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[Intervention Protocol]

Pharmacological interventions for the prevention of bleeding in people undergoing definitive fixation of hip, pelvic and long bone fractures: 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 review systematically the optimal administration and relative efficacy of pharmacological interventions for preventing blood loss in definitive surgical fixation of the hip, pelvic and long bones.

BACKGROUND

Description of the condition

Traumatic injury and fracture is one of the world's leading causes of death and disability (Haagsma 2016). Acute orthopaedic injuries, including soft tissue, muscle and bone injuries, are the most common injuries sustained in accidents and the most likely form of traumatic injury to require hospitalisation (Clay 2010; Lang 2014; Lee 2005). In addition, orthopaedic injury may result in important individual and social disability and is associated with substantial economic and social costs (Clay 2010; Lang 2014; Williamson 2009).

The ease with which bone fracture occurs is related to bone mineral density, which decreases with age. In younger people – with higher bone mineral density – high-impact accidents may result in fracture (Armas 2010); however, in older people – with lower bone mineral density and osteoporosis – lower energy accidents such as a simple fall from standing height may result in an important injury, for instance pelvic or hip fracture. In 2010, the number of people aged 50 years or more at high risk of osteoporotic fracture worldwide was estimated at 158 million and this figure is expected to double by 2040 (Odén 2015). As a consequence of an ageing population, globally the number of people with a hip fracture is expected to reach 6.26 million by 2050 (Dhanwal 2011). Studies in the UK report incidences of pelvic fracture in the region of 7.4 per 10,000; tibial fractures 8.8 per 10,000; and radius/ulna fractures 9.6 per 10,000 for men, and 41.2 per 10,000 for women (van der Velde 2016).

Pelvic, hip and long bones are highly vascular and fracture can result in significant bleeding. Blood loss from a closed femoral fracture is estimated to be between 1000 mL and 1500 mL, and for closed tibial fractures 500 mL and 1000 mL. For open fractures, when the skin is breached, these figures may double (Lee 2005). Surgical fixation techniques include plate and screws, intramedullary nailing (a rod placed down the middle of the bone) or a form of joint replacement. Determining which technique to use depends on the location of the injury, type of fracture and functional requirements of the person. Surgical fixation of pelvic, hip and long bones often results in a large amount of blood loss and this is combined with loss from the initial injury. Typically, people undergoing a hip hemiarthroplasty for fracture (half a hip replacement whereby the ball of the femur is replaced and the socket is left alone) lose between 300 mL and 500 mL of blood from surgery (Ahn 2008). For people undergoing revision total hip replacement for periprosthetic fracture (whereby the person has sustained a fracture around an existing hip replacement), blood loss from surgery is around 2000 mL (Moloney 2014). Long bone fixation with plate and screws or fixation with an intramedullary nail is thought to incur a blood loss between 550 mL and 1500 mL (Foss 2006), while the estimated blood loss for pelvic fixation with plate and screws is thought to be around 1200 mL (Odak 2013). Hip fractures treated with dynamic hip screw fixation typically result in a lower blood loss of between 300 mL to 400 mL (Baruah 2016), and fixation of humerus fractures results in blood loss of around 250 mL (Kurup 2011). Fixation of extremity fractures, such as fibula and radius fractures, results in even lower blood losses of around 170 mL (Ergol 2006), and 100 mL (Wei 2016), respectively.

Bleeding sustained from a bony fracture along with loss from surgical fixation increases the risk of blood transfusion and postoperative anaemia. In one Cochrane Review of people who had surgery for a neck of femur fracture, taking a liberal haemoglobin

transfusion threshold of approximately 100 g/L, 74% to 100% required a blood transfusion, and for a restrictive haemoglobin transfusion threshold of approximately 80 g/L, 11% to 45% required a blood transfusion (Brunskill 2015). Allogenic blood transfusions (donated blood from matched donors) are not without risk and have been shown to increase the risk of mortality (Vochteloo 2011). In addition, allogenic transfusion is associated with increased duration of hospital stay, which increases healthcare costs (Smeets 2018).

Presently, there are several effective pharmacological interventions available that help prevent blood loss during surgery (Schulman 2012). Pharmacological interventions offer the opportunity to reduce the risk of allogenic blood transfusion and associated complications, improve outcomes and decrease healthcare costs.

Description of the intervention

This review will focus on pharmacological interventions used to reduce bleeding during surgery to rejoin fractured bones permanently (definitive fixation). Pharmacological interventions to prevent bleeding provide the opportunity to reduce blood transfusion and the infection and compatibility complications associated with its use. The interventions will include antifibrinolytic drugs, desmopressin, factor VIIa and factor XIII, fibrinogen, and sealants (glues).

Antifibrinolytic interventions include tranexamic acid, aprotinin and epsilon-aminocaproic acid. Tranexamic acid and epsilon-aminocaproic acid are synthetic derivatives of lysine, while aprotinin is derived from bovine lung. Antifibrinolytics help to reduce blood loss through stabilising blood clots and reduce bleeding in major trauma, particularly when given early (Ker 2015).

Sealants (which are applied directly to the wound during surgery) will be grouped into those which contain fibrin and those which do not contain fibrin. Fibrin plays an important role in forming a blood clot, and sealants containing fibrin prevent bleeding during surgery. They are thought to be particularly effective when used in orthopaedic surgery where blood loss is high (Carless 2003). Non-fibrin sealants rely on fibrin found in normal blood, and tend to exert their effects through mechanical expansion which provides pressure to bleeding surfaces (Baird 2015).

The route by which the interventions can be administered is displayed in Table 1 and include intravenous, oral, topical and nasal modes.

How the intervention might work

Blood loss from surgical fixation of fractures can cause haemoglobin levels to fall significantly. Low haemoglobin levels are associated with the onset of symptoms such as fatigue, breathlessness and hypotension, which may reduce the blood available to perfuse organs. In these circumstances, blood transfusion may be required, even though it is associated with risk. The aim of the blood-saving interventions (listed below) is to reduce bleeding, and ultimately reduce blood loss and need for blood transfusion.

An explanation of how each intervention works with any potential risks is provided below.

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

Antifibrinolytics act by inhibiting the process that breaks down blood clots, resulting in the clot becoming more stable (Tengborn 2015). The most commonly used antifibrinolytics are tranexamic acid, aprotinin and epsilon-aminocaproic acid (Henry 2011). They may be administered orally, intravenously or topically (BNF 2018). Although most of these drugs cause few adverse effects, there is a theoretical increased risk of unwanted venous blood clots with their use (Levy 2018; Myers 2019), and at higher doses there is concern about the risk of seizures (Zhang 2016).

Desmopressin

Desmopressin stimulates the release of factor VIII (Pearson 2016), which in turn encourages blood clotting. Factor VIII, an important factor contained in blood, enables platelets to adhere to wound sites and form blood clots. It can be given intravenously, subcutaneously (under the skin) or intranasally (via the nose) (BNF 2018). Reported adverse effects include facial flushing, and the possibility of low blood sodium levels, particularly with repeated doses (Desborough 2017).

Recombinant factor VIIa and factor XIII

Recombinant factor VIIa (rFVIIa) is used to treat people with haemophilia, congenital factor VII deficiency and inhibitory alloantibodies. It has also been administered outside licensed use (off-licence) to prevent significant blood loss during surgery (Simpson 2012). However, despite its use, the efficacy of this drug in people who do not have haemophilia remains unclear.

Recombinant factor XIII (rFXIII) protects a developing clot during formation and, therefore, improves clot strength. This effect is likely to depend on dose and it has been suggested that maintaining high levels of rFXIII may prevent bleeding (Aleman 2014).

Both rFVIIa and rFXIII are administered intravenously (BNF 2018). The concern with rFVIIa is the potential increased risk of arterial blood clots, particularly in older people; however, there is limited evidence to confirm this risk (Goodnough 2016).

Fibrinogen

Fibrinogen is a soluble protein present in the bloodstream. During tissue and vessel injury it is converted by enzymes to fibrin (by thrombin) and then to a fibrin-based blood clot. The formation of the blood clot helps to prevent excessive bleeding. Fibrinogen is administered intravenously (BNF 2018). Since fibrinogen is obtained from blood, there is a potential risk, albeit small, of viral infection due to the manufacturing process (Franchini 2012).

Fibrin sealants

Fibrin sealants are surgical wound adhesives and are administered topically. They are mostly used during surgery and to aid haemostasis (halt bleeding), tissue sealing and wound healing. Sealants tend to originate from plasma and commonly contain fibrinogen, thrombin, factor XIII and calcium chloride. Fibrin sealants may include an antifibrinolytic agent (Fischer 2011), and their final composition may vary. They can be applied to actively bleeding bony surfaces and into the wound. Allergy is a rarely noted adverse effect (Aguilera 2013).

Non-fibrin sealants

Non-fibrin sealants are administered topically and tend to be liquids that combine to form a film that promotes platelet activation and formation of a cluster. Non-fibrin sealants help with blood clot formation, however, the functioning of the sealant is dependent on the individual's own fibrin contained within their blood. The term 'non-fibrin sealants' also encompasses internal dressings and powders, which may be an alternative to tourniquet use when this is not possible. The mechanism of action of many sealants in this group is through mechanical expansion and compression of tissues. Consequently, many reported adverse events are associated with this, including nerve compression (Baird 2015).

Why it is important to do this review

This review will aim to assess the effectiveness of various pharmacological interventions to prevent blood loss following definitive fixation of hip, pelvic and long bone fractures (definitive meaning a permanent fix of the broken bone as opposed to a temporary surgery). Although emergency blood transfusions provide a life-saving treatment for people who have lost blood from trauma, there are risks associated with allogenic blood transfusions, such as transfusion-transmitted infection and serious adverse transfusion reactions (WHO 2016). In 2017 in the UK, 21 people died from transfusion-related complications and there were 112 incidences of major morbidity associated with blood transfusion (SHOT 2018).

A global priority for the World Health Organization is to be able to provide safe access to blood products, and also to minimise unnecessary transfusions in order to preserve a scarce resource, reduce risk, and reduce costs (WHO 2016). One unit of red blood cells in the UK cost GBP 129 in April 2019, which is expected to rise to GBP 133 by 2020 (NCG 2018). By comparison, in 2018, an ampoule of tranexamic acid cost GBP 1.50, and an ampoule of desmopressin cost GBP 13.16 (BNF 2018). Embracing pharmacological treatments to prevent bleeding may reduce the need for blood transfusion, reduce costs, and potentially offer patients a lower risk profile.

Concerns around the adverse effect profile of pharmacological interventions may contribute to their limited uptake in clinical practice for people who require definitive fixation. Theoretically, interventions to prevent bleeding may also result in the formation of unwanted blood clots. This may be of particular concern in people with myocardial infarction or a pre-existing increased risk of stroke or pulmonary embolism (Danninger 2015). Knowing the optimal dose could help to limit adverse effects, as well as reduce treatment costs. In addition, the timing of the intervention is important. The CRASH-2 trial (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage 2; a large randomised controlled trial (RCT) of tranexamic acid versus placebo in people with major trauma) found that timing of the intervention was associated with outcome (Roberts 2013). Delivery of tranexamic acid within three hours of trauma improved the chance of survival, however, when tranexamic acid was delivered three hours after injury, there was an increased risk of death from bleeding.

Currently the optimal dose, route and timing of these interventions is unknown, which results in uncertainty for decision makers. We will carry out a network meta-analysis (NMA) of RCTs to provide the highest level of evidence for those treating people who

are undergoing definitive fixation for hip, pelvic and long bone fractures.

Description of network meta-analysis

NMA is a type of analysis that allows more than two treatments to be compared (Lu 2004). Network diagrams are used to represent the available evidence for each treatment comparison. Each treatment is represented by a node (vertex), and a line is used to connect the two treatments being compared (Jansen 2011). It is important to undertake a NMA like any other meta-analysis, using a rigorous systematic approach. The network diagram will contain a mix of solid and blank lines. Solid lines indicate 'direct' comparisons for which there is evidence from clinical trials. Blank (or absent lines) indicate 'indirect' comparisons, that is, those where no clinical trials have compared the interventions (Bucher 1997; Jansen 2011).

An NMA uses data from direct comparisons to estimate the effects of indirect comparisons that have not been assessed yet in a clinical trial (Caldwell 2005; Jansen 2011; Jansen 2013; Song 2003). This allows NMA to 'fill gaps' in the evidence by pooling data from direct clinical trial comparisons, and deduce information about missing comparisons in the network (Krahn 2013; Salanti 2014). To draw robust conclusions, the NMA assumes that all the people and trials included in the network are similar enough in terms of effect modifiers across all direct comparisons (Jansen 2013).

A further benefit of NMA is that it can aid clinical decision making by providing results in an accessible format. Outputs can be tabulated in a hierarchy to show results by treatment and outcome. This is particularly useful as all relevant evidence can be included in one table, indicating both benefits and risks of a given treatment (Hoaglin 2011; Jansen 2011; Sutton 2008; van der Valk 2009).

OBJECTIVES

To review systematically the optimal administration and relative efficacy of pharmacological interventions for preventing blood loss in definitive surgical fixation of the hip, pelvic and long bones.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs). If the process of randomisation is unclear, we will contact the trial authors to obtain further information. If we are unable to contact the authors, we will include the trial in the review and consider it to be at unclear risk of bias. To be eligible, trials must compare at least one of our interventions of interest (placebo versus active treatment, or active treatment versus another active treatment). We will use both abstracts and full-text publications if they report adequate information about study design, patient characteristics and interventions. We will only include trials that have been prospectively registered, unless the final trial report was published before 2010.

Types of participants

We will include people who have undergone surgery for definitive fixation of hip, pelvic and long bone (pelvis, tibia, femur, humerus, radius, ulna and clavicle) fractures. There will be no restrictions on gender, ethnicity or age.

Definitive fixation will include the following types of surgery:

- fixation with plate and screws, intramedullary nailing and joint replacement;
- joint replacement surgery:
 - * hip hemiarthroplasty;
 - * total hip replacement;
 - * total shoulder replacement;
 - * reverse shoulder replacement;
 - * total knee replacement; and
 - * total elbow replacement for the management of fractures;
- fixation of a fracture around an existing replacement (periprosthetic fractures).

If an eligible trial contains a mixed population of people (e.g. non-definitive surgery such as temporary external fixation), then we will only use data contributed from our population of interest. If no subgroup data are given, and we are unable to contact the corresponding author to provide this 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 participants if they were taking anticoagulant medication or antiplatelet therapy at the time of injury. We will exclude participants with known bleeding disorders, such as haemophilia.

Types of interventions

Eligible trials will 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;
- non-fibrin sealants.

We will not combine different interventions and treatments other than those listed above in the NMA. Trials must compare an intervention of interest versus placebo, or an intervention of interest versus another intervention of interest. We will include trials which use interventions of interest combined with another agent or blood product in each arm (e.g. tranexamic acid plus platelets versus placebo plus platelets), as we will consider the effect of the additional agent in both arms will cancel out.

To explore the optimal treatment pathway, we will consider interventions administered over a range of doses, as both single or multiple doses via intravenous, subcutaneous, intranasal, oral or topical routes, and at different timings.

The variations in dose, route and times for interventions may differ greatly. We expect that tranexamic acid will be the intervention most commonly assessed in our included trials, and therefore this is anticipated to be the focus of our NMA.

Types of outcome measures

We will use the outcome measures below to assess the relative hierarchy of our interventions.

Primary outcomes

- Proportion of participants receiving allogenic blood transfusions during or after surgery (up to 30 days)
- All-cause mortality (deaths occurring up to 30 days after the operation)

Secondary outcomes

- Mean number of red blood cell units transfused per person (within 30 days)
- Reoperation due to bleeding (within seven days)
- Adverse events:
 - * thromboembolism (deep vein thrombosis, pulmonary embolism, myocardial infarction, stroke) (within 30 days)
 - * transfusion reactions (acute) (within 24 hours)
 - * suspected serious adverse drug reactions (within 30 days)

For suspected serious adverse drug reactions we will use the International Conference on Harmonisation Good Clinical Practice definition of a serious adverse drug reaction ([ICH GCP 2018](#)). If studies report different measures, we will record and present the information to the expert panel prior to extracting data to decide an appropriate analysis strategy.

We will also collect and present any data on cost or resource information reported in the included trials. This will not constitute a formal economic evaluation, but it will provide a useful insight that may be of interest for those involved in decision-making.

Search methods for identification of studies

The Information Specialist (CD) from the Systematic Review Initiative will generate the search strategies in conjunction with the Cochrane Injuries Group.

Electronic searches

Bibliographic databases

We will produce thorough and sensitive search strategies to identify RCTs and systematic reviews in the following databases, from database inception to the date of search:

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

The search strategies produced for this review will be made up of index terms, text words and word variations for the concepts of population (definitive fixation of hip, pelvic and long bone fractures) and intervention or comparator (pharmacological

interventions for the prevention of bleeding). The searches will be combined in the MEDLINE, Embase and CINAHL databases with adaptations of the recommended Cochrane RCT filter ([Lefebvre 2011](#)), and of the Scottish Intercollegiate Guidelines Network (SIGN) systematic review filters (www.sign.ac.uk/search-filters.html). Language, year of publication and publication type will not be used to limit the searches. Search strategies for all databases are presented in [Appendix 1](#).

Searching other resources

To supplement the database searches, we will handsearch the bibliographies of all included trials, relevant review articles and other current evidence in order to identify additional trials missed by the electronic searches. We will also contact authors of ongoing trials to acquire any unpublished data. Authors will be contacted a maximum of three times.

We will check the reference list of included trials and relevant systematic reviews to identify any trials that were not found by the electronic searches. We will also check for relevant retraction statements and errata for included trials.

Data collection and analysis

We will undertake the systematic review using methods stated in Chapter 7 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). Analyses will be run using Review Manager 5 and Stata 15 ([Review Manager 2014](#); [Stata 2017](#)).

Selection of studies

Two review authors (VG and RC) will independently screen titles and abstracts of citations identified by the electronic searches for eligibility. If the title and abstract the citation is found to be irrelevant, we will exclude it at this stage. The same review authors will then independently screen the full-text articles of the citations thought to be eligible against the criteria set out in this protocol. We will resolve disagreements through discussion. If a disagreement is not resolved, we will consult a third review author (LE). If there is insufficient information with which to make a decision regarding eligibility, we will request further information from the corresponding author of the trial. We will contact the author up to three times within six weeks. If there is no response after six weeks of initial attempted contact, we will exclude the study. We will keep records of the study selection process and use the information to generate a PRISMA flowchart to show the flow of studies ([Moher 2009](#)). We will include reasons for exclusion of trials at the full-text stage in the 'Characteristics of excluded studies' table. If we encounter translation needs, we will use colleagues or Cochrane resources such as Task Exchange.

Data extraction and management

Two review authors (VG and RC) will independently use a standardised, piloted form to undertake data extraction of included trials. The form will be designed following methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011a](#)). The two review authors (VG and RC) will not be blinded to authors, institutions or outcomes of the trials they are extracting. Colleagues providing translation support will be expected to help extract data. We will pilot the data extraction forms on 10 included trials selected at random (equally split between the review authors). Following this process, if necessary, we will make amendments to the data extraction form.

If there is a discrepancy between the two review authors regarding the decision to include a trial, we will attempt to resolve this through discussion. If this is unsuccessful, we will consult a third review author (LE). We will contact corresponding authors up to three times to request further trial data. We will classify the data as unobtainable if there is no response from the authors within six weeks of the initial email request. If a conflict were to arise over data sources, we will give preference to published data over unpublished data, as published work is more likely to have undergone a rigorous peer-review process.

Table 1 illustrates the potential dose, route and timing combinations for each intervention. There are numerous treatment pathway combinations for each intervention, which will make deciding on an approach for data synthesis prior to data extraction difficult. To overcome this, we will use a staged approach to carry out data extraction. In the first stage, two review authors (VG and RC) will extract trial, participant and intervention characteristics. Using these data, we will convene an independent blinded external expert panel to categorise the clinically meaningful interventions by dose, route and timing, in order to decide which to compare. The external expert panel will also help us to create clinically meaningful groups ready for data analysis. Once this process has been completed, the two review authors (VG and RC) will independently extract the outcome data.

We will extract data for the following items and list these and the outcomes from each trial in the 'Characteristics of included studies' table.

- General information: name of review author carrying out data extraction, date of data extraction, study identifier, surname and contact address of first author, language of trial.
- Trial information: RCT trial design – location of where the trial was run, setting, sample size, duration of trial, power calculation, treatment arms, randomisation, inclusion and exclusion criteria, comparability of groups, length of study.
- Characteristics of participants: age, sex, breakdown of total numbers for those randomised and analysed, type of surgery, dropouts (percentage in each arm) with reasons and protocol violations, participants on anticoagulants or antiplatelet therapy at the time of injury, participants given tranexamic acid in the prehospital setting or on admission to the emergency department, duration of surgery, use of tourniquet and type of anaesthetic (spinal or general).
- Characteristics of interventions: number of treatment arms, description of experimental arm(s), description of control arm(s), timing, dose and route of administration of intervention, and other differences between intervention arms.
- Outcomes (all within 30 days of surgery unless otherwise specified): allogenic blood transfusion during or after surgery, mortality due to any cause, mean number of units of red blood cells transfused, reoperation due to bleeding (within seven days) and adverse effects (thromboembolism, transfusion reactions (within 24 hours) and adverse drug reactions). We will use the International Conference on Harmonisation Good Clinical Practice definition of serious adverse events (ICH GCP 2018). Where that definition is not used in the included studies we will extract information about how 'adverse effect' and 'serious adverse effect' were defined in each study.)

- Quality assessment: allocation concealment, blinding (participants, personnel, outcome assessors), incomplete outcome data, selective outcome reporting, other sources of bias.

We will extract arm-level data, rather than study-level data, from both abstracts and full-text papers. If there are multiple publications from the same trial, we will use one extraction form and obtain maximal data through extracting data from all available publications. If insufficient information is given in the full text, we will contact the corresponding author, study group or sponsor to obtain additional data. Where studies have multiple publications, we will collate the reports of the same study so that each study, rather than each report, is the unit of interest for the review, and such studies will have a single identifier with multiple references. We will conduct the review according to this published protocol and report any deviations from it in the 'Differences between protocol and review' section of the full review.

While extracting trial data, we will collect any data about cost, resource usage and quality of life given in the included studies. While this will not form a formal economic evaluation, it will offer useful information that may guide decision-making. Should any quality of life data be available, we will comment on these outcomes descriptively in our discussion.

We will list all treatment arms in each study in the 'Characteristics of included studies' table.

Two review authors (VG and RC) will independently enter data into Review Manager 5 (Review Manager 2014). Each review author will cross check the other review author's entries for accuracy.

Potential risk modifiers

We will extract data on the following characteristics which may behave as treatment risk modifiers.

- **Type of surgery:** different types of definitive fixation surgery are likely to result in different volumes of blood loss. We expect the effect of the interventions will be greater in surgery with greater blood loss, therefore, we will examine this through subgroup analysis according to the expected amount of blood loss in the different types of surgery:
 - * Group 1: pelvic fixation, revision joint replacement for periprosthetic hip/knee fracture, femoral fixation and neck of femur intramedullary nailing (highest risk of bleeding);
 - * Group 2: hip joint replacement surgery (hip hemiarthroplasty, total hip replacement) knee joint replacement (high risk of bleeding);
 - * Group 3: cannulated hip screws, dynamic hip screw, tibial fixation, shoulder replacement surgery, humerus fixation (lower risk of bleeding);
 - * Group 4: elbow replacement surgery, clavicle fixation, fibula fixation, radius fixation and ulna fixation (lowest risk of bleeding).
- **Incidence of preoperative anaemia:** after surgery, people with anaemia are likely to have a higher risk of blood transfusion (Sim 2018), an increased length of hospital stay (Abdullah 2017), and an increased risk of complications (Viola 2015). We expect that the effect of the interventions will vary depending on the presence or absence of preoperative anaemia, with the treatment being less effective and resulting in greater reported

complication rates in people with preoperative anaemia. We will examine this through subgroup analysis of participants with and without preoperative anaemia.

- **Consumption of anticoagulant or antiplatelet drugs at the time of injury:** people taking these medications are likely to bleed more. A previous review reported that desmopressin, an intervention of interest, may be effective at reducing the need for blood transfusion in people taking antiplatelet drugs (Desborough 2017). We anticipate that the interventions will be more effective in people taking anticoagulants or antiplatelets. We will examine this through subgroup analysis of participants taking these medications and those who are not.

Assessment of risk of bias in included studies

We will assess the quality of the included trials using the Cochrane 'Risk of bias' tool described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011b). We will test the tool on a random sample of trials. Two review authors (VG, RC) will independently assess the risk of bias within each trial and assign it a classification of low, high or unclear risk. We will compare the judgements of the two review authors and reach a consensus. If there is discrepancy, we will consult a third review author (LE). We will report our judgements in the 'Risk of bias' table for each trial.

Using the information generated, we will look for statistical heterogeneity in each trial and perform sensitivity analyses accordingly. We will assess risk of bias in 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); and
- other forms of bias.

Each of the domains above will be assigned a risk of bias classification as follows:

- 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.

Measures of treatment effect

When extracting data for dichotomous outcomes (proportion of participants needing an allogenic blood transfusion, mortality, reoperation due to bleeding, adverse events), we will record the number of participants and events in both the intervention and control arms. We will express the results as odds ratios with 95% confidence intervals.

However, when extracting arm-level data for continuous outcomes (e.g. mean number of allogenic blood transfusions per participant), we will record means, standard deviations (or medians with interquartile ranges) and the total number of participants in both the intervention and control arms. If only study-level data are available, we will note the reported effect size and standard errors. If the data allow, we will use Stata to do the quantitative analyses.

For continuous outcome data measured using the same scale, we will use mean difference with a 95% confidence interval (CI). However, if this outcome is measured using different scales, we will use standardised mean difference with 95% CI.

Unit of analysis issues

When performing pair-wise meta-analyses, we will treat trials with multiple treatment comparisons as individual, independent two-arm studies. However, this will not be the case in the NMA where we will include all comparisons, if and when there are adequate data to do so. These trials will be analysed by taking into account the respective treatment effects. The NMA method correctly accounts for correlations in relative effects from trials with more than two arms. We will analyse data with the participant as the unit of analysis.

Dealing with missing data

We will handle missing data using the approach discussed in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c). We will contact corresponding authors of studies to obtain missing data. We will keep a record of the number of participants lost to follow-up in each trial. If an included trial has a mixed population, we will only extract data from the relevant population. If it is not possible to do this, we will contact the authors up to three times to request additional information. If we are still unable to obtain the information, and the missing data are thought to lead to serious bias, we will perform a sensitivity analysis to assess the impact of the missing outcome data.

Assessment of heterogeneity

Assessment of clinical and methodological heterogeneity within treatment comparisons

If the extracted data appear to be homogeneous, we will amalgamate the data and undertake an NMA. We will look for clinical and methodological heterogeneity within each comparison by comparing trial and baseline characteristics across the included trials. If we find important clinical or methodological heterogeneity, we may not be able to perform a meta-analysis. If this is the case, we will provide a descriptive summary instead.

When performing the NMA, we will assume a common estimate for heterogeneity across all our comparisons, and we will estimate a value for the total I^2 value across the network. We will assess statistical heterogeneity across the whole network based on the magnitude of the heterogeneity variance parameter (τ^2), which we will estimate from the NMA models. We will perform a likelihood ratio test for the null hypothesis of no heterogeneity versus presence of heterogeneity.

For pair-wise meta-analyses, there may be different heterogeneity variances for each pair-wise comparison. We will assess the heterogeneity within each pair using the I^2 statistic and 95% CI (an I^2 statistic greater than 50% will indicate moderate heterogeneity), which demonstrates variability that is not due to random error. If we find that heterogeneity is present, we will investigate this by performing a subgroup meta-regression where possible (Deeks 2011).

Assessment of reporting biases

We will investigate the presence of small-study effects in the pair-wise meta-analyses through funnel plots and linear regression, if there are at least 10 studies. We will use a threshold of 0.10 or below for a P value to be statistically significant. Several factors can contribute to the association between study effect size and funnel plot asymmetry. We will differentiate between funnel plot asymmetry caused by publication bias using contour-enhanced funnel plots (Peters 2008). The contour lines in the plot demonstrate levels of statistical significance. We will assume that a lack of studies in areas of non-significance will show signs of publication bias.

Data synthesis

We will use Stata to undertake a multivariate NMA which will treat each comparison as a different outcome. The analyses will be done using the network package in Stata (Stata 2017). We will provide the estimated treatment effect for each comparison with a 95% CI. For pair-wise meta-analyses, we will perform direct treatment comparisons using methods described in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). Where data are homogeneous enough to do so, we will perform meta-analyses in Review Manager 5 (Review Manager 2014). Forest plots illustrating these results will be shown with 95% CIs for all analyses. Both review authors (VG and RC) will enter data into Review Manager 5, and will cross check each other's data entry for accuracy.

Where appropriate, we will categorise interventions into clinically meaningful groups during the first stage of data extraction. Each group will act as a single node within the network. We will run sensitivity analyses using different groupings. Each group will contain one type of pharmacological intervention, for example, only tranexamic acid, but may include a narrow dose range, route and timing variables, so as to have a pharmacologically similar predicted effect.

Summary of findings

We will create a 'Summary of findings' table for each intervention for the following outcomes: need for allogenic blood transfusion during or after surgery (within 30 days), all-cause mortality (deaths occurring within 30 days after the operation), mean number of red blood cell transfusion units per person (within 30 days), number of units of allogenic blood transfused, reoperation due to bleeding (within seven days), and adverse events (within 30 days).

We will use the study limitations, consistency of effect, imprecision, indirectness and publication bias (i.e. GRADE) to assess the certainty of the evidence contributing data to the analyses for the prespecified outcomes. We will use methods described in Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2017), and GRADEpro software (GRADEpro GDT).

Two review authors (VG, RC) will independently judge the certainty of the evidence. We will resolve disagreements by discussion or with a third review author (LE). We will provide justifications in the 'Summary of findings' table for any decisions made to downgrade the certainty of the evidence to aid the reader's understanding of the review and incorporate these judgements into the review for each outcome.

For the NMA, we will evaluate the confidence of the evidence using the CINeMA framework (Confidence in Network Meta-Analysis) (Salanti 2014). We will use the online CINeMA tool which assesses confidence for each comparison within the network and is based on: within-study bias, across-studies bias, indirectness, imprecision, heterogeneity and incoherence (CINeMA 2017).

We will create a 'Summary of findings' table before writing the 'Results' and 'Authors' conclusions' sections of our review.

Subgroup analysis and investigation of heterogeneity

Subgroup analysis

If the data allow, we will perform subgroup analyses and network meta-regression for the following variables, to explain any heterogeneity, inconsistency, or both:

- type of surgery;
- participants with preoperative anaemia;
- participants on anticoagulant or antiplatelet therapy at the time of injury.

The justification for the choice of subgroups is detailed within [Data extraction and management](#).

Investigation of heterogeneity

While performing pair-wise meta-analyses, we will evaluate heterogeneity in each pair-wise comparison using the I^2 statistic (with 95% CI). For the NMA, we will estimate the heterogeneity variance parameter τ^2 and use it to assess statistical heterogeneity within the network. We will also estimate a total I^2 statistic for the whole network (see [Assessment of heterogeneity](#)).

Assessment of statistical inconsistency

To gauge any inconsistency within each loop of the network, we will use the 'loop' inconsistency model of Lu and Ades (Lu 2006), using the luades option in Stata (Stata 2017). This will give an assessment of consistency within each loop of the network. If there are no closed loops, we will calculate transitivity to determine the presence of inconsistency. We will assume there is common heterogeneity within each loop. We will present results in a forest plot through the network graphs package in Stata. If we find evidence of global inconsistency, we will use the node-splitting method to explore this further (Dias 2010).

Sensitivity analysis

We will examine the strength of the overall results by performing sensitivity analyses, where appropriate, with and without the trials thought to be at high risk of bias. A sensitivity analysis is used to determine the robustness of an assessment by examining the extent to which results are affected by changing the methods or models of analysis, values of unmeasured variables or assumptions.

We will perform our main analyses using studies deemed at low risk of bias, and then undertake a sensitivity analysis which incorporates all the included studies. We will look at the effect of participant dropout, and will categorise the trials into groupings of:

- less than 20% dropout;
- 20% to 50% dropout and

- more than 50% dropout.

We will analyse each group separately. We will explore heterogeneity using a fixed-effect model to assess sensitivity.

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ADDITIONAL TABLES

Table 1. Table of intervention variables

Variable	TXA	Apro- tinin	Ep- silon-aminocaproic acid	Desmo- pressin	Factor VIIa	Factor XIII	Fibrino- gen	Fibrin sealants/ glue	Non- fibrin sealants
Timing									
Preoperative	✓	✓	✓	✓	✓	✓	✓	X	X
Intraoperative	✓	✓	✓	✓	✓	✓	✓	✓	✓
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	✓	✓	✓	✓	✓	✓

The table is for illustrative purposes only and replicated from [Gibbs 2019](#).

Table 1. Table of intervention variables *(Continued)*

Ticks indicate which intervention and timing/route/dose combinations are clinically possible; crosses indicate which intervention and timing/route/dose combinations are not clinically possible.

IV: intravenous; TXA: tranexamic acid.

APPENDICES

Appendix 1. Search strategies

CENTRAL (the Cochrane Library)

#1 MeSH descriptor: [Femoral Fractures] explode all trees

#2 MeSH descriptor: [Ankle Fractures] this term only

#3 MeSH descriptor: [Humeral Fractures] this term only

#4 MeSH descriptor: [Osteoporotic Fractures] this term only

#5 MeSH descriptor: [Periprosthetic Fractures] this term only

#6 MeSH descriptor: [Shoulder Fractures] explode all trees

#7 MeSH descriptor: [Tibial Fractures] this term only

#8 MeSH descriptor: [Ulna Fractures] this term only

#9 MeSH descriptor: [Radius Fractures] explode all trees

#10 MeSH descriptor: [Fractures, Bone] this term only

#11 ((pelvi* or sacrum or coccyx or ischium or pubis or pubic or ilium or tailbone or diaphys* or epiphys* or metaphys* or acetabulum or acetabular or femor* or femur* or hip* or thigh* or tibia* or fibula* or intertrochanteric or subtrochanteric or petrochanteric or intracapsular or subcapsular or subcapital or osteoporo* or osteoarthritis or orthop?edic) near/6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or "intramedullary nail" or "intramedullary nails")):ti,ab

#12 (("long bone" or "long bones" or long-bone* or humerus or humeral or "upper arm" or "upper arms" or shoulder* or clavicle* or clavicle* or "collar bone" or "collar bones" or ankle* or pilon or "lower leg" or "lower legs" or calf* or knee* or tibiofibular or menisci or meniscus or femoropatellar or patellofemoral or radial or radius or ulna or forearm* or elbow*) near/6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or "intramedullary nail" or "intramedullary nails")):ti,ab

#13 ((malleol* or talus or trochanteric or crural or crus or olecranon or antebrachial or monteggi* or bankart) near/6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or "intramedullary nail" or "intramedullary nails")):ti,ab

#14 ((wrist* or capitate or hamtae or lunate or carpal or metacarpal or pisiform or scaphoid or trapezium or triquetral) near/6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or "intramedullary nail" or "intramedullary nails")):ti,ab

#15 ((peri-implant or periprosthetic) near/1 fracture*)

#16 MeSH descriptor: [Pelvic Bones] explode all trees and with qualifier(s): [injuries - IN, surgery - SU]

#17 MeSH descriptor: [Leg Bones] explode all trees and with qualifier(s): [injuries - IN, surgery - SU]

#18 MeSH descriptor: [Arm Bones] explode all trees and with qualifier(s): [injuries - IN, surgery - SU]

#19 MeSH descriptor: [Clavicle] explode all trees and with qualifier(s): [injuries - IN, surgery - SU]

#20 MeSH descriptor: [Bones of Upper Extremity] this term only and with qualifier(s): [injuries - IN, surgery - SU]

#21 MeSH descriptor: [Bones of Lower Extremity] this term only and with qualifier(s): [injuries - IN, surgery - SU]

#22 MeSH descriptor: [Hip Joint] explode all trees and with qualifier(s): [surgery - SU]

#23 MeSH descriptor: [Shoulder Joint] this term only and with qualifier(s): [surgery - SU]

#24 MeSH descriptor: [Knee Joint] explode all trees and with qualifier(s): [surgery - SU]

#25 MeSH descriptor: [Ankle Joint] this term only and with qualifier(s): [surgery - SU]

- #26 MeSH descriptor: [Elbow Joint] this term only and with qualifier(s): [injuries - IN, surgery - SU]
- #27 MeSH descriptor: [Hip Injuries] explode all trees and with qualifier(s): [surgery - SU]
- #28 MeSH descriptor: [Knee Injuries] explode all trees and with qualifier(s): [surgery - SU]
- #29 MeSH descriptor: [Lower Extremity] this term only and with qualifier(s): [surgery - SU, injuries - IN]
- #30 MeSH descriptor: [Upper Extremity] this term only and with qualifier(s): [surgery - SU, injuries - IN]
- #31 ((hip* or shoulder* or knee*) near/5 (replac* or arthroplast* or hemiarthroplast* or hemi-arthroplast*)):ti,ab
- #32 MeSH descriptor: [Bones of Lower Extremity] explode all trees
- #33 MeSH descriptor: [Bones of Upper Extremity] explode all trees
- #34 #32 or #33
- #35 MeSH descriptor: [Fracture Fixation] explode all trees
- #36 (trauma* or fracture* or injur* or surg* or operat* or repair* or fixation):ti
- #37 #35 or #36
- #38 #34 and #37
- #39 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #38
- #40 MeSH descriptor: [Antifibrinolytic Agents] this term only
- #41 MeSH descriptor: [Tranexamic Acid] this term only
- #42 MeSH descriptor: [Aminocaproic Acid] explode all trees
- #43 (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 cyklokapon or femstrual or ugurol):ti,ab
- #44 (AMCHA or amchafibrin or amikapron or amstat or antivoff or caprilon or cl65336 or cyclocapron or cyclokapon or cyklocapron or cyklokapon or exacyl or frenolyse or fibrinon or hemostan or hexacapon):ti,ab
- #45 (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):ti,ab
- #46 (fibrinolysis near/2 inhibitor*):ti,ab
- #47 (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 Espencil 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 Nexmef 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 Temsyt-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 Tranexa or Tranfib 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):ti,ab
- #48 (ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or epsilonaminocapronsav or ethaaminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or neocaprol or resplamin or tachostyptan):ti,ab
- #49 (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):ti,ab
- #50 (aminohexanoic or aminocaproic or aminohexanoic or amino caproic or amino-caproic or amino-n-hexanoic):ti,ab
- #51 #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50
- #52 MeSH descriptor: [Aprotinin] this term only

#53 (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):ti,ab

#54 #52 or #53

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

#56 (factor viia or factor 7a or rfviia or fviiia or novoseven* or novo seven* or aryoseven or acet or eptacog* or proconvertin):ti,ab

#57 (activated near/1 (factor seven or factor vii or rfvii or fvii)):ti,ab

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

#59 #55 or #56 or #57 or #58

#60 MeSH descriptor: [Fibrinogen] this term only

#61 ("fibrinogen concentrate" or "factor I" or Haemocomplettan* or Riastap* or Fibryga* or Fibryna*):ti,ab

#62 #60 or #61

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

#64 (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):ti,ab

#65 #63 or #64

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

#67 (factor xiii or fxiii or fibrin stabili?ing factor* or Tretten* or Catridecacog):ti,ab

#68 #66 or #67

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

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

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

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

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

#74 ((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*)):ti,ab

#75 ((nonfibrin* or non-fibrin* or synthetic* or non-biological* or nonbiological* or biological*) near/3 (glue* or seal* or adhesive*)):ti,ab

#76 (surgical* near/3 (glue* or sealant* or adhesive*)):ti,ab

#77 ((fibrin* or collagen or cellulose or gelatin or thrombin) near/3 (hemosta* or haemosta*)):ti,ab

#78 (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 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 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):ti,ab

#79 (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):ti,ab

#80 (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):ti,ab

#81 (polysaccharide next (sphere* or hemostatic powder)):ti,ab

#82 MeSH descriptor: [Chitosan] this term only

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

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

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

#86 ((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*)):ti,ab

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

#88 (absorbable cellulose or resorbable cellulose or oxidized cellulose or carboxycellulose or oxycellulose or cellulosic acid or oxycel or oxidized regenerated cellulose):ti,ab

#89 (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):ti,ab

#90 (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):ti,ab

#91 #69 or #70 or #71 or #72 or #73 or #74 or #75 or #76 or #77 or #78 or #79 or #80 or #81 or #82 or #83 or #84 or #85 or #86 or #87 or #88 or #89 or #90

#92 MeSH descriptor: [Waxes] explode all trees

#93 (bonewax* or bone wax* or bone putty or hemasorb or ostene):ti,ab

#94 #92 or #93

#95 MeSH descriptor: [Blood Coagulation Factors] this term only

#96 (prothrombin near/5 (complex* or concentrate*))

#97 (PCC* or 3F-PCC* or 4F-PCC* or Beriplex* or Feiba* or Autoplex* or Ocplex* or Octaplex* or Kcentra* or Cofact or Prothrombinex* or "Proplex-T" or Prothroras* or Haemosolvex* or Prothromplex* or "HT Defix" or Facnyne* or Kaskadil* or Kedcom* or Confidex* or PPSB or Profil?ine* or Pronativ* or Proplex* or Prothar* or ProthoRAAS* or Protromplex* or "Pushu Laishi" or "Uman Complex")

#98 #95 or #96 or #97

#99 (((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*)):ti,ab

#100 #51 or #54 or #59 or #62 or #65 or #68 or #91 or #94 or #98 or #99

#101 #39 and #100

MEDLINE (OvidSP)

1. exp Femoral Fractures/

2. Ankle Fractures/
3. Humeral Fractures/
4. Osteoporotic Fractures/
5. Periprosthetic Fractures/
6. exp Shoulder Fractures/
7. Tibial Fractures/
8. exp Ulna Fractures/
9. Radius Fractures/
10. Fractures, Bone/
11. ((pelvi* or sacrum or coccyx or ischium or pubis or pubic or ilium or tailbone or diaphys* or epiphys* or metaphys* or acetabulum or acetabular or femor* or femur* or hip* or thigh* or tibia* or fibula* or intertrochanteric or subtrochanteric or petrochanteric or intracapsular or subcapsular or subcapital or osteoporo* or osteoarthritis or orthop?edic) adj6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or intramedullary nail*)).tw,kf.
12. ((long bone* or long-bone* or humerus or humeral or upper arm* or shoulder* or clavicle* or clavícula* or collar bone* or ankle* or pilon or lower leg* or calf* or knee* or tibiofibular or menisci or meniscus or femoropatellar or patellofemoral or radial or radius or ulna or forearm* or elbow*) adj6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or intramedullary nail*)).tw,kf.
13. ((malleol* or talus or trochanteric or crural or crus or olecranon or antebrachial or monteggia* or bankart) adj6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or intramedullary nail*)).tw,kf.
14. ((wrist* or capitate or hamtae or lunate or carpal or metacarpal or pisiform or scaphoid or trapezium or triquetral) adj6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or intramedullary nail*)).tw,kf.
15. ((peri-implant or periprosthetic) adj1 fracture*).tw,kf.
16. exp Pelvic Bones/in, su
17. exp Leg Bones/in, su
18. exp Arm Bones/in, su
19. Clavicle/in, su
20. "Bones of Upper Extremity"/in, su or "Bones of Lower Extremity"/in, su
21. exp Hip Joint/su or Shoulder Joint/su or exp Knee Joint/su
22. Ankle Joint/su or Elbow Joint/in, su
23. exp Hip Injuries/su or exp Knee Injuries/su
24. exp Arm Injuries/su or exp Shoulder Injuries/su
25. Lower Extremity/in, su or Hip/su or Thigh/su or Leg/su or Knee/su
26. Upper Extremity/in, su or Arm/su or Elbow/su or Forearm/su or Shoulder/su
27. ((hip* or shoulder* or knee*) adj5 (replac* or arthroplast* or hemiarthroplast* or hemi-arthroplast*)).mp.
28. exp Leg Bones/ or exp Arm Bones/ or Clavicle/ or exp Humerus/ or exp Pelvic Bones/ or exp Femur/ or Tibia/ or Fibula/ or "Bones of Upper Extremity"/ or "Bones of Lower Extremity"/
29. exp Fracture Fixation/ or (trauma* or fracture* or injur* or surg* or operat* or repair* or fixation).ti.

30. 28 and 29

31. (or/1-27) or 30

32. Antifibrinolytic Agents/

33. Tranexamic Acid/

34. Aminocaproic Acid/

35. (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 cyklokapron 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 hexacapron 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 adj2 inhibitor*).tw,kf.

36. (Agretax or Bio-Stat or Capiloc or Capitrax or Clip Inj or Clot-XL or Clotawin-T or Coastat or Cuti or Cymine or Dubatran or Espencil 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 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.

37. (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 caproleg 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,kf.

38. or/32-37

39. Aprotinin/

40. (antagasan 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.

41. (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.

42. or/39-41

43. Factor VIIa/

44. (factor viia or factor 7a or rfviia or fviia or novoseven* or novo seven* or aryoseven or acset or eptacog* or proconvertin).tw,kf.

45. ((activated adj2 factor seven) or (activated adj2 factor vii) or (activated adj3 rfvii) or (activated adj2 fvii)).tw,kf.

46. (factor seven or factor vii or factor 7).ti.

47. 43 or 44 or 45 or 46

48. Fibrinogen/ad, ae, de, sd, tu, th, to

49. *Fibrinogen/

50. (fibrinogen concentrate* or factor I or Haemocomplettan* or Riastap* or Fibryga* or Fibryna*).tw,kf.

51. 48 or 49 or 50

52. Deamino Arginine Vasopressin/

53. (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.
54. 52 or 53
55. exp Factor XIII/
56. (factor XIII or fXIII or fibrin stabili?ing factor* or Tretten* or Catridecacog).tw,kf.
57. 55 or 56
58. exp Tissue Adhesives/
59. *Adhesives/
60. Collagen/tu
61. Thrombin/tu
62. Gelatin/tu
63. Gelatin Sponge, Absorbable/
64. ((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.
65. ((nonfibrin* or non-fibrin* or synthetic* or non-biological* or nonbiological* or biological*) adj3 (glue* or seal* or adhesive*)).tw,kf.
66. (surgical* adj3 (glue* or sealant* or adhesive*)).tw,kf.
67. ((fibrin* or collagen or cellulose or gelatin or thrombin) adj3 (hemosta* or haemosta*)).tw,kf.
68. (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 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 Monoclote-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.
69. (Glubran or Gluetiss or Ifabond or Indermil or LiquiBand or TissuGlu).tw,kf.
70. (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.
71. (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.
72. (polysaccharide adj (sphere* or hemostatic powder)).tw,kf.
73. *Chitosan/
74. *Polyethylene Glycols/
75. *Hydrogel, Polyethylene Glycol Dimethacrylate/
76. Polyurethanes/ad, ae, pd, tu, to
77. ((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,kf.

78. Cellulose, Oxidized/

79. (absorbable cellulose or resorbable cellulose or oxidized cellulose or carboxycellulose or oxycellulose or cellulosic acid or oxycel or oxidized regenerated cellulose).tw,kf.

80. (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.

81. (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.

82. or/58-81

83. exp Waxes/

84. (bonewax* or bone wax* or bone putty or hemasorb or ostene).tw,kf.

85. 83 or 84

86. (((haemosta* or hemosta* or antihaemorrhag* or antihemorrhag* or anti haemorrhag* or anti-hemorrhag*) adj5 (drug* or agent* or treat* or therap*)) or ((coagulat* or clotting) adj factor)).tw,kf.

87. 38 or 42 or 47 or 51 or 54 or 57 or 82 or 85 or 86

88. 31 and 87

89. Systematic Review.pt.

90. Meta-Analysis.pt.

91. ((meta analy* or metaanaly*) and (trials or studies)).ab.

92. (meta analy* or metaanaly* or evidence-based).ti.

93. ((systematic* or evidence-based) adj2 (review* or overview*)).tw,kf.

94. (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.

95. Cochrane Database of systematic reviews.jn.

96. (additional adj (papers or articles or sources)).ab.

97. ((electronic* or online) adj (sources or resources or databases)).ab.

98. (relevant adj (journals or articles)).ab.

99. or/89-98

100. Review.pt.

101. exp Randomized Controlled Trials as Topic/

102. selection criteria.ab. or critical appraisal.tw.

103. (data adj (abstract* or extract* or analys*)).ab.

104. exp Randomized Controlled Trial/

105. or/101-104

106. 100 and 105

107. 99 or 106

108. exp Randomized Controlled Trial/

109. Controlled Clinical Trial/

110. (placebo or randomly or groups).ab.

111. (randomi* or trial).tw,kf.

112. exp Clinical Trial as Topic/

113. 107 or 108 or 109 or 110 or 111 or 112

114. exp animals/ not humans/

115. 113 not 114

116. 88 and 115

Embase (OvidSP)

1. exp leg fracture/

2. exp arm fracture/

3. exp pelvis fracture/

4. clavicle fracture/

5. fragility fracture/

6. periprosthetic fracture/

7. ((peli* or sacrum or coccyx or ischium or pubis or pubic or ilium or tailbone or diaphys* or epiphys* or metaphys* or acetabulum or acetabular or femor* or femur* or hip* or thigh* or tibia* or fibula* or intertrochanteric or subtrochanteric or petrochanteric or intracapsular or subcapsular or subcapital or osteoporo* or osteoarthritis or orthop?edic) adj6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or intramedullary nail*)).tw,kw.

8. ((long bone* or long-bone* or humerus or humeral or upper arm* or shoulder* or clavicle* or clavica* or collar bone* or ankle* or pilon or lower leg* or calf* or knee* or tibiofibular or menisci or meniscus or femoropatellar or patellofemoral or radial or radius or ulna or forearm* or elbow*) adj6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or intramedullary nail*)).tw,kw.

9. ((malleol* or talus or trochanteric or crural or crus or olecranon or antebrachial or monteggi* or bankart) adj6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or intramedullary nail*)).tw,kw.

10. ((wrist* or capitate or hamtae or lunate or carpal or metacarpal or pisiform or scaphoid or trapezium or triquetral) adj6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or intramedullary nail*)).tw,kw.

11. ((peri-implant or periprosthetic) adj1 fracture*).tw,kw.

12. exp long bone/su

13. exp pelvic girdle/su [Surgery]

14. exp "bones of the leg and foot"/su [Surgery]

15. exp "bones of the arm and hand"/su [Surgery]

16. exp fibula/su [Surgery]

17. exp femur/su [Surgery]

18. exp tibia/su
19. exp shoulder/su
20. exp knee/su
21. exp hip/su
22. exp elbow/su
23. exp ankle/su
24. exp humerus/su [Surgery]
25. exp hip injury/su [Surgery]
26. exp knee injury/su [Surgery]
27. exp arm injury/su [Surgery]
28. exp leg injury/su [Surgery]
29. exp pelvis injury/su [Surgery]
30. exp lower limb/su
31. exp upper limb/su
32. ((hip* or shoulder* or knee*) adj5 (replac* or arthroplast* or hemiarthroplast* or hemi-arthroplast*)).mp.
33. exp leg bone/
34. exp arm bone/
35. exp pelvic girdle/
36. exp long bone/
37. exp shoulder girdle/
38. 33 or 34 or 35 or 36 or 37
39. exp fracture treatment/
40. (trauma* or fracture* or injur* or surg* or operat* or repair* or fixation).ti.
41. 39 or 40
42. 38 and 41
43. (or/1-32) or 42
44. Antifibrinolytic Agent/
45. Tranexamic Acid/
46. Aminocaproic Acid/
47. (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 hexacapon 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,kw.

48. (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 Nicolida 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,kw.

49. (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 acikaprין 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,kw.

50. or/44-49

51. Aprotinin/

52. (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,kw.

53. (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,kw.

54. or/51-53

55. Blood Clotting Factor 7a/

56. (factor viia or factor 7a or rfviia or fviia or novoseven* or novo seven* or aryoseven or acset or eptacog* or proconvertin).tw,kw.

57. ((activated adj2 factor seven) or (activated adj2 factor vii) or (activated adj3 rfvi) or (activated adj2 fvii)).tw,kw.

58. (factor seven or factor vii or factor 7).ti.

59. 55 or 56 or 57 or 58

60. Fibrinogen Concentrate/

61. (fibrinogen concentrate* or factor I or Haemocomplettan* or Riastap* or Fibryga* or Fibryna*).tw,kw.

62. 60 or 61

63. Desmopressin/

64. (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,kw.

65. 63 or 64

66. Blood Clotting Factor 13/

67. (factor xiii or fxiii or fibrin stabili?ing factor* or Tretten* or Catridecagog).tw,kw.

68. 66 or 67

69. exp Tissue Adhesive/

70. *Adhesive Agent/

71. *Hemostatic Agent/

72. ((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,kw.
73. ((nonfibrin* or non-fibrin* or synthetic* or non-biological* or nonbiological* or biological*) adj3 (glue* or seal* or adhesive*)).tw,kw.
74. (surgical* adj3 (glue* or sealant* or adhesive*)).tw,kw.
75. ((fibrin* or collagen or cellulose or gelatin or thrombin) adj3 (hemosta* or haemosta*)).tw,kw.
76. (8Y or Aaact or Actif-VIII or Advate or Artiss or Raplixa or Evarrest or Aleivate 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 Humaclo or Humafactor-8 or Humate-P or Immunate or Innovate or Koate or Koate-DVI or Kogenate Bayer or Kogenate FS or Monoclade-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,kw.
77. (Glubran or Gluetiss or Ifabond or Indermil or LiquiBand or TissuGlu).tw,kw.
78. Collagen Sponge/ or Collagen Dressing/
79. Gelatin Sponge/ or Gelfoam/
80. (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,kw.
81. *Chitosan/
82. Hydrogel Dressing/
83. Fibrinogen plus Thrombin/
84. Polyvinyl Alcohol Sponge/
85. (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,kw.
86. (polysaccharide adj (sphere* or hemostatic powder)).tw,kw.
87. ((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,kw.
88. Oxidized Cellulose/
89. Oxidized Regenerated Cellulose/
90. Recombinant Thrombin/
91. Tachocomb/
92. (absorbable cellulose or resorbable cellulose or oxidi?ed cellulose or carboxycellulose or oxycellulose or cellulosic acid or oxycel or oxidi?ed regenerated cellulose).tw,kw.
93. (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).tw,kw.
94. (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,kw.
95. (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,kw.

96. or/69-95
97. Bone Wax/
98. (bonewax* or bone wax* or bone putty or hemasorb or ostene).tw,kw.
99. or/97-98
100. Prothrombin Complex/
101. (prothrombin adj5 (complex* or concentrate*)).tw,kw.
102. (PCC* or 3F-PCC* or 4F-PCC* or Beriplex* or Feiba* or Autoplex* or Ocplex* or Octaplex* or Kcentra* or Cofact or Prothrombinex* or "Proplex-T" or Prothroras* or Haemosolvex* or Prothromplex* or "HT Defix" or Facnyne* or Kaskadil* or Kedcom* or Confidex* or PPSB or Profil?ine* or Pronativ* or Proplex* or Prothar* or ProthoRAAS* or Protromplex* or "Pushu Laishi" or "Uman Complex").tw,kw.
103. or/100-102
104. (((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,kw.
105. 50 or 54 or 59 or 62 or 65 or 68 or 96 or 99 or 103 or 104
106. Meta Analysis/
107. (meta analy* or metaanaly* or evidence-based).ti.
108. ((meta analy* or metaanaly*) and (trials or studies)).ab.
109. Systematic Review/
110. ((systematic* or evidence-based) adj2 (review* or overview*)).tw,kw.
111. (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.
112. ((electronic* or online) adj (sources or resources or databases)).ab.
113. ((additional adj (papers or articles or sources)) or (relevant adj (journals or articles))).ab.
114. or/106-113
115. Review.pt.
116. (data extraction or selection criteria).ab.
117. 115 and 116
118. 114 or 117
119. Editorial.pt.
120. 118 not 119
121. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/
122. (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.
123. 120 or 121 or 122
124. (exp animal/ or nonhuman/) not exp human/
125. 123 not 124
126. 43 and 105 and 125

CINAHL (EBSCOhost)

S1 (MH "Femoral Fractures+") OR (MH "Ankle Fractures") OR (MH "Elbow Fractures") OR (MH "Fibula Fractures") OR (MH "Humeral Fractures+") OR (MH "Knee Fractures+") OR (MH "Osteoporotic Fractures") OR (MH "Pelvic Fractures") OR (MH "Periprosthetic Fractures") OR (MH "Radius Fractures") OR (MH "Shoulder Fractures+") OR (MH "Ulna Fractures+") OR (MH "Wrist Fractures+") OR (MH "Tibial Fractures+")

S2 T1 (((pelvi* or sacrum or coccyx or ischium or pubis or pubic or ilium or tailbone or diaphys* or epiphys* or metaphys* or acetabulum or acetabular or femor* or femur* or hip* or thigh* or tibia* or fibula* or intertrochanteric or subtrochanteric or petrochanteric or intracapsular or subcapsular or subcapital or osteoporo* or osteoarthritis or orthopedic or orthopaedic) N6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or intramedullary nail*))) OR AB (((pelvi* or sacrum or coccyx or ischium or pubis or pubic or ilium or tailbone or diaphys* or epiphys* or metaphys* or acetabulum or acetabular or femor* or femur* or hip* or thigh* or tibia* or fibula* or intertrochanteric or subtrochanteric or petrochanteric or intracapsular or subcapsular or subcapital or osteoporo* or osteoarthritis or orthopedic or orthopaedic) N6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or intramedullary nail*)))

S3 T1 (((long bone* or long-bone* or humerus or humeral or upper arm* or shoulder* or clavicle* or clavícula* or collar bone* or ankle* or pilon or lower leg* or calf* or knee* or tibiofibular or menisci or meniscus or femoropatellar or patellofemoral or radial or radius or ulna or forearm* or elbow*) N6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or implant* or fixation* or prosthes* or "plate and screw" or "plate and screws" or intramedullary nail*))) OR AB (((long bone* or long-bone* or humerus or humeral or upper arm* or shoulder* or clavicle* or clavícula* or collar bone* or ankle* or pilon or lower leg* or calf* or knee* or tibiofibular or menisci or meniscus or femoropatellar or patellofemoral or radial or radius or ulna or wrist* or forearm* or elbow*) N6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or implant* or fixation* or prosthes* or "plate and screw" or "plate and screws" or intramedullary nail*)))

S4 T1 (((malleol* or talus or trochanteric or crural or crus or olecranon or antebrachial or monteggi* or bankart) N6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or intramedullary nail*))) OR AB (((malleol* or talus or trochanteric or crural or crus or olecranon or antebrachial or monteggi* or bankart) N6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or intramedullary nail*)))

S5 T1 (((wrist* or capitate or hamtae or lunate or carpal or metacarpal or pisiform or scaphoid or trapezium or triquetral) N6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or intramedullary nail*))) OR AB (((wrist* or capitate or hamtae or lunate or carpal or metacarpal or pisiform or scaphoid or trapezium or triquetral) N6 (fracture* or break* or broke* or trauma* or injur* or surg* or operat* or repair* or reconstruct* or fixation* or implant* or prosthes* or "plate and screw" or "plate and screws" or intramedullary nail*)))

S6 T1 (((peri-implant or periprosthetic) N1 fracture*)) OR AB (((peri-implant or periprosthetic) N1 fracture*))

S7 (MH "Arm Bones+/IN/SU") OR (MH "Leg Bones+/IN/SU") OR (MH "Pelvic Bones+/IN/SU") OR (MH "Epiphyses/IN/SU") OR (MH "Diaphyses/IN/SU") OR (MH "Lower Extremity/IN/SU") OR (MH "Upper Extremity/IN/SU")

S8 (MH "Ankle Joint/IN/SU") OR (MH "Elbow Joint/IN/SU") OR (MH "Hip Joint/IN/SU") OR (MH "Knee Joint+/IN/SU") OR (MH "Shoulder Joint+/IN/SU")

S9 (MH "Knee Injuries+/SU") OR (MH "Hip Injuries+/SU") OR (MH "Ankle Injuries+/SU")

S10 (MH "Hip/IN/SU") OR (MH "Knee/IN/SU") OR (MH "Leg/IN/SU") OR (MH "Thigh/IN/SU") OR (MH "Lower Extremity/IN/SU")

S11 (MH "Arm Injuries+/SU") OR (MH "Shoulder Injuries+/SU")

S12 (MH "Arm/IN/SU") OR (MH "Elbow/IN/SU") OR (MH "Forearm/IN/SU") OR (MH "Shoulder/IN/SU")

S13 T1 (((hip* or shoulder* or knee*) N5 (replac* or arthroplast* or hemiarthroplast* or hemi-arthroplast*))) OR AB (((hip* or shoulder* or knee*) N5 (replac* or arthroplast* or hemiarthroplast* or hemi-arthroplast*)))

S14 (MH "Arm Bones+") OR (MH "Leg Bones+") OR (MH "Pelvic Bones+")

S15 (MH "Fractures+") OR (MH "Fracture Fixation+") OR T1 (trauma* or fracture* or injur* or surg* or operat* or repair* or fixation)

S16 S14 AND S15

S17 S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S16 S19 (MH "Antifibrinolytic Agents") OR (MH "Aminocaproic Acids") OR (MH "Tranexamic Acid")

S20 T1 ((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 anvitofof 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 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 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 anvitofof 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 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 N2 inhibitor*)))

S21 TI ((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)) OR AB ((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))

S22 S19 OR S20 OR S21

S23 (MH "Aprotinin")

S24 TI ((antagasan 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 AB ((antagasan 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))

S25 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))

S26 S23 OR S24 OR S25

S27 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 rfvi) or (activated N2 fvii)))

S28 TX (factor seven or factor vii or factor 7)

S29 S27 OR S28

S30 (MH "Fibrinogen")

S31 TX (fibrinogen concentrate* or factor I or Haemocomplettan* or Riastap* or Fibryga* or Fibryna*)

S32 S30 OR S31

S33 (MH "Desmopressin")

S34 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))

S35 S33 OR S34

S36 TX (factor XIII or fXIII or fibrin stabili?ing factor* or Tretten* or Catridecacog)

S37 (MH "Tissue Adhesives")

S38 (MH "Fibrin Tissue Adhesive")

S39 (MH "Collagen/TU")

S40 (MH "Thrombin/TU")

S41 (MH "Surgical Sponges")

S42 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*)))

S43 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*)))

S44 TI ((surgical* N3 (glue* or sealant* or adhesive*))) OR AB ((surgical* N3 (glue* or sealant* or adhesive*)))

S45 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*)))

S46 TI ((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 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 Monoclade-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)) 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 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 Monoclade-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))

S47 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))

S48 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))

S49 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))

S50 TX (polysaccharide NEXT (sphere* or hemostatic powder))

S51 (MM "Polyethylene Glycols")

S52 (MH "Hydrogel Dressings")

S53 (MH "Polyurethanes/AD/AE/TU/ST/DE")

S54 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 polyglusam 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 polyglusam 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*)))

S55 (MH "Cellulose/TU")

S56 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))

S57 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))

S58 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))

S59 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 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58

S60 (MH "Waxes/TU")

S61 TI ((bonewax* or bone wax* or bone putty or hemisorb or ostene)) OR AB ((bonewax* or bone wax* or bone putty or hemisorb or ostene))

S62 S60 OR S61

S63 TI ((((haemosta* or hemosta* or antihaemorrhag* 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 antihaemorrhag* or antihemorrhag* or anti haemorrhag* or anti-hemorrhag*) N5 (drug* or agent* or treat* or therap*)) or ((coagulat* or clotting) NEXT factor*)))

S64 S22 OR S26 OR S29 OR S32 OR S35 OR S59 OR S62 OR S63

S65 (MH Clinical Trials+)

S66 PT Clinical Trial

S67 TI ((controlled trial*) or (clinical trial*)) OR AB ((controlled trial*) or (clinical trial*))

S68 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*))

S69 TI randomi* OR AB randomi*

S70 MH RANDOM ASSIGNMENT

S71 TI ((phase three) or (phase III) or (phase three)) or AB ((phase three) or (phase III) or (phase three))

S72 (TI (random* N2 (assign* or allocat*))) OR (AB (random* N2 (assign* or allocat*))))

S73 MH PLACEBOS

S74 MH META ANALYSIS

S75 MH SYSTEMATIC REVIEW

S76 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*")

S77 TI ("literature review" OR "literature overview" OR "literature search*") OR AB ("literature review" OR "literature overview" OR "literature search*")

S78 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)

S79 TI placebo* OR AB placebo*

S80 MH QUANTITATIVE STUDIES

S81 S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73 or S74 or S75 or S76 or S77 or S78 or S79 or S80

S82 (MH "Blood Coagulation Factors") OR (MH "Prothrombin")

S83 TI ((prothrombin N5 (complex* or concentrate*))) OR AB ((prothrombin N5 (complex* or concentrate*)))

S84 TI ((PCC* or 3F-PCC* or 4F-PCC* or Beriplex* or Feiba* or Autoplex* or Ocplex* or Octaplex* or Kcentra* or Cofact or Prothrombinex* or "Proplex-T" or Prothroras* or Haemosolvex* or Prothromplex* or "HT Defix" or Facnyne* or Kaskadil* or Kedcom* or Confidex* or PPSB or Profil?ine* or Pronativ* or Proplex* or Prothar* or ProthoRAAS* or Protromplex* or "Pushu Laishi" or "Uman Complex")) OR AB ((PCC* or 3F-PCC* or 4F-PCC* or Beriplex* or Feiba* or Autoplex* or Ocplex* or Octaplex* or Kcentra* or Cofact or Prothrombinex* or "Proplex-T" or Prothroras* or Haemosolvex* or Prothromplex* or "HT Defix" or Facnyne* or Kaskadil* or Kedcom* or Confidex* or PPSB or Profil?ine* or Pronativ* or Proplex* or Prothar* or ProthoRAAS* or Protromplex* or "Pushu Laishi" or "Uman Complex"))

S85 S82 OR S83 OR S84

S86 S64 OR S85

S87 S18 AND S81 AND S86

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.go

1. Other terms: randomized or randomised OR randomly OR random

Condition: fracture OR long bone OR pelvic OR ischium OR pubis OR pubic OR ilium OR acetabular OR acetabulum OR diaphysis OR epiphysis OR metaphysis OR femoral OR femur OR hip OR knee OR shoulder OR clavicle OR humerus OR humeral OR tibia OR tibial OR fibula OR ankle OR pilon OR ulna OR radius OR radial OR elbow OR intertrochanteric OR subtrochanteric OR petrochanteric OR intracapsular OR subcapsular OR osteoporosis OR osteoporotic OR osteoarthritis OR orthopedic trauma OR surgical fixation OR hemiarthroplasty OR arthroplasty OR periprosthetic

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

Study Type: Interventional Studies (Clinical Trials)

2. Other terms: randomized or randomised OR randomly OR random

Condition: fracture OR long bone OR pelvic OR ischium OR pubis OR pubic OR ilium OR acetabular OR acetabulum OR diaphysis OR epiphysis OR metaphysis OR femoral OR femur OR hip OR knee OR shoulder OR clavicle OR humerus OR humeral OR tibia OR tibial OR fibula OR ankle OR pilon OR ulna OR radius OR radial OR elbow OR intertrochanteric OR subtrochanteric OR petrochanteric OR intracapsular OR subcapsular OR osteoporosis OR osteoporotic OR osteoarthritis OR orthopedic trauma OR surgical fixation OR hemiarthroplasty OR arthroplasty OR periprosthetic

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
Study Type: Interventional Studies (Clinical Trials)

3. Other terms: randomized or randomised OR randomly OR random

Condition: fracture OR long bone OR pelvic OR ischium OR pubis OR pubic OR ilium OR acetabular OR acetabulum OR diaphysis OR epiphysis OR metaphysis OR femoral OR femur OR hip OR knee OR shoulder OR clavicle OR humerus OR humeral OR tibia OR tibial OR fibula OR ankle OR pilon OR ulna OR radius OR radial OR elbow OR intertrochanteric OR subtrochanteric OR petrochanteric OR intracapsular OR subcapsular OR osteoporosis OR osteoporotic OR osteoarthritis OR orthopedic trauma OR surgical fixation OR hemiarthroplasty OR arthroplasty OR periprosthetic

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 hemisorb OR ostene
Study Type: Interventional Studies (Clinical Trials)

4. Other terms: randomized or randomised OR randomly OR random

Condition: fracture OR long bone OR pelvic OR ischium OR pubis OR pubic OR ilium OR acetabular OR acetabulum OR diaphysis OR epiphysis OR metaphysis OR femoral OR femur OR hip OR knee OR shoulder OR clavicle OR humerus OR humeral OR tibia OR tibial OR fibula OR ankle OR pilon OR ulna OR radius OR radial OR elbow OR intertrochanteric OR subtrochanteric OR petrochanteric OR intracapsular OR subcapsular OR osteoporosis OR osteoporotic OR osteoarthritis OR orthopedic trauma OR surgical fixation OR hemiarthroplasty OR arthroplasty OR periprosthetic

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
Study Type: Interventional Studies (Clinical Trials)

5. Other terms: randomized or randomised OR randomly OR random

Condition: fracture OR long bone OR pelvic OR ischium OR pubis OR pubic OR ilium OR acetabular OR acetabulum OR diaphysis OR epiphysis OR metaphysis OR femoral OR femur OR hip OR knee OR shoulder OR clavicle OR humerus OR humeral OR tibia OR tibial OR fibula OR ankle OR pilon OR ulna OR radius OR radial OR elbow OR intertrochanteric OR subtrochanteric OR petrochanteric OR intracapsular OR subcapsular OR osteoporosis OR osteoporotic OR osteoarthritis OR orthopedic trauma OR surgical fixation OR hemiarthroplasty OR arthroplasty OR periprosthetic

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

Study Type: Interventional Studies (Clinical Trials)

6. Other Terms: fracture OR long bone OR pelvic OR ischium OR pubis OR pubic OR ilium OR acetabular OR acetabulum OR diaphysis OR epiphysis OR metaphysis OR femoral OR femur OR hip OR knee OR shoulder OR clavicle OR humerus OR humeral OR tibia OR tibial OR fibula OR ankle OR pilon OR ulna OR radius OR radial OR elbow OR intertrochanteric OR subtrochanteric OR petrochanteric OR intracapsular OR subcapsular OR osteoporosis OR osteoporotic OR osteoarthritis OR orthopedic trauma OR surgical fixation OR hemiarthroplasty OR arthroplasty OR periprosthetic

Study Type: Interventional Studies (Clinical Trials)

Condition: bleeding OR haemorrhage 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]

World Health Organization International Clinical Trials Registry Platform

1. Title OR Condition: fracture OR long bone OR pelvic OR ischium OR pubis OR pubic OR ilium OR acetabular OR acetabulum OR femoral OR femur OR hip OR knee OR shoulder OR clavicle OR collar bone OR diaphysis OR epiphysis OR metaphysis OR humerus OR humeral OR tibia OR tibial OR fibula OR ankle OR pilon OR ulna OR radius OR radial OR elbow OR intertrochanteric OR subtrochanteric OR petrochanteric OR intracapsular OR subcapsular OR osteoporosis OR osteoporotic OR osteoarthritis OR orthopedic trauma OR surgical fixation OR hemiarthroplasty OR arthroplasty OR periprosthetic

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

Recruitment Status: ALL

2. Title OR Condition: fracture OR long bone OR pelvic OR ischium OR pubis OR pubic OR ilium OR acetabular OR acetabulum OR femoral OR femur OR hip OR knee OR shoulder OR clavicle OR collar bone OR diaphysis OR epiphysis OR metaphysis OR humerus OR humeral OR tibia OR tibial OR fibula OR ankle OR pilon OR ulna OR radius OR radial OR elbow OR intertrochanteric OR subtrochanteric OR petrochanteric OR intracapsular OR subcapsular OR osteoporosis OR osteoporotic OR osteoarthritis OR orthopedic trauma OR surgical fixation OR hemiarthroplasty OR arthroplasty OR periprosthetic

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

Recruitment Status: ALL

3. Title OR Condition: fracture OR long bone OR pelvic OR ischium OR pubis OR pubic OR ilium OR acetabular OR acetabulum OR femoral OR femur OR hip OR knee OR shoulder OR clavicle OR collar bone OR diaphysis OR epiphysis OR metaphysis OR humerus OR humeral OR tibia OR tibial OR fibula OR ankle OR pilon OR ulna OR radius OR radial OR elbow OR intertrochanteric OR subtrochanteric OR petrochanteric OR intracapsular OR subcapsular OR osteoporosis OR osteoporotic OR osteoarthritis OR orthopedic trauma OR surgical fixation OR hemiarthroplasty OR arthroplasty OR periprosthetic 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

Recruitment Status: ALL

4. Title OR Condition: fracture OR long bone OR pelvic OR ischium OR pubis OR pubic OR ilium OR acetabular OR acetabulum OR femoral OR femur OR hip OR knee OR shoulder OR clavicle OR collar bone OR diaphysis OR epiphysis OR metaphysis OR humerus OR humeral OR tibia OR tibial OR fibula OR ankle OR pilon OR ulna OR radius OR radial OR elbow OR intertrochanteric OR subtrochanteric OR petrochanteric OR intracapsular OR subcapsular OR osteoporosis OR osteoporotic OR osteoarthritis OR orthopedic trauma OR surgical fixation OR hemiarthroplasty OR arthroplasty OR periprosthetic

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

Recruitment Status: ALL

5. Title: fracture OR long bone OR pelvic OR ischium OR pubis OR pubic OR ilium OR acetabular OR acetabulum OR femoral OR femur OR hip OR knee OR shoulder OR humerus OR humeral OR tibia OR tibial OR fibula OR ankle OR pilon OR ulna OR radius OR radial OR elbow OR intertrochanteric OR subtrochanteric OR petrochanteric OR intracapsular OR subcapsular OR osteoporosis OR osteoporotic OR osteoarthritis OR orthopedic trauma OR surgical fixation OR hemiarthroplasty OR arthroplasty OR periprosthetic

Condition: bleeding OR hemorrhage OR haemorrhage OR blood loss OR bloodloss

Recruitment Status: ALL

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

CONTRIBUTIONS OF AUTHORS

VG: protocol development and content expertise.

RC: protocol development.

AN: protocol development.

CD: protocol development and developing the search strategy.

AP: protocol development and content expertise.

LE: protocol development and content expertise.

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RC: this review is funded by a NIHR Cochrane Programme Grant.

AN: none.

CD: none.

AP: none.

LE: none.

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