrombin-JMI or Thrombinar or Thrombogen or Thrombostat)

#52 (porcine gelatin or bovine collagen or bovine gelatin or nu-knit or arista or hemostase or vita sure or thrombin-jmi or thrombinjmi or avicel or vivagel or lyostypt or tabotamp or arterx or omnex or veriset)

#53 (polysaccharide next (sphere* or hemostatic powder))

#54 MeSH descriptor: [Chitosan] this term only

#55 MeSH descriptor: [Polyethylene Glycols] this term only and with qualifier(s): [therapeutic use - TU]

#56 MeSH descriptor: [Hydrogel, Polyethylene Glycol Dimethacrylate] explode all trees and with qualifier(s): [therapeutic use - TU]

#57 MeSH descriptor: [Polyurethanes] explode all trees and with qualifier(s): [pharmacology - PD, adverse effects - AE, toxicity - TO, administration & dosage - AD, therapeutic use - TU]

#58 ((polymer-derived elastic* or polymer tissue adhesive* or elastic hydrogel* or glutaraldehyde or PEG-based or polyurethane-based tissue or polyethylene glycol* or polyvinyl alcohol-based tissue or PVA-based tissue or natural biopolymer* or polypeptide-based or protein-based or polysaccharide-based or chitosan or poliglusam or cyanoacrylic or cyanoacrylate or cyacrin or dextran-based or chondroitin sulfate-based or mussel-inspired elastic* or glycol hydrogel or polymer-based) next (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste* or powder*))

#59 MeSH descriptor: [Cellulose, Oxidized] this term only

#60 (absorbable cellulose or resorbable cellulose or oxidized cellulose or carboxycellulose or oxycellulose or cellulosic acid or oxycel or oxidized regenerated cellulose)

#61 (BioGlue or Progel or Duraseal or Coseal or FocalSeal or ADAL-1 or AdvaSeal or Pleuraseal or Angio-Seal or Avitene or Instat or Helitene or Helistat or TDM-621 or Dermabond or Tissueseal or PolyStat or Raplixa or Spongostan or Surgicel or Surgilux or Tachosil or Traumstem)

#62 (collagen-thrombin or thrombin-collagen or gelatin-fibrinogen or fibrinogen-gelatin or gelatin-thrombin or thrombin-gelatin or fibrinogen-thrombin or thrombin-fibrinogen or collagen-fibrinogen or fibrinogen-collagen or microfibrillar collagen or CoStasis or "GRF Glue" or GR-Dial or Algosterile or TraumaStat or HemCon or ChitoFlex or Celox or QuikClot or WoundStat or Vitagel or TachSeal or TachoComb or Cryoseal)

#63 #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62

#64 MeSH descriptor: [Waxes] explode all trees

#65 (bonewax* or bone wax* or bone putty or hemasorb or ostene)

#66 #64 or #65

#67 (((haemosta* or hemosta* or antihaemorrhag* or antihemorrhag* or anti haemorrhag* or anti-hemorrhag*) next (drug* or agent* or treat* or therap*)) or ((coagulat* or clotting) next factor*))

#68 #23 or #26 or #31 or #34 or #37 or #40 or #63 or #66 or #67

#69 #11 and #68

MEDLINE (Ovid)

1. Arthroplasty, Replacement, Hip/

2. Hip/su

3. Osteoarthritis, Hip/su

4. Arthroplasty, Replacement, Knee/

5. exp Knee Injuries/su

6. Knee/su

7. Osteoarthritis, Knee/su

8. ((hip* or knee* or femur or femoral) adj10 (replac* or operat* or surg* or arthroplast* or reconstruct* or repair* or osteotom* or alloplast* or plast* or resurfac* or implant* or prosthes*)) .tw,kf.

9. (acetabuloplast* or acetabulum arthroplast*) .tw,kf.

10. (THA or THR or TKA or TKR or UKA or UKR).tw.
11. or/1-10
12. Antifibrinolytic Agents/
13. Tranexamic Acid/
14. Aminocaproic Acid/
15. (antifibrinolytic* or anti-fibrinolytic* or antifibrinolysin* or antiplasmin* or plasmin inhibitor* or tranexamic or tranhexamic or cyclohexanecarboxylic acid* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or "kabi 2161" or transamin or amchafibrin or anvitoff or spotof or cyklokapon or cyclo-F or femstrual or ugurol or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanoic acid or amstat or antivoff or caprilon or cl?65336 or cl65336 or cyclocapron or cyclokapon or cyklokapon or cyklokapon or exacyl or frenolyse or fibrinon or hemostan or hexacapon or hexakapon or kalnex or lysteda or rikaparin or ronex or theranex or tranexam or tranexanic or tranexic or trans achma or tranexamic or trenaxin or TXA or (fibrinolysis adj2 inhibitor*)).tw,kf.
16. (Agretax or Bio-Stat or Capiloc or Capitrax or Clip Inj or Clot-XL or Clotawin-T or Coastat or Cuti or Cymin or Dubatran or Espercil or Examic or Existat or Extam or Fibran or Gynae-Pil or Hemstate or Kapron or Menogia or Monitex or Nestran or Nexamic or Nexi-500 or Nexmeff or Nicolda or Nixa-500 or Pause or Rheonex or Sylstep TX or Synostat or T-nex or T Stat or T Stat or Tanmic or Temsyl-T or Texakind or Texanis or Texapar or Texid or Thams or Tonopan or Traklot or Tramic or Tramix or Tranarest or Trance Inj or Tranecid or Tranee or Tranemic or Tranex or Tranexa or Tranfib or Tranlok or Transtat or Transys or Transcam or Tranxi or Traptic or Traxage or Traxamic or Traxyl or Trenaxa or Trexamic or Trim Inj or Tx-1000 or Tx 500 or Wistran or X-Tran or Xamic).tw,kf.
17. (6-aminohexanoic or amino?caproic or amino?hexanoic or amino caproic or amino-caproic or amino-n-hexanoic or cy-116 or cy116 or lederle or acikaprin or afibrin or amicar or caprocid or capracid or capramol or caprogel or caprolest or caprolisin* or caprolysin* or capromol or epsikapron or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid or cl 10304 or cl10304 or ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or epsilonaminocapronsav or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or resplamin or tachostyptan).tw,kf.
18. or/12-17
19. Aprotinin/
20. (antagosan or antilysin* or aprotimbin or apronitin* or aprotinin* or bayer a128 or contrical or contrycal or contrykal or dilmintal or frey inhibitor or kontrycal or Kunitz inhibitor or gordox or haemoprot or kallikrein-trypsin inactivator).tw,kf.
21. (iniprol or kontrikal or kontrykal or kunitz pancreatic trypsin inhibitor or midran or pulmin or tracylol or trascolan or trasilol or tra?ylol or traskolan or zymofren or pancreas antitrypsin or protinin or riker 52g or Rivilina zymofren).tw,kf.
22. or/19-21
23. Factor VIIa/
24. (factor viia or factor 7a or rfviia or fviia or novoseven* or novo seven* or aryoseven or acet or eptacog* or proconvertin).tw,kf.
25. ((activated adj2 factor seven) or (activated adj2 factor vii) or (activated adj3 rfvii) or (activated adj2 fvii)).tw,kf.
26. (factor seven or factor vii or factor 7).ti.
27. 23 or 24 or 25 or 26
28. Fibrinogen/ad, ae, de, sd, tu, th, to
29. *Fibrinogen/
30. (fibrinogen concentrate* or factor I or Haemocomplettan* or Riastap* or Fibryga* or Fibryna*).tw,kf.
31. 28 or 29 or 30
32. Deamino Arginine Vasopressin/
33. (desmopressin* or vasopressin deamino or D-amino D-arginine vasopressin or deamino-8-d-arginine vasopressin or vasopressin 1-desamino-8-arginine or desmotabs or DDAVP or desmogalen or adin or adiuretin or concentraid or d-void or dav ritter or deamino 8 dextro arginine vasopressin or deamino 8d arginine vasopressin or deamino dextro arginine vasopressin or deaminovasopressin or defirin or defirin melt or desmirin or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin or minirinette or minirinmelt or minrin or minurin or miram or nictur or noctisson or nocturin or nocutil or nordurine or novidin or nucotil or octim or octostim or presinex or stimate or wetirin).tw,kf.
34. 32 or 33
35. exp Factor XIII/
36. (factor XIII or fXIII or fibrin stabili?ing factor* or Tretten* or Catridecacog).tw,kf.
37. 35 or 36

38. exp Tissue Adhesives/
39. *Adhesives/
40. Collagen/tu
41. Thrombin/tu
42. Gelatin/tu
43. Gelatin Sponge, Absorbable/
44. ((fibrin* or collagen or cellulose or gelatin or gel or thrombin* or albumin or hemostatic* or haemostatic*) adj3 (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste or powder*)).tw,kf.
45. ((nonfibrin* or non-fibrin* or synthetic* or non-biological* or nonbiological* or biological*) adj3 (glue* or seal* or adhesive*)).tw,kf.
46. (surgical* adj3 (glue* or sealant* or adhesive*)).tw,kf.
47. ((fibrin* or collagen or cellulose or gelatin or thrombin) adj3 (hemosta* or haemosta*)).tw,kf.
48. (8Y or Aafact or Actif-VIII or Advate or Artiss or Bioglue or Biocol or Collaseal or Omrixil or Transglutine or Raplixa or Evarrest or Aleviate or Alphanate or Amofil or Beriate or Beriplast or Biostat or Bolheal or Cluvot or Conco-Eight-HT or Crosseal or Crosseal or Crosseight or Emoclot or Evarrest or Evicel or Factane or Fanhdi or Fibrogammin P or Green VIII or Green VIII Factor or Greengene or Greenmono or Greenplast or Haemate or Haemate P or Haemate P or Haemate P500 or Haemate-P or Haemoctin or Haemoctin SDH or Haemoctin-SDH or Hemaseel or Hemaseal or Hemofil M or Hemoraas or Humaclo or Humafactor-8 or Humate-P or Immunate or Innovate or Koate or Koate-DVI or Kogenate Bayer or Kogenate FS or Monoclate-P or NovoThirteen or Octafil or Octanate or Octanate or Optivate or Quixil or Talate or Tisseel or Tisseal or Tissel or Tissucol or Tricos or Vivostat or Voncento or Wilate or Wilnativ or Wilstart or Xyntha).tw,kf.
49. (Glubran or Gluetiss or Ifabond or Indermil or LiquiBand or TissuGlu).tw,kf.
50. (Evithrom or Floseal or Hemopatch or Gel-Flow or Gelfoam or Gelfilm or Recothrom or Surgifoam or Surgiflo* or "rh Thrombin" or Thrombi-Gel or Thrombi-Pad or Thrombin-JMI or Thrombinar or Thrombogen or Thrombostat).tw,kf.
51. (porcine gelatin or bovine collagen or bovine gelatin or nu-knit or arista or hemostase or vita sure or thrombin-jmi or thrombinjmi or avicel or vivagel or lyostypt or tabotamp or arterx or omnex or veriset).tw,kf.
52. (polysaccharide adj (sphere* or hemostatic powder)).tw,kf.
53. *Chitosan/
54. *Polyethylene Glycols/
55. *Hydrogel, Polyethylene Glycol Dimethacrylate/
56. Polyurethanes/ad, ae, pd, tu, to
57. ((polymer-derived elastic* or polymer tissue adhesive* or elastic hydrogel* or glutaraldehyde or PEG-based or polyurethane-based tissue or polyethylene glycol* or polyvinyl alcohol-based tissue or PVA-based tissue or natural biopolymer* or polypeptide-based or protein-based or polysaccharide-based or chitosan or polyglusam or cyanoacrylic or cyanoacrylate or cyacrin or dextran-based or chondroitin sulfate-based or mussel-inspired elastic* or glycol hydrogel or polymer-based) adj3 (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste* or powder*)).tw,kf.
58. Cellulose, Oxidized/
59. (absorbable cellulose or resorbable cellulose or oxidized cellulose or carboxycellulose or oxycellulose or cellulosic acid or oxycel or oxidized regenerated cellulose).tw,kf.
60. (BioGlue or Progel or Duraseal or Coseal or FocalSeal or ADAL-1 or Advaseal or Pleuraseal or Angio-Seal or Avitene or Instat or Helitene or Helistat or TDM-621 or Dermabond or Tissueseal or PolyStat or Raplixa or Spongostan or Surgicel or Surgilux or Tachosil or Traumstem).tw,kf.
61. (collagen-thrombin or thrombin-collagen or gelatin-fibrinogen or fibrinogen-gelatin or gelatin-thrombin or thrombin-gelatin or fibrinogen-thrombin or thrombin-fibrinogen or collagen-fibrinogen or fibrinogen-collagen or microfibrillar collagen or CoStasis or "GRF Glue" or GR-Dial or Algosterile or TraumaStat or HemCon or ChitoFlex or Celox or QuikClot or WoundStat or Vitagel or TachSeal or TachoComb or Cryoseal).tw,kf.
62. or/38-61
63. exp Waxes/
64. (bonewax* or bone wax* or bone putty or hemasorb or ostene).tw,kf.
65. 63 or 64
66. (((haemosta* or hemosta* or antihemorrhag* or antihemorrhag* or anti haemorrhag* or anti-hemorrhag*) adj5 (drug* or agent* or treat* or therap*)) ((coagulat* or clotting) adj factor*)).tw,kf.
67. 18 or 22 or 27 or 31 or 34 or 37 or 62 or 65 or 66

68. 11 and 67
69. Meta-Analysis.pt.
70. ((meta analy* or metaanaly*) and (trials or studies)).ab.
71. (meta analy* or metaanaly* or evidence-based).ti.
72. ((systematic* or evidence-based) adj2 (review* or overview*)).tw,kf.
73. (evidence synthes* or 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.
74. Cochrane Database of systematic reviews.jn.
75. (additional adj (papers or articles or sources)).ab.
76. ((electronic* or online) adj (sources or resources or databases)).ab.
77. (relevant adj (journals or articles)).ab.
78. or/69-77
79. Review.pt.
80. exp Randomized Controlled Trials as Topic/
81. selection criteria.ab. or critical appraisal.tw.
82. (data adj (abstract* or extract* or analys*)).ab.
83. exp Randomized Controlled Trial/
84. or/80-83
85. 79 and 84
86. 78 or 85
87. Randomized Controlled Trial.pt.
88. Controlled Clinical Trial.pt.
89. (placebo or randomly or groups).ab.
90. (randomi* or trial).tw,kf.
91. exp Clinical Trial as Topic/
92. 86 or 87 or 88 or 89 or 90 or 91
93. exp animals/ not humans/
94. 92 not 93
95. 68 and 94

Embase (Ovid)

1. exp Hip Surgery/
2. exp Hip Disease/su
3. exp Knee Surgery/
4. exp Knee Disease/su
5. ((hip* or knee* or femur or femoral) adj10 (replac* or operat* or surg* or arthroplast* or reconstruct* or repair* or osteotom* or alloplast* or plast* or resurfac* or implant* or prosthes*)).tw.
6. (acetabuloplast* or acetabulum arthroplast*).tw.
7. or/1-6
8. Antifibrinolytic Agent/
9. Tranexamic Acid/
10. Aminocaproic Acid/
11. (antifibrinolytic* or anti-fibrinolytic* or antifibrinolysin* or antiplasmin* or plasmin inhibitor* or tranexamic or tranhexamic or cyclohexanecarboxylic acid* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or "kabi 2161" or transamin or amchafibrin or anvitoff or spotof or cyklokapon or cyclo-F or femstrual or ugurol or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or antivoff or caprilon or cl?65336 or cl65336 or cyclocapron or cyclokapon or cyklokapon or cyklokapon or exacyl or frenolyse or fibrinon or hemostan or hexacapron or hexakapon or kalnex or lysteda or rikaparin or ronex or theranex or tranexam or tranexanic or tranexic or trans achma or transexamic or trenaxin or TXA or (fibrinolysis adj2 inhibitor*)).tw.

12. (Agretax or Bio-Stat or Capiloc or Capitrax or Clip Inj or Clot-XL or Clotawin-T or Coastat or Cuti or Cymin or Dubatran or Espercil or Examic or Existat or Extam or Fibrin or Gynae-Pil or Hemstate or Kapron or Menogia or Monitex or Nestran or Nexamic or Nexi-500 or Nexmeff or Nicolda or Nixa-500 or Pause or Rheonex or Sylstep TX or Synostat or T-nex or T Stat or T Stat or Tanmic or Temsyl-T or Texakind or Texanis or Texapar or Texid or Thams or Tonopan or Traklot or Tramic or Tramix or Tranarest or Trance Inj or Tranecid or Tranee or Tranemic or Tranex or Tranexa or Tranfib or Tranlok or Transtat or Transys or Transcam or Tranxi or Trapic or Traxage or Traxamic or Traxyl or Trenaxa or Trexamic or Trim Inj or Tx-1000 or Tx 500 or Wistran or X-Tran or Xamic).tw.
13. (6-aminohexanoic or amino?caproic or amino?hexanoic or amino caproic or amino-caproic or amino-n-hexanoic or cy-116 or cy116 or lederle or acikaprin or afibrin or amicar or caprocid or capracid or capramol or caprogel or caprolest or caprolisin* or caprolysin* or capromol or epsikapron or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid or cl 10304 or cl10304 or ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or epsilonaminocapronsav or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd:177 or neocaprol or nsc:26154 or resplamin or tachostyptan).tw.
14. or/8-13
15. Aprotinin/
16. (antagosan or antilysin* or aprotimbin or apronitin* or aprotinin* or bayer a128 or contrical or contrycal or contrykal or dilmintal or frey inhibitor or kontrycal or Kunitz inhibitor or gordox or haemoprot or kallikrein-trypsin inactivator).tw.
17. (iniprol or kontrikal or kontrykal or kunitz pancreatic trypsin inhibitor or midran or pulmin or tracylol or trascolan or trasilol or tra?ylol or traskolan or zymofren or pancreas antitrypsin or protinin or riker 52g or Rivilina zymofren).tw.
18. or/15-17
19. Blood Clotting Factor 7a/
20. (factor viia or factor 7a or rfviia or fviiia or novoseven* or novo seven* or aryoseven or acet or eptacog* or proconvertin).tw.
21. ((activated adj2 factor seven) or (activated adj2 factor vii) or (activated adj3 rfvii) or (activated adj2 fvii)).tw.
22. (factor seven or factor vii or factor 7).ti.
23. 19 or 20 or 21 or 22
24. Fibrinogen Concentrate/
25. (fibrinogen concentrate* or factor I or Haemocomplettan* or Riastap* or Fibryga* or Fibryna*).tw.
26. 24 or 25
27. Desmopressin/
28. (desmopressin* or vasopressin deamino or D-amino D-arginine vasopressin or deamino-8-d-arginine vasopressin or vasopressin 1-desamino-8-arginine or desmotabs or DDAVP or desmogalen or adin or adiuretin or concentraid or d-void or dav ritter or deamino 8 dextro arginine vasopressin or deamino 8d arginine vasopressin or deamino dextro arginine vasopressin or deaminovasopressin or defirin or defirin melt or desmirin or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin or minirinette or minirinmelt or minrin or minurin or miram or nictur or noctisson or nocturin or nocutil or nordurine or novidin or nucotil or octim or octostim or presinex or stimate or wetirin).tw.
29. 27 or 28
30. Blood Clotting Factor 13/
31. (factor xiii or fxiii or fibrin stabili?ing factor* or Tretten* or Catridecacog).tw.
32. 30 or 31
33. exp Tissue Adhesive/
34. *Adhesive Agent/
35. *Hemostatic Agent/
36. ((fibrin* or collagen or cellulose or gelatin or gel or thrombin* or albumin or hemostatic* or haemostatic*) adj3 (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste or powder*)).tw.
37. ((nonfibrin* or non-fibrin* or synthetic* or non-biological* or nonbiological* or biological*) adj3 (glue* or seal* or adhesive*)).tw.
38. (surgical* adj3 (glue* or sealant* or adhesive*)).tw.
39. ((fibrin* or collagen or cellulose or gelatin or thrombin) adj3 (hemosta* or haemosta*)).tw.
40. (8Y or Aafact or Actif-VIII or Advate or Artiss or Raplixa or Evarrest or Aleviate or Alphanate or Amofil or Beriate or Beriplast or Biostate or Bolheal or Cluvot or Conco-Eight-HT or Crosseel or Crosseal or Crosseight or Emoclot or Evarrest or Evicel or Factane or Fanhdi or Fibrogammin P or Green VIII or Green VIII Factor or Greengene or Greenmono or Greenplast or Haemate or Haemate P or Haemate P or Haemate P500 or Haemate-P or Haemoctin or Haemoctin SDH or Haemoctin-SDH or Hemaseel or Hemaseal or Hemofil M or Hemoraas or Humacloct or Humafactor-8 or Humate-P or Immunate or Innovate or Koate or Koate-DVI or Kogenate

- Bayer or Kogenate FS or Monoclate-P or NovoThirteen or Octafil or Octanate or Octanate or Optivate or Quixil or Talate or Tisseel or Tisseal or Tissel or Tissucol or Tricos or Vivostat or Voncento or Wilate or Wilnativ or Wilstart or Xyntha).tw.
41. (Glubran or Gluetiss or Ifabond or Indermil or LiquiBand or TissuGlu).tw.
 42. Collagen Sponge/ or Collagen Dressing/
 43. Gelatin Sponge/ or Gelfoam/
 44. (Evithrom or Floseal or Hemopatch or Gel-Flow or Gelfoam or Gelfilm or Recothrom or Surgifoam or Surgiflo* or "rh Thrombin" or Thrombi-Gel or Thrombi-Pad or Thrombin-JMI or Thrombinar or Thrombogen or Thrombostat).tw.
 45. *Chitosan/
 46. Hydrogel Dressing/
 47. Fibrinogen plus Thrombin/
 48. Polyvinyl Alcohol Sponge/
 49. (porcine gelatin or bovine collagen or bovine gelatin or nu-knit or arista or hemostase or vita sure or thrombin-jmi or thrombinjmi or avicel or vivagel or lyostypt or tabotamp or arterx or omnex or veriset).tw.
 50. (polysaccharide adj (sphere* or hemostatic powder)).tw.
 51. ((polymer-derived elastic* or polymer tissue adhesive* or elastic hydrogel* or glutaraldehyde or PEG-based or polyurethane-based tissue or polyethylene glycol* or polyvinyl alcohol-based tissue or PVA-based tissue or natural biopolymer* or polypeptide-based or protein-based or polysaccharide-based or chitosan or poliglusam or cyanoacrylic or cyanoacrylate or cyacrin or dextran-based or chondroitin sulfate-based or mussel-inspired elastic* or glycol hydrogel or polymer-based) adj3 (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste* or powder*)).tw.
 52. Oxidized Cellulose/
 53. Oxidized Regenerated Cellulose/
 54. Recombinant Thrombin/
 55. Tachocomb/
 56. (absorbable cellulose or resorbable cellulose or oxidized cellulose or carboxycellulose or oxycellulose or cellulosic acid or oxycel or oxidized regenerated cellulose).tw.
 57. (BioGlue or Progel or Duraseal or Coseal or FocalSeal or ADAL-1 or AdvaSeal or Pleuraseal or Angio-Seal or Avitene or Instat or Helitene or Helistat or TDM-621 or Dermabond or Tissuseal or PolyStat or Raplixa or Spongostan or Surgicel).tw.
 58. (Tachosil or Traumstem or CoStasis or "GRF Glue" or GR-Dial or Algosterile or TraumaStat or HemCon or ChitoFlex or Celox or QuikClot or WoundStat or Vitagel or TachSeal or TachoComb or Cryoseal).tw.
 59. (collagen-thrombin or thrombin-collagen or gelatin-fibrinogen or fibrinogen-gelatin or gelatin-thrombin or thrombin-gelatin or fibrinogen-thrombin or thrombin-fibrinogen or collagen-fibrinogen or fibrinogen-collagen or microfibrillar collagen).tw.
 60. or/33-59
 61. Bone Wax/
 62. (bonewax* or bone wax* or bone putty or hemasorb or ostene).tw.
 63. or/61-62
 64. (((haemosta* or hemosta* or antihemorrhag* or antihemorrhag* or anti haemorrhag* or anti-hemorrhag*) adj5 (drug* or agent* or treat* or therap*)) or ((coagulat* or clotting) adj factor*)).tw.
 65. 14 or 18 or 23 or 26 or 29 or 32 or 60 or 63 or 64
 66. 7 and 65
 67. Meta Analysis/
 68. (meta analy* or metaanaly* or evidence-based).ti.
 69. ((meta analy* or metaanaly*) and (trials or studies)).ab.
 70. Systematic Review/
 71. ((systematic* or evidence-based) adj2 (review* or overview*)).tw.
 72. (evidence syntheses* or 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.
 73. ((electronic* or online) adj (sources or resources or databases)).ab.
 74. ((additional adj (papers or articles or sources)) or (relevant adj (journals or articles))).ab.
 75. or/67-74
 76. Review.pt.
 77. (data extraction or selection criteria).ab.
 78. 76 and 77

79. 75 or 78
80. Editorial.pt.
81. 79 not 80
82. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/
83. (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.
84. 82 or 83
85. 81 or 84
86. 66 and 85

CINAHL (EBSCOhost)

S1 (MH "Arthroplasty, Replacement, Hip")
 S2 (MH "Osteoarthritis, Hip")
 S3 (MH "Arthroplasty, Replacement, Knee+")
 S4 (MH "Knee Injuries+/SU")
 S5 (MH "Knee/SU") OR (MH "Hip/SU")
 S6 (MH "Osteoarthritis, Knee/SU")
 S7 TI (((hip* or knee* or femur or femoral) N10 (replac* or operat* or surg* or arthroplast* or reconstruct* or repair* or osteotom* or alloplast* or plast* or resurfac* or implant* or prosthes*))) OR AB (((hip* or knee* or femur or femoral) N10 (replac* or operat* or surg* or arthroplast* or reconstruct* or repair* or osteotom* or alloplast* or plast* or resurfac* or implant* or prosthes*)))
 S8 TI ((acetabuloplast* or acetabulum arthroplast*)) OR AB ((acetabuloplast* or acetabulum arthroplast*)) OR TI ((THA or THR or TKA or TKR or UKA or UKR)) OR AB ((THA or THR or TKA or TKR or UKA or UKR))
 S9 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
 S10 (MH "Antifibrinolytic Agents") OR (MH "Aminocaproic Acids") OR (MH "Tranexamic Acid")
 S11 TI ((antifibrinolytic* or anti-fibrinolytic* or antifibrinolysin* or antiplasmin* or plasmin inhibitor* or tranexamic or tranhexamic or cyclohexanecarboxylic acid* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or "kabi 2161" or transamin or amchafibrin or anvitoff or spotof or cyklokapon or cyclo-F or femstrual or ugurol or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanoic acid or amstat or antivoff or caprilon or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or frenolyse or fibrinon or hemostan or hexacapon or hexakapron or kalnex or lysteda or rikaparin or ronex or theranex or tranexam or tranexanic or tranexic or trans achma or transexamic or trenaxin or TXA or (fibrinolysis N2 inhibitor*))) OR AB ((antifibrinolytic* or anti-fibrinolytic* or antifibrinolysin* or antiplasmin* or plasmin inhibitor* or tranexamic or tranhexamic or cyclohexanecarboxylic acid* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or "kabi 2161" or transamin or amchafibrin or anvitoff or spotof or cyklokapon or cyclo-F or femstrual or ugurol or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanoic acid or amstat or antivoff or caprilon or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or frenolyse or fibrinon or hemostan or hexacapon or hexakapron or kalnex or lysteda or rikaparin or ronex or theranex or tranexam or tranexanic or tranexic or trans achma or transexamic or trenaxin or TXA or (fibrinolysis N2 inhibitor*)))
 S12 TI ((6-aminoheptanoic or amino?caproic or amino?hexanoic or amino caproic or amino-caproic or amino-n-hexanoic or cy-116 or cy116 or lederle or acikaprin or afibrin or amicar or caprocid or capracid or capramol or caprogel or caprolest or caprolisin* or caprolysin* or capromol or epsikapron or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid or cl 10304 or cl10304 or ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or epsilonaminocaproinsav or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177 or neocaprol or nsc?26154 or resplamin or tachostyptan)) OR AB ((6-aminoheptanoic or amino?caproic or amino?hexanoic or amino caproic or amino-caproic or amino-n-hexanoic or cy-116 or cy116 or lederle or acikaprin or afibrin or amicar or caprocid or capracid or capramol or caprogel or caprolest or caprolisin* or caprolysin* or capromol or epsikapron or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid or cl 10304 or cl10304 or ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or

epsilonaminocaproic or epsilonaminocaproic or etha?aminocaproic or ethaaminocaproic or emocaprol or hepin or ipsilon or jd? 177 or neocaprol or nsc?26154 or resplamin or tachostyptan))

S13 S10 OR S11 OR S12

S14 (MH "Aprotinin")

S15 TI ((antagasan or antilysin* or aprotimbin or apronitin* or aprotinin* or bayer a128 or contrical or contrykal or contrykal or dilmintal or frey inhibitor or kontrykal or Kunitz inhibitor or gordox or haemoprot or kallikrein-trypsin inactivator)) OR AB ((antagasan or antilysin* or aprotimbin or apronitin* or aprotinin* or bayer a128 or contrical or contrykal or contrykal or dilmintal or frey inhibitor or kontrykal or Kunitz inhibitor or gordox or haemoprot or kallikrein-trypsin inactivator))

S16 TI ((iniprol or kontrikal or kontrykal or kunitz pancreatic trypsin inhibitor or midran or pulmin or tracylol or trascolan or trasilol or tra?ylol or traskolan or zymofren or pancreas antitrypsin or protinin or riker 52g or Rivilina zymofren)) OR AB ((iniprol or kontrikal or kontrykal or kunitz pancreatic trypsin inhibitor or midran or pulmin or tracylol or trascolan or trasilol or tra?ylol or traskolan or zymofren or pancreas antitrypsin or protinin or riker 52g or Rivilina zymofren))

S17 S14 OR S15 OR S16

S18 TX ((factor viia or factor 7a or rfviia or fviiia or novoseven* or novo seven* or aryoseven or acet or eptacog* or proconvertin)) OR TX (((activated N2 factor seven) or (activated N2 factor vii) or (activated N3 rfvii) or (activated N2 fvii))

S19 TX (factor seven or factor vii or factor 7)

S20 S18 OR S19

S21 (MH "Fibrinogen")

S22 TX (fibrinogen concentrate* or factor I or Haemocomplettan* or Riastap* or Fibryga* or Fibryna*)

S23 S21 OR S22

S24 (MH "Desmopressin")

S25 TI ((desmopressin* or vasopressin deamino or D-amino D-arginine vasopressin or deamino-8-d-arginine vasopressin or vasopressin 1-desamino-8-arginine or desmotabs or DDAVP or desmogalen or adin or adiuretin or concentraid or d-void or dav ritter or deamino 8 dextro arginine vasopressin or deamino 8d arginine vasopressin or deamino dextro arginine vasopressin or deaminovasopressin or defirin or defirin melt or desmirin or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin or minirinette or minirinmelt or minrin or minurin or miram or nictur or noctisson or nocturin or nocutil or nordurine or novidin or nucotil or octim or octostim or presinex or stimate or wetirin)) OR AB ((desmopressin* or vasopressin deamino or D-amino D-arginine vasopressin or deamino-8-d-arginine vasopressin or vasopressin 1-desamino-8-arginine or desmotabs or DDAVP or desmogalen or adin or adiuretin or concentraid or d-void or dav ritter or deamino 8 dextro arginine vasopressin or deamino 8d arginine vasopressin or deamino dextro arginine vasopressin or deaminovasopressin or defirin or defirin melt or desmirin or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin or minirinette or minirinmelt or minrin or minurin or miram or nictur or noctisson or nocturin or nocutil or nordurine or novidin or nucotil or octim or octostim or presinex or stimate or wetirin))

S26 S24 OR S25

S27 TX (factor XIII or fXIII or fibrin stabilizing factor* or Tretten* or Catridecacog)

S28 (MH "Tissue Adhesives")

S29 (MH "Fibrin Tissue Adhesive")

S30 (MH "Collagen/TU")

S31 (MH "Thrombin/TU")

S32 (MH "Surgical Sponges")

S33 TI (((fibrin* or collagen or cellulose or gelatin or gel or thrombin* or albumin or hemostatic* or haemostatic*) N3 (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste or powder*))) OR AB (((fibrin* or collagen or cellulose or gelatin or gel or thrombin* or albumin or hemostatic* or haemostatic*) N3 (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste or powder*)))

S34 TI (((nonfibrin* or non-fibrin* or synthetic* or non-biological* or nonbiological* or biological*) N3 (glue* or seal* or adhesive*))) OR AB (((nonfibrin* or non-fibrin* or synthetic* or non-biological* or nonbiological* or biological*) N3 (glue* or seal* or adhesive*)))

S35 TI ((surgical* N3 (glue* or sealant* or adhesive*))) OR AB ((surgical* N3 (glue* or sealant* or adhesive*)))

S36 TI (((fibrin* or collagen or cellulose or gelatin or thrombin) N3 (hemosta* or haemosta*))) OR AB (((fibrin* or collagen or cellulose or gelatin or thrombin) N3 (hemosta* or haemosta*)))

S37 TI ((8Y or Aafact or Actif-VIII or Advate or Artiss or Biogluce or Biocol or Collaseal or Omrixil or Transglutine or Raplixa or Evarrest or Aleviate or Alphanate or Amofil or Beriate or Beriplast or Biostate or Bolheal or Cluvot or Conco-Eight-HT or Crosseel or

Crosseal or Crosseight or Emoclot or Evarrest or Evicel or Factane or Fanhdi or Fibrogammin P or Green VIII or Green VIII Factor or Greengene or Greenmono or Greenplast or Haemate or Haemate P or Haemate P or Haemate P500 or Haemate-P or Haemoctin or Haemoctin SDH or Haemoctin-SDH or Hemaseel or Hemaseal or Hemofil M or Hemoraas or Humaclot or Humafactor-8 or Humate-P or Immunate or Innovate or Koate or Koate-DVI or Kogenate Bayer or Kogenate FS or Monoclate-P or NovoThirteen or Octafil or Octanate or Octanate or Optivate or Quixil or Talate or Tisseal or Tisseal or Tissel or Tissucol or Tricos or Vivostat or Voncento or Wilate or Wilmativ or Wilstart or Xyntha) OR AB ((8Y or Aafact or Actif-VIII or Advate or Artiss or Bioglue or Biocol or Collaseal or Omrixil or Transglutine or Raplixa or Evarrest or Aleviate or Alphanate or Amofil or Beriate or Beriplast or Biostat or Bolheal or Cluvot or Conco-Eight-HT or Crosseal or Crosseal or Crosseight or Emoclot or Evarrest or Evicel or Factane or Fanhdi or Fibrogammin P or Green VIII or Green VIII Factor or Greengene or Greenmono or Greenplast or Haemate or Haemate P or Haemate P or Haemate P500 or Haemate-P or Haemoctin or Haemoctin SDH or Haemoctin-SDH or Hemaseel or Hemaseal or Hemofil M or Hemoraas or Humaclot or Humafactor-8 or Humate-P or Immunate or Innovate or Koate or Koate-DVI or Kogenate Bayer or Kogenate FS or Monoclate-P or NovoThirteen or Octafil or Octanate or Octanate or Optivate or Quixil or Talate or Tisseal or Tisseal or Tissel or Tissucol or Tricos or Vivostat or Voncento or Wilate or Wilmativ or Wilstart or Xyntha)

S38 TI ((Glubran or Gluetiss or Ifabond or Indermil or LiquiBand or TissuGlu) OR AB ((Glubran or Gluetiss or Ifabond or Indermil or LiquiBand or TissuGlu))

S39 TI ((Evithrom or Floseal or Hemopatch or Gel-Flow or Gelfoam or Gelfilm or Recothrom or Surgifoam or Surgiflo* or “rh Thrombin” or Thrombi-Gel or Thrombi-Pad or Thrombin-JMI or Thrombinar or Thrombogen or Thrombostat) OR AB ((Evithrom or Floseal or Hemopatch or Gel-Flow or Gelfoam or Gelfilm or Recothrom or Surgifoam or Surgiflo* or “rh Thrombin” or Thrombi-Gel or Thrombi-Pad or Thrombin-JMI or Thrombinar or Thrombogen or Thrombostat))

S40 TI ((porcine gelatin or bovine collagen or bovine gelatin or nu-knit or arista or hemostase or vita sure or thrombin-jmi or thrombinjmi or avicel or vivagel or lyostypt or tabotamp or arterx or omnex or veriset) OR AB ((porcine gelatin or bovine collagen or bovine gelatin or nu-knit or arista or hemostase or vita sure or thrombin-jmi or thrombinjmi or avicel or vivagel or lyostypt or tabotamp or arterx or omnex or veriset))

S41 TX (polysaccharide NEXT (sphere* or hemostatic powder))

S42 (MM “Polyethylene Glycols”)

S43 (MH “Hydrogel Dressings”)

S44 (MH “Polyurethanes/AD/AE/TU/ST/DE”)

S45 TI (((polymer-derived elastic* or polymer tissue adhesive* or elastic hydrogel* or glutaraldehyde or PEG-based or polyurethane-based tissue or polyethylene glycol* or polyvinyl alcohol-based tissue or PVA-based tissue or natural biopolymer* or polypeptide-based or protein-based or polysaccharide-based or chitosan or poliglusam or cyanoacrylic or cyanoacrylate or cyacrin or dextran-based or chondroitin sulfate-based or mussel-inspired elastic* or glycol hydrogel or polymer-based) N3 (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste* or powder*))) OR AB (((polymer-derived elastic* or polymer tissue adhesive* or elastic hydrogel* or glutaraldehyde or PEG-based or polyurethane-based tissue or polyethylene glycol* or polyvinyl alcohol-based tissue or PVA-based tissue or natural biopolymer* or polypeptide-based or protein-based or polysaccharide-based or chitosan or poliglusam or cyanoacrylic or cyanoacrylate or cyacrin or dextran-based or chondroitin sulfate-based or mussel-inspired elastic* or glycol hydrogel or polymer-based) N3 (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste* or powder*)))

S46 (MH “Cellulose/TU”)

S47 TI ((absorbable cellulose or resorbable cellulose or oxidized cellulose or carboxycellulose or oxycellulose or cellulosic acid or oxycel or oxidized regenerated cellulose)) OR AB ((absorbable cellulose or resorbable cellulose or oxidized cellulose or carboxycellulose or oxycellulose or cellulosic acid or oxycel or oxidized regenerated cellulose))

S48 TI ((BioGlue or Progel or Duraseal or Coseal or FocalSeal or ADAL-1 or AdvaSeal or Pleuraseal or Angio-Seal or Avitene or Instat or Helitene or Helistat or TDM-621 or Dermabond or Tissueseal or PolyStat or Raplixa or Spongostan or Surgicel or Surgilux or Tachosil or Traumstem) OR AB ((BioGlue or Progel or Duraseal or Coseal or FocalSeal or ADAL-1 or AdvaSeal or Pleuraseal or Angio-Seal or Avitene or Instat or Helitene or Helistat or TDM-621 or Dermabond or Tissueseal or PolyStat or Raplixa or Spongostan or Surgicel or Surgilux or Tachosil or Traumstem))

S49 TI ((collagen-thrombin or thrombin-collagen or gelatin-fibrinogen or fibrinogen-gelatin or gelatin-thrombin or thrombin-gelatin or fibrinogen-thrombin or thrombin-fibrinogen or collagen-fibrinogen or fibrinogen-collagen or microfibrillar collagen or CoStasis or “GRF Glue” or GR-Dial or Algosterile or TraumaStat or HemCon or ChitoFlex or Celox or QuikClot or WoundStat or Vitagel or TachSeal or TachoComb or Cryoseal) OR AB ((collagen-thrombin or thrombin-collagen or gelatin-fibrinogen or fibrinogen-gelatin or gelatin-thrombin or thrombin-gelatin or fibrinogen-thrombin or thrombin-fibrinogen or collagen-fibrinogen or fibrinogen-collagen or microfibrillar collagen or CoStasis or “GRF Glue” or GR-Dial or Algosterile or TraumaStat or HemCon or ChitoFlex or Celox or QuikClot or WoundStat or Vitagel or TachSeal or TachoComb or Cryoseal))

or microfibrillar collagen or CoStasis or “GRF Glue” or GR-Dial or Algosterile or TraumaStat or HemCon or ChitoFlex or Celox or QuikClot or WoundStat or Vitagel or TachSeal or TachoComb or Cryoseal)

S50 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 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49

S51 (MH “Waxes/TU”)

S52 TI ((bonewax* or bone wax* or bone putty or hemasorb or ostene)) OR AB ((bonewax* or bone wax* or bone putty or hemasorb or ostene))

S53 S51 OR S52

S54 TI ((((haemosta* or hemosta* or antihemorrhag* or antihemorrhag* or anti haemorrhag* or anti-hemorrhag*) N5 (drug* or agent* or treat* or therap*)) or ((coagulat* or clotting) NEXT factor*))) OR AB ((((haemosta* or hemosta* or antihemorrhag* or antihemorrhag* or anti haemorrhag* or anti-hemorrhag*) N5 (drug* or agent* or treat* or therap*)) or ((coagulat* or clotting) NEXT factor*)))

S55 S13 OR S17 OR S20 OR S23 OR S26 OR S50 OR S53 OR S54

S56 S9 AND S55

S57 (MH Clinical Trials+)

S58 PT Clinical Trial

S59 TI ((controlled trial*) or (clinical trial*)) OR AB ((controlled trial*) or (clinical trial*))

S60 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*))

S61 TI randomi* OR AB randomi*

S62 MH RANDOM ASSIGNMENT

S63 TI ((phase three) or (phase III) or (phase three)) or AB ((phase three) or (phase III) or (phase three))

S64 (TI (random* N2 (assign* or allocat*))) OR (AB (random* N2 (assign* or allocat*))))

S65 MH PLACEBOS

S66 MH META ANALYSIS

S67 MH SYSTEMATIC REVIEW

S68 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*”)

S69 TI (“literature review” OR “literature overview” OR “literature search*”) OR AB (“literature review” OR “literature overview” OR “literature search*”)

S70 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)

S71 TI placebo* OR AB placebo*

S72 MH QUANTITATIVE STUDIES

S73 S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72

S74 S56 AND S73

Transfusion Evidence Library

Clinical Specialty: Orthopaedic Surgery

AND

Subject Areas: Alternatives to Blood/Antifibrinolytics OR Alternatives to Blood/Fractionated Blood Products OR Alternatives to Blood/Recombinant Coagulation Factors

ClinicalTrials.gov

1. Other Terms: (hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR THA OR TKA) AND (randomized or randomised OR randomly OR random) AND

Intervention: hemostatic OR antifibrinolytic OR tranexamic OR EACA OR aminocaproic OR aprotinin OR desmopressin OR DDAVP OR factor viia OR novoseven OR arioseven OR fibrinogen OR haemocomplettan OR Riastap OR Fibryna OR Fibryga OR factor XIII OR Tretten

2. Other Terms: (hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR THA OR TKA) AND (randomized or randomised OR randomly OR random) AND Intervention: sealant OR adhesive OR collagen OR cellulose OR gelatin OR glue OR matrix OR sponge OR fleece OR foam OR scaffold OR patch OR sheet OR gelfoam OR chitosan OR hydrogel OR polyethylene glycol OR tachocomb OR BioGlue OR Surgicel OR Veriset

3. Other Terms: (hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR THA OR TKA) AND (randomized or randomised OR randomly OR random) AND Intervention: Evithrom OR Floseal OR Tachosil OR Cryoseal OR Hemopatch OR Progel OR Duraseal OR Coseal OR FocalSeal OR Algosterile OR TraumaStat OR HemCon OR ChitoFlex OR Celox OR QuikClot OR WoundStat OR Vitagel OR TachSeal OR bonewax OR hemasorb OR ostene

4. Other Terms: (hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR THA OR TKA) AND (randomized or randomised OR randomly OR random) AND Intervention: iniprol or kontrikal OR CloSys OR Glubran OR Gluetiss OR Ifabond OR Indermil OR LiquiBand OR Octafil OR Octanate OR Optivate OR Quixil OR Tisseel OR Tissucol OR TissuGlu OR Thrombi-Gel OR Vivostat OR Voncento OR Wilate OR Wilnativ OR Wilstart

5. Other Terms: (hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR THA OR TKA) AND (randomized or randomised OR randomly OR random) AND Title: hemostasis OR hemostatic OR antifibrinolytic OR factor OR fibrinogen OR thrombin OR collagen OR gelatin OR cellulose

6. Other Terms: (hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR THA OR TKA) AND (randomized or randomised OR randomly OR random) AND Condition: bleeding OR hemorrhage OR blood loss OR bloodloss

7. 1 OR 2 OR 3 OR 4 OR 5 OR 6 [N.B. combined and de-duplicated in EndNote]

WHO ICTRP

1. Title OR Condition: hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR TKA OR THA
Intervention: hemostatic OR antifibrinolytic OR tranexamic OR EACA OR aminocaproic OR aprotinin OR desmopressin OR DDAVP OR factor viia OR novoseven OR arioseven OR fibrinogen OR haemocomplettan OR Riastap OR Fibryna OR Fibryga OR factor XIII OR Tretten

2. Title OR Condition: hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR TKA OR THA
Intervention: sealant OR adhesive OR collagen OR cellulose OR gelatin OR glue OR matrix OR sponge OR fleece OR foam OR scaffold OR patch OR sheet OR gelfoam OR chitosan OR hydrogel OR polyethylene glycol OR tachocomb OR BioGlue OR Surgicel OR Veriset

3. Title OR Condition: hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR TKA OR THA
Intervention: Evithrom OR Floseal OR Tachosil OR Cryoseal OR Hemopatch OR Progel OR Duraseal OR Coseal OR FocalSeal OR Algosterile OR TraumaStat OR HemCon OR ChitoFlex OR Celox OR QuikClot OR WoundStat OR Vitagel OR TachSeal OR bonewax OR hemasorb OR ostene

4. Title OR Condition: hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR TKA OR THA
Intervention: iniprol or kontrikal OR CloSys OR Glubran OR Gluetiss OR Ifabond OR Indermil OR LiquiBand OR Octafil OR Octanate OR Optivate OR Quixil OR Tisseel OR Tissucol OR TissuGlu OR Thrombi-Gel OR Vivostat OR Voncento OR Wilate OR Wilnativ OR Wilstart

5. Title OR Condition: hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR TKA OR THA

Intervention OR Title: hemostasis OR hemostatic OR antifibrinolytic OR factor OR fibrinogen OR thrombin OR collagen OR gelatin OR cellulose

6. 1 OR 2 OR 3 OR 4 OR 5 [N.B. combined and de-duplicated in EndNote]

CONTRIBUTIONS OF AUTHORS

Victoria N Gibbs: protocol development and content expertise

Rita Champaneria: protocol development

Antony Palmer: protocol development and content expertise

Carolyn Doree: protocol development and design of the searching strategy

Lise J Estcourt: protocol development and content expertise

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