Draft for Consultation

Transfusion

Blood transfusion

NICE guideline

Appendices H-I

18 May 2015

Draft for consultation

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Appendix H: Clinical evidence tables

H.1 Erythropoietin and iron

Study (subsidiary papers)	Anon 1993[18] (Laupacis 1996[89])
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=208)
Countries and setting	Conducted in Canada
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: Patients scheduled for an elective unilateral hip-joint replacement
Subgroup analysis within study	Post-hoc subgroup analysis
Inclusion criteria	To be eligible for the trial patients had to be scheduled for an elective unilateral hip-joint replacement, be less than 86 years of age, and to have given informed consent.
Exclusion criteria	Pre-operative Hb of <110 or >160 g/dl, a systolic blood pressure above 180 mm Hg; a diastolic blood pressure above 100 mm Hg; a history of any seizure or venographically proven proximal deep vein thrombosis; a myocardial infarction or stroke within the previous year; any condition that might interfere with the response to erythropoietin (e.g. iron deficiency) or any systemic illness.
Recruitment/selection of patients	Patients were recruited from 5 Canadian University affiliated centres between March 9, 1990 and Dec 20, 1991.
Age, gender and ethnicity	Age - Mean (SD): Group 1: 63 (12); Group 2 64 (12); Group 3: 63 (15). Gender (M:F): 50/50 (%). Ethnicity: Not stated
Further population details	1. Anaemia at baseline: Not anaemic at baseline ; Hb level at baseline: Hb level >11 g/dl (mean for study: 13.7 g/dl;. Type of surgery : Orthopaedic surgery
Extra comments	Patients were randomised 11 days before surgery.in to one of the 3 groups: group 1, 14 days for placebo; group 2: 14 days of erythropoietin; group 3 , placebo for days 10 to 6 pre-operatively and erythropoietin for 9 days from the fifth pre-operative to the third post-operative day.

Indirectness of population	No indirectness
Interventions	(n=77) Intervention 1: Erythropoietin - Erythropoietin (alfa). All patients received recombinant erythropoietin daily, starting 10 days before surgery and continuing until the third day after surgery. Dose of EPO: 300 units/kg per dose (to a maximum of 30,000 units administered subcutaneously. The concentration used was 10,000 units per ml. Duration 14 days of erythropoietin. Concurrent medication/care: Iron sulphate (300 mg) starting 21 days before surgery. One tablet was taken on the first day, 2 tablets the second day, and then one tablet 3 three times daily until the day of surgery. It was suggested that patients be given iron at least until the day of discharge. Further details: Hb trigger/threshold for transfusion: Hb threshold 8-10 g/dl (stable patients would not be given blood post-operatively unless their Hb was less than 90 g/litre). The use of transfusion protocol : The use of transfusion protocol -Pre-defined cutoff points (Stable patients would not receive blood intra-operatively Unless they had lost more than 15% of their intravascular volume (calculated on the basis of their sex and body weight), and stable patients would not be given blood post-operatively unless their Hb was less than 90 g/litre). Comments: Stable patients would not receive blood intra-operative Unless they had lost more than 15% of their intravascular volume (calculated on the basis of their sex and body weight), and stable patients would not be given blood post-operatively unless their Hb was less than 90 g/litre. (n=53) Intervention 2: Erythropoietin - Erythropoietin (alfa). All patients received recombinant erythropoietin daily, starting 10 days before surgery and continuing until the third day after surgery. Dose of EPO: 300 units/kg per dose (to a maximum of 30,000 units administered subcutaneously. The concentration used was 10,000 units per ml. Duration Placebo for days 10 to 6 pre-operatively and erythropoietin for 9 days from the fifth pre-operative to the third post-operative day. Concurrent medication/care: Iron sulphate (300 mg) starting 21 days before surgery. One tablet was taken on the first day, 2 tablets the second day, and then one tablet 3 three times daily until the day of surgery. It was suggested that patients be given iron at least until the day of discharge. (n=78) Intervention 3: Placebo. Placebo. Duration 14 days pre-operatively. Concurrent medication/care: Iron sulphate (300 mg) starting 21 days before surgery. One tablet was taken on the first day, 2 tablets the second day, and then one tablet 3 three times daily until the day of surgery. It was suggested that patients be given iron at least until the day of discharge.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (14 DAYS) VERSUS PLACEBO	

Protocol outcome 1: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients transfused at 7 days post-operatively; Group 1: 24/77, Group 2: 52/78; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Thrombosis at end of follow-up - Actual outcome: Deep vein thrombosis at 7 days post-operatively; Group 1: 8/77, Group 2: 5/78; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (9 DAYS) VERSUS PLACEBO Protocol outcome 1: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients transfused at 7 days post-operatively; Group 1: 40/53, Group 2: 52/78; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Thrombosis at end of follow-up - Actual outcome: Deep vein thrombosis at 7 days post-operatively; Group 1: 8/53, Group 2: 5/78; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Number of units transfused at end of follow-up

Study	**Bisbe 2014[14]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=122)
Countries and setting	Conducted in Spain; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Post-operative

Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients >18 years who underwent total knee arthroplasty (TKA) at the University Hospital, Barcelona, Spain. TKA (Total knee arthroplasty) patients with post-operative anaemia.
Exclusion criteria	Patients with known hypersensitivity or contraindications to iron, liver insufficiency, bronchial asthma, presence of acute or chronic infection, severe heart disease, significant history of allergies, or anti-anaemia patient treatment within 15 days before surgery. Also pregnant or nursing women were excluded.
Recruitment/selection of patients	Adult patients were recruited at the scheduled pre-operative visit (21-30 days prior to surgery). On the day after surgery eligible patients with anaemia (Hb <12 g/dl), iron deficiency or both randomly assigned to either oral iron or IV iron groups.
Age, gender and ethnicity	Age - --: . Gender (M:F): Define. Ethnicity: Not stated
Further population details	1. Anaemia at baseline: Anaemic at baseline 2. Cardiovascular disease: No cardiovascular disease 3. Hb level at baseline: Hb level 9 to 11 g/dl 4. Respiratory disease: No respiratory disease 5. Type of surgery : Orthopaedic surgery
Extra comments	Pre-operatively anaemic patients were treated with iron, subcutaneous EPO or both
Indirectness of population	No indirectness
Interventions	(n=62) Intervention 1: Oral iron. Ferrous glycine sulphate (FS) was given as a once daily oral dose of 100 mg iron from the day of discharge (day 7) to the rehabilitation visit 30 days after surgery. . Duration From day 7 after discharge to 30 days after surgery. Concurrent medication/care: Antithrombotic treatment was initiated 6 hours after the operation. During surgery patients could receive TXA before tourniquet release. Further details:. Duration of treatment: 2-4 weeks (oral iron) Comments: Patients with intra-operative or immediate post-operative transfusion, severe post-operative anaemia (Hb <8.5 g/dl) or a risk of transfusion within the next hours were not randomised to the study. (n=59) Intervention 2: IV iron. Ferric carboxymaltose (FCM) was given the day after surgery as a single IV dose. Duration Single dose on the day of the surgery. Concurrent medication/care: Not stated Further details: Duration of treatment: once a week (IV iron) Comments: Pre-operatively triggers of RBC transfusion were Hb <8 g/dl or occurrence of acute anaemia symptoms
Funding	Other
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL IRON VERSUS IV IRON Protocol outcome 1: Quality of life at end of follow-up	

- Actual outcome for Post-operative: Quality of life- total EQ-5D at end of follow-up; Group 1: mean 0.6 (SD 0.17); n=62, Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Post-operative: Number of patients transfused at end of follow-up; Group 1: 2/62, Group 2: 3/59; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Length of hospital stay at end of follow-up - Actual outcome for Post-operative: Length of hospital stay at end of follow-up; Group 1: mean 7.6 (SD 0.9); n=62, Group 2: mean 7.9 (SD 1.7); n=59; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Serious adverse events (as described in studies) at end of follow-up - Actual outcome for Post-operative: Deep vein thrombosis at end of follow-up; Group 1: 0/62, Group 2: 1/59; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all causes) at 30 days; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Bleeding at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Number of units transfused at end of follow-up

Study	**Crosby 1994[35]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=128)
Countries and setting	Conducted in USA; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 2 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Haemoglobin level
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Male patients or post-menopausal female patients; age > 50 years; admitted for elective coronary bypass surgery

Exclusion criteria	Patients undergoing concomitant procedures such as left ventricular aneurysm resection and valve surgery; Patients with acute myocardial infarction and/or a history of previous open heart surgery, known cancer, rheumatoid arthritis, kidney failure, recent infection, anaemia. Post-operative exclusion criteria included any patients that had received more than three units of homologous blood transfusion, had prolonged or complicated post-operative course of greater than 9 days, or a haematocrit of greater than 31% on post-operative day 6.
Recruitment/selection of patients	Consecutive patients who gave consent for participating in the study.
Age, gender and ethnicity	Age - Mean (SD): Age in years (SD) for: Oral iron-50 mg: 65(9.9); Oral iron-200 mg 64(7.6); Placebo-65(7.2). Gender (M:F): 100:21. Ethnicity: NR
Further population details	1. Anaemia at baseline: 2. Cardiovascular disease: 3. Hb level at baseline: 4. Respiratory disease: 5. Type of surgery :
Extra comments	None of the outcomes listed in the review protocol were reported in or able to be extracted from this study
Indirectness of population	Serious indirectness: Population included all patients undergoing cardio-pulmonary bypass surgery and is indirect to target population of all patients receiving blood transfusions.
Interventions	(n=62) Intervention 1: Oral iron. Oral iron: 50 mg elemental iron +60 mg ascorbic acid daily (Geroitol, SmithKline Beecham)200 mg elemental iron (Feosol, SmithKline Beecham). Duration 8 weeks. Concurrent medication/care: None Comments: Of 62 randomised, 28 received 50 mg iron and 34 received 200 mg iron. (n=26) Intervention 2: Placebo. NA. Duration 8 weeks. Concurrent medication/care: None
Funding	Academic or government funding (Grant from Allegheny Singer Research Institute)
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Number of units transfused at end of follow-up

Study	**D'Ambra 1997[37]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	not applicable (n=182)
Countries and setting	Conducted in USA; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 month after hospital discharge
Method of assessment of guideline condition	Unclear method of assessment/diagnosis: No information reported on how it was decided when to transfuse
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged >=18 years, scheduled for initial or repeat elective coronary artery bypass grafting (CABG). Females required to have been: postmenopausal for >1 year; surgically sterile; or to have had negative birth test and to be using a reliable method of birth control.
Exclusion criteria	Haematocrit (HCT) >45%; clinically significant laboratory abnormalities or diseases or dysfunction of the nervous, pulmonary, endocrine, gastrointestinal, or genitourinary systems; a history of primary haematologic disease, seizures, or uncontrolled hypertension (diastolic blood pressure >=100 mmHg); congestive heart failure (New York Heart Association class III or IV); clinically significant ongoing blood loss; drug or alcohol abuse within past 2 years; peripheral vascular disease; medical conditions or therapies known to interfere with erythropoiesis; scheduled valve replacement; or lactation. Patients also eligible if they had received blood transfusion or androgen therapy or had participated in an experimental study within previous month. Attempts made to exclude patients with iron deficiency (e.g. serum ferritin level <20 ng/ml, total iron-binding capacity >360 micrograms/dl, and serum iron to total iron-binding capacity ratio <16%).
Recruitment/selection of patients	Only reports patients scheduled for major elective CABG enrolled at nine study sites in USA between November 1988 and December 1990. Not indicated if these were consecutive patients or all patients meeting the criteria.
Age, gender and ethnicity	Age - Mean (SD): Epoetin alfa 300 IU/kg: 60.3+/-8.9; Epoetin alfa 150 IU/kg: 62.6+/-7.8; Placebo: 62.1+/-8.1. Gender (M:F): 162/20. Ethnicity: not reported
Further population details	1. Anaemia at baseline: Not anaemic at baseline 2. Cardiovascular disease: Not applicable / Not stated / Unclear (Only reports excluding patients with congestive heart failure). 3. Hb level at baseline: Not applicable / Not stated / Unclear (Epoetin alfa 300 IU/kg: 14.1+/-1.1; Epoetin alfa 150 IU/kg: 14.2+/-1.0; Placebo: 14.1+/-1.1 reported for population as a whole and not subgrouped). 4. Respiratory disease: Not applicable / Not stated / Unclear 5. Type of surgery : Cardiovascular surgery (Elective initial or repeat coronary artery bypass grafting).
Indirectness of population	No indirectness

Interventions	(n=63) Intervention 1: Erythropoietin - Erythropoietin (alfa). 300 IU/kg per day. Duration 5 days pre-operatively, 2 days post-operatively. Concurrent medication/care: Oral iron supplements: 325 mg 3x per day as soon as possible pre-operatively and continuing throughout treatment period Further details: 1. Dosage: Not applicable / Not stated / Unclear (Epoetin alfa 300 IU/kg per day. Total of 8 doses to be administered). 2. Duration of treatment: Not applicable / Not stated / Unclear (Daily for 5 days pre-operatively and 2 days post-operatively). 3. Hb trigger/threshold for transfusion: Not applicable / Not stated / Unclear (not reported). 4. The use of transfusion protocol: No transfusion protocol/ based on clinical judgment (No transfusion protocol reported in the study). (n=63) Intervention 2: Erythropoietin - Erythropoietin (alfa). 150 IU/kg per day. Duration 5 days pre-operatively, 2 days post-operatively. Concurrent medication/care: Oral iron supplements: 325 mg 3x per day as soon as possible pre-operatively and continuing throughout treatment period Further details: 1. Dosage: Not applicable / Not stated / Unclear (Epoetin alfa 150 IU/kg per day. Total of 8 doses to be administered). 2. Duration of treatment: Not applicable / Not stated / Unclear (Daily for 5 days pre-operatively and 2 days post-operatively). 3. Hb trigger/threshold for transfusion: Not applicable / Not stated / Unclear (not reported). 4. The use of transfusion protocol : No transfusion protocol/ based on clinical judgment (No transfusion protocol reported in the study. Policy not to transfuse patients with a haematocrit value >24% after CABG). (n=56) Intervention 3: Placebo. Placebo defined as equivalent volume to drug under investigation. Duration 5 days pre-operatively, 2 days post operatively. Concurrent medication/care: Oral iron supplements: 325 mg 3x per day as soon as possible pre-operatively and continuing throughout treatment period Further details: 1. Dosage: Not applicable / Not stated / Unclear 2. Duration of treatment: Not applicable / Not stated / Unclear (5 days pre-operatively, 2 days post operatively). 3. Hb trigger/threshold for transfusion: Not applicable / Not stated / Unclear (not reported). 4. The use of transfusion protocol: No transfusion protocol/ based on clinical judgment (No transfusion protocol reported in the study).
Funding	Study funded by industry (Part funded by grants from R.W. Johnson Pharmaceutical Research Institute, Raritan, NJ and Rowland Foundation, Cambridge, MA.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (ALFA) 300 IU VERSUS ERYTHROPOIETIN (ALFA) 150 IU

Protocol outcome 1: Number of units transfused at end of follow-up
- Actual outcome: Mean number of units transfused at not reported; Group 1: mean 1.37 IU/kg (SD 2.78); n=59, Group 2: mean 1.72 IU/kg (SD 3.64); n=60; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Mortality (all causes) at 30 days
- Actual outcome: Death During study period, within 2 months of discontinuation of treatment or 3 months after operation; Group 1: 7/63, Group 2: 4/63; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Number of patients needing transfusions at end of follow-up
- Actual outcome: No. patients requiring transfusion at not reported; Group 1: 19/59, Group 2: 17/60; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Serious adverse events (as described in studies) at end of follow-up
- Actual outcome: Serious or unexpected adverse events described as patients removed from study due to adverse events. Mortality added to numbers. at not reported; Group 1: 7/63, Group 2: 6/63; Risk of bias: High; Indirectness of outcome: Serious indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (ALFA) 300 IU VERSUS PLACEBO

Protocol outcome 1: Number of units transfused at end of follow-up
- Actual outcome: Mean number of units transfused at not reported; Group 1: mean 1.37 IU/kg (SD 2.78); n=59, Group 2: mean 1.33 IU/kg (SD 2.01); n=52; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Mortality (all causes) at 30 days
- Actual outcome: Death During study period, within 2 months of discontinuation of treatment or 3 months after operation; Group 1: 7/63, Group 2: 0/56; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Number of patients needing transfusions at end of follow-up
- Actual outcome: No. patients requiring transfusion at not reported; Group 1: 19/59, Group 2: 25/52; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Serious adverse events (as described in studies) at end of follow-up
- Actual outcome: Serious or unexpected adverse events described as patients removed from study due to adverse events. Mortality added to numbers. at not reported; Group 1: 7/63, Group 2: 2/56; Risk of bias: High; Indirectness of outcome: Serious indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (ALFA) 150 IU VERSUS PLACEBO

Protocol outcome 1: Number of units transfused at end of follow-up
- Actual outcome: Mean number of units transfused at not reported; Group 1: mean 1.72 IU/kg (SD 3.64); n=60, Group 2: mean 1.33 IU/kg (SD 2.01); n=52; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Mortality (all causes) at 30 days

- Actual outcome: Death During study period, within 2 months of discontinuation of treatment or 3 months after operation; Group 1: 4/63, Group 2: 0/56; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Number of patients needing transfusions at end of follow-up - Actual outcome: No. patients requiring transfusion at not reported; Group 1: 17/60, Group 2: 25/52; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Serious adverse events (as described in studies) at end of follow-up - Actual outcome: Serious or unexpected adverse events described as patients removed from study due to adverse events. Mortality added to numbers. at not reported; Group 1: 6/63, Group 2: 2/56; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Length of hospital stay at end of follow-up

Study	**De Andrade 1996[44]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=316)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Hb levels and clinical need
Stratum	Overall: Hb level: stratum 1 - Hb <=10 g/dl; stratum 2 - Hb >10 to <=13 g/dl; stratum 3 - Hb >13 g/dl
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Major elective orthopaedic surgery of hip or knee; general good health with no abnormal laboratory values; expected to require at least 2 units of blood without having participated in pre-operative autologous blood programme; >=18 years old; Hb level <=15 g/dl; serum iron to total iron binding capacity (TIBC) ratio >=15%; serum ferrin level >=50 ng/ml
Exclusion criteria	Major systemic disease or dysfunction; any condition that may interfere with response to Epoetin alfa; seizures; uncontrolled hypertension (that is, diastolic blood pressure >=100 mmHg); recent gastrointestinal or intracranial bleeding; any contraindications to warfarin use; drug or alcohol abuse; active inflammatory disease excluding

	osteoarthritis; autoimmune haemolysis; positive values for hep B surface antigen or HIV; exposure to blood transfusion within 30 days of study entry; exposure to androgen therapy; erythropoietic-suppressing medication or an experimental drug device within 1 month of study entry; previous exposure to Epoetin alfa; pregnancy or lactation; contraindications to blood transfusions.
Recruitment/selection of patients	Patients enrolled at 26 US study sites between 18 April 1993 and 30 August 1994
Age, gender and ethnicity	Age - Mean (SD): 66.51 (12.45). Gender (M:F): Define. Ethnicity: not reported
Further population details	1. Anaemia at baseline: Not applicable / Not stated / Unclear (Mixed). 2. Cardiovascular disease: Not applicable / Not stated / Unclear 3. Hb level at baseline: Not applicable / Not stated / Unclear (<=15 g/dl). 4. Respiratory disease: Not applicable / Not stated / Unclear 5. Type of surgery : Orthopaedic surgery
Extra comments	Patients "expected" to require at least 2 units of blood . Stratified then randomised. Baseline details reported for study overall. Groups comprise: stratum 1=2 patients; stratum 2=96; stratum 3=218 patients. More women in stratum 2 (84%) than stratum 3 (52%) because baseline Hb levels.
Indirectness of population	No indirectness
Interventions	(n=112) Intervention 1: Erythropoietin - Erythropoietin (alfa). Epoetin alfa 300 IU/kg by subcutaneous injection for 10 consecutive days pre-operatively, day of surgery and 4 days post-operatively for a total of 15 doses. Epoetin alfa concentration of 10,000 IU/ml in diluent with 2.5 mg/ml human serum albumin. Duration 15 days. Concurrent medication/care: Oral elemental iron >=150 mg / day from first day of study treatment until hospital discharge Further details: 1. Dosage : Not applicable / Not stated / Unclear (type of epoetin alfa not stated). 2. Duration of treatment: Not applicable / Not stated / Unclear 3. Hb trigger/threshold for transfusion: Hb threshold <8 g/dl (Hb <9 g/dl). 4. The use of transfusion protocol: Transfusion protocol +clinical need (Hb <9g/dl or clinical need). (n=101) Intervention 2: Erythropoietin - Erythropoietin (alfa). Epoetin alfa 300 IU/kg by subcutaneous injection for 10 consecutive days pre-operatively, day of surgery and 4 days post-operatively for a total of 15 doses. Epoetin alfa concentration of 10000 IU/ml in diluent with 2.5 mg/ml human serum albumin. Duration 15 days. Concurrent medication/care: Oral elemental iron >=150 mg / day from first day of study treatment until hospital discharge Further details: 1. Dosage : Not applicable / Not stated / Unclear (type of epoetin alfa not stated). 2. Duration of treatment: Not applicable / Not stated / Unclear 3. Hb trigger/threshold for transfusion: Hb threshold <8g/dl (Hb <9g/dl). 4. The use of transfusion protocol: Transfusion protocol +clinical need (Hb <9g/dl or clinical need). (n=103) Intervention 3: Placebo. Placebo identical to epoetin alfa diluent. Duration 15 days. Concurrent medication/care: Oral elemental iron >=150 mg / day from first day of study treatment until hospital discharge Further details: 1. Dosage : Not applicable / Not stated / Unclear (type of epoetin alfa not stated). 2. Duration of

	treatment: Not applicable / Not stated / Unclear 3. Hb trigger/threshold for transfusion: Hb threshold <8g/dl (Hb <9g/dl). 4. The use of transfusion protocol : Transfusion protocol +clinical need (Hb <9 g/dl or clinical need).
Funding	Study funded by industry (R.W. Johnson Pharmaceutical Research Institute)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (ALFA) HIGH DOSE VERSUS ERYTHROPOIETIN (ALFA) LOW DOSE

Protocol outcome 1: Number of units transfused at end of follow-up
- Actual outcome: Number of allogeneic units transfused per patient in Stratum 2 (baseline Hb >10 to <=13g/dl) at 6 week follow up; Group 1: mean 0.45 (SD 1.207); n=31, Group 2: mean 0.42 (SD 0.945); n=26; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: Number of allogeneic units transfused per patient in Stratum 3 (baseline Hb >13g/dl) at 6 week follow up; Group 1: mean 0.26 (SD 0.956); n=68, Group 2: mean 0.13 (SD 0.544); n=68; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Mortality (all causes) at 30 days
- Actual outcome: Mortality at 6 week follow up; Group 1: 1/112, Group 2: 0/101; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Serious adverse events (as described in studies) at end of follow-up
- Actual outcome: Serious adverse events as classified by the sponsor, no more detail provided. Includes death. at 6 week follow up; Group 1: 7/112, Group 2: 6/101; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (ALFA) HIGH DOSE VERSUS PLACEBO

Protocol outcome 1: Number of units transfused at end of follow-up
- Actual outcome: Number of allogeneic units transfused per patient in Stratum 2 (baseline Hb >10 to <=13g/dl) at 6 week follow up; Group 1: mean 0.45 (SD 1.207); n=31, Group 2: mean 1.14 (SD 1.432); n=29; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: Number of allogeneic units transfused per patient in Stratum 3 (baseline Hb >13g/dl) at 6 week follow up; Group 1: mean 0.26 (SD 0.956); n=68, Group 2: mean 0.33 (SD 0.911); n=67; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Mortality (all causes) at 30 days
- Actual outcome: Mortality at 6 week follow up; Group 1: 1/112, Group 2: 0/103; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Serious adverse events (as described in studies) at end of follow-up
- Actual outcome: Serious adverse events as classified by the sponsor, no more detail provided. Includes death. at 6 week follow up; Group 1: 7/112, Group 2: 8/103; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (ALFA) LOW DOSE VERSUS PLACEBO Protocol outcome 1: Number of units transfused at end of follow-up - Actual outcome: Number of allogeneic units transfused per patient in Stratum 2 (baseline Hb >10 to <=13g/dl) at 6 week follow up; Group 1: mean 0.42 (SD 0.945); n=26, Group 2: mean 1.14 (SD 1.432); n=29; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Number of allogeneic units transfused per patient in Stratum 3 (baseline Hb >13g/dl) at 6 week follow up; Group 1: mean 0.13 (SD 0.544); n=68, Group 2: mean 0.33 (SD 0.911); n=67; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Mortality (all causes) at 30 days - Actual outcome: Mortality at 6 week follow up; Group 1: 0/101, Group 2: 0/103; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Serious adverse events (as described in studies) at end of follow-up - Actual outcome: Serious adverse events as classified by the sponsor, no more detail provided. Includes death. at 6 week follow up; Group 1: 6/101, Group 2: 8/103; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Bleeding at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Length of hospital stay at end of follow-up

Study (subsidiary papers)	**Devon 2009[46] (Heiss 1996[70], Kettelhack 1998[81], Christodoulakis 2005[29], Qvist 1999[129])**
Study type	Systematic Review
Number of studies (number of participants)	4 (n=421 (in pooled analysis))
Countries and setting	Conducted in Denmark, Germany, Greece; Setting: Secondary care (hospital setting)
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable

Inclusion criteria	Randomised controlled trials of erythropoietin versus placebo or no treatment/standard of care were eligible for inclusion. The study must have reported one of the primary or secondary outcomes and included anaemic patients undergoing surgery for colorectal cancer.
Exclusion criteria	The Cochrane review excluded non randomised studies, studies which did not provide any information on colorectal cancer and studies where patients were treated beyond discharge from hospital.
Age, gender and ethnicity	Age - Mean (SD): As reported per study. Gender (M:F): Provided per study. Ethnicity: Not reported
Further population details	-
Indirectness of population	No indirectness
Interventions	(n=243) Intervention 1: Erythropoietin - Erythropoietin (alfa). Studies included in the review included patients on erythropoietin therapy. The doses differed between studies as listed below: Christodoulakis 2005: 2 groups of patients in this study received erythropoietin; one group received 150 IU/kg/day of subcutaneous epoetin alfa from 10 days pre-operatively till post-operative day one. The second group received 300 IU/kg/day from 10 days pre-operatively till post-operative day one. Heiss 1996: 150 IU/kg erythropoietin every two days beginning 10 days pre-operatively till two days post-operatively. Kettelhack 1998: Subcutaneous epoetin beta 20000 units per day from 5 to 10 days pre-operatively till fourth day post-operatively for a minimum treatment of 10days.Qvist 1999: Subcutaneous erythropoietin 300 IU/kg for four days pre-operatively and then 150 IU/kg daily until post-operative day three. Duration Pre- and post-operative period. Concurrent medication/care: All patients received concomitant therapy with oral iron or IV iron. The dosage differed according to the studies. Christodoulakis 2005: Oral iron 200 mg/day plus 40 g IV post-operatively until discharge if needed and folic acid 15 mg/day for 10 days post-operatively. Heiss 1996: 200 mg oral iron plus 5 mg folate daily until day of operation. Kettelhack 1998: Oral iron in case of deficiency plus 15 mg IV iron on post-operative day one. Qvist 1999: Oral iron 200 mg/day for four days pre-operatively. Comments: the number of patients randomised refers to the total number randomised to receive EPO across all four studies. (n=178) Intervention 2: Placebo. 3 of the studies (Heiss 1996, Kettelhack 1998, Qvist 1999) compared erythropoietin to placebo; One study (Christodoulakis 2005) compared erythropoietin with standard care. Heiss 1996: Subcutaneous placebo every 2 days beginning 10 days pre-operatively until 2 days post-operatively. Kettelhack 1998: Subcutaneous placebo beginning 5-10 days pre-operatively until fourth day post-operatively for a minimum treatment duration of 10 days. Christodoulakis 2005: patients received standard care. Qvist 1999: placebo preparation subcutaneously for 4 days pre-operatively. Duration Pre-operatively through to post-operative period. Concurrent medication/care: Heiss 1996: Both groups received 200 mg oral iron plus 5 mg folate daily until day of operation.Kettelhack1998: Oral iron in case of deficiency plus 40 mg iron intravenously on post-operative day one. Qvist 1999: Oral iron 200 mg/day. Christodoulakis

	2005: All patients received oral iron 200 mg/day plus 40 mg IV iron post-operatively until discharge and Folic acid 15 mg/day for 10 days. Further details: 1. Dosage : Systematic review: mixed 2. Duration of treatment: Systematic review: mixed 3. Hb trigger/threshold for transfusion: Systematic review: mixed (Transfusion protocol varied across studies with threshold for transfusion being Hb level was < 10 g/dl (Christodoulakis 2005), <9 g/dl (Heiss 1996), < 7.5 g/dl (Kettelhack 1998); One study (Qvist1999) did not have a threshold and transfusion was at the discretion of the anaesthetist). 4. The use of transfusion protocol : Systematic review: mixed (Transfusion protocol varied across studies with threshold for transfusion being Hb level was < 10 g/dl(Christodoulakis 2005), <9 g/dl (Heiss 1996), < 7.5 g/dl (Kettelhack 1998); One study (Qvist1999) did not have a threshold and transfusion was at the discretion of the anaesthetist). Comments: Number randomised is for all patients randomised to the control placebo (and standard care) group across all four studies.
Funding	Academic or government funding
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Number of units transfused at end of follow-up

Study	**Dousias 2003[49]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=50)
Countries and setting	Conducted in Greece; Setting: outpatient clinic and hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: Before patients underwent abdominal total hysterectomy
Subgroup analysis within study	Post-hoc subgroup analysis
Inclusion criteria	The study included mildly anaemic healthy women before they underwent abdominal total hysterectomy for uterine

	leiomyomas. Eligibility criteria included absence of major medical illness (including haemoglobinopathies, other blood disorders and malignancies), age between 30 and 60 years, baseline Hb >9 and <12 g/dl, body weight between 50 and 80 kg, ferritin >50ng/ml and uterine leiomyomas demonstrated by means of ultrasonography.
Exclusion criteria	Not reported.
Recruitment/selection of patients	Mildly anaemic women with benign uterine pathology.
Age, gender and ethnicity	Age - Mean (SD): Group A: 48.2 (4.1) years; Group B: 49.2 (4.7) years. Gender (M:F): All women. Ethnicity: NR
Further population details	1. Anaemia at baseline: Anaemic at baseline 2. Cardiovascular disease: Not applicable / Not stated / Unclear 3. Hb level at baseline: Hb level >11 g/dl (Baseline level - >9 and <12). 4. Respiratory disease: Not applicable / Not stated / Unclear 5. Type of surgery : Major abdominal surgery (excluding cancer)
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: Oral iron + Erythropoietin. Recombinant human erythropoietin (rHuEPO) 600 U/ml subcutaneously once weekly for 3 weeks (pre-operative days -14,-7 and the morning before the operation). . Duration 3 weeks before surgery. Concurrent medication/care: Oral iron 200 mg/day (throughout the study period - 3 weeks before and 2 weeks after surgery) Further details: 1. Dosage : Epoetin alfa (Erythropoietin) Binocrit- 600 units/kg every week for 3 weeks before surgery and on day of surgery or 300 units/kg daily for 15 days starting 10 days before surgery 2. Duration of treatment: Once a week (Erythropoietin) 3. Hb trigger/threshold for transfusion: Not applicable / Not stated / Unclear 4. The use of transfusion protocol : Not applicable / Not stated / Unclear (n=27) Intervention 2: Oral iron. Oral iron 200 mg/day (throughout the study period - 3 weeks before and 2 weeks after surgery). Duration Throughout the study period - 3 weeks before and 2 weeks after surgery. Concurrent medication/care: Oral iron 200 mg/day (throughout the study period - 3 weeks before and 2 weeks after surgery) Further details: 1. Dosage : 2. Duration of treatment: 3. Hb trigger/threshold for transfusion: 4. The use of transfusion protocol :
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL IRON + ERYTHROPOIETIN VERSUS ORAL IRON Protocol outcome 1: Number of units transfused at end of follow-up - Actual outcome: Number of units transfused at 2 weeks post-operatively; Risk of bias: High; Indirectness of outcome: No indirectness	

Protocol outcome 2: Length of hospital stay at end of follow-up - Actual outcome: Length of hospital stay at end of follow-up; Group 1: mean 7.6 days (SD 0.5); n=23, Group 2: mean 7.8 days (SD 0.9); n=27; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Number of patients needing transfusions at end of follow-up - Actual outcome: Number patients needing transfusion at 2 weeks post-operatively; Group 1: 0/23, Group 2: 5/27; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (transfusion related) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Mortality (all causes) at 30 days

Study	**Edwards 2009[52]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=62)
Countries and setting	Conducted in United Kingdom; Setting: Secondary care (pre-operative), single centre study
Line of therapy	1st line
Duration of study	Intervention + follow up: From 14 days before surgery to discharge of patient
Method of assessment of guideline condition	Method of assessment /diagnosis not stated: Haematocrit levels assessed but threshold for blood transfusion not reported
Stratum	Overall: Population stratified according to pre-recruitment Hb status: normal (Hb level 13.5 g/dl in males and 12.5 g/dl in females), anaemic or unknown (no test within 2 months of recruitment)
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with Colorectal cancer surgery Hb: at least 13.5 g/dl in men and 12.5 g/dl in women
Exclusion criteria	Define
Recruitment/selection of patients	Volunteers from all patients scheduled to undergo surgery

Age, gender and ethnicity	Age - Median (range): Iron group=67 years; Placebo group 70 years, Range not reported. Gender (M:F): Define. Ethnicity: Not reported
Further population details	1. Anaemia at baseline: Not anaemic at baseline 2. Cardiovascular disease: Not applicable / Not stated / Unclear 3. Hb level at baseline: Not applicable / Not stated / Unclear (Iron group= 13.4 (10.8-15.9) g/dl; Placebo=13.7 (9.2-16.8)g/dl). 4. Respiratory disease: Not applicable / Not stated / Unclear 5. Type of surgery : Cancer surgery
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: IV iron. 600 mg iron sucrose (total dose)- 2 doses of 300 mg iron sucrose made up to 250 ml with 0.9% saline; Provided as 15 ml ferric hydroxide with sucrose in a 2 per cent solution (Venofer, syner-Med, Purley, UK); Minimum time between each infusion was 24 hours and all infusions were completed within a minimum period of 14 days before surgery. Duration 7 days or until discharge (whichever was earlier). Concurrent medication/care: None Further details: 1. Dosage : Not applicable / Not stated / Unclear (600 mg iron sucrose (total dose)- 2 doses of 300 mg iron sucrose made up to 250 ml with 0.9% saline;). 2. Duration of treatment: Twice a week (IV iron) (2 divided doses of 300 mg each given 14 days before surgery). 3. Hb trigger/threshold for transfusion: Hb threshold <8g/dl (If Hb <8g/dl, transfused to a target of 10 g/dl; patients were also transfused if Hb level 8-10 g/dl and patients had abnormal ECG, ischaemic heart disease, obstructive lung disease or were unable to absorb oral iron). 4. The use of transfusion protocol : The use of transfusion protocol -Pre-defined cutoff points (If Hb <8g/dl, transfused to a target of 10 g/dl; patients were also transfused if Hb level 8-10 g/dl and patients had abnormal ECG, ischaemic heart disease, obstructive lung disease or were unable to absorb oral iron.) (n=27) Intervention 2: Placebo. 2 infusions of 250 ml of 0.9% saline (intravenous placebo). Duration 14 days before surgery . Concurrent medication/care: None Further details: 1. Dosage: Not applicable / Not stated / Unclear 2. Duration of treatment: Not applicable / Not stated / Unclear 3. Hb trigger/threshold for transfusion: Hb threshold <8g/dl (If Hb <8g/dl, transfused to a target of 10 g/dl; patients were also transfused if Hb level 8-10 g/dl and patients had abnormal ECG, ischaemic heart disease, obstructive lung disease or were unable to absorb oral iron). 4. The use of transfusion protocol : The use of transfusion protocol - Pre-defined cutoff points (If Hb <8g/dl, transfused to a target of 10 g/dl; patients were also transfused if Hb level 8-10 g/dl and patients had abnormal ECG, ischaemic heart disease, obstructive lung disease or were unable to absorb oral iron).
Funding	Equipment / drugs provided by industry (Syner-Med Pharmaceutical Products Limited (provided Venofer and funded blood tests))
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IRON (600 MG IRON SUCROSE GIVEN IN 2 DIVIDED DOSES 14 DAYS BEFORE SURGERY) VERSUS PLACEBO	

Protocol outcome 1: Number of units transfused at end of follow-up - Actual outcome: Median number of units transfused at peri-operative period; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Length of hospital stay at end of follow-up - Actual outcome: Median length of hospital stay at Discharge of patient; Risk of bias:Low --; Indirectness of outcome: No indirectness Protocol outcome 3: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients needing transfusions at Peri-operative period; Group 1: 2/34, Group 2: 5/26; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Mortality (all causes) at 30 days

Study	**Faris 1996[56]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in USA; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled for a major orthopaedic surgery. All patients were more than 18 years old.
Exclusion criteria	If patients had a history of primary haematological disease, clinically important disease or dysfunction of other major organ systems, seizures, uncontrolled hypertension, or an active infectious or neoplastic disease or if they were candidates for autologous blood donation

Recruitment/selection of patients	The patients participating in this trial were scheduled to have a major orthopaedic procedure. The selection of patients was limited to those who could not or did not choose to donate autologous blood pre-operatively.
Age, gender and ethnicity	Age - Mean (SD): 66 (13.3). Gender (M:F): 67/133. Ethnicity: NR
Further population details	1. Anaemia at baseline: Not anaemic at baseline 2. Cardiovascular disease: 3. Hb level at baseline: Hb level >11 g/dl (Haemoglobin <100 g/litre; Haemoglobin >100 <130 g/litre; Haemoglobin >130 g/litre). 4. Respiratory disease: 5. Type of surgery:
Extra comments	The women had been post-menopausal for at least 1 year, were sterile, or were using a reliable method of birth control and had a negative pregnancy test immediately before being enrolled in the study. . Haemoglobin: mean (SE) g/litre- 131 (16)
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: Erythropoietin - Erythropoietin (alfa). Recombinant human erythropoietin 300 IU per kg of body weight per day administered subcutaneously. The medication was administered for 15 consecutive days, beginning 10 days before the operation and extending through the day of the operation through the 4th day post-operative day. . Duration 15 days. Concurrent medication/care: All patients received iron supplementation (ferrous sulfate 325 milligrams or the equivalent, three times per day) orally throughout the study. Further details: 1. Dosage : 2. Duration of treatment: 3. Hb trigger/threshold for transfusion: 4. The use of transfusion protocol : Transfusion protocol +clinical need (Intra operative and post-operative blood transfusions were performed at the discretion of the surgeon; however every effort was made to avoid transfusion if the haematocrit level was more than 0.27, unless the clinical situation warranted it). Comments: Intra operative and post-operative blood transfusions were performed at the discretion of the surgeon; however every effort was made to avoid transfusion if the haematocrit level was more than 0.27, unless the clinical situation warranted it. (n=71) Intervention 2: Erythropoietin - Erythropoietin (alfa). Recombinant human erythropoietin 100 IU per kg of body weight per day administered subcutaneously. The medication was administered for 15 consecutive days, beginning 10 days before the operation and extending through the day of the operation through the 4th day post-operative day . Duration 15 days. Concurrent medication/care: All patients received iron supplementation (ferrous sulfate 325 milligrams or the equivalent, three times per day) orally throughout the study. (n=69) Intervention 3: Placebo. Placebo medication. Duration 15 days. Concurrent medication/care: All patients received iron supplementation (ferrous sulfate 325 milligrams or the equivalent, three times per day) orally throughout the study.

Funding	Study funded by industry

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (HIGH DOSE) VERSUS PLACEBO

Protocol outcome 1: Number of units transfused at end of follow-up
- Actual outcome: Number of units transfused per patient at 4 weeks post-operatively; Group 1: mean 0.37 (SD 0.96); n=54, Group 2: mean 1.42 (SD 1.67); n=67; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of patients needing transfusions at end of follow-up
- Actual outcome: Number of patients who received a transfusion at 4 weeks post-operatively; Group 1: 9/54, Group 2: 36/67; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: Number of patients who received transfusion (baseline Hb<100 g/litre) at 4 weeks post-operatively; Group 1: 2/3, Group 2: 1/1; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: Number of patients who received transfusion (baseline Hb >100 < 130 g/litre) at 4 weeks post-operatively; Group 1: 3/22, Group 2: 21/27; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: Number of patients who received transfusion (baseline Hb >130 g/litre) at 4 weeks post-operatively; Group 1: 4/29, Group 2: 14/39; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Serious adverse events (as described in studies) at end of follow-up
- Actual outcome: Serious adverse events (thrombotic and vascular events including MI,angina, DVT, superficial phlebitis and peripheral arterial thrombosis) at 4 weeks post-operatively; Group 1: 2/54, Group 2: 6/67; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (LOW DOSE) VERSUS PLACEBO

Protocol outcome 1: Number of units transfused at end of follow-up
- Actual outcome: Number of units transfused per patient at 4 weeks post-operatively; Group 1: mean 0.58 (SD 1.15); n=64, Group 2: mean 1.42 (SD 1.67); n=67; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of patients needing transfusions at end of follow-up
- Actual outcome: Number of patients who received a transfusion at 4 weeks post-operatively; Group 1: 16/64, Group 2: 36/67; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome: Number of patients who received transfusion (baseline Hb<100 g/litre) at 4 weeks post-operatively; Group 1: 3/5, Group 2: 1/1; Risk of bias: High; Indirectness of outcome: No indirectness

- Actual outcome: Number of patients who received transfusion (baseline Hb >100 < 130 g/litre) at 4 weeks post-operatively; Group 1: 9/23, Group 2: 21/27; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome: Number of patients who received transfusion (baseline Hb> 130 g/litre) at 4 weeks post-operatively; Group 1: 4/36, Group 2: 14/39; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Serious adverse events (as described in studies) at end of follow-up - Actual outcome: Serious adverse events (thrombotic and vascular events including MI, angina, DVT, superficial phlebitis and peripheral arterial thrombosis) at 4 weeks post-operatively; Group 1: 3/71, Group 2: 6/69; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Length of hospital stay at end of follow-up

Study	**Feagan 2000[57]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=216)
Countries and setting	Conducted in Canada; Setting: Secondary care
Line of therapy	1st line
Duration of study	Intervention time: from at least 42 days before surgery until discharge
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Haemoglobin concentration 98-137g/litre
Exclusion criteria	Autologous blood donation; rheumatoid arthritis; recent gastrointestinal or intracranial bleeding; iron deficiency; seizures; blood dyscrasias; uncontrolled hypertension (diastolic blood pressure >100 mmHg); patients requiring revision hip arthroplasty; and patients in whom red cell salvage devices were considered essential.
Recruitment/selection of patients	Recruited from 13 teaching hospitals and 4 community hospitals across Canada from May 1996 to April 1999

Age, gender and ethnicity	Age - Mean (SD): Epoetin alfa 40,000: 67.3+/-11.0; Epoetin alfa 20,000: 68.9+/-10.8; Placebo: 67.8+/-11.9. Gender (M:F): 21/180. Ethnicity: not applicable
Further population details	1. Anaemia at baseline: 2. Cardiovascular disease: Not applicable / Not stated / Unclear 3. Hb level at baseline: Not applicable / Not stated / Unclear (Epoetin alfa 40,000: 126.1 +/-7.6; Epoetin alfa 20,000: 125.1+/-8.8; Placebo: 125.7+/-7.0 g/litre. Data related to population (males and females together) and not subgrouped). 4. Respiratory disease: Not applicable / Not stated / Unclear 5. Type of surgery :
Indirectness of population	No indirectness
Interventions	(n=46) Intervention 1: Erythropoietin - Erythropoietin (alfa). 40,000 U - 4 doses starting 4 weeks pre-operatively. Duration 4 weeks. Concurrent medication/care: Oral iron (150 mg 3x/day) started at least 42 days pre-operatively and continued until hospital discharge (Niferex-150 - Schwarz Pharma, Mequon, Wisconsin). Further details: 1. Dosage : Not applicable / Not stated / Unclear (40,000 U - 4 doses starting 4 weeks pre-operatively). 2. Duration of treatment: Once a week (Erythropoietin) 3. Hb trigger/threshold for transfusion: Not applicable / Not stated / Unclear (Usual policy in Canada is not to perform transfusion in asymptomatic patients on the basis of a specific threshold). 4. The use of transfusion protocol: The use of transfusion protocol -Pre-defined cutoff points (Transfusion performed according to usual practice of attending surgeons and anaesthesiologists. Usual policy in Canada is not to perform transfusion in asymptomatic patients. No other criteria established for transfusion.). Comments: Study drug withheld if haemoglobin concentration >=150 g/litre, systolic blood pressure >=200 mHg, or diastolic blood pressure >=105 mHg (n=86) Intervention 2: Erythropoietin - Erythropoietin (alfa). 20,000 U - 4 doses starting 4 weeks pre-operatively. Duration 4 weeks. Concurrent medication/care: Oral iron (150 mg 3x/day) started at least 42 days pre-operatively and continued until hospital discharge (Niferex-150 - Schwarz Pharma, Mequon, Wisconsin). Further details: 1. Dosage : Not applicable / Not stated / Unclear (20,000 U - 4 doses starting 4 weeks pre-operatively). 2. Duration of treatment: Once a week (Erythropoietin) 3. Hb trigger/threshold for transfusion: Not applicable / Not stated / Unclear (Usual policy in Canada is not to perform transfusion in asymptomatic patients on the basis of a specific threshold). 4. The use of transfusion protocol: The use of transfusion protocol -Pre-defined cutoff points (Transfusion performed according to usual practice of attending surgeons and anaesthesiologists. Usual policy in Canada is not to perform transfusion in asymptomatic patients. No other criteria established for transfusion.). Comments: Study drug withheld if haemoglobin concentration >=150 g/litre, systolic blood pressure >=200 mHg, or diastolic blood pressure >=105 mHg (n=82) Intervention 3: Placebo. Placebo . Duration 4 weeks. Concurrent medication/care: Oral iron (150 mg 3x/day) started at least 42 days pre-operatively and continued until hospital discharge (Niferex-150 - Schwarz Pharma, Mequon,

	Wisconsin). Further details: Hb trigger/threshold for transfusion: Not applicable / Not stated / Unclear (Usual policy in Canada is not to perform transfusion in asymptomatic patients on the basis of a specific threshold). 4. The use of transfusion protocol : The use of transfusion protocol -Pre-defined cutoff points (Transfusion performed according to usual practice of attending surgeons and anaesthesiologists. Usual policy in Canada is not to perform transfusion in asymptomatic patients. No other criteria established for transfusion.). Comments: Study drug withheld if haemoglobin concentration >=150 g/litre, systolic blood pressure >=200 mHg, or diastolic blood pressure >=105 mHg
Funding	Study funded by industry (Sponsored by Janssen-Ortho Inc. Two of the authors are employed by Janssen-Ortho Inc, manufacturer of epoetin alfa and own shares in the company.)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (ALFA) HIGH DOSE VERSUS ERYTHROPOIETIN (ALFA) LOW DOSE

Protocol outcome 1: Number of units transfused at end of follow-up
- Actual outcome: Units of blood transfused at not reported; Group 1: mean 0.3 (SD 0.7); n=44, Group 2: mean 0.4 (SD 0.9); n=79; Risk of bias: Unclear; Indirectness of outcome: No indirectness
- Actual outcome for Post-operative: Units of blood transfused at not reported; Group 1: mean 0.1 (SD 0.3); n=44, Group 2: mean 0.1 (SD 0.4); n=79; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of patients needing transfusions at end of follow-up
- Actual outcome: Number of patients who received a blood transfusion at not reported; Group 1: 5/44, Group 2: 18/79; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 3: Thrombosis at end of follow-up
- Actual outcome: Any deep vein thrombosis or pulmonary embolism diagnosed by duplex ultrasonography at not reported; Group 1: 2/44, Group 2: 5/79; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (ALFA) HIGH DOSE VERSUS PLACEBO

Protocol outcome 1: Number of units transfused at end of follow-up
- Actual outcome: Units of blood transfused at not reported; Group 1: mean 0.3 (SD 0.7); n=44, Group 2: mean 1 (SD 1.2); n=78; Risk of bias: Unclear; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of patients needing transfusions at end of follow-up

- Actual outcome: Number of patients who received a blood transfusion at not reported; Group 1: 5/44, Group 2: 35/78; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Thrombosis at end of follow-up - Actual outcome: Any deep vein thrombosis or pulmonary embolism diagnosed by duplex ultrasonography at not reported; Group 1: 2/44, Group 2: 6/78; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (ALFA) LOW DOSE VERSUS PLACEBO Protocol outcome 1: Number of units transfused at end of follow-up - Actual outcome: Units of blood transfused at not reported; Group 1: mean 0.4 (SD 0.9); n=79, Group 2: mean 1 (SD 1.2); n=78; Risk of bias: Unclear; Indirectness of outcome: No indirectness - Actual outcome for Intra operative: Units of blood transfused at during surgery; Group 1: mean 0.1 (SD 0.4); n=79, Group 2: mean 0.1 (SD 0.4); n=78; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients who received a blood transfusion at not reported; Group 1: 18/79, Group 2: 35/78; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 3: Thrombosis at end of follow-up - Actual outcome: Any deep vein thrombosis or pulmonary embolism diagnosed by duplex ultrasonography at not reported; Group 1: 5/79, Group 2: 6/78; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Length of hospital stay at end of follow-up

Study	**Garrido-martin 2012[63]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=210)
Countries and setting	Conducted in Spain; Setting: Secondary care

Line of therapy	1st line
Duration of study	Intervention + follow up: One month (approximately)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Haematocrit levels and blood transfusion following protocol
Stratum	Overall: Cardiac surgery
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients older than 18 years of age, elective cardiac surgery under extracorporeal circulation (EC), without previous anaemia, susceptible to treatment, without pre-operative blood transfusion, able to complete all study visits per protocol and providing written informed consent.
Exclusion criteria	Elective cardiac surgery patients without EC, treatment with fibrinolytic therapy 48 hours before CPB surgery, history of impaired renal function (creatinine clearance <50 ml/min), previous surgery for active endocarditis, redo-surgery patients, pregnant or lactating, signs of active gastrointestinal bleeding, vitamin B12 deficit, ferropenic anaemia, clinical history of asthma or allergy, active infection, included in another clinical study, hepatic disease, history of allergy to iron, unlikely to adhere to protocol follow up, unable to comply with the study protocol
Age, gender and ethnicity	Age - Mean (SD): IV iron: 65(11), Oral iron: 65(10), Placebo: 65(12). Gender (M:F): Define. Ethnicity: Not reported
Further population details	Type of surgery : cardiac surgery
Indirectness of population	No indirectness
Interventions	(n=71) Intervention 1: IV iron. Intravenous iron (III)-hydroxide sucrose complex (Venofer; Uriach Lab.)- 3 doses of 100 mg of intravenous iron/24 hours (in 200 ml of isotonic saline injected slowly over 1 hour) during pre-and post-operative hospitalisation+ 1 pill/24 hours of oral placebo during the same period and during 1 month after discharge. Duration During hospitalisation (pre-and post-operative period). Concurrent medication/care: None Further details: 1. Dosage : Not applicable / Not stated / Unclear (3 doses of 100 mg of intravenous iron/24 hours (in 200 ml of isotonic saline injected slowly over 1 hour)). 2. Duration of treatment: 3 doses of 100 mg of intravenous iron/24 hours during pre-and post-operative period. 3. Hb trigger/threshold for transfusion: Hb threshold <8g/dl (Hb level < 8 g/dl in coronary patients and <7 g/dl in valve surgery patients). 4. The use of transfusion protocol -Pre-defined cutoff points (Hb level < 8 g/dl in coronary patients and <7 g/dl in valve surgery patients). (n=73) Intervention 2: Oral iron. Ferrous fumarate iron- 105 mg of iron- 1 pill/24 hours orally pre-and post-operatively and during one month after discharge +intravenous placebo while hospitalised. Duration Pre and post-operatively and for one month after discharge. Concurrent medication/care: None Further details: 1. Dosage : Not applicable / Not stated / Unclear (Ferrous fumarate iron- 105 mg of iron- 1 pill/24 hours

	orally). 2. Duration of treatment: 4-6 weeks (oral iron) (pre- and post-operatively and for one month after discharge). 3. Hb trigger/threshold for transfusion: Hb threshold <8g/dl (Hb<8g/dl for coronary patients and Hb < 7g/dl in valve surgery patients). 4. The use of transfusion protocol : Pre-defined cutoff points (Hb<8g/dl for coronary patients and Hb < 7g/dl in valve surgery patients). (n=66) Intervention 3: Placebo. Oral and intravenous placebo given pre and post operatively (during hospitalisation). Duration Pre and post operatively. Concurrent medication/care: None Further details: 1. Dosage : Not applicable / Not stated / Unclear 2. Duration of treatment: Not applicable / Not stated / Unclear 3. Hb trigger/threshold for transfusion: Hb threshold <8g/dl (Hb<8g/dl for coronary patients and Hb < 7g/dl in valve surgery patients). 4. The use of transfusion protocol : The use of transfusion protocol -Pre-defined cutoff points (Hb<8g/dl for coronary patients and Hb < 7g/dl in valve surgery patients).
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IRON (3 DOSES OF 100 mg IV IRON DAILY DURING PRE-AND POST-OPERATIVE HOSPITALISATION) VERSUS PLACEBO Protocol outcome 1: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients transfused at end of follow up; Group 1: 20/54, Group 2: 26/52; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL IRON (FERROUS FUMARATE 105 MG DAILY FOR ONE MONTH POST-OPERATIVELY VERSUS IV IRON (3 DOSES OF 100 mG IV IRON DAILY DURING PRE-AND POST-OPERATIVE HOSPITALISATION) Protocol outcome 1: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients transfused at end of follow up; Group 1: 27/53, Group 2: 20/54; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL IRON (FERROUS FUMARATE 105 MG DAILY FOR ONE MONTH POST-OPERATIVELY VERSUS PLACEBO Protocol outcome 1: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients transfused at end of follow up; Group 1: 27/53, Group 2: 26/52; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and

	septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Number of units transfused at end of follow-up

Study	**Karkouti 2006[77]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=38)
Countries and setting	Conducted in Canada
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Haemoglobin concentration and clinical indication
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Open heart surgery, spinal fusion or total hip arthroplasty; Hb between 70 to 90 g/litre on post-operative day 1; aged >=18 years
Exclusion criteria	Pre-operative anaemia (Hb<120 g/litre in women and 140 g/litre in men); pre-operative autologous blood donation, IV iron or erythropoietin therapy; active infection; pregnancy or lactation; major comorbidities (previous history of stroke, transient ischemic attacks, or seizures; significant respiratory disease [FEV <50% predicted], renal disease [creatinine >200 micromol/litre] or liver disease [hepatitis, cirrhosis]; uncontrolled hypertension [systolic >180, diastolic > 100 mm Hg]); any haematological diseases (e.g. thromboembolic events, haemoglobinopathy, coagulopathy, or haemolytic disease); ongoing haemorrhage or evidence of organ dysfunction on post-operative day 1
Recruitment/selection of patients	Patients enrolled from October 2001 to September 2003
Age, gender and ethnicity	Age - Mean (SD): Erythropoietin + IV iron: 56 (15); IV iron: 62 (11); Placebo: 62 (5). Gender (M:F): 23/8. Ethnicity: not reported
Further population details	Type of surgery : cardiac surgery
Indirectness of population	No indirectness
Interventions	(n=12) Intervention 1: IV iron +Erythropoietin. Erythropoietin (Eprex). Doses: 300 U/kg IV + 300 U/kg SC on post-

	operative day 1; 600 U/kg SC on post-operative day 3 for a total of 1200 U/kg. ANDIV iron sucrose 200 mg (Venofer) on post-operative days 1,2 & 3 for a total of 600 mg. Preparation diluted in 200 ml of normal saline and given over 1 hour. . Duration 3 days. Concurrent medication/care: Oral iron (150 mg / day, polysaccharide-iron compound (Niferex) as soon as able to tolerate oral intake after surgery Further details: 1. Dosage : Not applicable / Not stated / Unclear 2. Duration of treatment: Not applicable / Not stated / Unclear (3 doses over 3 days post-operatively). 3. Hb trigger/threshold for transfusion: Not applicable / Not stated / Unclear (Hb level <70 g/litre or clinical indication for transfusion). 4. The use of transfusion protocol : The use of transfusion protocol -Pre-defined cutoff points (Hb level <70 g/litre or clinical indication for transfusion). Comments: IV solution draped with opaque cover and IV tubing covered by translucent tape. (n=13) Intervention 2: IV iron. IV iron sucrose 200 mg (Venofer) on post-operative days 1,2 & 3 for a total of 600 mg. Preparation diluted in 200 ml of normal saline and given over 1 hour. Duration 3 days. Concurrent medication/care: Oral iron (150 mg / day, polysaccharide-iron compound (Niferex) as soon as able to tolerate oral intake after surgery Further details: 1. Dosage : Not applicable / Not stated / Unclear 2. Duration of treatment: Not applicable / Not stated / Unclear (3 doses over 3 days post-operatively). 3. Hb trigger/threshold for transfusion: Not applicable / Not stated / Unclear (Hb level <70 g/litre or clinical indication for transfusion). 4. The use of transfusion protocol : The use of transfusion protocol -Pre-defined cutoff points (Hb level <70 g/litre or clinical indication for transfusion). Comments: IV solution draped with opaque cover and IV tubing covered by translucent tape. (n=13) Intervention 3: Placebo. IV and SC injections of normal saline. Duration 3 days. Concurrent medication/care: Oral iron (150 mg / day, polysaccharide-iron compound (Niferex) as soon as able to tolerate oral intake after surgery Further details: 1. Dosage : Not applicable / Not stated / Unclear 2. Duration of treatment: Not applicable / Not stated / Unclear (3 doses over 3 days post-operatively). 3. Hb trigger/threshold for transfusion: Not applicable / Not stated / Unclear (Hb level <70 g/litre or clinical indication for transfusion). 4. The use of transfusion protocol : The use of transfusion protocol -Pre-defined cutoff points (Hb level <70 g/litre or clinical indication for transfusion). Comments: IV solution draped with opaque cover and IV tubing covered by translucent tape.
Funding	Other (Physicians' Services Incorporated, Ontario Canada funded the study. Ortho Biotech donated recombinant erythropoietin.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IRON +ERYTHROPOIETIN VERSUS IV IRON Protocol outcome 1: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients receiving a transfusion at 42 days; Group 1: 2/10, Group 2: 2/11; Risk of bias: Very high; Indirectness of outcome: No indirectness	

Protocol outcome 2: Serious adverse events (as described in studies) at end of follow-up - Actual outcome: Serious adverse events (undefined) at 42 days; Group 1: 0/10, Group 2: 0/11; Risk of bias: Very high; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IRON +ERYTHROPOIETIN VERSUS PLACEBO Protocol outcome 1: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients receiving a transfusion at 42 days; Group 1: 2/10, Group 2: 2/11; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Serious adverse events (as described in studies) at end of follow-up - Actual outcome: Serious adverse events (undefined) at 42 days; Group 1: 0/10, Group 2: 0/10; Risk of bias: Very high; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IRON VERSUS PLACEBO Protocol outcome 1: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients receiving a transfusion at 42 days; Group 1: 2/11, Group 2: 4/10; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Serious adverse events (as described in studies) at end of follow-up - Actual outcome: Serious adverse events (undefined) at 42 days; Group 1: 0/11, Group 2: 0/10; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Number of units transfused at end of follow-up

Study	**Kateros 2010[78]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=79)
Countries and setting	Conducted in Greece; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with intertrochanteric fractures.
Exclusion criteria	Clinically significant systemic diseases or laboratory chemistry abnormalities such as primary haematologic diseases, history of seizure diseases, uncontrolled hypertension, recent gastrointestinal or intra cranial bleeding, or any contra indication to anti-coagulant use as Hb level higher than 13 g/dl.
Recruitment/selection of patients	Between December 2002 and January 2007, 256 patients were admitted with an intertrochanteric fracture. Of the 256 patients 118 patients were excluded because of clinically significant systemic diseases or laboratory chemistry abnormalities, which limited the use of epoetin alfa.
Age, gender and ethnicity	Age - Mean (range): 77.8 years (67-96 years). Gender (M:F): 21/58. Ethnicity: Not stated
Further population details	1. Anaemia at baseline: Anaemic at baseline 2. Cardiovascular disease: Not applicable / Not stated / Unclear 3. Hb level at baseline: Hb level 9 to 11 g/dl 4. Respiratory disease: Not applicable / Not stated / Unclear 5. Type of surgery : Orthopaedic surgery
Extra comments	Patients with intertrochanteric fractures. All fractures managed with sliding crew and plating. Mean time interval between day of admission and day of operation was 3.1 days (days 1-5 days). Pre-treatment Hb level of 10.2 g/dl (range 9.6-2.7 g/dl)
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: IV iron +Erythropoietin. 10 daily doses of 20,000 IU of epoetin alfa and 100 mg of parenteral iron from the day of admission. Duration 3.1 days (range 1-5 days). Concurrent medication/care: Not reported Further details: The use of transfusion protocol : Transfusion protocol +clinical need Comments: Patients with Hb lower than 9g/dl or in patients with any discomfort or pathologic signs from cardiovascular, central nervous or renal system related to anaemia were transfused with allogeneic blood. (n=41) Intervention 2: IV iron. Placebo+ 100 mg of parenteral iron daily from the day of admission. Duration 3 days (range 1-6 days). Concurrent medication/care: Not reported Further details: The use of transfusion protocol : Transfusion protocol +clinical need
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IRON +ERYTHROPOIETIN VERSUS IV IRON Protocol outcome 1: Serious adverse events (as described in studies) at end of follow-up - Actual outcome for Post-operative: Serious adverse events at end of follow-up; Group 1: 0/38, Group 2: 0/41; Risk of bias: High; Indirectness of outcome: No indirectness -Number of units of blood transfused, (No SD) EPO+IV iron : 1.5 (range 0-3) IV iron: 2.5 (range 1-4) Length of hospital stay, mean (no. SD) days Risk of bias: high; Indirectness of outcome: No indirectness EPO+IV iron : 6.7 days (range 5-10 days) IV iron: 6.9 days (range 5-10 days) Risk of bias: high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Bleeding at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Number of units transfused at end of follow-up

Study	**Kosmadakis 2003**[86]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=63)
Countries and setting	Conducted in Greece; Setting: Medical school

Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: Peri-operative erythropoietin administration
Subgroup analysis within study	Not applicable
Inclusion criteria	Diagnosis of non-metastatic gastrointestinal malignancy (stomach 15; colon 38; rectum 22), age between 40 and 90 years, and moderate anaemia (haemoglobin values 8.5-13 g/dl).
Exclusion criteria	Severe concomitant disease, history of thromboembolic disease, pregnancy, history of hepatic or kidney dysfunction, systemic haematologic disease and blood transfusions within 30 days before surgery, or haemoglobin values more than 13 or less than 8.5 g/dl.
Recruitment/selection of patients	Patients with no metastatic cancer of the gastrointestinal tract treated in the Athens medical school were included in the study
Age, gender and ethnicity	Age - Mean (SD): Study group: 67.1 (2.1); Control group: 66.4 (2). Gender (M:F): Study group: 15/16; Control group: 19/13. Ethnicity: not stated
Further population details	Hb level at baseline: Hb level >11 g/dl (Hb in study group: 10.6 (0.18) g/dl ; control group: 11.1 (0.19) g/dl) Type of surgery : Cancer surgery
Extra comments	Patients with gastrointestinal tract cancer and moderate anaemia. Hb in study group: 10.6 (0.18) g/dl ; control group: 11.1 (0.19) g/dl
Indirectness of population	No indirectness
Interventions	(n=31) Intervention 1: Erythropoietin - Erythropoietin (alfa). 300 iv/kg body weight Erythropoietin alfa subcutaneously each day. Duration 14 days pre-operatively, starting 7 days before the operation. Concurrent medication/care: All patients were given 100 mg iron intravenously. Further details: Hb trigger/threshold for transfusion: Hb threshold 8-10 g/dl (Indication for blood transfusion was a Hb value of 8.5 g/dl or less). The use of transfusion protocol : Pre-defined cutoff points (Indication for blood transfusion was a Hb value of 8.5 g/dl or less). (n=32) Intervention 2: Placebo. IV iron plus placebo . Duration 14 days pre-operatively, starting 7 days before the operation. Concurrent medication/care: All patients were given 100 mg iron intravenously.

	Comments: The indication for blood transfusion was a haemoglobin value of 8.5 g/dl or less.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (ALFA) VERSUS PLACEBO Protocol outcome 1: Number of units transfused at end of follow-up - Actual outcome: Number of blood units transfused at Not specified (intervention period-7 days pre-operatively and 7 days post-operatively); Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Length of hospital stay at end of follow-up - Actual outcome: Length of hospital stay at end of follow-up; Group 1: mean 10 days (SD 0.5); n=31, Group 2: mean 13 days (SD 0.9); n=32; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients transfused at Not specified (intervention period-7 days pre-op and 7 days post-op); Group 1: 10/31, Group 2: 28/32; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Thrombosis at end of follow-up - Actual outcome: Deep vein thrombosis at Not specified (intervention period-7 days pre-operatively and 7 days post-operatively); Group 1: 2/31, Group 2: 1/32; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Mortality (all causes) at 30 days

Study	**Larson 2001[87]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=32)
Countries and setting	Conducted in Denmark; Setting: Outpatient clinic

Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: Anaemic female patients scheduled for hysterectomy
Subgroup analysis within study	Not applicable
Inclusion criteria	Healthy women with Hb less than 12 g/dl.
Exclusion criteria	Not mentioned
Recruitment/selection of patients	Not mentioned
Age, gender and ethnicity	Age - Mean (SD): Group 1: 46 (1) years; Group 2 : 44 (1) years. Gender (M: F): All women. Ethnicity: Not stated
Further population details	1. Anaemia at baseline: 2. Cardiovascular disease: 3. Hb level at baseline: Hb level 9 to 11 g/dl (Group 1: Hb 9.8 (1.5); Group 2: Hb 10 (1.2)). 4. Respiratory disease: 5. Type of surgery :
Extra comments	No transfusion protocol.
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Oral iron + Erythropoietin. Erythropoietin beta 500 units twice a week + oral iron 100 mg bid (iron succinate). Duration Treatment was given 4 weeks prior to the surgery. Concurrent medication/care: None Further details: No transfusion protocol/ based on clinical judgment (n=16) Intervention 2: Oral iron. oral iron 100 mg bid (iron succinate). Duration: Treatment was given 4 weeks prior to the surgery. Concurrent medication/care: None
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL IRON + ERYTHROPOIETIN VERSUS ORAL IRON Protocol outcome 1: Number of units transfused at end of follow-up - Actual outcome: Number of units transfused at During surgery (4 weeks after treatment); Group 1: mean 0 (SD 0); n=15, Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Length of hospital stay at end of follow-up	

- Actual outcome: Length of hospital stay at end of follow-up ; Group 1: mean 6.4 (SD 2.4); n=15, Group 2: mean 8.1 (SD 7.1); n=16; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery - Actual outcome: Infections at During surgery (4 weeks after treatment); Group 1: 1/16, Group 2: 2/16; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients needing transfusions at During surgery (4 weeks after treatment); Group 1: 0/15, Group 2: 1/16; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (transfusion related) at 30 days ; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Mortality (all causes) at 30 days

Study	**Lidder 2007[92]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=45)
Countries and setting	Conducted in United Kingdom; Setting: Out-patient clinics and secondary care (hospital)
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Assessment of intra-operative haematocrit and transfusion based on protocol
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients diagnosed with colorectal cancer and fit for surgery.
Exclusion criteria	Not reported.

Recruitment/selection of patients	Not reported.
Age, gender and ethnicity	Age - Mean (range): Iron group: 69 (47-89); Non-iron group: 72 (57-80). Gender (M:F): Iron group: 14:8; Non-iron group: 14:9. Ethnicity: Not stated
Further population details	Type of surgery : cancer surgery
Extra comments	Greater proportion of anaemic patients in the non-iron group even after randomisation (Iron group: 6/24; Non-iron group: 14/25).No difference in haemoglobin concentration at recruitment between groups, however, there was a significant difference in haemoglobin concentration at admission between the two groups- Iron group: 13.1 g/dl, Non-iron group: 11.8 g/dl (p=0.04)
Indirectness of population	No indirectness
Interventions	(n=24) Intervention 1: Oral iron. Ferrous sulphate 200 mg thrice daily for 14 days (until surgery)Patients received blood transfusion according to a protocol. Duration 14 days. Concurrent medication/care: None Further details: 1. Dosage: Ferrous sulfate 200 mg -dried (oral iron) (Ferrous sulphate 200 mg thrice daily for 14 days). 2. Duration of treatment: 2-4 weeks (oral iron) (Median (range)=14 days(12-56)). 3. Hb trigger/threshold for transfusion: Hb threshold <8 g/dl (Hb level <8 g/dl OR if patients had abnormal ECG, ischaemic heart disease, obstructive lung disease, or were unable to absorb oral iron, transfusion given if Hb level 8-10 g/dl; also transfused at anaesthetists discretion). 4. The use of transfusion protocol : The use of transfusion protocol -Pre-defined cutoff points (Transfused in Hb level <8 g/dl or if patients had abnormal ECG, ischaemic heart disease, obstructive lung disease, or were unable to absorb oral iron, transfusion given if Hb level 8-10 g/dl; also transfused at anaesthetists discretion). (n=25) Intervention 2: No treatment. Standard treatment with no iron therapy. Duration 14 days. Concurrent medication/care: None Further details: Hb trigger/threshold for transfusion: Hb threshold <8 g/dl . The use of transfusion protocol : The use of transfusion protocol -Pre-defined cutoff points (Transfused in Hb level <8 g/dl or if patients had abnormal ECG, ischaemic heart disease, obstructive lung disease, or were unable to absorb oral iron, transfusion given if Hb level 8-10 g/dl).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL IRON (FERROUS SULPHATE 200 MG THRICE DAILY FOR 14 DAYS) VERSUS NO TREATMENT

Protocol outcome 1: Number of units transfused at end of follow-up
- Actual outcome: Median units transfused (range) at peri-operative period; Risk of bias: --; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients needing allogeneic transfusions at peri-operative period; Group 1: 6/24, Group 2: 13/25; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Length of hospital stay at end of follow-up

Study	**Madi-jebara 2004[96]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in Lebanon; Setting: Secondary care
Line of therapy	1st line
Duration of study	Follow up (post intervention):
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Haemoglobin levels post-operatively
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Elective cardiac surgery patients using cardiopulmonary bypass (American Society of Anaesthesiologists grade II or III) with a post-operative haemoglobin range between 7 and 10 g/dl
Exclusion criteria	Transfusion of allogeneic blood intra-operatively; unstable haemodynamic status post-operatively; ejection fraction <40%; pre-operative anaemia of any cause such as renal failure, hypothermic bypass, and contraindications for parental iron such as rheumatoid arthritis, history of allergic drug reactions to iron, haemosiderosis, and liver disease.
Recruitment/selection of patients	Recruited between August 1998 and December 1999. Not reported if consecutive patients.
Age, gender and ethnicity	Age - Mean (SD): r-HuEPO + IV iron: 57.55+/-10.07; IV iron: 55.3+/-9.48; Placebo: 59.18+/-9.12. Gender (M:F): Define. Ethnicity: not reported
Further population details	Type of surgery : cardiac surgery

Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: IV iron +Erythropoietin. recombinant-human erythropoietin (r-HuEPO) 300 U/kg given in 1 dose subcutaneously at day 1 and Iron III-hydroxide sucrose complex (IHSC) (Venofer), 200 mg/day parenteral starting day 1 to reach total iron deficit (TID) calculated as TID (mg)=2.4 x body weight (kg) x (target haemoglobin [Hb]-lowest Hb) g/dl. Target Hb level fixed at 12 g/dl. . Duration not reported. Concurrent medication/care: none Further details: Hb trigger/threshold for transfusion: 7 g/dl The use of transfusion protocol: Pre-defined cutoff points (Only information reported states that if at any time during study the lowest Hb level <7 g/dl then patient was transfused and excluded from study.). (n=40) Intervention 2: IV iron. Iron III-hydroxide sucrose complex (IHSC) (Venofer), 200 mg/day parenteral starting day 1 to reach total iron deficit (TID) calculated as TID (mg)=2.4 x body weight (kg) x (target haemoglobin [Hb]-lowest Hb) g/dl. Target Hb level fixed at 12 g/dl. Placebo subcutaneous rHuEPO. Duration not reported. Concurrent medication/care: none Further details: Dosage : Iron sucrose (20 mg/ml) of iron (IV iron) . Hb trigger/threshold for transfusion: <7 g/dl The use of transfusion protocol : Pre-defined cutoff points (Only information reported states that if at any time during study the lowest Hb level <7 g/dl then patient was transfused and excluded from study). (n=40) Intervention 3: Placebo. Placebo IV iron and placebo subcutaneous rHuEPO. Duration not reported. Concurrent medication/care: none Further details: Hb trigger/threshold for transfusion: <7 g/dl. The use of transfusion protocol : Pre-defined cutoff points (Only information reported states that if at any time during study the lowest Hb level <7 g/dl then patient was transfused and excluded from study).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IRON +ERYTHROPOIETIN VERSUS IV IRON

Protocol outcome 1: Mortality (all causes) at 30 days
- Actual outcome: Mortality at 30 days; Group 1: 0/40, Group 2: 0/40; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of patients needing transfusions at end of follow-up
- Actual outcome: Number of patients transfused at 30 days; Group 1: 7/40, Group 2: 10/40; Risk of bias: High; Indirectness of outcome: No indirectness

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IRON +ERYTHROPOIETIN VERSUS PLACEBO

Protocol outcome 1: Mortality (all causes) at 30 days - Actual outcome: Mortality at 30 days; Group 1: 0/40, Group 2: 0/40; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients transfused at 30 days; Group 1: 7/40, Group 2: 9/40; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IRON VERSUS PLACEBO Protocol outcome 1: Mortality (all causes) at 30 days - Actual outcome: Mortality at 30 days; Group 1: 0/40, Group 2: 0/40; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients transfused at 30 days; Group 1: 10/40, Group 2: 9/40; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Number of units transfused at end of follow-up

Study	**Na 2011[114]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=113)
Countries and setting	Conducted in China; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Post-hoc subgroup analysis

Inclusion criteria	Hb level of more than 100 g/litre and either a serum ferritin level of less than 100 mg/ml or a ferritin level of between 100 and 300 ng/ml with a transferrin saturation of less than 20% on the mornings of the operation days.
Exclusion criteria	Haematologic disease, thromboembolic disease, hepatic or renal disease, coagulation disorder, infection, malignancy, anticoagulant therapy, hypersensitivity to iron sucrose or rHuEPO, PABD, the use of iron or rHuEPO, and a history of a blood transfusion within the previous 1 month.
Recruitment/selection of patients	Women of physical status I or II by the ASA selected.
Age, gender and ethnicity	Age - Mean (SD): Study group: 69.4 (4.1); control group: 67.9 (5.2). Gender (M:F): All women. Ethnicity: Not stated
Further population details	1. Anaemia at baseline: 2. Cardiovascular disease: 3. Hb level at baseline: Hb level >11 g/dl (Group 1: Hb 121 (13) g/litre; Group 2: Hb 121 (12) g/litre). 4. Respiratory disease: 5. Type of surgery :
Extra comments	Patients undergoing total knee replacement arthroplasty.
Indirectness of population	No indirectness
Interventions	(n=56) Intervention 1: IV iron +Erythropoietin. 200 mg of iron sucrose diluted with 100 ml of normal saline given intravenously over 1 hour and the 3000 IU of recombinant erythropoietin beta injected subcutaneously. Duration once during surgery and not more than 2 times in the post-operative period. Concurrent medication/care: none Further details: Hb trigger/threshold for transfusion: Hb threshold <8 g/dl (The RBC transfusion guideline was applied to all the participants independent of the group: 1 unit of RBCs when the Hb level was between 69 g/litre and 2 units of RBCs when the Hb level was between 50 and 59 g/litre). The use of transfusion protocol : Pre-defined cutoff points (The RBC transfusion guideline was applied to all the participants independent of the group: 1 unit of RBCs when the Hb level was between 69 g/litre and 2 units of RBCs when the Hb level was between 50 and 59 g/litre). Comments: The RBC transfusion guideline was applied to all the participants independent of the group: 1 unit of RBCs when the Hb level was between 69 g/litre and 2 units of RBCs when the Hb level was between 50 and 59 g/litre. (n=57) Intervention 2: No treatment. Duration same as the duration of intervention group. Concurrent medication/care: none
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IRON +ERYTHROPOIETIN VERSUS NO TREATMENT Protocol outcome 1: Number of units transfused at end of follow-up - Actual outcome: Number patients who received transfusion at 6 weeks post-operatively; Group 1: mean 0.2 (SD 0.5); n=54, Group 2: mean 0.8 (SD 0.8); n=54; Risk of bias: High; Indirectness of outcome: No indirectness	

Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome: Number patients who received transfusion at 6 weeks post-operatively; Group 1: 12/54, Group 2: 41/54; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Length of hospital stay at end of follow-up

Study	**Olijhoek 2001[121]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in Australia, Belgium, Germany, Italy, Netherlands; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged ≥18 years of age and scheduled for an elective orthopaedic surgery that was estimated to require 2 to 4 units (900 to 1800 ml) of blood.
Exclusion criteria	Patients were excluded for clinically significant systemic infections, or neoplastic disease, significant ongoing blood loss, laboratory abnormalities, androgen therapy within 1 month of study entry, history of drug or alcohol abuse within the past 2 years, or previous exposure to epoetin alfa.
Age, gender and ethnicity	Age - Mean (SD): 65.7 (13.4) years. Gender (M:F): 11/99. Ethnicity: Not stated
Further population details	1. Anaemia at baseline: Anaemic at baseline 2. Cardiovascular disease: No cardiovascular disease 3. Hb level at baseline: Hb level >11 g/dl 4. Respiratory disease: No respiratory disease 5. Type of surgery : Orthopaedic surgery

Extra comments	Each patient had pre-treatment Hb level ≥10 to ≤13 g/dl and was in generally good health.
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: Oral iron + IV iron + Erythropoietin. Epoetin alfa was administered subcutaneously on days 1 and 8 of the 14 day of the study; surgery was scheduled for day 15. IV iron saccharate (200 mg) was administered on days 1 and 8, and oral iron (200 mg) was given daily for 14 days beginning on day 1. If the Hb level was ≥15 g/dl before the second dose, epoetin alfa was withheld; however the iron supplement was administered. IV iron was administered before dosing with epoetin alfa or placebo. Duration EPO and IV iron on days 1 and 8 of the 14 day study. Oral iron was given daily for 14 days. Concurrent medication/care: Not reported Further details: The use of transfusion protocol: No transfusion protocol/ based on clinical judgment (n=52) Intervention 2: Oral iron + IV iron. Placebo was administered subcutaneously on days 1 and 8 of the 14 day of the study; surgery was scheduled for day 15. IV iron saccharate (200 mg) was administered on days 1 and 8, and oral iron (200 mg) was given daily for 14 days beginning on day 1. . Duration Placebo and IV iron on days 1 and 8 of the 14 day study. Oral iron was given daily for 14 days. Concurrent medication/care: Not reported Further details: The use of transfusion protocol : No transfusion protocol/ based on clinical judgment
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL IRON + IV IRON + ERYTHROPOIETIN VERSUS ORAL IRON + IV IRON Protocol outcome 1: Serious adverse events (as described in studies) at end of follow-up - Actual outcome for Post-operative: Serious adverse events at end of follow-up; Group 1: 0/48, Group 2: 1/52; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Thrombosis at end of follow-up - Actual outcome for Post-operative: Thrombotic events at end of follow-up; Group 1: 0/48, Group 2: 0/48; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Bleeding at end of follow-up; Mortality (all causes) at 1 year; Number of units transfused at end of follow-up

Study	Podesta 2000[128]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in Italy; Setting: Outpatient clinic and hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall: Pre-operative
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with valvular and coronary disease undergoing open heart surgery.
Exclusion criteria	Haematocrit more than 42%, age over 79, and pathologies like insulin dependent diabetes, untreated hypertension, severe peripheral vascular disease.
Recruitment/selection of patients	60 patients undergoing open heart surgery between Feb 1997 and May 1998 were selected for the study.
Age, gender and ethnicity	Age - Mean (SD): Group A: 61 (15); Group B: 72 (11). Gender (M:F): Group A: 24/6 ;Group B: 24/6. Ethnicity: Not stated
Further population details	1. Anaemia at baseline: 2. Cardiovascular disease: 3. Hb level at baseline: Hb level >11 g/dl (Group A: 14.2 (1.04) ; Group B: 13.9 (1.23)). 4. Respiratory disease: 5. Type of surgery : open heart surgery.
Extra comments	Hb at baseline [mean (SD)] - Group A: 14.2 (1.04) ; Group B: 13.9 (1.23). The 2 groups were comparable for gender, age, weight and blood values before treatment.
Indirectness of population	No
Interventions	(n=30) Intervention 1: Oral iron + Erythropoietin. 10,000 IU epoetin-alpha subcutaneously twice a week for 3 weeks. . Duration 3 weeks. Concurrent medication/care: All patients received pre-operatively 525 mg ferrous sulphate 3 times a day for 3 weeks. Further details: No transfusion protocol/ based on clinical judgment (n=30) Intervention 2: Oral iron. 525 mg ferrous sulphate pre-operatively 3 times a day for 3 weeks. Duration 3 weeks. Concurrent medication/care: All patients (in both the groups) received pre-operatively 525 mg ferrous sulphate 3 times a day for 3 weeks.

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL IRON + ERYTHROPOIETIN VERSUS ORAL IRON Protocol outcome 1: Number of units transfused at end of follow-up - Actual outcome: Number of blood units transfused at 7 days post-operatively; Group 1: mean 2 (SD 0); n=30, Group 2: mean 2.4 (SD 1.98); n=30; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Mortality (all causes) at 30 days - Actual outcome: Mortality (intra-operatively) at During surgery; Group 1: 1/30, Group 2: 0/0; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients needing transfusions at 7 days post-operatively; Group 1: 1/30, Group 2: 26/30; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Length of hospital stay at end of follow-up

Study	**Scott 2002[145]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=58)
Countries and setting	Conducted in USA; Setting: University of Iowa hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were required to be >18 years of age, have a pre-study Hb level >10 g/dl and <13.5 g/dl, have their surgical procedure scheduled at least 10 days from the date of potential study enrolment, and have provided informed consent.
Exclusion criteria	Primary haematologic disease seizure disorder, uncontrolled hypertension, recent history of thromboembolic disease (within 1 year), other clinically significant systemic disease, an active infectious process, pregnancy, ongoing blood loss, scheduled autologous blood donation or blood transfusion within the previous 30 days.
Recruitment/selection of patients	Patients scheduled for major head and neck oncologic surgery.
Age, gender and ethnicity	Age - Mean (SD): Epoetin alfa: 67.6 (11.01). Placebo: 61.8 (10.75). Gender (M:F): Epoetin alfa: 16/13. Placebo: 18/11. Ethnicity: NR
Further population details	1. Anaemia at baseline: 2. Cardiovascular disease: 3. Hb level at baseline: Hb level >11 g/dl (12.2 g/dl). 4. Respiratory disease: 5. Type of surgery : major head and neck oncologic surgery.
Extra comments	Haemoglobin (g/dl): Epoetin alfa - 12.2 (1.04); Placebo- 12.3 (1.15)
Indirectness of population	No indirectness of population
Interventions	(n=29) Intervention 1: Erythropoietin - Erythropoietin (alfa). Epoetin alfa 600 IU 3 doses. The initial dose was given between pre-operative days 10 and 19, the second dose was given between pre-operative days 6 and 12, and the final dose was given the day of surgery. Duration Maximum 19 days before surgery till the day of the surgery. Concurrent medication/care: All patients received oral iron supplementation (150 mg ferrous sulfate per day) beginning with the first dose of the study medication and continuing until the day of the surgery. Further details: Hb trigger/threshold for transfusion: Hb threshold 8-10 g/dl (Allogeneic blood transfusions were performed at the discretion of the attending surgeon; however an effort was made not to transfuse patients with Hb values >9 g/dl unless clinically indicated). The use of transfusion protocol: Pre-defined cut off points (Allogeneic blood transfusions were performed at the discretion of the attending surgeon; however an effort was made not to transfuse patients with Hb values >9 g/dl unless clinically indicated). Comments: Allogeneic blood transfusions were performed at the discretion of the attending surgeon; however an effort was made not to transfuse patients with Hb values >9 g/dl unless clinically indicated. (n=29) Intervention 2: Placebo. 3 doses of placebo medication. The initial dose was given between pre-operative days 10 and 19, the second dose was given between pre-operative days 6 and 12, and the final dose was given the day of surgery. Duration Maximum 19 days before surgery till the day of the surgery. Concurrent medication/care: All patients received oral iron supplementation (150 mg ferrous sulfate per day) beginning with the first dose of the study

	medication and continuing until the day of the surgery.
Funding	Study funded by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (ALFA) VERSUS PLACEBO Protocol outcome 1: Number of units transfused at end of follow-up - Actual outcome: Mean number of units transfused per patient for all patients requiring transfusion at 21 days post-operatively; Group 1: mean 3.16 (SD 2.87); n=29, Group 2: mean 4.12 (SD 2.86); n=29; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients transfused at 21 days post-operatively; Group 1: 19/29, Group 2: 24/29; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Serious adverse events (as described in studies) at end of follow-up - Actual outcome: Serious adverse events (thrombotic/vascular events) at 21 days post-operatively ; Group 1: 2/29, Group 2: 0/29; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Length of hospital stay at end of follow-up.

Study	**Serrano-Trenas 2011[147]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in Spain; Setting: Secondary care (Orthopaedic and trauma surgery unit of hospital)
Line of therapy	1st line
Duration of study	Intervention + follow up: One month
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Haematocrit levels

Stratum	Overall
Subgroup analysis within study	Not stratified but pre-specified: Analysis by Hb level at baseline
Inclusion criteria	Patients >65 years of age, undergoing hip fracture surgery between October 2006 and October 2008.
Exclusion criteria	Diseases diagnosed before admission of the patient (iron overload disorders, hypersensitivity to oral or parenteral iron preparations, asthma or other severe atopic conditions, active infection, neoplasm), treatment with clopidogrel or acetylsalicylic acid at dose rates greater than 150 mg/24 hours, no surgical indication for the current fracture, disorders of impaired coagulation (partial thromboplastin time>2.5%, international normalised ratio >1.5), liver disorders with elevated transaminases, chronic kidney failure patients on dialysis.
Recruitment/selection of patients	Consecutive patients admitted for surgery
Age, gender and ethnicity	Age - Mean (SD): IV iron: 83.46(7.11); No treatment: 82.53 (6.37). Gender (M:F): IV iron=20:79; No treatment= 20:77. Ethnicity: Not reported
Further population details	1. Anaemia at baseline: Anaemic at baseline (Mean Hb level 11.9 (79.4% female) and 12.1 g/dl (79.8% female)). 2. Cardiovascular disease: 3. Hb level at baseline: Hb level >11 g/dl (Patients with admission Hb level >12 g/dl (both males and females)). 4. Respiratory disease: 5. Type of surgery : Orthopaedic surgery
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: IV iron. Intravenous iron sucrose- 600 mg (Venofer, Vifor Frnace Company, Levallois-Perret, France) in 3 doses of 200 mg each at 48 hour intervals starting on day of admission; administration was by slow perfusion of two 100 mg ampoules diluted in 250 ml of 0.95 saline solution over a 90 minute period; first dos given on admission and always pre-operatively and following doses administered before or after surgery depending on time of surgery. Duration Pre- and post-operative period. Concurrent medication/care: Intervention was administered in addition to standard protocolised treatment (no treatment). Further details: 1. Dosage : Not applicable / Not stated / Unclear (Iron sucrose 600 mg (3 doses- each dose of 200 mg diluted in 250 ml 0.9% saline solution)). 2. Duration of treatment: Three times a week (IV iron) (200 mg dose given every 48 hours). 3. Hb trigger/threshold for transfusion: Hb threshold <8g/dl (Pre-operative haemoglobin level of less than 10 g/dl, post-operative Hb level of less than 8 g/dl or less than 9 g/dl in patients with a history of cardiorespiratory conditions or any Hb level in patients with symptoms of untreated anaemia). 4. The use of transfusion protocol : Pre-defined cutoff points (Pre-operative haemoglobin level of less than 10 g/dl, post-operative Hb level of less than 8 g/dl or less than 9 g/dl in patients with a history of cardiorespiratory conditions or any Hb level in patients with symptoms of untreated anaemia). (n=100) Intervention 2: No treatment. Standard protocolised treatment. Duration Pre- and post-operative period of

	hospitalisation. Concurrent medication/care: None
Funding	Academic or government funding (Spanish Ministry of Health and Consumer Affairs)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IRON VERSUS NO TREATMENT Protocol outcome 1: Length of hospital stay at end of follow-up - Actual outcome: Total length of hospital stay at Follow up period ; Group 1: mean 13.5 Days (SD 7.1); n=100, Group 2: mean 12.9 Days (SD 6.9); n=100; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Mortality (all causes) at 30 days - Actual outcome: Mortality at During follow up period (within 30 days); Group 1: 11/100, Group 2: 10/100; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery - Actual outcome: Infections at Follow up period ; Group 1: 16/100, Group 2: 13/100; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients receiving transfusions at Intra and post-operative period ; Group 1: 33/100, Group 2: 41/100; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (transfusion related) at 30 days; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Number of units transfused at end of follow-up

Study	**Sowade 1997[159]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=76)
Countries and setting	Conducted in Germany
Line of therapy	1st line

Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Hb/Hct levels and clinical need
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Elective open-heart surgery with contraindications for autologous blood donations; aged 18 to 80 years
Exclusion criteria	Diastolic blood pressure >100 mm Hg; haematocrit (Hct) >0.45; convulsions or epilepsy; platelet count >450 x 10 to the power of 9 /litre; malignant tumour; acute infections; pregnancy; lactation; inadequate contraception.
Age, gender and ethnicity	Age - Mean (SD): Epoetin Beta: 54.3+/-8.6; Placebo: 57.0+/-8.8. Gender (M:F): 56/16. Ethnicity: not reported
Further population details	1. Anaemia at baseline: 2. Cardiovascular disease: No cardiovascular disease (elective cardiac surgery). 3. Hb level at baseline: Not applicable / Not stated / Unclear (Epoetin Beta: 14.31+/-0.98; Placebo: 13.78+/-1.03). 4. Respiratory disease: Not applicable / Not stated / Unclear 5. Type of surgery : cardiac surgery
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Erythropoietin - Erythropoietin (beta). IV Epoetin Beta, 500 U/kg body weight administered on pre-operative days 14, 10, 7, 5 and 2. Duration 14 days. Concurrent medication/care: Iron: 300 mg /day oral iron-glycine-sulfate Further details: 1. Dosage : Epoetin beta (Erythropoietin) NeoRecormon 2. Duration of treatment: Two times a week (Erythropoietin) (5 doses over 14 days). 3. Hb trigger/threshold for transfusion: Not applicable / Not stated / Unclear (Intra-operatively: Hb <6.9 g/dl or Hct <0.21; Post-operatively: Hb <8.5 g/dl or Hct <0.26). 4. The use of transfusion protocol : Pre-defined cut-off points (Thresholds above and clinical need in accordance with severity of heart disease). Comments: Trial medication not administered if: Hct >0.50, increase in Hct >0.6 over baseline; platelet count >500 x 10 to the power of 9 g/litre; adverse events rendering continuation of treatment unacceptable from a medical point of view; diastolic blood pressure >110 mm Hg; convulsion. (n=38) Intervention 2: Placebo. IV placebo, 500 U/kg body weight administered on pre-operative days 14, 10, 7, 5 and 2. Duration 14 days. Concurrent medication/care: Iron: 300 mg /day oral iron-glycine-sulfate Further details:. Duration of treatment: Two times a week (Erythropoietin) (5 doses over 14 days). Hb trigger/threshold for transfusion: Hb threshold <8g/dl (Intra-operatively: Hb <6.9 g/dl or Hct <0.21; Post-operatively: Hb <8.5 g/dl or Hct <0.26). 4. The use of transfusion protocol: Pre-defined cutoff points (Thresholds above and clinical need in accordance with severity of heart disease). Comments: Trial medication not administered if: Hct >0.50, increase in Hct >0.6 over baseline; platelet count >500 x 10 to the power of 9 g /litre; adverse events rendering continuation of treatment unacceptable from a medical point of

	view; diastolic blood pressure >110 mm Hg; convulsion.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (BETA) VERSUS PLACEBO Protocol outcome 1: Mortality (all causes) at 30 days - Actual outcome: Mortality during study at 7 days post-operatively; Group 1: 4/38, Group 2: 4/38; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients receiving allogeneic blood transfusions at 7 days post-operatively; Group 1: 4/36, Group 2: 19/36; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Serious adverse events (as described in studies) at end of follow-up - Actual outcome: Serious adverse events reported as: mortality osteomyelitis, arterial bleeding, myocardial infarction, ventricular fibrillation, hypocoagulation at 7 days post-operatively; Group 1: 6/38, Group 2: 9/38; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (transfusion related) at 30 days ; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Number of units transfused at end of follow-up

Study	**Stowell 2009[164]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=680)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall

Subgroup analysis within study	Not applicable
Inclusion criteria	All adult patients >18 years scheduled for elective spinal surgery with at least 3 weeks lead time were eligible if the anticipated peri-operative blood loss was 2 to 4 U and haemoglobin was >10 to ≤13 g/dl.
Exclusion criteria	Patients were excluded if they had clinically significant systemic disease or laboratory chemistry abnormalities, primary haematologic disease, history of deep vein thrombosis or pulmonary embolism, history of seizure disorder, uncontrolled hypertension, or recent gastrointestinal or intracranial bleeding. Patients were also excluded if they were scheduled to receive peri-operative pharmacologic anti-coagulation.
Recruitment/selection of patients	The study was conducted in 80 centres in the USA between April 1998 and May 2006.
Age, gender and ethnicity	Age - Mean (SD): 59.8 (14.24) years. Gender (M:F): 78/601 - 1 unknown. Ethnicity: Not stated
Further population details	1. Anaemia at baseline: Not anaemic at baseline 2. Cardiovascular disease: No cardiovascular disease 3. Hb level at baseline: Hb level >11 g/dl 4. Respiratory disease: No respiratory disease 5. Type of surgery: Orthopaedic surgery (Elective spinal surgery).
Extra comments	Baseline Haemoglobin 12.2 (0.80) g/dl
Indirectness of population	No
Interventions	(n=340) Intervention 1: Oral iron + Erythropoietin. Patients received epoetin alfa 600 micrograms/kg administered subcutaneously once weekly x 4 doses (days -21, -14, -7, and 0) plus standard care of treatment. All patients received oral iron from day -21 to day 0. Duration 21 days prior to surgery. Concurrent medication/care: Not stated Further details:. The use of transfusion protocol : Not applicable / Not stated / Unclear Comments: No pre-operative autologous blood donation was permitted after the first dose of epoetin alfa. (n=340) Intervention 2: Oral iron. Patients received oral iron from day -21 to day 0. . Duration 21 days prior to surgery. Concurrent medication/care: Not stated
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ORAL IRON + ERYTHROPOIETIN VERSUS ORAL IRON

Protocol outcome 1: Mortality (all causes) at 30 days
- Actual outcome for Post-operative: Serious adverse events (wound infection) at 30 days after surgery; Group 1: 1/340, Group 2: 2/340; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Serious adverse events (as described in studies) at end of follow-up - Actual outcome for Post-operative: Serious adverse events (wound infection) at 30 days after surgery; Group 1: 4/340, Group 2: 1/340; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Thrombosis at end of follow-up - Actual outcome for Post-operative: Deep vein thrombosis at 30 days after surgery; Group 1: 16/340, Group 2: 7/340; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Post-operative: Other thrombovascular events at 30 days after surgery; Group 1: 12/340, Group 2: 7/340; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (transfusion related) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Bleeding at end of follow-up; Mortality (all causes) at 1 year; Number of units transfused at end of follow-up.

Study	**Weltert 2010[185]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=320)
Countries and setting	Conducted in Italy
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients with a diagnosis of isolated coronary vessel disease
Exclusion criteria	Presence of high Hb values (>14.5 g/dl), confirmed renal impairment (creatinine >2 mg/dl), or the need for on-pump revascularisation.
Recruitment/selection of patients	All patients with a diagnosis of isolated coronary vessel disease at the European Hospital were considered for the study

Age, gender and ethnicity	Age - Mean (SD): HRE: 66.9 (9.11) years; control: 66.4 (10.8). Gender (M:F): Males- 84% in HRE group and 83% in the control group . Ethnicity: Not stated
Further population details	1. Anaemia at baseline: Not applicable / Not stated / Unclear 2. Cardiovascular disease: Cardiovascular disease 3. Hb level at baseline: Hb level >11 g/dl 4. Respiratory disease: No respiratory disease 5. Type of surgery : Cardiovascular surgery
Extra comments	Baseline Hb: Recombinant human erythropoietin (HRE): 13.18±1.21 g/dl and control group: 13.44±1.20
Indirectness of population	No indirectness
Interventions	(n=158) Intervention 1: Erythropoietin - Erythropoietin (alfa). Patients received 14,000 IU via subcutaneous administration 2 days before the operation, 14,000 IU on the next day, 8000 IU on the morning of the operation, 8000 IU day after the operation, and 8000 IU on post-operative day 2. . Duration 2 days before the operation to 2 days post-operatively. Concurrent medication/care: Not stated Further details: Duration of treatment: Once a week (Erythropoietin) 3. Hb trigger/threshold for transfusion: Hb threshold 8-10 g/dl . The use of transfusion protocol : Pre-defined cut-off points Comments: Transfusion need was triggered by Hb levels less than 8g/dl for both the groups. (n=162) Intervention 2: No treatment. The control group received no treatment. Duration No treatment. Concurrent medication/care: Not stated Further details: Hb trigger/threshold for transfusion: Hb threshold 8-10 g/dl. The use of transfusion protocol : The use of transfusion protocol -Pre-defined cut-off points
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (ALFA) VERSUS NO TREATMENT

Protocol outcome 1: Mortality (all causes) at 30 days
- Actual outcome for Post-operative: Mortality (45 days) at end of follow-up ; Group 1: 3/158, Group 2: 3/162; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery
- Actual outcome for Post-operative: Infections (Pneumonia) at end of follow-up ; Group 1: 0/158, Group 2: 0/162; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Number of patients needing transfusions at end of follow-up
- Actual outcome for Post-operative: Patients transfused in ICU at end of follow-up ; Group 1: 35/158, Group 2: 59/162; Risk of bias: Low; Indirectness of outcome: No

indirectness Protocol outcome 4: Thrombosis at end of follow-up - Actual outcome for Post-operative: Deep vein thrombosis at end of follow-up ; Group 1: 0/158, Group 2: 1/162; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (transfusion related) at 30 days ; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Number of units transfused at end of follow-up

Study	**Wurnig 2001[188]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=194)
Countries and setting	Conducted in Austria, France, Portugal, Sweden; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with haematocrit value <42%, not eligible for autologous blood donation, scheduled for elective surgery where blood loss was expected to be >1 litre and the resulting RBC transfusion requirement would be 2-3 U.
Exclusion criteria	Patients with haematocrit <30%, uncontrolled diastolic hypertension (>110 mm Hg), epilepsy, chronic inflammatory disease, thrombocytosis, malignancy, acute infection, renal insufficiency, vitamin B12 or folic acid deficiency, a serum ferritin level <20 ng/ml, hypersensitivity to epoetin beta, or had been administered any other investigational drug in the previous 30 days. In addition women were excluded from the study if pregnant, lactating or if considered to be using unreliable methods of contraception.
Recruitment/selection of patients	Adult patients not eligible for autologous blood donation and scheduled for elective surgery (mainly orthopaedic or cardiac procedures).

Age, gender and ethnicity	Age - Other: Group 1: 62.5 years; Group 2: 66 years; Group 3: 62 years. Gender (M:F): Group 1 : 14/56; Group 2: 20/44; Group 3: 23/37. Ethnicity: NR
Further population details	1. Anaemia at baseline: 2. Cardiovascular disease: 3. Hb level at baseline: Hb level >11 g/dl (Hb 13.5 (group 1); Hb 13.2 (group 2); Hb 12.7 (group 3)). 4. Respiratory disease: 5. Type of surgery : orthopaedic or cardiac
Indirectness of population	Not applicable
Interventions	(n=70) Intervention 1: Erythropoietin - Erythropoietin (beta). Epoetin beta dose 50,000 and 100,000 IU, 125 IU/kg once weekly. . Duration Pre-operative treatment phase of 3-4 weeks. Concurrent medication/care: All patients received concomitant oral iron supplementation (200-300 mg elemental iron/day) Further details: 1. Dosage : 2. Duration of treatment: 3. Hb trigger/threshold for transfusion: Hb threshold 8-10 g/dl (A haemoglobin value of 8.5 g/dl was regarded as the intervention threshold). 4. The use of transfusion protocol : Transfusion protocol +clinical need (Intra and post-operative RBC transfusions were administered at the discretion of the treating physician (anaesthesiologist or surgeon) upon clinical indication. A haemoglobin value of 8.5 g/dl was regarded as the intervention threshold). Comments: Intra and post-operative RBC transfusions were administered at the discretion of the treating physician (anaesthesiologist or surgeon) upon clinical indication. A haemoglobin value of 8.5 g/dl was regarded as the intervention threshold. (n=64) Intervention 2: Erythropoietin - Erythropoietin (beta). Epoetin beta dose 50,000 and 100,000 IU, 250 IU/kg once weekly. Duration Pre-operative treatment phase of 3-4 weeks. Concurrent medication/care: All patients received concomitant oral iron supplementation (200-300 mg elemental iron/day) (n=60) Intervention 3: Placebo. Placebo. Duration Pre-operative treatment phase of 3-4 weeks. Concurrent medication/care: All patients received concomitant oral iron supplementation (200-300 mg elemental iron/day)
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (LOW DOSE) VERSUS ERYTHROPOIETIN (HIGH DOSE)

Protocol outcome 1: Mortality (all causes) at 30 days
- Actual outcome: Mortality at 10 days after study completion; Group 1: 0/65, Group 2: 0/59; Risk of bias: Very high; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of patients needing transfusions at end of follow-up

- Actual outcome: Number of patients transfused at 6 days post-operatively; Group 1: 19/65, Group 2: 22/59; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Thrombosis at end of follow-up - Actual outcome: Deep vein thrombosis at 6 days post-operatively; Group 1: 2/65, Group 2: 2/59; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (LOW DOSE) VERSUS PLACEBO Protocol outcome 1: Mortality (all causes) at 30 days - Actual outcome: Mortality at 10 days after study completion; Group 1: 0/65, Group 2: 1/60; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients transfused at 6 days post-operatively; Group 1: 19/65, Group 2: 28/51; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Thrombosis at end of follow-up - Actual outcome: Deep vein thrombosis at 6 days post-operatively; Group 1: 2/65, Group 2: 0/60; Risk of bias: High; Indirectness of outcome: No indirectness RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ERYTHROPOIETIN (HIGH DOSE) VERSUS PLACEBO Protocol outcome 1: Mortality (all causes) at 30 days - Actual outcome: Mortality at 10 days after study completion; Group 1: 0/59, Group 2: 1/60; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients transfused at 6 days post-operatively; Group 1: 22/59, Group 2: 28/51; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Thrombosis at end of follow-up - Actual outcome: Deep vein thrombosis at 6 days post-operatively; Group 1: 2/59, Group 2: 0/60; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (transfusion related) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Number of units transfused at end of follow-up.

Study	**Yoo 2011[190]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=74)
Countries and setting	Conducted in South Korea
Line of therapy	1st line
Duration of study	Intervention time: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Haemoglobin concentrations
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Valvular heart surgery patients with pre-operative anaemia (Hb concentration < 12 g/dl in women and < 13 g/dl in men)
Exclusion criteria	Pre-existing uncontrolled hypertension (diastolic blood pressure more than 100 mmHg); platelet count more than 450,000/mm^3; history of thromboembolism, seizure, malignant disease, liver dysfunction, confirmed renal impairment (serum creatinine [Cr] >2 mg/dl), aplastic or iron deficiency anaemia and/or acute hyperparathyroidism; hypersensitivity to iron therapy
Recruitment/selection of patients	Yonsei University Health System, Seoul between April 2009 and April 2010
Age, gender and ethnicity	Age - Mean (SD): rHuEPO: 56 (12); Placebo: 59 (12). Gender (M:F): 27/47. Ethnicity: not reported
Further population details	Type of surgery : cardiac surgery
Indirectness of population	No indirectness
Interventions	(n=37) Intervention 1: IV iron +Erythropoietin. Recombinant human erythropoietin (rHuEPO) 50 IU/kg (Epocain prefilled) via intravenous bolus AND200 mg IV iron sucrose (Venoferrum) mixed with 100 ml saline all administered at the same time over 1 hour. Duration 1 dose 16 to 24 hours pre-operatively. Concurrent medication/care: none Further details: Hb trigger/threshold for transfusion: <7 mg/dl during surgery and <8 mg/dl after surgery. The use of transfusion protocol : Pre-defined cut-off points (n=37) Intervention 2: Placebo. Equivalent volume of normal saline. Duration 1 dose 16 to 24 hours pre-operatively. Concurrent medication/care: none Further details: Hb trigger/threshold for transfusion: 7 mg/dl during surgery and <8 mg/dl after surgery). The use of transfusion protocol : Pre-defined cut-off points

Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: IV IRON +ERYTHROPOIETIN VERSUS PLACEBO Protocol outcome 1: Number of units transfused at end of follow-up - Actual outcome: Number of units per patient transfused with erythrocyte during surgery at Peri-operatively (surgery and the 4 post-operative days combined); Group 1: mean 1 (SD 1.1); n=37, Group 2: mean 3.3 (SD 2.2); n=37; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Length of hospital stay at end of follow-up - Actual outcome: Duration of hospital stay at not applicable; Group 1: mean 11.3 (SD 4.1); n=37, Group 2: mean 13.5 (SD 8); n=37; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Mortality (all causes) at 30 days - Actual outcome: Mortality at 30 days; Group 1: 0/37, Group 2: 1/37; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Number of patients needing transfusions at end of follow-up - Actual outcome: Number of patients transfused with erythrocyte at Peri-operatively (surgery and the 4 post-operative days combined); Group 1: 22/37, Group 2: 32/37; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Bleeding at end of follow-up; Serious adverse events (as described in studies) at end of follow-up; Mortality (all causes) at 1 year; Thrombosis at end of follow-up; Mortality (transfusion related) at 30 days.

H.2 Alternatives to blood transfusion

Study	**Abdelameen 2013**
Study type	RCT
Number of studies (number of participants)	n=1 (n=740)

Countries and setting	Conducted in Egypt; Setting: Women's Health Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Pregnant women with singleton foetus at ≤37 weeks gestation were eligible for the study.
Exclusion criteria	Women were considered ineligible if they had any of the following: history of medical disorders, pre-eclampsia, antepartum haemorrhage, history of thromboembolic disorders, polyhydramnios, macrosomia, history of sensitivity to TXA and patients taking anti-coagulant therapy.
Recruitment/selection of patients	All pregnant women who were scheduled to have elective caesarean section (CS) were approached for possible inclusion in the study.
Age, gender and ethnicity	TXA (n=373) Control (n=367) Age (years) 26.34 (5.16) 26.62 (5.05) All females
Further population details	Type of surgery: elective caesarean section (CS) TXA (n=373) Control (n=367) Gestational age (weeks) 39.32 (1.15) 39.31 (1.17) Proportion of women with anaemia (Hb <11g/dl) 205 (55%) 239 (65.1%) There were no significant differences both groups regard to parity, gestational age, type of anaesthesia and mean birth weight.
Indirectness of population	No indirectness
Interventions	TXA (n=373) Patients received TXA 1 g, given slowly intravenously over 10 minutes before the operation commenced. TXA injection was prepared by diluting 1 g (10 ml) TXA with 20 ml of 5% glucose.

	Control group (n=367) No TXA. The control group did received nothing.
Funding	Not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS CONTROL Length of stay in hospital (days) TXA:2±0.52 days control: 2±0.54 days Risk of bias: low; Indirectness of outcome: No indirectness Thromboembolic events TXA:0/373 control:0/367 Risk of bias: low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Infections, Number of patients needing transfusions, Number of units of allogeneic blood transfused / volume of allogeneic blood transfused (in ml), Serious adverse events (as defined by study)

Study	**Aghdaii 2012**[5]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)

Countries and setting	Conducted in Iran
Line of therapy	Not applicable
Duration of study	Intervention +Follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Primary, elective on-pump CABG surgery; age between 30 and 70 years; left ventricular ejection fraction >=45%; pump time <2 hours; aortic clumping time <45 minutes.
Exclusion criteria	Known coagulation disorders; redo or emergency surgery; patients on warfarin, heparin or other systemic anticoagulant drugs and antiplatelet drugs such as aspirin preoperatively (patients either took no aspirin or a maximum dose of 80mg/day); coexisting diseases (renal and hepatic disease diabetes mellitus, hypertension, and endocrine and hematology disorders).
Recruitment/selection of patients	not reported
Age, gender and ethnicity	Age - Mean (SD): cell salvage group: 58+/-5.4, no cell salvage group: 55+/-14. Gender (M:F): 33/17. Ethnicity: not reported
Further population details	1. Type of surgery : Cardiovascular surgery (Coronary artery by pass graft).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Intra-operative cell salvage therapy + Post-operative cell salvage therapy . Blood

	aspirated from wound area, operative field, cardiopulmonary bypass circuit and heart-lung machine collected in cell-saver reservoir primed with 150ml of normal saline and 30,000 IU heparin/L, washed and concentrated with continuous-flow cell saver before retransfusion. Cell-saver device started prior to skin incision using 1000ml saline as a washing solution. Reinfusion of cell-salvage blood was done regardless of postoperative hematocrit levels. . Duration not applicable. Concurrent medication/care: none reported Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (During surgery: haemoglobin <7 g/dL (hematocrit <21%); After surgery trigger in no cell salvage group: Hb <8 g/dL (hematocrit <24%)). (n=25) Intervention 2: No cell salvage therapy. Homologous blood transfusions based on haemoglobin and haematocrit levels. Duration not applicable. Concurrent medication/care: none reported Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (During surgery: haemoglobin <7 g/dL (hematocrit <21%); After surgery trigger in no cell salvage group: Hb <8 g/dL (hematocrit <24%)).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-OPERATIVE CELL SALVAGE THERAPY + POST-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY

Protocol outcome 1: Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up
- Actual outcome: Number of units transfused per patient at up to discharge; Group 1: mean 0.4 mL (SD 0.8); n=25, Group 2: mean 0.7 mL (SD 1); n=25; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Mortality (all causes) at 30 days
- Actual outcome: Mortality at up to discharge; Group 1: 0/25, Group 2: 0/25; Risk of bias: Low; Indirectness of outcome: Serious indirectness

Protocol outcome 3: Number of patients needing transfusions at End of follow-up
- Actual outcome: Number of patients requiring transfusion of allogenic red blood cells postoperatively at up to discharge; Group 1: 7/25, Group 2: 8/25;

Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Serious adverse events of donor blood transfusion. at End of follow-up; Serious adverse events of cell salvage therapy at End of follow-up; Length of hospital stay at End of follow-up

Study	**Aguilera 2013**
Study type	RCT (single centre, parallel, open clinical trial)
Number of studies (number of participants)	n= 1 (n=87) [n=172 in the study. The study included 4 arms: those receiving, fibrin glue, Tissucol, TXA, Control. We have included only 2 arms of the study]
Countries and setting	Conducted in Spain; Setting: Surgery (Hospital)
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients (>18 years) scheduled for elective primary scheduled for elective primary total knee arthroplasty and who agreed to participate.
Exclusion criteria	Allergy to TXA or to aprotinin, a history of coagulopathy or a thromboembolic event, previous vascular or cardiac bypass

	surgery, treatment with an anti-coagulant or contraceptives, presence of a cardiovascular prosthesis, and patients who declined to participate.
Recruitment/selection of patients	Consecutive patients scheduled for elective primary total knee arthroplasty from June 2010 to October 2011 were recruited for the study.
Age, gender and ethnicity	TXA (n=44) / Control (n=43) Age (years) 72.4±6.6 / 74.9±7.0 Females 40 / 36
Further population details	Type of surgery: elective primary total knee arthroplasty TXA (n=44) / Control (n=43) ASA class 1/2/3 1/24/16 / 0/28/14
Indirectness of population	No indirectness
Interventions	TXA (n=41) Patients received two 1 g doses by intravenous bolus. The first dose was administered 15 to 30 minutes before the pneumatic tourniquet was inflated, and the second dose was given when the tourniquet was removed (60 to 90 minutes after the first dose). Control (n=32) The control group received routine haemostasis only, consisting of electrocoagulation of all possible bleeding points or vessels. Note: Transfusion of packed red blood cells was indicated when haemoglobin was <8 g/dl, when haemoglobin was <8.5 g/dl in patients with heart disease or older than 70 years, and when haemoglobin was between 8.5 and 9 g/dl in patients who had low orthostatic tolerance.
Funding	Funded principally by a grant from the Ministry of Health and Social Policy of Spain, with additional support from the Blood and Tissue Bank of Catalonia.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS CONTROL	

No. of patients requiring allogeneic transfusions TXA: 2/41 control: 12/42 Risk of bias: high; Indirectness of outcome: No indirectness No. of units transfused (no standard deviations reported) TXA: 9 control: 30 Risk of bias: high; Indirectness of outcome: No indirectness Length of hospital stay (days) TXA: 6.8±2.4 control: 7.5±2.6 Risk of bias: high ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Infections, Thrombotic complications, Serious adverse events (as defined by study)

Study	**Ahn 2012**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=76)
Countries and setting	Conducted in Japan; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults

Subgroup analysis within study	Not applicable
Inclusion criteria	76 pre-operatively anaemic patients (Hb <130 g/litre for males and <120 g/litre for females) treated with aspirin and clopidogrel until within 5 days of cardio pulmonary bypass.
Exclusion criteria	Patients with impaired renal function, hepatic dysfunction, neurologic dysfunction or haematologic disorders were excluded.
Age, gender and ethnicity	Age - Mean (SD): TXA: 69 (7); control: 67 (7). Gender (M:F): TXA: 23/15; control: 18/20. Ethnicity: Not stated
Further population details	Type of surgery: cardio pulmonary bypass
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Tranexamic acid. TXA 1g for 20 min before skin incision with subsequent continuous infusion at 200 mg/h during the operation. Duration Before and during surgery. Concurrent medication/care: Systemic heparinisation with 100 IU/kg of porcine heparin to reach a target activated clotting time >250 seconds. Comments: Transfusion protocol: Allogeneic packed RBC were transfused when the Hb level was <85 g/litre throughout the study period. (n=38) Intervention 2: Placebo. Patients in control group received the equivalent amount of saline solution at the same rate as TXA. Duration Before and during surgery. Concurrent medication/care: Systemic heparinisation with 100 IU/kg of porcine heparin to reach a target activated clotting time >250 seconds.
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO

Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up
- Actual outcome for Adults: Number of units transfused- RBC at end of follow-up; Group 1: mean 0.8 units (SD 0.8); n=38, Group 2: mean 1.4 units (SD 1.2); n=38; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of patients needing transfusions at end of follow-up
- Actual outcome for Adults: Number of patients needing transfusion- RBC at end of follow-up; Group 1: 20/38, Group 2: 27/38; Risk of bias: Low; Indirectness of

outcome: No indirectness Protocol outcome 3: Thrombosis at end of follow-up - Actual outcome for Adults: Other thrombosis at end of follow-up; Group 1: 0/38, Group 2: 0/38; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Bleeding at end of follow-up - Actual outcome for Adults: Total blood loss at Before and after surgery; Group 1: mean 986 (SD 520); n=38, Group 2: mean 944 (SD 482); n=38; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Length of hospital stay at end of follow-up

Study	Antinolfi 2014
Study type	RCT (Patient randomised; prospective)
Number of studies (number of participants)	1 (n=40) (n=20 TXA; n=20 placebo)
Countries and setting	Conducted in Italy; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients affected by primary knee osteoarthritis and candidates to receive primary TKA(total knee arthroplasty)
Exclusion criteria	TXA allergy, history of thromboembolism, previous surgery to the knee, bleeding disorders, platelet or bone marrow disorders, level of creatinine more than 250 mol/l,
Age, gender and ethnicity	Age - Mean (SD) years: TXA : 71.9 (5.1); Placebo : 70.7 (7.3) Gender (M: F): male: TXA-11/20; Control: 10/20. Ethnicity: Not stated
Further population details	Type of surgery: Primary Total knee arthroplasty
Extra comments	No significant difference between the groups for demographic characteristics and pre-operative blood parameters
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Tranexamic acid. At the end of the surgical procedure 500 mg of TXA was injected inside the joint. (n=20) Intervention 2: Control. Control group did not receive any treatment.
Funding	Not reported

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS CONTROL

Protocol outcome 1: Number of units transfused (red cells)/volume in ml in children
- Group 1: (mean± SD) units 0.8 (0.8) ; n=20, Group 2: (mean± SD) units : 2.2 (1.0) ; n=20; Risk of bias: high ; Indirectness of outcome: No indirectness

Protocol outcome 2: Thrombosis (DVT/PE) at end of follow-up - Actual outcome for Adults; Thrombosis (DVT/PE): Group 0/20: , Group 2:0/20 ; Risk of bias: High ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Number of patients transfused; Infection; Mortality at 30days; Quality of life at End of follow-up; Serious adverse events related to transfusion at End of follow-up;; Length of hospital stay at End of follow-up

Study	**Atay 2010-1**[10]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=74)
Countries and setting	Conducted in Turkey
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	First time arthroplasty because of hip osteoarthritis and unilateral surgery
Exclusion criteria	Patients operated simultaneous bilaterally, who had hematologic, chronic metabolic, infectious and/or rheumatologic

	diseases, with preoperative hemoglobin level below 12 g/dL, using anticoagulant therapy, with previous history of non-arthroplasty surgery in the same area, and planned revision hip arthroplasty were excluded from the study
Recruitment/selection of patients	December 2008 to April 2009
Age, gender and ethnicity	Age - Mean (SD): Cell salvage: 59.78+/-15.43; No cell salvage: 58.95+/-13.6. Gender (M:F): 12/24. Ethnicity: not reported
Further population details	1. Type of surgery : Orthopaedic surgery
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Post-operative cell salvage therapy . Blood transfused at the end of the 4th postoperative hour. Autotransfusion set (Translog, Heim Medizintechnik, Germany). Set could collect approximately 1000ml of blood in 240 microns bag. No anticoagulation included in the system. Routine hemovac drain used postoperatively after transfusion and removed at the end of the 48th hour. . Duration until discharge. Concurrent medication/care: Subcutaneous low molecular weight heparin with adjusted dose according to weight used for deep vein thrombosis prophylaxis and continued for 10 days. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Haemoglobin <8 g/dL (hematocrit <25%)). Comments: No blood transfused during surgery (n=19) Intervention 2: No cell salvage therapy. Routine hemovac drain used postoperatively after transfusion and removed at the end of the 48th hour.. Duration until discharge. Concurrent medication/care: Subcutaneous low molecular weight heparin with adjusted dose according to weight used for deep vein thrombosis prophylaxis and continued for 10 days. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Haemoglobin <8 g/dL (hematocrit <25%)). Comments: No blood transfused during surgery
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POST-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY

Protocol outcome 1: Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up

- Actual outcome: Number of units of blood transfused per patient at up to discharge; Group 1: mean 0.82 (SD 1.07); n=17, Group 2: mean 1.68 (SD 1.44); n=19; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at End of follow-up - Actual outcome: Number of patients needing allogenic blood transfusion at up to discharge; Group 1: 9/17, Group 2: 15/19; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Serious adverse events of donor blood transfusion. at End of follow-up - Actual outcome: Complications related to allogenic transfusion: febril reaction at up to discharge; Group 1: 0/17, Group 2: 2/19; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Serious adverse events of cell salvage therapy at End of follow-up - Actual outcome: Complications related to autotransfusion at up to discharge; Group 1: 0/17, Group 2: 0/19; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Length of hospital stay at End of follow-up

Study	**Atay 2010-2[10]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=41)
Countries and setting	Conducted in Turkey
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cell salvage:

Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	First time arthroplasty because of knee osteoarthritis and unilateral surgery
Exclusion criteria	Patients operated simultaneous bilaterally, who had hematologic, chronic metabolic, infectious and/or rheumatologic diseases, with preoperative hemoglobin level below 12 g/dL, using anticoagulant therapy, with previous history of non-arthroplasty surgery in the same area, and planned revision knee arthroplasty were excluded from the study
Recruitment/selection of patients	December 2008 to April 2009
Age, gender and ethnicity	Age - Mean (SD): Cell salvage: 65.25+/-12.57; No cell salvage: 68.19+/-6.62. Gender (M:F): 9/32. Ethnicity: not reported
Further population details	1. Type of surgery : Orthopaedic surgery
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Post-operative cell salvage therapy . Blood transfused at the end of the 4th postoperative hour. Autotransfusion set (Translog, Heim Medizintechnik, Germany). Set could collect approximately 1000ml of blood in 240 microns bag. No anticoagulation included in the system. Routine hemovac drain used postoperatively after transfusion and removed at the end of the 48th hour.. Duration until discharge. Concurrent medication/care: Subcutaneous low molecular weight heparin with adjusted dose according to weight used for deep vein thrombosis prophylaxis and continued for 10 days. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Haemoglobin <8 g/dL (hematocrit <25%)). Comments: No blood transfused during surgery (n=21) Intervention 2: No cell salvage therapy. Routine hemovac drain used postoperatively after transfusion and removed at the end of the 48th hour.. Duration until discharge. Concurrent medication/care: Subcutaneous low molecular weight heparin with adjusted dose according to weight used for deep vein thrombosis prophylaxis and continued for 10 days. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Haemoglobin <8 g/dL (hematocrit <25%)). Comments: No blood transfused during surgery

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POST-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY Protocol outcome 1: Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up - Actual outcome: Number of units of blood transfused per patient at up to discharge; Group 1: mean 0.05 (SD 0.22); n=20, Group 2: mean 0.71 (SD 0.96); n=21; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at End of follow-up - Actual outcome: Number of patients needing allogenic blood transfusion at up to discharge; Group 1: 1/20, Group 2: 8/21; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Serious adverse events of donor blood transfusion. at End of follow-up - Actual outcome: Complications related to allogenic transfusion: febril reaction at up to discharge; Group 1: 0/0, Group 2: 1/21; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Serious adverse events of cell salvage therapy at End of follow-up - Actual outcome: Complications related to auto transfusion at up to discharge; Group 1: 0/20, Group 2: 0/21; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Length of hospital stay at End of follow-up

Study	**Auvinen 1987[11] – No outcomes were reported by this study**
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Bleeding at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of

	units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up

Study	**Bidolegui 2014**
Study type	Prospective randomised controlled trial
Number of studies (number of participants)	n= 1(n=50)
Countries and setting	Conducted in Argentina; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with a diagnosis of osteoarthritis scheduled to have primary, unilateral TKA (total knee arthroplasty)
Exclusion criteria	If patients had allergy to TXA, a prior history of thromboembolic disease, congenital or acquired coagulopathy, renal or liver dysfunction, myocardial infarction within the last 6 months or retinopathy.
Recruitment/selection of patients	Patients were enrolled in a consecutive prospective manner on a voluntary basis. The study was conducted between September 2011 and July 2012.
Age, gender and ethnicity	Mean age was 71.5±9.4 years (range 43-90 years) in the treatment group and 72±6.8 years (range 61-84) in the control group, p=ns. Female gender was prevalent in both groups (60% for treatment and 80% for control group; p=ns).
Further population details	Type of surgery: unilateral TKA (total knee arthroplasty) Pre-operative risk according to the ASA was as follows: ASA II in 47 patients and ASA III in 3, without significant differences between treatment groups.
Indirectness of population	No indirectness

Interventions	TXA (n=25) TXA 15mg/kg (diluted in 100cc of normal saline) 10 minute intravenous infusion twice, the first dose during induction of anaesthesia and a second three hours later. Placebo (n=25) No further information provided
Funding	Not stated

RESULTS (NUMBERS ANALYSED AND RISK OF BIAS FOR COMPARISON): TRANEXAMIC ACID VERSUS CONTROL

No. of patients requiring allogeneic transfusions
TXA: 0/25
control: 8/25
Risk of bias: high; Indirectness of outcome: No indirectness

Length of hospital stay (days)
TXA:4.1±8.3 (range 3-7) days
control:3.8±9.4 (range 3-7)days
Risk of bias: high; Indirectness of outcome: No indirectness

DVT
TXA:0/25
control:0/25
Risk of bias: high; Indirectness of outcome: No indirectness

Infections
TXA:0/25
control:0/25
Risk of bias: high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Number of units of allogeneic blood transfused / volume of allogeneic blood transfused (in ml), Serious adverse events (as defined by study)

Study	**Bowley 2006[16]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=44)
Countries and setting	Conducted in South Africa
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Penetrating trauma injury requiring laparotomy with hypotension (<90mmHg) either preohospital or on arrival and were considered to have significant blood loss
Exclusion criteria	Patients <18 years old; injury >6 hours old
Recruitment/selection of patients	Emergency room
Age, gender and ethnicity	Age - Range: 20 to 54 years. Gender (M:F): 40/4. Ethnicity: not reported
Further population details	1. Type of surgery : Major abdominal surgery (includes obstetrics and gyanecological)
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Intra-operative cell salvage therapy . Intraoperative cell salvage therapy using a Saver 4 machine (Haemonetics, Braintree, MA, USA). Duration during surgery. Concurrent medication/care: none reported Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: No transfusion protocol

	Comments: 9/21 patients did not have a sample of cell saved blood taken before reinfusion (n=23) Intervention 2: No cell salvage therapy. Duration during surgery. Concurrent medication/care: none reported Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: No transfusion protocol
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY Protocol outcome 1: Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up - Actual outcome: Mean number of allogenic units transfused at up to 24 hours post injury; Group 1: mean 6.47 (SD 5.14); n=21, Group 2: mean 11.17 (SD 6.06); n=23; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Mortality (all causes) at 30 days - Actual outcome: Mortality at up to discharge; Group 1: 14/21, Group 2: 15/23; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery - Actual outcome: Postoperative sepsis in patients who did not die of exsanguination at up to discharge; Group 1: 5/13, Group 2: 7/13; Risk of bias: ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Number of patients needing transfusions at End of follow-up; Serious adverse events of donor blood transfusion. at End of follow-up; Serious adverse events of cell salvage therapy at End of follow-up; Length of hospital stay at End of follow-up

Study	Bradshaw 2012
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=46)
Countries and setting	Conducted in Australia; Setting: Surgery (Hospital)
Line of therapy	1st line
Duration of study	Intervention + follow up: Surgery and follow up at 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing primary total knee replacement for osteoarthritis of the knee
Exclusion criteria	History of thromboembolic events, anticoagulation that could not be ceased within the recommended time frame before surgery, peripheral vascular disease, oral contraception, pregnancy, current bleeding at any site, immunocompromise from a known medical condition or medical therapy, known hypersensitivity to the study medication, creatinine clearance of less than 30 ml/minute, or significant hepatic disease.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Tranexamic acid: 67.1(9.4); placebo: 68.2 (9.8). Gender (M:F): Tranexamic acid=14:12; placebo=13:7. Ethnicity: Caucasian
Further population details	Type of surgery: primary total knee replacement for osteoarthritis of the knee
Indirectness of population	No indirectness
Interventions	(n=26) Intervention 1: Tranexamic acid. Pre-operative self-administered three oral doses of 1500mg of encapsulated tranexamic acid. 2 of these doses were taken before admission and the third dose was taken 2 hours before planned surgery. A fourth dose was given 6 hours post-operatively.. Duration Before and after surgery. Concurrent medication/care: None

	(n=20) Intervention 2: Placebo. Medication identical in appearance but inactive was given. Duration Before and after surgery. Concurrent medication/care: None
Funding	Equipment / drugs provided by industry (Pfizer Australia provided medication used in the study)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery - Actual outcome for Adults: Infections at Post-operative; Group 1: 1/26, Group 2: 1/20; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome for Adults: Number of patients needing transfusions at Post-operative; Group 1: 0/26, Group 2: 1/20; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 3: Thrombosis at end of follow-up - Actual outcome for Adults: Deep vein thrombosis at Post-operative period; Group 1: 0/26, Group 2: 1/20; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Bleeding at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up

Study (subsidiary papers)	**Carless 2010[20] (Klein 2008[84], Laub 1993[88], Mcgill 2002[103], Abuzakuk 2007[1], Adalberth 1998[2], Altinel 2007[7], Amin 2008[8], Axford 1994[12], Ayers 1995[13], Bouboulis 1994[15], Cheng 2005[26], Clagett 1999[31], Dalrymple-hay 1999[38], Damgaard 2006[39], Davies 1987[42], Dietrich 1989[48], Dramis 2006[51], Ekback 1995[53], Elawad 1991[54], Eng 1990[55], Fragnito 1995[60], Gannon 1991[62], Goel 2007[64], Healy 1994[66], Heddle 1992[68], Kelley-patteson 1993[79], Kirkos 2006[83], Koopman-van gemert 1993[85], Lepore 1989[90], Lorentz 1991[94], Mah 1995[97], Majkowski 1991[98], Martin 2000[100], Mauerhan 1993[102], Menges 1992[104], Mercer 2004[105], Moonen 2007[108], Murphy 2004[109], Murphy 2005[110], Naumenko 2003[115], Newman 1997[116], Niranjan**

	2006[118], Page 1989[123], Parrot 1991[124], Pleym 2005[127], Riou 1994[134], Ritter 1994[135], Rollo 1995[136], Rosencher 1994[137], Sait 1999[139], Schaff 1978[141], Schmidt 1997[143], Schonberger 1993[144], Shenolikar 1997[150], Shirvani 1991[151], Simpson 1994[152], Sirvinskas 2007[153], Slagis 1991[154], Smith 2007[157], So-osman 2006[158], Spark 1997[160], Tempe 1996[165], Tempe 2001[166], Thomas 2001[167], Thurer 1979[169], Tripkovic 2008[173], Unsworth-white 1996[175], Ward 1993[183], Westerberg 2004[186], Wiefferink 2007[187], Zacharopoulos 2007[191], Zhang 2008[192], Zhao 1996[193], Zhao 2003[194])
Study type	Systematic Review
Number of studies (number of participants)	75 (n=6025)
Countries and setting	Conducted in Multiple countries
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Systematic review – pre-specified in protocol: type of surgery, use of transfusion protocols, active concomitant treatment, timing of cell salvage
Inclusion criteria	Elective or non-urgent surgical patients
Exclusion criteria	studies not reporting data on either the number of patients transfused with red cells or the volume of blood transfused
Age, gender and ethnicity	Age - Other: not reported. Gender (M:F): not reported. Ethnicity:
Further population details	1. Type of surgery: Mixed (orthopaedic, cardiac, vascular).
Indirectness of population	No indirectness
Interventions	(n=3048) Intervention 1: Mixed: intraoperative, postoperative or intraoperative + post operative cell salvage therapy. Intraoperative + postoperative cell salvage therapy . Duration not reported. Concurrent medication/care: Mixture with some studies having active background treatment Further details: 1. Active treatment: Mixed 2. Transfusion protocol: Mixed (n=2977) Intervention 2: No cell salvage therapy. No cell salvage therapy. Duration not reported. Concurrent medication/care: Mixture with some studies having active background treatment

	Further details: 1. Active treatment: Mixed 2. Transfusion protocol: Mixed
Funding	Academic or government funding
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Length of hospital stay at End of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Number of patients needing transfusions at End of follow-up; Serious adverse events of donor blood transfusion. at End of follow-up; Serious adverse events of cell salvage therapy at End of follow-up; Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up

Study	**Chareancholvanich 2012**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=240)
Countries and setting	Conducted in Thailand; Setting: Surgery (Hospital)
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not stratified but pre-specified: Study compared combination of clamping/non-clamping of drains with use of tranexamic acid/placebo by randomising patients into 4 groups. For the purpose of this review, groups have not been differentiated based on clamping.
Inclusion criteria	Patients undergoing unilateral primary total knee arthroplasty (TKA); aged less than 85 years; diagnosed with primary osteoarthritis of the knee
Exclusion criteria	Patients with secondary osteoarthritis (such as rheumatoid arthritis, post-traumatic arthritis, gouty arthritis, post-septic

	arthritis), high risk medical co-morbidity, history of thromboembolic disease, bleeding disorder, known allergy to tranexamic acid, patients receiving anti-coagulant drugs.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Tranexamic acid=69.7(6.8), Placebo=69.3(6.9). Gender (M: F): Tranexamic acid=17:103; Placebo=18:102. Ethnicity: Asian
Further population details	Type of surgery: unilateral primary total knee arthroplasty (TKA);
Indirectness of population	No indirectness
Interventions	(n=120) Intervention 1: Tranexamic acid. 10mg/kg of intravenous tranexamic acid (Transamine; 250mg/5ml, OLIC, Thailand) was administered 10 minutes before inflating the tourniquet and 10mg/kg at 3 hours post-operatively. 1500 mg per day of oral formed tranexamic acid (Transamine 250 mg/capsule, OLIC, Thailand) was given for 5 days after the operation.. Duration Post-operative period. Concurrent medication/care: Patients receiving tranexamic acid were in two different groups- both groups had a number 10 gauge drain placed intra-articularly and this was connected to a pressure drainage bottle; in one group this drain was clamped and released intermittently at every 3 hour interval and the drain in the other group was released following release of the tourniquet pressure. Further details: Transfusion protocol: Transfusion protocol (Patients received transfusions if their haemoglobin levels decreased to <10 g/dl or if compromised clinical criteria (tachycardia, hypotension, symptoms of anaemia that were relative to the pre-operative medical condition of the patient) necessitated transfusion.). 5. Type of surgery: Orthopaedic surgery (Total knee arthroplasty). (n=120) Intervention 2: Placebo. Equivalent volume of physiological saline and starch capsule administered as placebo. Duration Post-operative period. Concurrent medication/care: The placebo group was also divided into 2 groups like the tranexamic acid group into those whose post-operative drains were clamped or not clamped.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up - Actual outcome for Adults: Number of units of packed red cells transfused at Post-operative period; Group 1: mean 0.55 units (SD 0.62); n=120, Group 2: mean 1.55 units (SD 0.98); n=120; Risk of bias: Low; Indirectness of outcome: No indirectness	

Protocol outcome 2: Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery - Actual outcome for Adults: Infections at Post-operative; Group 1: 2/120, Group 2: 1/120; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Number of patients needing transfusions at end of follow-up - Actual outcome for Adults: Number of patients requiring blood transfusions at Post-operative period; Group 1: 57/120, Group 2: 102/120; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Thrombosis at end of follow-up - Actual outcome for Adults: Venous thromboembolism at Post-operative; Group 1: 0/120, Group 2: 0/120; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Bleeding at end of follow-up - Actual outcome for Adults: Volume of blood drained (blood loss) at Post-operative; Group 1: mean 625 ml (SD 254.4); n=120, Group 2: mean 1002 ml (SD 416.9); n=120; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Length of hospital stay at end of follow-up

Study	**Chareancholvanich 2011**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=100)
Countries and setting	Conducted in Thailand; Setting: Surgery (hospital)
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable

Inclusion criteria	Patients with primary osteoarthritis who underwent unilateral cemented total knee arthroplasty; aged less than 85 years
Exclusion criteria	Patients with secondary osteoarthritis (rheumatoid arthritis, gouty arthritis, post-traumatic arthritis, post-septic arthritis), patients with high risk medical co-morbidity, simultaneous bilateral total knee arthroplasty, history of thromboembolic disease, bleeding disorders, known allergy to tranexamic acid, receiving anti-coagulant treatment
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Tranexamic acid: 69.2(6.13); Placebo: 68.8(6.12). Gender (M: F): Tranexamic acid=7:43; Placebo=8:42. Ethnicity: Asian
Further population details	Type of surgery: unilateral cemented total knee arthroplasty
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Tranexamic acid. Intravenous tranexamic acid 10mg/kg administered 10 minutes before tourniquet inflation and again 3 hours post-operatively and then oral tranexamic acid (250 mg/capsule, two capsules three times daily)for 5 days. Duration Post-operative period. Concurrent medication/care: None (n=50) Intervention 2: Placebo. Intravenous saline 10 minutes before surgery and 3 hours post-operatively and then oral placebo (two capsules three times daily) for 5 days. Duration Post-operative period. Concurrent medication/care: None
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO

Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up
- Actual outcome for Adults: Number of units of packed red cells transfused at Post-operative period; Group 1: mean 0.71 units (SD 0.78); n=50, Group 2: mean 1.89 units (SD 0.87); n=50; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery
- Actual outcome for Adults: Infections at Post-operative period; Group 1: 1/50, Group 2: 1/50; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Number of patients needing transfusions at end of follow-up

- Actual outcome for Adults: Number of patients transfused at Post-operative period; Group 1: 28/50, Group 2: 45/50; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Thrombosis at end of follow-up - Actual outcome for Adults: Deep vein thrombosis at Post-operative period; Group 1: 0/50, Group 2: 0/50; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Bleeding at end of follow-up - Actual outcome for Adults: Volume of blood drained (blood loss) at Post-operative period; Group 1: mean 727.5 ml (SD 234); n=50, Group 2: mean 1208.77 ml (SD 421); n=50; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Length of hospital stay at end of follow-up

Study	**Chauhan 2003**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=120)
Countries and setting	Conducted in India; Setting: Surgery(Hospital)
Line of therapy	1st line
Duration of study	Intervention + follow up: 24 hours after surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children: Included children from 2 months to 14 years of age
Subgroup analysis within study	Not applicable
Inclusion criteria	Children with cyanotic congenital heart disease undergoing corrective surgery; included patients on heparin or aspirin
Exclusion criteria	Patients with renal impairment, previous neurological events or congenital bleeding disorders
Recruitment/selection of patients	Consecutive patients were enrolled

Age, gender and ethnicity	Age - Mean (SD): In years: TXA group: 4.2(3.3); control group: 4.4 (3.6). Gender (M:F): Not reported. Ethnicity: Asian Indian
Further population details	Type of surgery: cardiac surgery
Indirectness of population	Serious indirectness: Study also included patients less than 1 year of age but mean age in each group >4 years
Interventions	(n=96) Intervention 1: Tranexamic acid. Tranexamic acid (Traxmic, Systopic, Labs, New Delhi) given as:10mg/kg after anaesthetic induction, 10mg/kg on cardio-pulmonary bypass, 10mg/kg after protamine reversal of heparin. Duration Before, during and after surgery. Concurrent medication/care: Some patients were on heparin or aspirin, number not reported. (n=24) Intervention 2: Placebo. Control group with no treatment. Concurrent medication/care: None
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Bleeding at end of follow-up - Actual outcome for Children: Post-operative blood loss at 24 hours after surgery; Group 1: mean 20 ml/kg/24hours (SD 9); n=96, Group 2: mean 36 ml/kg/24hours (SD 12); n=24; Risk of bias: Unclear; Indirectness of outcome: Serious indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up

Study	**Choi 2009- No outcomes were reported by this study**
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Bleeding at end of follow-

	up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up.

Study	**Cip 2013[30]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=151)
Countries and setting	Conducted in Austria
Line of therapy	Not applicable
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Primary elective total knee arthroplasty for osteoarthritis
Exclusion criteria	Not defined as an priori list. Reports numbers of patients excluded prior to randomisation from a total of 223 total knee arthroplasties carried out at the centre: unwillingness to participate (53); revision arthroplasty (19).
Recruitment/selection of patients	From December 2007 to January 2009
Age, gender and ethnicity	Age - Mean (SD): 70 years. Gender (M:F): Define. Ethnicity: not reported
Further population details	1. Type of surgery : Orthopaedic surgery
Indirectness of population	No indirectness
Interventions	(n=76) Intervention 1: Intra-operative cell salvage therapy + Post-operative cell salvage therapy . Intraoperative and postoperative cell salvage therapy. Re-transfusion system that processed blood by completing anticoagulation, filtering,

	washing and centrifugation steps. Orthopaedic Perioperative Autotransfusion System (OrthoPAT, Haemonetics Corp, Braintree, MA, USA) used for cell salvage and re-transfusions.. Duration Auto transfusion system used for 6 hours after total skin incision (intraoperatively and postoperatively). . Concurrent medication/care: Antithrombotic prophylaxis: 40mg low molecular weight heparin from 1 day before surgery to 42 days post-operatively.Intravenous perioperative infection prophylaxis: 1500mg cefuoxime. Further details:Transfusion protocol: Transfusion protocol (Signs of anaemia (vertigo, nausea, vomiting, hypotension, tachycardia) or haemoglobin level <8 g/dL). Comments: After re-transfusion of blood patients continued with a drainage system without blood for 48 hours. (n=75) Intervention 2: No auto transfusion. Duration unclear. Concurrent medication/care: Antithrombotic prophylaxis: 40mg low molecular weight heparin from 1 day before surgery to 42 days postoperatively. Intravenous perioperative infection prophylaxis: 1500mg cefuoxime. Further details: 1. Active treatment: Mixed 2. Transfusion protocol: Transfusion protocol (Signs of anaemia (vertigo, nausea, vomiting, hypotension, tachycardia) or haemoglobin level <8 g/dL).
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-OPERATIVE CELL SALVAGE THERAPY + POST-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY Protocol outcome 1: Number of patients needing transfusions at End of follow-up - Actual outcome: Number of patients having allogenic blood transfusions at up to discharge; Group 1: 23/70, Group 2: 23/70; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Length of hospital stay at End of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Serious adverse events of donor blood transfusion. at End of follow-up; Serious adverse events of cell salvage therapy at End of follow-up; Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up

Study	Crescenti 2011
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in Italy; Setting: University hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients older than 18 years undergoing radical retropubic prostatectomy (associated lymph node dissection when required for oncological radicality) and who provided written informed consent were eligible for the trial.
Exclusion criteria	Atrial fibrillation, coronary artery disease treated with drug eluting stent, severe chronic renal failure (serum creatinine >180 mmol/litre), congenital or acquired thrombophilia, and known or suspected allergy to tranexamic acid.
Age, gender and ethnicity	Age - Mean (SD): TXA: 64 (7.4); control: 64 (7.8). Gender (M:F): All males. Ethnicity: Not stated
Further population details	Type of surgery: radical retropubic prostatectomy
Extra comments	200 patients older than 18 years and undergoing radical prostatectomy.
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: Tranexamic acid. A loading dose of 500 mg of TXA diluted in 100 ml of saline was infused slowly intravenously 20 minutes before surgery and a continuous intravenous infusion of tranexamic acid was given at a rate of 250mg/h from surgical incision until skin closure. . Duration 20 minutes before surgery. Concurrent medication/care: None Further details: 1No Transfusion protocol 5. Type of surgery: Any other type of surgery (radical retropubic

	prostatectomy). Comments: No form of cell salvage was allowed during and after surgery. (n=100) Intervention 2: Placebo. Patients received placebo (saline) with identical volumes and rates of infusion as tranexamic acid. Duration 20 minutes before surgery. Concurrent medication/care: None
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Length of hospital stay at end of follow-up - Actual outcome for Adults: Length of hospital stay at end of follow-up; Group 1: mean 9 days (SD 4.3); n=100, Group 2: mean 9 days (SD 4.3); n=100; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Mortality (all causes) at 30 days - Actual outcome for Adults: Mortality at 6 months; Group 1: 0/100, Group 2: 0/100; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Number of patients needing transfusions at end of follow-up - Actual outcome for Adults: No. of patients transfused at end of follow-up; Group 1: 34/100, Group 2: 55/100; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Thrombosis at end of follow-up - Actual outcome for Adults: Deep vein thrombosis at 6 months; Group 1: 1/100, Group 2: 3/100; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Bleeding at end of follow-up - Actual outcome for Adults: Total intra-operative blood loss at During surgery; Group 1: mean 1103 (SD 500.8); n=100, Group 2: mean 1335 (SD 686.5); n=100; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up

Study	Dakir 2014
Study type	RCT
Number of studies (number of participants)	n= 1 (n=12)
Countries and setting	Conducted in India; setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Male patients between the age 20-40 years, with pan facial fractures, with normal bleeding, clotting and prothrombin time, with no other medical complications were included in the study.
Exclusion criteria	Not stated
Recruitment/selection of patients	The study was conducted between November 2009 and October 2011.
Age, gender and ethnicity	Not stated
Further population details	Not stated
Indirectness of population	No indirectness
Interventions	TXA (n=6) TXA 10 mg/kg intravenously 15 minutes before surgery Control group (n=6) 60.9% Normal saline 15 minutes before surgery All patients received fluid replacement to maintain urine output greater than 0.5 ml/kg/hour. RBC transfusion was done

	when the blood loss was greater than one fourth of the blood volume (70 ml/kg for males, 65 ml/kg for females) or haemoglobin level was less than 8 g/dl.
Funding	Not stated
RESULTS (NUMBERS ANALYSED): TRANEXAMIC ACID VERSUS CONTROL No. of patients requiring allogeneic transfusions TXA: 0/6 control: 2/6 Risk of bias: high ; Indirectness of outcome: No indirectness Length of hospital stay There was no difference in length of hospital stay between the TXA and control groups Risk of bias: high ; Indirectness of outcome: No indirectness Thrombotic complications TXA:0/6 Placebo:0/6 Risk of bias: high ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Infections, Number of units of allogeneic blood transfused / volume of allogeneic blood transfused (in ml), Serious adverse events (as defined by study).

Study	**Esfandiari 2014**
Study type	RCT (Prospective randomised placebo controlled study)
Number of studies (number of participants)	n=1 (n=150)
Countries and setting	Conducted in: Iran; Setting: Hospital (Kashani hospital)
Line of therapy	1st line

Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients planned for primary isolated elective for coronary artery bypass surgery.
Exclusion criteria	Patients who had an emergency surgery, rheumatic fever, bleeding diathesis (haemophilia or platelet count <100 x10^9 litres), known allergy or contraindication to Tranexamic acid (TXA) (acquired visual defect, subarachnoid haemorrhage, gall bladder disease, emboli, venous thrombosis), recent (<7 days before surgery) intake of Plavix or heparin, or streptokinase administration within 48 hours of operation, were excluded from the study.
Recruitment/selection of patients	There were 150 patients (60 men and 15 women) who satisfied the inclusion criteria. They were informed about the use of TXA during surgery and its side effects, and their informed consent was obtained.
Age, gender and ethnicity	Mean age was 54.6±10.4 years in the placebo group and 54.2±9.7 years in the TXA group. There was no significant difference in terms of age or sex based on the t-test (p=0.94).
Further population details	Type of surgery: emergency surgery
Indirectness of population	No indirectness
Interventions	TXA: n=75 Patients received 10 mg/kg of TXA added to the priming solution and a bolus dose of 1 mg/kg after weaning from cardiopulmonary bypass and infusion of protamine sulphate. Placebo: n=75 Patients received 100ml of normal saline per procedure. Note: If haematocrit levels were <24% or the haemoglobin levels <8 mg/dl in the post-operative period, a blood transfusion was carried out.
Funding	No funding obtained for the study
RESULTS AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO	

No. of patients requiring allogeneic transfusions TXA: 22/75 Placebo: 43/75 Risk of bias: high; Indirectness of outcome: No indirectness Thrombotic complications (CVA) TXA: 3/75 Placebo: 5/75 Risk of bias: high; Indirectness of outcome: No indirectness Mortality TXA: 2/75 Placebo: 2/75 Risk of bias: high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life, Length of stay (hospitalisation), Infections, Number of units of allogeneic blood transfused / volume of allogeneic blood transfused, Serious adverse events.

Study	**Eftekharian 2015**
Study type	RCT (Patient randomised; double blind)
Number of studies (number of participants)	1 (n=56) (n= 28 TXA; n=28 placebo)
Countries and setting	Conducted in Iran ; Setting: Hospital
Line of therapy	1st line

Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged 15 to 45 years, with American Society of Anaesthesiologists physical status I who were scheduled to undergo bimaxillary osteotomy for correction of Class II or Class III skeletal deformity.
Exclusion criteria	Patients who had coagulopathy or used anticoagulants, patients requiring additional procedures such as genioplasty, bone grafting or augmentation, segmental surgery, or Lefort II and III surgery were excluded from the study.
Age, gender and ethnicity	Age - Mean (SD): TXA: 22.71±6 ; Placebo : 21.64±3.81 Gender (M: F): male: TXA – 13/28; Control: 14/28. Ethnicity: Not stated
Further population details	Type of surgery: Orthognathic surgery Pre-operative Hb (mg/dl): TXA: 13.70±1.54; control: 13.89±1.43
Extra comments	A total of 56 patients who were scheduled to undergo bimaxillary osteotomy at the Shiraz University of medical sciences between April 1 2011, and April 1, 2013 were enrolled to participate in the study.
Indirectness of population	No indirectness
Interventions	(n= 28) Intervention 1: Tranexamic acid. Patients received topical TXA solution, 1,000 mg (20 ml) in 1 litre of 0.9% normal saline. (n= 28) Intervention 2: Control. Participants received 0.9% normal saline for tissue irrigation and cooling of the

	instruments.
Funding	Not reported
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID versus CONTROL Protocol outcome 1: Intra-operative blood loss - Group 1: (mean± SD) ml: 575± 286.90 ; n= 28, Group 2: (mean± SD) units: 817±261.83; n= 28; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Infection at end of follow-up - Group 1: 0/28 , Group 2: 0/28; Risk of bias: High; Indirectness of outcome: No indirectness Number of patients needing transfusion - Group 1: 0/28, Group 2: 0/28; Risk of bias: High; Indirectness of outcome: No indirectness Thrombotic events - Group 1: 0/28, Group 2: 0/28; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up, Number of units transfused, Serious adverse events related to transfusion at End of follow-up; Length of hospital stay at End of follow-up

Study	**Farrokhi 2011**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=76)
Countries and setting	Conducted in India; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who were enrolled to undergo a spinal fixation surgery. Patients aged 40 to 80 years, with physical status I and II were eligible to participate.
Exclusion criteria	History of bleeding disorders, platelet count <150,000, abnormal prothrombin time and partial thromboplastin time, body mass index >30 kg/m2, previous thromboembolic event, severe allergy to TXA, pre-existing renal disorders, heart disease, using drugs interfering with blood haemostasis, uncontrolled hypertension or high blood pressure (BP>160/90), and ASA physical status >3.
Recruitment/selection of patients	The patients were enrolled from Dec 2008 to Dec 2009 to undergo spinal fixation surgery in Chamran Hospital, Iran
Age, gender and ethnicity	Age - Mean (SD): TXA: 51.4 (11.6); control: 45.5 (11.6). Gender (M: F): TXA: 27/11; control group: 31/7. Ethnicity: Not stated
Further population details	Type of surgery: spinal fixation surgery
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Tranexamic acid. TXA 10mg/kg at the initiation of induction of anaesthesia during 10 minutes followed by a maintenance dose of intravenous infusion of 1 mg/kg/h by a syringe infusion pump during surgery. Duration 10 minutes before surgery. Concurrent medication/care: None (n=38) Intervention 2: Placebo. Equivalent volume of normal saline. Duration 10 minutes before surgery. Concurrent medication/care: None
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up - Actual outcome for Adults: Total Transfused packed cell (ml) at end of follow-up; Group 1: mean 675 (SD 382); n=38, Group 2: mean 600 (SD 220); n=38; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome for Adults: No. of patients needing blood transfusion at end of follow-up; Group 1: 10/38, Group 2: 15/38; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Drug related adverse events at end of follow-up - Actual outcome for Adults: Side effects of TXA (including nausea, diarrhoea, orthostatic reactions, MI, cerebral infarction, stroke, DVT, renal failure, cerebral infarction, granulomatous liver disease, jaundice and pyrexia) at end of follow-up; Group 1: 0/38, Group 2: 0/38; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Thrombosis at end of follow-up - Actual outcome for Adults: Deep vein thrombosis at end of follow-up; Group 1: 0/38, Group 2: 0/38; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 5: Bleeding at end of follow-up - Actual outcome for Adults: Total intra-operative blood loss at During surgery; Group 1: mean 1268.9 ml (SD 690); n=38, Group 2: mean 1335.9 ml (SD 550); n=38; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Length of hospital stay at end of follow-up.

Study	**Ghaffari Nejad 2012**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Iran; Setting: Hospital

Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	On-pump CABG and patients acceptance
Exclusion criteria	History of haemorrhagic tendency and blood dyscrasia, history of plavix usage, known hepatic, renal and metabolic diseases, use of other anti-coagulation drugs like coumadin for valvular disease and arrhythmias and streptokinase, emergency surgery, rheumatic heart disease, known allergy to aprotinin or transamine and prohibition for their use like: acquired visual defects and retinal disease, subarachnoid haemorrhage, disseminated intravascular coagulation, gall bladder disease, leukaemia, embolisation and vein thrombosis.
Age, gender and ethnicity	Age - Mean (SD): TXA: 54.6 (10.4); Control: 54.2 (9.7). Gender (M:F): TXA: 41/9; control: 35/15. Ethnicity: Not stated
Further population details	Type of surgery: Cardiac surgery
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Tranexamic acid. 1 g of Transamine was added to pump prime solution and another 1 g was used intravenously after discontinuation of pump. . Duration NR. Concurrent medication/care: All patients received 300 IU/kg of bovine lung heparin. Additional heparin was administered for activated clotting times less than 400 seconds. Comments: Packed red cell was transfused for a haematocrit concentration under 30% and fresh frozen plasma was transfused based on abnormal prothrombin time and the rate of bleeding. Platelet transfusion threshold was a platelet count of 1000000 or less and bleeding tendency. (n=50) Intervention 2: Placebo. 250 cc of normal saline (no more details). Duration not reported. Concurrent medication/care: All patients received 300 IU/kg of bovine lung heparin. Additional heparin was administered for activated clotting times less than 400 seconds.
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Mortality (all causes) at 30 days - Actual outcome for Adults: Mortality at end of follow-up; Group 1: 0/50, Group 2: 0/50; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome for Adults: Number of patients needing transfusions at end of follow-up; Group 1: 15/50, Group 2: 23/50; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Bleeding at end of follow-up - Actual outcome for Adults: Bleeding after 48 hours at 48 hours after surgery; Group 1: mean 432 (SD 210.3); n=50, Group 2: mean 649 (SD 365.3); n=50; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up

Study	**Ghavidel 2014**
Study type	RCT (Patient randomised; double blind)

Number of studies (number of participants)	1 (n=200) (n=100 TXA; n=100 placebo)
Countries and setting	Conducted in Iran; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients older than 18 years scheduled to undergo non-emergent CABG
Exclusion criteria	Patients with serum creatinine level of >2 mg/dl, previous history of bleeding or coagulation disorders, taking oral anticoagulation medications within 72 hours of the surgery and allergy to the study medications
Age, gender and ethnicity	Age - Mean (SD): TXA: 58±9 ; Placebo : 59±10 Gender (M: F): male: TXA- 70/100; Control: 65/100. Ethnicity: Not stated
Further population details	Type of surgery: cardiac surgery
Extra comments	-
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: Tranexamic acid . The primary dose of TXA 10 mg/kg via prime solution and the maintenance dose of 0.5-2 mg/kg/h in proportion to serum creatinine were given.

	(n=100) Intervention 2: Placebo. Placebo consisted of 0.9% normal saline solution. The control group received the placebo solution in a similar way to the study medications. Comment: Normal saline and study medications were prepared in equivalent volume in 50 ml syringes with a coded label by a nurse who was not included in the study. Under general anaesthesia cardiopulmonary bypass (CPB) machine was established after heparin (3 mg/kg) administration. Additional dose of heparin was used during CPB to maintain the activated coagulation time higher than 380 seconds.
Funding	Not reported

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID versus PLACEBO

Protocol outcome 1: Number of units transfused (red cells)/volume in ml in children during ICU stay
- Group 1: (mean± SD) units: 1.25±0.53 ; n=100, Group 2: (mean± SD) units: 1.65±0.55; n=100; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Infection at end of follow-up
- Actual outcome for Adults; Deep wound Infection: Group 1: 1/100, Group 2: 2/100; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Number of patients needing transfusions during ICU stay
- Group 1:60 /100, Group 2: 74/100; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Post-op MI at end of follow-up
- Group 1: 8/100, Group 2: 6/100; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at End of follow-up; Serious adverse events related to transfusion at End of follow-up; Thrombosis at End of follow-up; Length of hospital stay at End of follow-up

Study	**Greiff 2012**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=64)
Countries and setting	Conducted in Norway; Setting: University hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients scheduled for combined AVR and CABG surgery were included in the study after giving written informed consent. Included patients were 70 years or older.
Exclusion criteria	Patients were excluded if they were receiving treatment with heparin or low molecular weight heparin, oral anti-coagulants, non- steroidal anti-inflammatory drugs, platelet inhibitors other than aspirin or systemic glucocorticoids. Patients with abnormal kidney function (serum creatinine >140 mmol/litre) or liver dysfunction with INR >1.5 were excluded.
Age, gender and ethnicity	Age - Mean (SD): TXA: 77; control group: 77. Gender (M:F): TXA group: 18/12; placebo: 19/14. Ethnicity: NR
Further population details	Type Of surgery: CABG
Extra comments	Patients on aspirin: the aspirin dose was either 75 mg (11 in the TXA group and 14 in the placebo group) or 160 mg (19 in the TXA group and 19 in the placebo group)
Indirectness of population	No indirectness

Interventions	(n=30) Intervention 1: Tranexamic acid. TXA 10mg/kg as a bolus injection followed by an infusion of 1mg/kg/h. The bolus injection was given before the skin incision, and the infusion was started immediately after the bolus injection and continued till the end of surgery. . Duration before surgery. Concurrent medication/care: None (n=33) Intervention 2: Placebo. Placebo group received 10 mg/kg of 0.9%. Duration before surgery. Concurrent medication/care: None Comments: Increased post-operative bleeding was treated with an infusion of FFP or platelets. The decision to give platelets or FFP was left to the attending physician, but treatment was considered only when patients had persistent post-operative bleeding of >200 ml/h.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up - Actual outcome for Adults: Total no. of units of platelets given per patient at During the entire hospital stay; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Total no. of units of FFP given per patient at During the entire hospital stay; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Total no. of units of red blood cells given per patient at During the entire hospital stay; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Bleeding at end of follow-up - Actual outcome for Adults: Total post-operative bleeding at Every 4 hours and for 16 hours post-operatively; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Length of hospital stay at end of follow-up

Study	**Gungorduk 2011**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=660)
Countries and setting	Conducted in Turkey; Setting: Teaching hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were eligible for the trial if the foetus was more than 38 weeks estimated gestational age and they required elective caesarean section delivery. Elective caesarean section was defined as caesarean section performed before the onset of labour.
Exclusion criteria	Women were excluded if they had risk factors associated with an increased risk factors associated with an increased risk of post-partum haemorrhage such as anaemia (Hb <7 g%), multiple gestation, antepartum haemorrhage (placenta praevia or placental abruption), abnormal placentation, uterine fibroids, polyhydramnios, emergency caesarean, a history of uterine atony and postpartum bleeding and a current previous history of significant disease including heart diseases, liver, renal disorders or a known coagulopathy.
Age, gender and ethnicity	Age - Mean (SD): TXA group: 26.3 (3.5); control group: 26.6 (3.6). Gender (M:F): All women. Ethnicity: Not stated
Further population details	Type of surgery: Caesarean section delivery
Indirectness of population	No indirectness
Interventions	(n=330) Intervention 1: Tranexamic acid. 1 g/10 ml transamine diluted with 20 ml of 5% glucose. TXA was slowly administered intravenously over a 5 minute period at least 10 minutes prior to skin incision. Duration Before skin incision. Concurrent medication/care: After delivery both TXA and placebo groups received a 5 IU intravenous bolus of prepared oxytocin, and then 30 IU oxytocin in 500 ml lactated Ringers solution was infused at a rate of 125 ml/hour. An antibiotic 1 g cefazolin diluted in 20 ml normal saline was administered over a 5 minute period. (n=330) Intervention 2: Placebo. 30 ml of 5% glucose. This was slowly administered intravenously over a 5 minute

	period at least 10 minutes prior to skin incision. Duration: Before skin incision. Concurrent medication/care: After delivery both TXA and placebo groups received a 5 IU intravenous bolus of prepared oxytocin, and then 30 IU oxytocin in 500 ml lactated Ringers solution was infused at a rate of 125 ml/hour. An antibiotic 1 g cefazolin diluted in 20ml normal saline was administered over a 5 minute period.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Length of hospital stay at end of follow-up - Actual outcome for Adults: Length of hospital stay at end of follow-up; Group 1: mean 2 (SD 0); n=330, Group 2: mean 2 (SD 0.1); n=330; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome for Adults: Number of patients needing transfusions at end of follow-up; Group 1: 2/330, Group 2: 7/330; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Thrombosis at end of follow-up - Actual outcome for Adults: Deep vein thrombosis at 6 weeks after surgery; Group 1: 0/330, Group 2: 0/330; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Bleeding at end of follow-up - Actual outcome for Adults: Total blood loss at Intra and post-operative; Group 1: mean 499.9 ml (SD 206.4); n=330, Group 2: mean 600.7 ml (SD 215.7); n=330; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up.

Study	**Henry 2011 (included studies- Tanaka 2001 , Karski 2005 , MacGillivray , Pleym 2003 , Mehr-Aein 2007 , Casati 2002 , Johansson 2005 , Benoni 2001 ,Vanek 2005 , Casati 2004 , Jimenez 2007 ,Casati 2001 , Wong 2008 , Shore-Lesserson ,**

	Katsaros 1996 , Niskanen 2005 , Husted 2003 , Benoni 2000 , Sadeghi 2007 , Benoni 1996 , Gill 2009 , Lemay 2004 , Hardy 1998 , Orpen 2006, Coffey 1995 , Mansour 2004 , Taghaddomi 2009 , Good 2003 , Penta de Peppo 1995 , Ellis 2001 , Claeys 2007 , Blauhut 1994 , Pinosky 1997 , Jares 2003, Engel 2001, Katoh 1997 , Armellin 2001 , Wei 2006 , Menichetti 1996 , Ekback 2000 , Garneti 2004, Zohar 2004 , Corbeau 1995 , Jansen 1999 , Isetta 1993 , Caglar 2008 , Speekenbrink 1995 , Veien 2002 , Kazemi 2010 , Sorin 1999 , Brown 1997 , Pugh 1995 , Kuitunen 2005 , Horrow 1995 , Dalmau 2000 , Hiipala 1995 , Murphy 2006 , Hiipala 1997 , Later 2009 , Horrow 1991 , Diprose 2005 , Santos 2006 , Andreasen 2004 , Wu 2006 , Yamasaki 2004)
Study type	Systematic review
Number of studies (number of participants)	n=65 (n=4842 patients)
Countries and setting	Conducted in United States, Germany, UK, Canada, Italy, Spain, Belgium, France, Turkey, Australia, Sweden, The Netherlands, Japan, China, Austria, Israel, Switzerland, Finland, Czech Republic, Denmark, Taiwan, Ireland, Greece, Poland, Brazil, Chile, Dubai, Egypt, India, Norway, Oman, Saudi Arabia and South Africa; setting: hospitals.
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	• the type of surgery, • the use of transfusion protocols, • dose regimen, and • trial methodological quality.
Inclusion criteria	Randomised controlled trials (RCTs) with a concurrent control group, or randomised head-to-head comparative trials. The study participants were adults (over 18 years). Trials were included if participants aged less than 18 years were enrolled, but the type of surgery was predominantly carried out in adult patients. The surgery performed was primarily elective but trials were included if urgent cases were proportionately similar across trial arms. The interventions considered: tranexamic acid (TXA),
Exclusion criteria	Not stated

Recruitment/selection of patients	
Age, gender and ethnicity	
Further population details	Of the 65 trials that studied the efficacy of TXA versus placebo or control- 34 involved cardiac surgery, 27 involved orthopaedic surgery, two involved liver surgery, one trial involved gynaecological surgery and one trial involved vascular surgery. Dose regimens for TXA varied significantly between trials with varying dose sizes and time frames for drug delivery.
Indirectness of population	No indirectness
Interventions	TXA (n=2528) TXA Control (n=2314) Patients did not receive TXA
Funding	Academic funding

Study	**Horstmann 2014**
Study type	Open Randomised controlled study
Number of studies (number of participants)	n=1 (n=115)
Countries and setting	Conducted in The Netherlands; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up. Patients attended the out-patient clinic- pre-operatively and were followed during their stay in hospital and at 6 weeks and 3 months post-operatively.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing primary total knee arthroplasty (TKA) and provided informed consent.

Exclusion criteria	Coagulation disorders including deep vein thrombosis and pulmonary embolism, malignancy, on-going infections, untreated hypertension, unstable angina pectoris, myocardial infarction within the past 12 months, coronary bypass operation within the past 12 months, intake of anticoagulants or participation in other clinical trials dealing with any drugs that affect blood loss.
Recruitment/selection of patients	Patients were enrolled between 2007 and February 2009.
Age, gender and ethnicity	Autotransfusion group (n=59) / No drainage (n=56) Mean age (years): 68 (9) / 69 (8) Female/Male: 42/17 / 39/17
Further population details	Autotransfusion group (n=59) / No drainage (n=56) Intra-operative blood loss (ml): 10 (26) / 15 (37) Drainage 0-6 hours post-operative (ml): 531 (294) / - Drainage 0-24 hours post-operative (ml): 702 (377) / -
Indirectness of population	No indirectness
Interventions	Auto transfusion group (PCS) (n=59) A drain was inserted in the knee joint at the end of the operative procedure. Low suction drainage was started 30 minutes after the operation and the drained blood was re-transfused within 6 hours of surgery. In accordance with the manufacturer's guidelines, no more than 1,500 ml of blood could be re-transfused. Drains were removed 24 hours after surgery. No drainage group (control) (n=56)
Funding	Not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PCS VERSUS CONTROL

No. of patients requiring allogeneic transfusions
PCS: 6/59
control: 11/56
Risk of bias: High; Indirectness of outcome: No indirectness

Length of hospital stay (no SD reported) PCS: 6.7 days control: 6.6 days Risk of bias: High; Indirectness of outcome: No indirectness Infections (pneumonia) PCS: 1/59 control: 0/56 Risk of bias: High; Indirectness of outcome: No indirectness Thrombotic complications (Pulmonary Embolism) PCS: 1/59 Control: 0/56 Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life, Number of units of allogeneic blood transfused / volume of allogeneic blood transfused(in ml), Serious adverse events (as defined by study)

Study	**Horstmann 2014 A**
Study type	Open, double blind, randomised controlled single centre study
Number of studies (number of participants)	n=1 (n=118)
Countries and setting	Conducted in The Netherlands; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	Adults		
Subgroup analysis within study	Not applicable		
Inclusion criteria	Patients scheduled for primary THA (total hip arthroplasty) and written informed consent.		
Exclusion criteria	Coagulation disorders, including deep vein thrombosis and pulmonary embolism, malignancy, on-going infections, untreated hypertension, unstable angina pectoris, myocardial infarction within the past 12 months, coronary artery bypass surgery within the past 12 months, renal dysfunction, anti-coagulant intake or participation in other clinical trials dealing with any drugs that affect blood loss.		
Recruitment/selection of patients	Patients were operated at Isala clinics, Zwolle, The Netherlands.		
Age, gender and ethnicity		ABT (n=56)	Drain group (n=62)
	Mean age (years)	67.6 (9.1)	69.3 (9.5)
	M/F	36/20	42/20
Further population details	Type of surgery: primary THA (total hip arthroplasty) The groups were statistically homogeneous with respect to gender, age, BMI, medical history and indication for operation.		
Indirectness of population	No indirectness		
Interventions	ABT group (intra and post-operative autologous blood re-transfusion)[ICS+PCS (intra-operative cell salvage + post-operative cell salvage) n=56 In the ABT group, blood collected during the operation was subsequently re-transfused after filtering through 200-, 80-, and 40-micrometre filters consecutively, and a drain with a post-operative re-transfusion unit was inserted. Post-operatively drained blood was re-transfused within 6 hours of surgery. Control (high vacuum closed-suction drainage) n=62 A closed suction high-vacuum drain was inserted, intra-operatively suctioned blood was not re-transfused in this group. In both groups, the drains were removed 24 hours post-operatively. Note: Venous thromboembolism prophylaxis was carried out using fondaparinux subcutaneously once daily. Administration of NSAIDs was stopped one day before surgery. Additional allogeneic blood transfusions were given based on the Dutch allogeneic blood transfusion guideline.		

Funding	Not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : ICS + PCS vs. control No. of patients requiring allogeneic transfusions ICS+PCS: 2/56 control: 4/62 Risk of bias: low ; Indirectness of outcome: No indirectness Length of hospital stay (days) ICS+PCS: 4.5±1.2 Control: 4.3±1.0 Risk of bias: low ; Indirectness of outcome: No indirectness Infections (pneumonia) ICS+PCS: 1/56 control: 0/62 Risk of bias: low ; Indirectness of outcome: No indirectness mortality (not related to operation) ICS+PCS: 1/56 control: 0/62 Risk of bias: low ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life, Number of units of allogeneic blood transfused / volume of allogeneic blood transfused(in ml), Thrombotic complications, Serious adverse events (as defined by study)

Study	**Aghdaii 2012[5]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Iran
Line of therapy	Not applicable
Duration of study	Intrevention+follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Primary, elective on-pump CABG surgery; age between 30 and 70 years; left ventricular ejection fraction >=45%; pump time <2 hours; aortic clumping time <45 minutes.
Exclusion criteria	Known coagulation disorders; redo or emergency surgery; patients on warfarin, heparin or other systemic anticoagulant drugs and antiplatelet drugs such as aspirin preoperatively (patients either took no aspirin or a maximum dose of 80mg/day); coexisting diseases (renal and hepatic disease diabetes mellitus, hypertension, and endocrine and hematology disorders).
Recruitment/selection of patients	not reported
Age, gender and ethnicity	Age - Mean (SD): cell salvage group: 58+/-5.4, no cell salvage group: 55+/-14. Gender (M:F): 33/17. Ethnicity: not reported
Further population details	1. Type of surgery : Cardiovascular surgery (Coronary artery by pass graft).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Intra-operative cell salvage therapy + Post-operative cell salvage therapy . Blood aspirated from wound area, operative field, cardiopulmonary bypass circuit and heart-lung machine collected in cell-saver reservoir primed with 150ml of normal saline and 30,000 IU heparin/L, washed and concentrated with continuous-flow cell saver before retransfusion. Cell-saver device started prior to skin incision using 1000ml saline as a washing solution. Reinfusion of cell-salvage blood was done regardless of postoperative hematocrit levels. . Duration not applicable. Concurrent medication/care: none reported Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (During surgery:

	haemoglobin <7 g/dL (hematocrit <21%); After surgery trigger in no cell salvage group: Hb <8 g/dL (hematocrit <24%)). (n=25) Intervention 2: No cell salvage therapy. Homologous blood transfusions based on haemoglobin and haematocrit levels. Duration not applicable. Concurrent medication/care: none reported Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (During surgery: haemoglobin <7 g/dL (hematocrit <21%); After surgery trigger in no cell salvage group: Hb <8 g/dL (hematocrit <24%).
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-OPERATIVE CELL SALVAGE THERAPY + POST-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY Protocol outcome 1: Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up - Actual outcome: Number of units transfused per patient at up to discharge; Group 1: mean 0.4 mL (SD 0.8); n=25, Group 2: mean 0.7 mL (SD 1); n=25; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Mortality (all causes) at 30 days - Actual outcome: Mortality at up to discharge; Group 1: 0/25, Group 2: 0/25; Risk of bias: Low; Indirectness of outcome: Serious indirectness Protocol outcome 3: Number of patients needing transfusions at End of follow-up - Actual outcome: Number of patients requiring transfusion of allogenic red blood cells postoperatively at up to discharge; Group 1: 7/25, Group 2: 8/25; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Serious adverse events of donor blood transfusion. at End of follow-up; Serious adverse events of cell salvage therapy at End of follow-up; Length of hospital stay at End of follow-up

Study	Atay 2010-1[10]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=74)
Countries and setting	Conducted in Turkey
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	First time arthroplasty because of hip osteoarthritis and unilateral surgery
Exclusion criteria	Patients operated simultaneous bilaterally, who had hematologic, chronic metabolic, infectious and/or rheumatologic diseases, with preoperative hemoglobin level below 12 g/dL, using anticoagulant therapy, with previous history of non-arthroplasty surgery in the same area, and planned revision hip arthroplasty were excluded from the study
Recruitment/selection of patients	December 2008 to April 2009
Age, gender and ethnicity	Age - Mean (SD): Cell salvage: 59.78+/-15.43; No cell salvage: 58.95+/-13.6. Gender (M:F): 12/24. Ethnicity: not reported
Further population details	1. Type of surgery : Orthopaedic surgery
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Post-operative cell salvage therapy . Blood transfused at the end of the 4th postoperative hour. Autotransfusion set (Translog, Heim Medizintechnik, Germany). Set could collect approximately 1000ml of blood in 240 microns bag. No anticoagulation included in the system. Routine hemovac drain used postoperatively after transfusion and removed at the end of the 48th hour. . Duration until discharge. Concurrent medication/care: Subcutaneous low molecular weight heparin with adjusted dose according to weight used for deep vein thrombosis prophylaxis and continued for 10 days. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Haemoglobin

	<8 g/dL (hematocrit <25%)). Comments: No blood transfused during surgery (n=19) Intervention 2: No cell salvage therapy. No cell salvage therapy. Routine hemovac drain used postoperatively after transfusion and removed at the end of the 48th hour.. Duration until discharge. Concurrent medication/care: Subcutaneous low molecular weight heparin with adjusted dose according to weight used for deep vein thrombosis prophylaxis and continued for 10 days. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Haemoglobin <8 g/dL (hematocrit <25%)). Comments: No blood transfused during surgery
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POST-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY

Protocol outcome 1: Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up
- Actual outcome: Number of units of blood transfused per patient at up to discharge; Group 1: mean 0.82 (SD 1.07); n=17, Group 2: mean 1.68 (SD 1.44); n=19; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of patients needing transfusions at End of follow-up
- Actual outcome: Number of patients needing allogenic blood transfusion at up to discharge; Group 1: 9/17, Group 2: 15/19; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Serious adverse events of donor blood transfusion. at End of follow-up
- Actual outcome: Complications related to allogenic transfusion: febril reaction at up to discharge; Group 1: 0/17, Group 2: 2/19; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Serious adverse events of cell salvage therapy at End of follow-up
- Actual outcome: Complications related to autotransfusion at up to discharge; Group 1: 0/17, Group 2: 0/19; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at End of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Length of hospital stay at End of follow-up

Study	Atay 2010-2[10]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=41)
Countries and setting	Conducted in Turkey
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cell salvage:
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	First time arthroplasty because of knee osteoarthritis and unilateral surgery
Exclusion criteria	Patients operated simultaneous bilaterally, who had hematologic, chronic metabolic, infectious and/or rheumatologic diseases, with preoperative hemoglobin level below 12 g/dL, using anticoagulant therapy, with previous history of non-arthroplasty surgery in the same area, and planned revision knee arthroplasty were excluded from the study
Recruitment/selection of patients	December 2008 to April 2009
Age, gender and ethnicity	Age - Mean (SD): Cell salvage: 65.25+/-12.57; No cell salvage: 68.19+/-6.62. Gender (M:F): 9/32. Ethnicity: not reported
Further population details	1. Type of surgery : Orthopaedic surgery
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Post-operative cell salvage therapy . Blood transfused at the end of the 4th postoperative hour. Autotransfusion set (Translog, Heim Medizintechnik, Germany). Set could collect approximately 1000ml of blood in 240 microns bag. No anticoagulation included in the system. Routine hemovac drain used postoperatively after transfusion and removed at the end of the 48th hour.. Duration until discharge. Concurrent medication/care: Subcutaneous low molecular weight heparin with adjusted dose according to weight used for deep vein thrombosis prophylaxis and continued for 10 days. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Haemoglobin <8 g/dL (hematocrit <25%)).

	Comments: No blood transfused during surgery (n=21) Intervention 2: No cell salvage therapy. No cell salvage therapy. Routine hemovac drain used postoperatively after transfusion and removed at the end of the 48th hour.. Duration until discharge. Concurrent medication/care: Subcutaneous low molecular weight heparin with adjusted dose according to weight used for deep vein thrombosis prophylaxis and continued for 10 days. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Haemoglobin <8 g/dL (hematocrit <25%)). Comments: No blood transfused during surgery
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POST-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY Protocol outcome 1: Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up - Actual outcome: Number of units of blood transfused per patient at up to discharge; Group 1: mean 0.05 (SD 0.22); n=20, Group 2: mean 0.71 (SD 0.96); n=21; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at End of follow-up - Actual outcome: Number of patients needing allogenic blood transfusion at up to discharge; Group 1: 1/20, Group 2: 8/21; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Serious adverse events of donor blood transfusion. at End of follow-up - Actual outcome: Complications related to allogenic transfusion: febril reaction at up to discharge; Group 1: 0/0, Group 2: 1/21; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Serious adverse events of cell salvage therapy at End of follow-up - Actual outcome: Complications related to autotransfusion at up to discharge; Group 1: 0/20, Group 2: 0/21; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site

infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Length of hospital stay at End of follow-up

Study	Bowley 2006[16]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=44)
Countries and setting	Conducted in South Africa
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Penetrating trauma injury requiring laparotomy with hypotension (<90mmHg) either preohospital or on arrival and were considered to have significant blood loss
Exclusion criteria	<18 years old; injury >6 hours old
Recruitment/selection of patients	Emergency room
Age, gender and ethnicity	Age - Range: 20 to 54 years. Gender (M:F): 40/4. Ethnicity: not reported
Further population details	1. Type of surgery : Major abdominal surgery (includes obstetrics and gyanecological)
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: Intra-operative cell salvage therapy. Intraoperative cell salvage therapy using a Saver 4 machine (Haemonetics, Braintree, MA, USA). Duration during surgery. Concurrent medication/care: none reported Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: No transfusion protocol Comments: 9/21 patients did not have a sample of cell saved blood taken before reinfusion (n=23) Intervention 2: No cell salvage therapy. Duration during surgery. Concurrent medication/care: none reported Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: No transfusion protocol

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY Protocol outcome 1: Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up - Actual outcome: Mean number of allogenic units transfused at up to 24 hours post injury; Group 1: mean 6.47 (SD 5.14); n=21, Group 2: mean 11.17 (SD 6.06); n=23; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Mortality (all causes) at 30 days - Actual outcome: Mortality at up to discharge; Group 1: 14/21, Group 2: 15/23; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery - Actual outcome: Postoperative sepsis in patients who did not die of exsanguination at up to discharge; Group 1: 5/13, Group 2: 7/13; Risk of bias: ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Number of patients needing transfusions at End of follow-up; Serious adverse events of donor blood transfusion. at End of follow-up; Serious adverse events of cell salvage therapy at End of follow-up; Length of hospital stay at End of follow-up

Study (subsidiary papers)	**Carless 2010[20] (Klein 2008[84], Laub 1993[88], Mcgill 2002[103], Abuzakuk 2007[1], Adalberth 1998[2], Altinel 2007[7], Amin 2008[8], Axford 1994[12], Ayers 1995[13], Bouboulis 1994[15], Cheng 2005[26], Clagett 1999[31], Dalrymple-hay 1999[38], Damgaard 2006[39], Davies 1987[42], Dietrich 1989[48], Dramis 2006[51], Ekback 1995[53], Elawad 1991[54], Eng 1990[55], Fragnito 1995[60], Gannon 1991[62], Goel 2007[64], Healy 1994[66], Heddle 1992[68], Kelley-patteson 1993[79], Kirkos 2006[83], Koopman-van gemert 1993[85], Lepore 1989[90], Lorentz 1991[94], Mah 1995[97], Majkowski 1991[98], Martin 2000[100], Mauerhan 1993[102], Menges 1992[104], Mercer 2004[105], Moonen 2007[108], Murphy 2004[109], Murphy 2005[110], Naumenko 2003[115], Newman 1997[116], Niranjan 2006[118], Page 1989[123], Parrot 1991[124], Pleym 2005[127], Riou 1994[134], Ritter 1994[135], Rollo 1995[136], Rosencher 1994[137], Sait 1999[139], Schaff 1978[141], Schmidt 1997[143], Schonberger 1993[144], Shenolikar 1997[150], Shirvani 1991[151], Simpson 1994[152], Sirvinskas 2007[153], Slagis 1991[154], Smith 2007[157], So-osman 2006[158], Spark 1997[160], Tempe 1996[165], Tempe 2001[166], Thomas 2001[167], Thurer 1979[169], Tripkovic 2008[173], Unsworth-white 1996[175], Ward 1993[183], Westerberg 2004[186], Wiefferink 2007[187], Zacharopoulos 2007[191], Zhang 2008[192], Zhao 1996[193], Zhao 2003[194])**
Study type	Systematic Review
Number of studies (number of participants)	75 (n=6025)
Countries and setting	Conducted in Multiple countries
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Systematic review – pre-specified in protocol: type of surgery, use of transfusion protocols, active concomitant treatment, timing of cell salvage
Inclusion criteria	Elective or non-urgent surgical patients
Exclusion criteria	studies not reporting data on either the number of patients transfused with red cells or the volume of blood transfused
Age, gender and ethnicity	Age - Other: not reported. Gender (M:F): not reported. Ethnicity:
Further population details	Type of surgery : Mixed (orthopaedic, cardiac, vascular).
Indirectness of population	No indirectness
Interventions	(n=3048) Intervention 1: Mixed: intraoperative, postoperative or intraoperative + post operative cell salvage therapy.

	Intraoperative + postoperative cell salvage therapy . Duration not reported. Concurrent medication/care: Mixture with some studies having active background treatment Further details: 1. Active treatment: Mixed 2. Transfusion protocol: Mixed (n=2977) Intervention 2: No cell salvage therapy. No cell salvage therapy. Duration not reported. Concurrent medication/care: Mixture with some studies having active background treatment Further details: 1. Active treatment: Mixed 2. Transfusion protocol: Mixed
Funding	Academic or government funding
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Length of hospital stay at End of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Number of patients needing transfusions at End of follow-up; Serious adverse events of donor blood transfusion. at End of follow-up; Serious adverse events of cell salvage therapy at End of follow-up; Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up

Study	Cip 2013[30]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=151)
Countries and setting	Conducted in Austria
Line of therapy	Not applicable
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Primary elective total knee arthroplasty for osteoarthritis
Exclusion criteria	Not defined as an priori list. Reports numbers of patients excluded prior to randomisation from a total of 223 total knee arthroplasties carried out at the centre: unwillingness to participate (53); revision arthroplasty (19).
Recruitment/selection of patients	From December 2007 to January 2009
Age, gender and ethnicity	Age - Mean (SD): 70 years. Gender (M:F): Define. Ethnicity: not reported
Further population details	1. Type of surgery : Orthopaedic surgery
Indirectness of population	No indirectness
Interventions	(n=76) Intervention 1: Intra-operative cell salvage therapy + Post-operative cell salvage therapy . Intraoperative and postoperative cell salvage therapy. Retransfusion system that processed blood by completing anticoagulation, fitering, washing and centrifugation steps. Orthopaedic Perioperative Autotransfusion System (OrthoPAT, Haemonetics Corp, Braintree, MA, USA) used for cell salvage and retransfusions.. Duration Autotransfusion system used for 6 hours after total skin incision (intraoperatively and postoperatively). . Concurrent medication/care: Antithrombotic prophylaxis: 40mg low molecular weight heparin from 1 day before surgery to 42 days postoperatively.Intrvavenous perioperative infection prophylaxis: 1500mg cefuoxime. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Signs of anaemia (vertigo, nausea, vomiting, hypotension, tachycardia) or hemoglobin level <8 g/dL).

	Comments: After retransfusion of blood patients continued with a drainage system without blood for 48 hours. (n=75) Intervention 2: No cell salvage therapy. No autotransfusion. Duration unclear. Concurrent medication/care: Antithrombotic prophylaxis: 40mg low molecular weight heparin from 1 day before surgery to 42 days postoperatively.Intrvavenous perioperative infection prophylaxis: 1500mg cefuoxime. Further details: 1. Active treatment: Mixed 2. Transfusion protocol: Transfusion protocol (Signs of anaemia (vertigo, nausea, vomiting, hypotension, tachycardia) or hemoglobin level <8 g/dL).
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-OPERATIVE CELL SALVAGE THERAPY + POST-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY Protocol outcome 1: Number of patients needing transfusions at End of follow-up - Actual outcome: Number of patients having allogenic blood transfusions at up to discharge; Group 1: 23/70, Group 2: 23/70; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Length of hospital stay at End of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Serious adverse events of donor blood transfusion. at End of follow-up; Serious adverse events of cell salvage therapy at End of follow-up; Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up

Study	Horstmann 2013[74]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=204)
Countries and setting	Conducted in Netherlands
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	pirmary total hip replacement
Exclusion criteria	coagulation disorders including venous thromboembolism; malignancy; ongoing infections; untreated hypertension; unstable angina pectoris; myocardial infarction with the past 12 months; coronary artery bypass surgery within the past 12 months; renal dysfunction; use of anticoagulants.
Recruitment/selection of patients	Recruited between August 2009 and April 2011
Age, gender and ethnicity	Age - Mean (SD): Cell salvage: 67.3(9.3); no cell salvage: 67.6(9.4). Gender (M:F): 57/147. Ethnicity: not reported
Further population details	1. Type of surgery : Orthopaedic surgery
Indirectness of population	No indirectness
Interventions	(n=102) Intervention 1: Intra-operative cell salvage therapy + Post-operative cell salvage therapy . Intraoperative and postoperative blood retransfused after sequential filtering through 200um, 80um and 40um filters. Blood collected intraoperatively retransfused within 6 hours of surgery. Manufacturers guidelines state not to retransfuse >1500ml of introperatively collected blood and >1000ml of postoperatively drained blood. Drains removed 24 hours postoperatively. (Sangvia, autologous blood salvage, low vacuum, 100 to 150mmHg, Astratech, Molndal, Sweden).. Duration not reported. Concurrent medication/care: Fondaparinux (2.5mg/0.5ml) starting 6 to 8 hours after surgery and continued for 5 weeks once daily. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Triggers: Hb

	6.4g/dL for American Society of Anesthesiologists (ASA) grade 1 patients; 8.0g/dL for ASA grade 2/3 patients; 9.6g/dL for ASA grade 4 patients (and in patients who failed to increase their cardiac output to compensate for dilution).). (n=102) Intervention 2. No cell salvage therapy. No drain was inserted for postoperative period. . Duration not reported. Concurrent medication/care: Fondaparinux (2.5mg/0.5ml) starting 6 to 8 hours after surgery and continued for 5 weeks once daily. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Triggers: Hb 6.4g/dL for American Society of Anesthesiologists (ASA) grade 1 patients; 8.0g/dL for ASA grade 2/3 patients; 9.6g/dL for ASA grade 4 patients (and in patients who failed to increase their cardiac output to compensate for dilution).).
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-OPERATIVE CELL SALVAGE THERAPY + POST-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY Protocol outcome 1: Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up - Actual outcome: Number of units of homologous blood transfused per patient at not reported; Group 1: mean 2 (SD 0); n=102, Group 2: mean 2 (SD 0); n=102; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Length of hospital stay at End of follow-up - Actual outcome: Length of hospital stay at days; Group 1: mean 4.8 (SD 1.7); n=102, Group 2: mean 5.1 (SD 2.3); n=102; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Number of patients needing transfusions at End of follow-up - Actual outcome: Number of patients needing homologous blood transfusions at not reported; Group 1: 4/102, Group 2: 9/102; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Serious adverse events of donor blood transfusion. at End of follow-up; Serious adverse events of cell salvage therapy at End of follow-up; Mortality (all causes) at 30 days

Study	Aghdaii 2012[5]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Iran
Line of therapy	Not applicable
Duration of study	Intervention+follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Primary, elective on-pump CABG surgery; age between 30 and 70 years; left ventricular ejection fraction >=45%; pump time <2 hours; aortic clumping time <45 minutes.
Exclusion criteria	Known coagulation disorders; redo or emergency surgery; patients on warfarin, heparin or other systemic anticoagulant drugs and antiplatelet drugs such as aspirin preoperatively (patients either took no aspirin or a maximum dose of 80mg/day); coexisting diseases (renal and hepatic disease diabetes mellitus, hypertension, and endocrine and hematology disorders).
Recruitment/selection of patients	not reported
Age, gender and ethnicity	Age - Mean (SD): cell salvage group: 58+/-5.4, no cell salvage group: 55+/-14. Gender (M:F): 33/17. Ethnicity: not reported

Further population details	1. Type of surgery: Cardiovascular surgery (Coronary artery by pass graft).
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Intra-operative cell salvage therapy + Post-operative cell salvage therapy . Blood aspirated from wound area, operative field, cardiopulmonary bypass circuit and heart-lung machine collected in cell-saver reservoir primed with 150ml of normal saline and 30,000 IU heparin/L, washed and concentrated with continuous-flow cell saver before retransfusion. Cell-saver device started prior to skin incision using 1000ml saline as a washing solution. Reinfusion of cell-salvage blood was done regardless of postoperative hematocrit levels. . Duration not applicable. Concurrent medication/care: none reported Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (During surgery: haemoglobin <7 g/dL (hematocrit <21%); After surgery trigger in no cell salvage group: Hb <8 g/dL (hematocrit <24%). (n=25) Intervention 2: No cell salvage therapy. Homologous blood transfusions based on haemoglobin and haematocrit levels. Duration not applicable. Concurrent medication/care: none reported Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (During surgery: haemoglobin <7 g/dL (hematocrit <21%); After surgery trigger in no cell salvage group: Hb <8 g/dL (hematocrit <24%)).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-OPERATIVE CELL SALVAGE THERAPY + POST-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY

Protocol outcome 1: Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up
- Actual outcome: Number of units transfused per patient at up to discharge; Group 1: mean 0.4 mL (SD 0.8); n=25, Group 2: mean 0.7 mL (SD 1); n=25; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Mortality (all causes) at 30 days - Actual outcome: Mortality at up to discharge; Group 1: 0/25, Group 2: 0/25; Risk of bias: Low; Indirectness of outcome: Serious indirectness Protocol outcome 3: Number of patients needing transfusions at End of follow-up - Actual outcome: Number of patients requiring transfusion of allogenic red blood cells postoperatively at up to discharge; Group 1: 7/25, Group 2: 8/25; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Serious adverse events of donor blood transfusion. at End of follow-up; Serious adverse events of cell salvage therapy at End of follow-up; Length of hospital stay at End of follow-up

Study	Atay 2010-1[10]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=74)
Countries and setting	Conducted in Turkey
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	First time arthroplasty because of hip osteoarthritis and unilateral surgery
Exclusion criteria	Patients operated simultaneous bilaterally, who had hematologic, chronic metabolic, infectious and/or rheumatologic diseases, with preoperative hemoglobin level below 12 g/dL, using anticoagulant therapy, with previous history of non-arthroplasty surgery in the same area, and planned revision hip arthroplasty were excluded from the study
Recruitment/selection of patients	December 2008 to April 2009
Age, gender and ethnicity	Age - Mean (SD): Cell salvage: 59.78+/-15.43; No cell salvage: 58.95+/-13.6. Gender (M:F): 12/24. Ethnicity: not reported

Further population details	1. Type of surgery : Orthopaedic surgery
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: Post-operative cell salvage therapy. Blood transfused at the end of the 4th postoperative hour. Autotransfusion set (Translog, Heim Medizintechnik, Germany). Set could collect approximately 1000ml of blood in 240 microns bag. No anticoagulation included in the system. Routine hemovac drain used postoperatively after transfusion and removed at the end of the 48th hour. . Duration until discharge. Concurrent medication/care: Subcutaneous low molecular weight heparin with adjusted dose according to weight used for deep vein thrombosis prophylaxis and continued for 10 days. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Haemoglobin <8 g/dL (hematocrit <25%)). Comments: No blood transfused during surgery (n=19) Intervention 2: No cell salvage therapy. Routine hemovac drain used postoperatively after transfusion and removed at the end of the 48th hour. Duration until discharge. Concurrent medication/care: Subcutaneous low molecular weight heparin with adjusted dose according to weight used for deep vein thrombosis prophylaxis and continued for 10 days. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Haemoglobin <8 g/dL (hematocrit <25%)). Comments: No blood transfused during surgery
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POST-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY

Protocol outcome 1: Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up
- Actual outcome: Number of units of blood transfused per patient at up to discharge; Group 1: mean 0.82 (SD 1.07); n=17, Group 2: mean 1.68 (SD 1.44); n=19; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of patients needing transfusions at End of follow-up - Actual outcome: Number of patients needing allogenic blood transfusion at up to discharge; Group 1: 9/17, Group 2: 15/19; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Serious adverse events of donor blood transfusion. at End of follow-up - Actual outcome: Complications related to allogenic transfusion: febril reaction at up to discharge; Group 1: 0/17, Group 2: 2/19; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Serious adverse events of cell salvage therapy at End of follow-up - Actual outcome: Complications related to autotransfusion at up to discharge; Group 1: 0/17, Group 2: 0/19; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Length of hospital stay at End of follow-up

Study	Atay 2010-2[10]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=41)
Countries and setting	Conducted in Turkey
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Cell salvage:
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	First time arthroplasty because of knee osteoarthritis and unilateral surgery
Exclusion criteria	Patients operated simultaneous bilaterally, who had hematologic, chronic metabolic, infectious and/or rheumatologic diseases, with preoperative hemoglobin level below 12 g/dL, using anticoagulant therapy, with previous history of non-arthroplasty surgery in the same area, and planned revision knee arthroplasty were excluded from the study
Recruitment/selection of patients	December 2008 to April 2009
Age, gender and ethnicity	Age - Mean (SD): Cell salvage: 65.25+/-12.57; No cell salvage: 68.19+/-6.62. Gender (M:F): 9/32. Ethnicity: not reported

Further population details	1. Type of surgery : Orthopaedic surgery
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Post-operative cell salvage therapy. Blood transfused at the end of the 4th postoperative hour. Autotransfusion set (Translog, Heim Medizintechnik, Germany). Set could collect approximately 1000ml of blood in 240 microns bag. No anticoagulation included in the system. Routine hemovac drain used postoperatively after transfusion and removed at the end of the 48th hour.. Duration until discharge. Concurrent medication/care: Subcutaneous low molecular weight heparin with adjusted dose according to weight used for deep vein thrombosis prophylaxis and continued for 10 days. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Haemoglobin <8 g/dL (hematocrit <25%)). Comments: No blood transfused during surgery (n=21) Intervention 2: No cell salvage therapy. Routine hemovac drain used postoperatively after transfusion and removed at the end of the 48th hour. Duration until discharge. Concurrent medication/care: Subcutaneous low molecular weight heparin with adjusted dose according to weight used for deep vein thrombosis prophylaxis and continued for 10 days. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Haemoglobin <8 g/dL (hematocrit <25%)). Comments: No blood transfused during surgery
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: POST-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY

Protocol outcome 1: Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up
- Actual outcome: Number of units of blood transfused per patient at up to discharge; Group 1: mean 0.05 (SD 0.22); n=20, Group 2: mean 0.71 (SD 0.96); n=21; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of patients needing transfusions at End of follow-up - Actual outcome: Number of patients needing allogenic blood transfusion at up to discharge; Group 1: 1/20, Group 2: 8/21; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Serious adverse events of donor blood transfusion. at End of follow-up - Actual outcome: Complications related to allogenic transfusion: febril reaction at up to discharge; Group 1: 0/0, Group 2: 1/21; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Serious adverse events of cell salvage therapy at End of follow-up - Actual outcome: Complications related to autotransfusion at up to discharge; Group 1: 0/20, Group 2: 0/21; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Length of hospital stay at End of follow-up

Study	Bowley 2006[16]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=44)
Countries and setting	Conducted in South Africa
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Penetrating trauma injury requiring laparotomy with hypotension (<90mmHg) either preohospital or on arrival and were considered to have significant blood loss
Exclusion criteria	<18 years old; injury >6 hours old
Recruitment/selection of patients	Emergency room
Age, gender and ethnicity	Age - Range: 20 to 54 years. Gender (M:F): 40/4. Ethnicity: not reported
Further population details	1. Type of surgery : Major abdominal surgery (includes obstetrics and gyanecological)
Indirectness of population	No indirectness

Interventions	(n=21) Intervention 1: Intra-operative cell salvage therapy. Intraoperative cell salvage therapy using a Saver 4 machine (Haemonetics, Braintree, MA, USA). Duration during surgery. Concurrent medication/care: none reported Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: No transfusion protocol Comments: 9/21 patients did not have a sample of cell saved blood taken before reinfusion (n=23) Intervention 2: No cell salvage therapy. Duration during surgery. Concurrent medication/care: none reported Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: No transfusion protocol
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY Protocol outcome 1: Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up - Actual outcome: Mean number of allogenic units transfused at up to 24 hours post injury; Group 1: mean 6.47 (SD 5.14); n=21, Group 2: mean 11.17 (SD 6.06); n=23; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Mortality (all causes) at 30 days - Actual outcome: Mortality at up to discharge; Group 1: 14/21, Group 2: 15/23; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery - Actual outcome: Postoperative sepsis in patients who did not die of exsanguination at up to discharge; Group 1: 5/13, Group 2: 7/13; Risk of bias: ; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Number of patients needing transfusions at End of follow-up; Serious adverse events of donor blood transfusion. at End of follow-up; Serious adverse events of cell salvage therapy at End of follow-up; Length of hospital stay at End of follow-up

Study (subsidiary papers)	**Carless 2010[20] (Klein 2008[84], Laub 1993[88], Mcgill 2002[103], Abuzakuk 2007[1], Adalberth 1998[2], Altinel 2007[7], Amin 2008[8], Axford 1994[12], Ayers 1995[13], Bouboulis 1994[15], Cheng 2005[26], Clagett 1999[31], Dalrymple-hay 1999[38], Damgaard 2006[39], Davies 1987[42], Dietrich 1989[48], Dramis 2006[51], Ekback 1995[53], Elawad 1991[54], Eng 1990[55], Fragnito 1995[60], Gannon 1991[62], Goel 2007[64], Healy 1994[66], Heddle 1992[68], Kelley-patteson 1993[79], Kirkos 2006[83], Koopman-van gemert 1993[85], Lepore 1989[90], Lorentz 1991[94], Mah 1995[97], Majkowski 1991[98], Martin 2000[100], Mauerhan 1993[102], Menges 1992[104], Mercer 2004[105], Moonen 2007[108], Murphy 2004[109], Murphy 2005[110], Naumenko 2003[115], Newman 1997[116], Niranjan 2006[118], Page 1989[123], Parrot 1991[124], Pleym 2005[127], Riou 1994[134], Ritter 1994[135], Rollo 1995[136], Rosencher 1994[137], Sait 1999[139], Schaff 1978[141], Schmidt 1997[143], Schonberger 1993[144], Shenolikar 1997[150], Shirvani 1991[151], Simpson 1994[152], Sirvinskas 2007[153], Slagis 1991[154], Smith 2007[157], So-osman 2006[158], Spark 1997[160], Tempe 1996[165], Tempe 2001[166], Thomas 2001[167], Thurer 1979[169], Tripkovic 2008[173], Unsworth-white 1996[175], Ward 1993[183], Westerberg 2004[186], Wiefferink 2007[187], Zacharopoulos 2007[191], Zhang 2008[192], Zhao 1996[193], Zhao 2003[194])**
Study type	Systematic Review
Number of studies (number of participants)	75 (n=6025)
Countries and setting	Conducted in Multiple countries
Line of therapy	Not applicable
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Systematic review – pre-specified in protocol: type of surgery, use of transfusion protocols, active concomitant treatment, timing of cell salvage

Inclusion criteria	Elective or non-urgent surgical patients
Exclusion criteria	studies not reporting data on either the number of patients transfused with red cells or the volume of blood transfused
Age, gender and ethnicity	Age - Other: not reported. Gender (M:F): not reported. Ethnicity:
Further population details	Type of surgery : Mixed (orthopaedic, cardiac, vascular).
Indirectness of population	No indirectness
Interventions	(n=3048) Intervention 1: Mixed: intraoperative, postoperative or intraoperative + post operative cell salvage therapy. Intraoperative + postoperative cell salvage therapy. Duration not reported. Concurrent medication/care: Mixture with some studies having active background treatment Further details: 1. Active treatment: Mixed 2. Transfusion protocol: Mixed (n=2977) Intervention 2: No cell salvage therapy. Duration not reported. Concurrent medication/care: Mixture with some studies having active background treatment Further details: 1. Active treatment: Mixed 2. Transfusion protocol: Mixed
Funding	Academic or government funding
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Length of hospital stay at End of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Number of patients needing transfusions at End of follow-up; Serious adverse events of donor blood transfusion. at End of follow-up; Serious adverse events of cell salvage therapy at End of follow-up; Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up

Study	Cip 2013[30]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=151)
Countries and setting	Conducted in Austria
Line of therapy	Not applicable
Duration of study	Intervention time:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Primary elective total knee arthroplasty for osteoarthritis
Exclusion criteria	Not defined as an priori list. Reports numbers of patients excluded prior to randomisation from a total of 223 total knee arthroplasties carried out at the centre: unwillingness to participate (53); revision arthroplasty (19).
Recruitment/selection of patients	From December 2007 to January 2009
Age, gender and ethnicity	Age - Mean (SD): 70 years. Gender (M:F): Define. Ethnicity: not reported
Further population details	Type of surgery : Orthopaedic surgery

Indirectness of population	No indirectness
Interventions	(n=76) Intervention 1: Intra-operative cell salvage therapy + Post-operative cell salvage therapy . Intraoperative and postoperative cell salvage therapy. Retransfusion system that processed blood by completing anticoagulation, fitering, washing and centrifugation steps. Orthopaedic Perioperative Autotransfusion System (OrthoPAT, Haemonetics Corp, Braintree, MA, USA) used for cell salvage and retransfusions.. Duration Autotransfusion system used for 6 hours after total skin incision (intraoperatively and postoperatively). . Concurrent medication/care: Antithrombotic prophylaxis: 40mg low molecular weight heparin from 1 day before surgery to 42 days postoperatively.Intrvavenous perioperative infection prophylaxis: 1500mg cefuoxime. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Signs of anaemia (vertigo, nausea, vomiting, hypotension, tachycardia) or hemoglobin level <8 g/dL). Comments: After retransfusion of blood patients continued with a drainage system without blood for 48 hours. (n=75) Intervention 2: No cell salvage therapy. No autotransfusion. Duration unclear. Concurrent medication/care: Antithrombotic prophylaxis: 40mg low molecular weight heparin from 1 day before surgery to 42 days postoperatively.Intrvavenous perioperative infection prophylaxis: 1500mg cefuoxime. Further details: 1. Active treatment: Mixed 2. Transfusion protocol: Transfusion protocol (Signs of anaemia (vertigo, nausea, vomiting, hypotension, tachycardia) or hemoglobin level <8 g/dL).
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-OPERATIVE CELL SALVAGE THERAPY + POST-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY

Protocol outcome 1: Number of patients needing transfusions at End of follow-up
- Actual outcome: Number of patients having allogenic blood transfusions at up to discharge; Group 1: 23/70, Group 2: 23/70; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at End of follow-up; Length of hospital stay at End of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Serious adverse events of donor blood transfusion. at End of follow-up; Serious adverse events of cell salvage therapy at End of follow-up; Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up

Study	Horstmann 2013[74]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=204)
Countries and setting	Conducted in Netherlands
Line of therapy	Not applicable
Duration of study	Not clear:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Primary total hip replacement
Exclusion criteria	coagulation disorders including venous thromboembolism; malignancy; ongoing infections; untreated hypertension; unstable angina pectoris; myocardial infarction with the past 12 months; coronary artery bypass surgery within the past 12 months; renal dysfunction; use of anticoagulants.
Recruitment/selection of patients	Recruited between August 2009 and April 2011
Age, gender and ethnicity	Age - Mean (SD): Cell salvage: 67.3(9.3); no cell salvage: 67.6(9.4). Gender (M:F): 57/147. Ethnicity: not reported
Further population details	Type of surgery : Orthopaedic surgery

Indirectness of population	No indirectness
Interventions	(n=102) Intervention 1: Intra-operative cell salvage therapy + Post-operative cell salvage therapy . Intraoperative and postoperative blood retransfused after sequential filtering through 200um, 80um and 40um filters. Blood collected intraoperatively retransfused within 6 hours of surgery. Manufacturers guidelines state not to retransfuse >1500ml of introperatively collected blood and >1000ml of postoperatively drained blood. Drains removed 24 hours postoperatively. (Sangvia, autologous blood salvage, low vacuum, 100 to 150mmHg, Astratech, Molndal, Sweden).. Duration not reported. Concurrent medication/care: Fondaparinux (2.5mg/0.5ml) starting 6 to 8 hours after surgery and continued for 5 weeks once daily. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Triggers: Hb 6.4g/dL for American Society of Anesthesiologists (ASA) grade 1 patients; 8.0g/dL for ASA grade 2/3 patients; 9.6g/dL for ASA grade 4 patients (and in patients who failed to increase their cardiac output to compensate for dilution).). (n=102) Intervention 2: No cell salvage therapy. No drain was inserted for postoperative period. . Duration not reported. Concurrent medication/care: Fondaparinux (2.5mg/0.5ml) starting 6 to 8 hours after surgery and continued for 5 weeks once daily. Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: Transfusion protocol (Triggers: Hb 6.4g/dL for American Society of Anesthesiologists (ASA) grade 1 patients; 8.0g/dL for ASA grade 2/3 patients; 9.6g/dL for ASA grade 4 patients (and in patients who failed to increase their cardiac output to compensate for dilution).).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-OPERATIVE CELL SALVAGE THERAPY + POST-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY

Protocol outcome 1: Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up

- Actual outcome: Number of units of homologous blood transfused per patient at not reported; Group 1: mean 2 (SD 0); n=102, Group 2: mean 2 (SD 0); n=102; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Length of hospital stay at End of follow-up - Actual outcome: Length of hospital stay at days; Group 1: mean 4.8 (SD 1.7); n=102, Group 2: mean 5.1 (SD 2.3); n=102; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Number of patients needing transfusions at End of follow-up - Actual outcome: Number of patients needing homologous blood transfusions at not reported; Group 1: 4/102, Group 2: 9/102; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Serious adverse events of donor blood transfusion. at End of follow-up; Serious adverse events of cell salvage therapy at End of follow-up; Mortality (all causes) at 30 days

Study	Rainaldi 1998[130]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=68)
Countries and setting	Conducted in Italy
Line of therapy	Not applicable
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Caesarian section
Exclusion criteria	not reported
Recruitment/selection of patients	not reported
Age, gender and ethnicity	Age - Mean (range): 32.7 (16-43). Gender (M:F): 0/100. Ethnicity: not reported
Further population details	1. Type of surgery : Major abdominal surgery (includes obstetrics and gyanecological)
Extra comments	Indications for caesarean section: foetal distress (11 patients); foetal malposition (11); repeat caesarian section (23); small pelvis (3); multiple pregnancy (8); elderly pirmipara (4); preclampsia (4); placenta praevia

	(4)
Indirectness of population	No indirectness
Interventions	(n=34) Intervention 1: Intra-operative cell salvage therapy . Intraoperative blood salvage (Dideco machine, Mironadola, Modena, Italy). Blood salvaged after extraction of fetoplacental unit.. Duration during surgery. Concurrent medication/care: none reported Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: No transfusion protocol Comments: Study reports in order to test blood 15 patients blood was salvaged but not reinfused. It does not report from which group of patients the blood was taken. (n=34) Intervention 2: No cell salvage. Duration during surgery. Concurrent medication/care: none reported Further details: 1. Active treatment: No active treatment 2. Transfusion protocol: No transfusion protocol
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY Protocol outcome 1: Length of hospital stay at End of follow-up - Actual outcome: Length of hospital stay at as per result; Group 1: mean 5.3 days (SD 1.9); n=34, Group 2: mean 7.3 days (SD 4); n=34; Risk of bias: Very high; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at End of follow-up - Actual outcome: Number of patients needing blood transfusions at up to hospital discharge; Group 1: 1/34, Group 2: 8/34; Risk of bias: Very high; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Serious adverse events of

	donor blood transfusion. at End of follow-up; Serious adverse events of cell salvage therapy at End of follow-up; Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up

Study	Thomassen 2012[168]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=227)
Countries and setting	Conducted in Austria, Netherlands, Norway, Spain
Line of therapy	Not applicable
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Primary or revision total hip arthroplasty and classified as American Society of Anesthesiology (ASA) class I, II or III.
Exclusion criteria	Previous randomization in this study; involvement in the planning and/or conduct of this studyl; participation in an interfering study; symptoms of hemophilia; contraindications for autologous blood useg; known malignancy in the last five years; expected use of cytotoxic drugs; untreated anemia (hemoglobin (Hb) level <11 g/dL); revision total hip arthroplasties with expected serious bone grafting; use of other alternatives for blood conservation such as recombinant erythropoietin, fibrin sealant, aprotinin and other autologous blood transfusion.
Recruitment/selection of patients	Patients enrolled between May 2009 and April 2010

Age, gender and ethnicity	Age - Mean (SD): Cell salvage: 67 (11); no cell salvage: 65 (12). Gender (M:F): Define. Ethnicity: not reported
Further population details	1. Type of surgery : Orthopaedic surgery
Indirectness of population	No indirectness
Interventions	(n=113) Intervention 1: Intra-operative cell salvage therapy + Post-operative cell salvage therapy . Intraoperative and postoperative cell salvage transfusion (Sangvia Blood Management System, Astra Tech AB, Moldal, Sweden). Duration up until first postoperative morning. Concurrent medication/care: Use of tranexamic acid permitted if routinely used in the individual clinic and therefore equally randomised between groups.Postoperative drains used in both groups. Further details: 1. Active treatment: Mixed (Use of tranexamic acid depended on the individual clinic.). 2. Transfusion protocol: Transfusion protocol (Trigger: Hb <8.5 g/dL or significant clinical symptoms of anaemia.). (n=114) Intervention 2: No cell salvage therapy. Duration up until first postoperative morning. Concurrent medication/care: Use of tranexamic acid permitted if routinely used in the individual clinic and therefore equally randomised between groups.Postoperative drains used in both groups. Further details: 1. Active treatment: Mixed (Use of tranexamic acid depended on the individual clinic). 2. Transfusion protocol: Transfusion protocol (Trigger: Hb <8.5 g/dL or significant clinical symptoms of anaemia.).
Funding	Study funded by industry (Astra Tech AB, Moldal, Sweden)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: INTRA-OPERATIVE CELL SALVAGE THERAPY + POST-OPERATIVE CELL SALVAGE THERAPY versus NO CELL SALVAGE THERAPY

Protocol outcome 1: Quality of life at End of follow-up
- Actual outcome: EQ-5D at 2 months; Risk of bias: Flawed; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of units of blood transfused (i.e. donor blood of red cells, platelets, FFP and Cryoprecipitate) at End of follow-up - Actual outcome: Number of units of allogenic blood transfused at up to hospital discharge; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Number of patients needing transfusions at End of follow-up - Actual outcome: Number of patients needing allogenic blood transfusion at up to hospital discharge; Group 1: 9/96, Group 2: 13/101; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Serious adverse events of donor blood transfusion. at End of follow-up; Serious adverse events of cell salvage therapy at End of follow-up; Length of hospital stay at End of follow-up

Study	Hosseini 2014
Study type	RCT (Prospective double blind study)
Number of studies	n=1
Countries and setting	Conducted in Iran; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who underwent the first time elective off-pump CABG.
Exclusion criteria	Clotting disorders, kidney failure (Cr<1.7), allergy to TXA, consumption of anti-platelet drugs, prescription of heparin 48h prior to surgery and patients with ejection fraction (EF<40).
Recruitment/selection of patients	All patients who underwent the first time elective off-pump CABG from Sep to March 2011 in Yazd Afshr Hospital were selected for the study.
Age, gender and ethnicity	TXA group: n=35 Placebo group: n=36 53 males (74.65) and 18 females (25.4%). The mean age of the sample was 60.56±10.96 with an age range of 40-89 years.
Further population details	Type of surgery: elective off-pump CABG The mean body index was not statistically different in the two group (p=0.888). EF (Ejection Fraction) was 46.3±10.2 in the TXA group and 47.48±9.6 in the control group.
Indirectness of population	No indirectness
Interventions	TXA: 1g of TXA IN 100ml of normal saline solution was applied to the pericardium and mediastinal cavity at the end of the

	surgery. Control: Only 100ml of normal saline was applied as placebo Note: All patients received heparin 150 IU/kg after separating the internal mammary artery. A repeated surgery was performed to control blood loss when the drainage of the chest tubes was more than 300 ml during 2 hours while observing simultaneously the patients correct clotting tests.
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : TRANEXAMIC ACID VERSUS PLACEBO Thrombotic complications (CVA) TXA:0/35 Placebo: 0/36 Risk of bias: low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Length of stay (hospitalisation), Infections, No. of patients requiring allogeneic transfusions ,Number of units of allogeneic blood transfused / volume of allogeneic blood transfused, Serious adverse events (as defined by study).

Study	**Imai 2012**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=117)
Countries and setting	Conducted in Japan; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults:
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing total hip arthroplasty for treatment of osteoarthritis of the hip joint
Exclusion criteria	Patients with a history of ischemic heart disease, severe chronic heart failure, hepatic dysfunction, chronic renal failure on haemodialysis, cerebral infarction, bleeding disorder, patients currently receiving anti-coagulant therapy
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (range): Tranexamic acid: 63.3 (47-85); Placebo: 60.2 (54-72). Gender (M:F): Tranexamic acid:16:79; Control= 5:17. Ethnicity: Not stated
Further population details	Type of surgery: total hip arthroplasty
Indirectness of population	No indirectness
Interventions	(n=95) Intervention 1: Tranexamic acid. Study evaluated the effectiveness of different doses and timings of administration of tranexamic acid (pooled effects presented for 4 groups in the analysis). The four groups included: i) 1 g of tranexamic acid administered 10 minutes before skin closure to avoid fibrinolytic inhibition during the phase operation and to exploit the effect of tranexamic acid maximally in the post-operative phase. ii) 1 g of tranexamic acid administered 10 minutes before skin closure and again at 6 hours after first administration. iii) 1 g of tranexamic acid administered 10 minutes before surgery. iv) 1 g of tranexamic acid administered 10 minutes before surgery and again at 6 hours after first administration. Duration: Intra-operative and post-operative. Concurrent medication/care: None Further details: Route of administration: IV route (n=22) Intervention 2: Placebo. Control group (no drug was administered). Duration Intra-operative and Post-operative period. Concurrent medication/care: None
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Number of patients needing transfusions at end of follow-up	

- Actual outcome for Adults: Number of patients receiving allogeneic transfusions at end of follow up; Group 1: 0/95, Group 2: 0/22; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Thrombosis at end of follow-up - Actual outcome for Adults: Venous thromboembolism at end of follow up; Group 1: 10/95, Group 2: 3/22; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Bleeding at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up.

Study	**Kakar 2009**
Study type	RCT
Number of studies (number of participants)	n=1 (n=50)
Countries and setting	Conducted in India; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing primary cemented total knee arthroplasties (both unilateral and bilateral).
Exclusion criteria	Patients were excluded if they had one of the following criteria: known or suspected allergy to medications used, inherited or acquired haemostatic diseases, abnormal coagulation screening tests (platelet count, prothrombin time,

	activated partial thromboplastin time), ingestion of aspirin or other non-steroidal anti-inflammatory drugs within seven days of surgery, renal or hepatic insufficiency, pregnancy, history of deep vein thrombosis (DVT), or pulmonary embolism or history of ocular pathology or ophthalmological procedure other than corrective lenses.		
Recruitment/selection of patients	Not stated		
Age, gender and ethnicity		TXA (n=25)	placebo (n=25)
	M/F	7/18	7/18
	Age (years)	63.13 (16.8)	67.15 (6.9)
Further population details	All patients underwent a pre-anaesthetic check-up and were pre-medicated with oral ranitidine 150 mg, alprazolam 0.25 mg and metoclopramide 10 mg HS and in morning of surgery.		
Indirectness of population	No indirectness		
Interventions	Tranexamic acid (TXA) (n=25) TXA was given immediately before inflation of the tourniquet. After a test dose of 1 ml, patients received a dose of 10 mg/kg IV followed by an infusion of 1 mg/kg/hour until skin closure. Normal saline (n=25) Patients received an equivalent volume of physiologic saline.		
Funding	Not stated		

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : TRANEXAMIC ACID VERSUS PLACEBO

Number of units transfused:
4 units in TXA group
26 units in the placebo group
Risk of bias: High; Indirectness of outcome: No indirectness

Thrombotic events (DVT/PE)
TXA: 0/25
Placebo: 0/25
Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Length of stay (hospitalisation), Infections, Number of patients needing transfusions, Serious adverse events (as defined by study)

Study	**Karimi 2012**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=32)
Countries and setting	Conducted in Iran; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	All ASA class I patients between 18 and 40 years of age scheduled for bimaxillary osteotomy between August 2010 and January 2011 were consecutively recruited to the study after written informed consent.
Exclusion criteria	Exclusion criteria were patients with uncontrolled systemic diseases, anticoagulant consumption, simultaneous TMJ surgery or rhinoplasty, concomitant craniofacial surgery, bone disease or massive autogenous graft.
Age, gender and ethnicity	Age - Mean (SD): TXA: 22.8 (12.8); control: 23.9 (12.2). Gender (M:F): TXA: 6/10; control: 7/9. Ethnicity: Not stated
Further population details	Type of surgery: bimaxillary osteotomy
Indirectness of population	No indirectness
Interventions	(n=16) Intervention 1: Tranexamic acid. TXA 20 mg/kg intravenously just before induction of anaesthesia. Duration Just before induction of anaesthesia. Concurrent medication/care: Patients were pre-medicated with 1 mg of midazolam and 3mg/kg of fentanyl intravenously.

	(n=16) Intervention 2: Placebo. Normal saline just before induction of anaesthesia (same volume as TXA). Duration Just before induction of anaesthesia. Concurrent medication/care: Patients were pre-medicated with 1 mg of midazolam and 3mg/kg of fentanyl intravenously.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Length of hospital stay at end of follow-up - Actual outcome for Adults: Length of hospital stay at end of follow-up; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome for Adults: Number of patients needing transfusions at end of follow-up; Group 1: 0/16, Group 2: 1/16; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Bleeding at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up.

Study	**Ker 2013 (included studies- Abdullah 2012, Abul-Azm 2006, Albirmawy 2013, Alshryda 2013, Athanasiadis 2007, Baric 2007, Blinder 1999, Canata 2012, De Bonis 2000, Dell'Amore 2012, Fawzy 2009, Georgiadis 2013, Gersel-Pedersen 1979, Ishida 2011, Jabalameli 2006, Kaewpradub 2011, Krohn 2002, Kurt 2011, Nouraei 2013, Ramstrom 1993, Roy 2012, Saberi 2010, Sa-Ngasoongsong 2011, Seo 2012, Sindet-Pedersen 1989, Tibbelin 1995, Van Elst 2013, Wong 2010, Yasim 2005)**
Study type	Systematic Review
Number of studies (number of participants)	28 (n=2612)
Countries and setting	Conducted in Australia, Belgium, Canada, Croatia, Denmark, Egypt, India, Iran, Israel, Italy, Japan, Norway, Saudi Arabia,

	South Korea, Sweden, Thailand, Turkey, United Kingdom, USA
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	--
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	RCTs People of all ages with bleeding of any severity. Topical administration of tranexamic acid versus no tranexamic acid or placebo.
Exclusion criteria	-
Age, gender and ethnicity	
Further population details	Twenty-eight trials assessed the effect of topical tranexamic acid in surgical patients. Of these trials, nine involved knee arthroplasty, six cardiac surgery, four dental surgery, two spinal surgery, one hip arthroplasty, one prostate resection, one pulmonary resection, three otolaryngological surgery and one orthognathic surgery. The single non-surgical trial assessed the effect of topical tranexamic acid for epistaxis.
Indirectness of population	No indirectness
Interventions	(n=1000) Intervention 1: Tranexamic acid (n=1612) Intervention 2: Placebo. In 23 of the 28 surgical trials, tranexamic acid was administered in saline solution directly on to the operative site, either by pouring or spraying into the surgical wound or as a mouthwash in the dental surgery trials. In four of the trials involving knee arthroplasty and the one trial of hip arthroplasty, tranexamic acid was given via an intra-articular injection. In all of these trials tranexamic acid was applied at the end of surgery, prior to wound closure. Twenty-five trials were placebo-controlled. In the remaining three trials, topical tranexamic acid was compared with a no treatment control group. Risk of bias: Low; Indirectness of outcome: No indirectness

Funding	National Institute for Health Research, UK.

Study	**Kim 2014**
Study type	Prospective RCT
Number of studies (number of participants)	n= 1(n=342)
Countries and setting	Conducted in Korea; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with a diagnosis of primary osteoarthritis (OA) scheduled for unilateral primary total knee arthroplasty (TKA) and simultaneous primary bilateral total knee arthroplasty
Exclusion criteria	Patients with a diagnosis other than OA, those with an acquired or congenital coagulopathy, those on current anticoagulation therapy, those with pre-operative hepatic or renal dysfunction or severe ischaemic heart disease and those with a history of thromboembolic disease.
Recruitment/selection of patients	342 consecutive patients scheduled for 187 unilateral primary TKA and 155 simultaneous primary bilateral TKAs during the period between October 2009 and May 2011 for the eligibility of this study.
Age, gender and ethnicity	Unilateral TKA: TXA (n=90) Control (n=90) Female 79 (88%) 78 (87%) Age (year) 73.5 (5.5) 71.9 (5.9)

	Bilateral TKA:		
		TXA (n=73)	Control (n=73)
	Female	72 (99%)	70 (96%)
	Age (year)	74.3 (5.3)	73.9 (5.1)
Further population details	Type of surgery: unilateral primary total knee arthroplasty (TKA) and simultaneous primary bilateral total knee arthroplasty There were no significant differences in the demographic data, pre-operative haematologic values and tourniquet time between TXA and control groups in both unilateral and bilateral TKAs		
Indirectness of population	No indirectness		
Interventions	TXA: Patients undergoing unilateral TKA were given TXA at 10 mg/kg of body weight 30 minutes before tourniquet deflation, and the same amount was repeated 3 hours after the commencement of the first injection. Calculated dose of TXA was mixed in 100 ml of normal saline and given as a slow intravenous injection. In simultaneous bilateral TKAs, the same amount of TXA was administered 30 minutes before tourniquet deflation for the 1st operation, then 30 minutes before tourniquet deflation for the 2nd operation, and finally the same amount was repeated 3 hours after the commencement of the second injection. Control: Patients did not receive placebo or saline. Patients diagnosed with anaemia were prescribed with oral iron forms to correct anaemia unless other underlying diseases were suspected.		
Funding	Not stated		
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : TRANEXAMIC ACID VERSUS PLACEBO No. of patients requiring allogeneic transfusions TXA:1/90 Placebo:6/90 Risk of bias: High; Indirectness of outcome: No indirectness			

Thromboembolic events (DVT/PE) TXA:0/90 Placebo:1/90 Risk of bias: High; Indirectness of outcome: No indirectness No. of patients requiring allogeneic transfusions TXA:5/73 Placebo:20/73 Risk of bias: High; Indirectness of outcome: No indirectness Thromboembolic events (DVT/PE) TXA:0/73 Placebo:0/73 Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Length of stay (hospitalisation), Infections, Number of units of allogeneic blood transfused / volume of allogeneic blood transfused(in ml), Serious adverse events (as defined by study)

Study	**Lee 2013A**
Study type	Prospective randomised double blinded trial
Number of studies (number of participants)	n=1 (n=68)
Countries and setting	Conducted in Korea; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	Adults		
Subgroup analysis within study	Not applicable		
Inclusion criteria	Adult patients with ASA physical status 1 and 2 patients scheduled to undergo primary unilateral cement less total hip replacement.		
Exclusion criteria	Patients older than 70 years, those with previous hip surgery, drug sensitivity, anaemia (Hb <12 g/dl for men and <11 g/dl for women), coagulopathy, thrombocytopenia, hepatic renal failure, history of deep vein thrombosis (DVT) or embolism, severe aortic or mitral valve stenosis or neurological or cerebrovascular disease were excluded.		
Recruitment/selection of patients	A total of 68 adult, ASA physical status 1 and 2 patients scheduled to undergo primary unilateral cement less total hip replacement were selected for the study.		
Age, gender and ethnicity		TXA (n=34)	Placebo (n=34)
	Age (years)	52.8 (10.7)	51.4 (11.2)
	M/F	20/14	22/12
Further population details	Duration of anaesthesia, surgery, controlled hypotension, length of hospital stay, amount of infused fluid, urine output, body temperature, and number of DVTs were comparable between the groups.		
Indirectness of population	No indirectness		
Interventions	TXA (n=34) Patients first received a bolus dose of 15 mg/kg of TXA (mixed in normal saline, total volume=50 ml), administered slowly 10 minutes before the surgical incision was made, then a continuous infusion of 15 mg/kg of TXA until skin closure. Placebo (n=34) Patients received normal saline in place of TXA in the same manner and the same volume as the TXA group. Note: Transfusion of packed red blood cells was given if Hct was <30 % during or after surgery.		
Funding	Not stated		
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON TRANEXAMIC ACID VERSUS PLACEBO			

No. of patients requiring allogeneic transfusions TXA:9/34 Placebo:20/34 Risk of bias: low; Indirectness of outcome: No indirectness Length of stay TXA: 15.4±3.3 Placebo: 15.2±3.1 Risk of bias: low; Indirectness of outcome: No indirectness Deep vein thrombosis (DVT) TXA:0/34 Placebo:0/34 Risk of bias: low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Infections, Number of units of allogeneic blood transfused/volume of allogeneic blood transfused (in ml), Serious adverse events (as defined by study).

Study	**Lundin 2014**
Study type	RCT (Double blind placebo controlled multi-centre study)
Number of studies (number of participants)	n=1 (n=100)
Countries and setting	Conducted in Sweden; Setting: 2 University Hospitals and 2 central hospitals
Line of therapy	1st line
Duration of study	Intervention + follow up (5 weeks)

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Women who were admitted to the participating units for presumed (clinically and/or radiologically) or confirmed advanced ovarian cancer and scheduled for explorative laparotomy with the aim of radical debulking surgery. Additional inclusion criteria: >18 years of age with an American Society of Anaesthesiologists score <3, who speak Swedish fluently.
Exclusion criteria	Allergy to TXA, treatment with anti-coagulants within the last month, a history or present laboratory signs of bleeding disorders, coagulopathy or thromboembolic events, a history of myocardial infarction within the last year, present unstable angina or severe coronary disease, reduced renal function with plasma creatinine levels above 250 micromoles/litre, and severe psychiatric or mental disorder.
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	TXA (n=50) Placebo (n=50) Age (years) 63 64.5 All women
Further population details	Type of surgery: explorative laparotomy with the aim of radical debulking surgery RBC transfusion pre-operatively: TXA group: 3/50 Placebo: 3/50
Indirectness of population	No indirectness
Interventions	TXA: n=50 15 mg/kg body weight, 100 mg/ml Cyklokapron) Control: n=50 Same volume of saline (0.9% NaCl) was added to a 100ml saline solution plastic bag. The patients received the study medication before the start of the operation as an intravenous infusion given in 15-20 min, starting the infusion immediately after the general anaesthesia had been established.

Funding	The study was supported financially by grants from the Medical Research Council of South East Sweden; Linkoping University and the County Council of Osterogotland.
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : TRANEXAMIC ACID VERSUS PLACEBO No. of patients requiring allogeneic transfusions TXA:15/50 Placebo:22/50 Risk of bias: High; Indirectness of outcome: No indirectness Thromboembolic events TXA:2/50 Placebo:5/50 Risk of bias: High; Indirectness of outcome: No indirectness Infections TXA:10/50 Placebo:16/50 Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Length of stay (hospitalisation), Number of units of allogeneic blood transfused / volume of allogeneic blood transfused(in ml), Serious adverse events (as defined by study)

Study	**Malhotra 2011**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in India; Setting: Hospital

Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing unilateral, cementless total hip arthroplasty.
Exclusion criteria	Patients with a history of severe ischemic heart disease, chronic renal failure, cirrhosis of the liver, and bleeding disorders, as well as those who were currently receiving anti-coagulant therapy.
Age, gender and ethnicity	Age - Mean (SD): TXA: 52.6; Placebo: 54.7. Gender (M: F): TXA: 10/15; Placebo: 12/13. Ethnicity: NR
Further population details	Type of surgery: total hip arthroplasty
Extra comments	Mean surgical time in minutes: TXA- 87.7; Placebo- 84.6
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Tranexamic acid. Patients received a bolus intravenous dose of 15 mg/kg of TXA 15 minutes before the incision. Duration 15 minutes before the incision. Concurrent medication/care: None (n=25) Intervention 2: Placebo. Normal saline intravenously. Duration 15 minutes before incision. Concurrent medication/care: None
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up - Actual outcome for Adults: Total units of allogeneic blood transfusion at 24 hours; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery	

- Actual outcome for Adults: Infections at 3rd post-operative day; Group 1: 0/25, Group 2: 0/25; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Thrombosis at end of follow-up - Actual outcome for Adults: Deep vein thrombosis at 10th post-operative day; Group 1: 0/25, Group 2: 0/25; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Bleeding at end of follow-up - Actual outcome for Adults: Intra-operative blood loss at during surgery; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Post-operative blood loss at 24 hours after surgery; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Number of patients needing transfusions at end of follow-up; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Length of hospital stay at end of follow-up

Study	**Mansouri 2012**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in Iran; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention +follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Age >18 years, not pregnant, elective operation, absence of known or suspected allergy to TXA, absence of previous strenotomy, pre-existing renal dysfunction , pre-operative coagulation defects, prothrombin time >18 seconds or activated partial prothrombin time >50 seconds, recent ingestion of acetylsalicylic acid, thrombolytic therapy, anticoagulant therapy, autologous pre-donation of blood, history of thrombotic events such as DVT, disseminated

	intravascular coagulation and cerebral thromboembolic accident in the previous 6 months or unstable angina.
Exclusion criteria	Not stated
Age, gender and ethnicity	Age - Mean (SD): TXA: 48.3 (15.5); control: 48.3 (13.5). Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	Type of surgery: cardiac surgery
Extra comments	Patients with normal renal function. Exclusion criteria were as follows: pump time >120 min, bleeding with a surgical source (identified at post-operative re-operation)
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: Tranexamic acid. 30 mg/kg TXA intravenously in 50 ml of normal saline over 20 minutes and TXA infusion was continued during CPB (cardio pulmonary bypass) at 1 mg/kg in 50 ml of normal saline. Duration Before and during surgery. Concurrent medication/care: Heparinisation (n=30) Intervention 2: Placebo. 50 ml of normal was administered intravenously over 20 minutes and 100 ml of normal saline was added to the priming fluid. . Duration Before and during surgery. Concurrent medication/care: Heparinisation
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up - Actual outcome for Adults: Number of units transfused- RBC at end of follow-up; Group 1: mean 2.06 unit (SD 1.28); n=21, Group 2: mean 3 unit (SD 2.31); n=30; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Bleeding at end of follow-up - Actual outcome for Adults: Post-operative bleeding at First 24 hours; Group 1: mean 283.3 ml (SD 156.9); n=30, Group 2: mean 841.6 ml (SD 696.9); n=30; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial

	embolism) at end of follow-up; Length of hospital stay at end of follow-up.

Study	**Martin 2014**		
Study type	RCT (Prospective stratified, randomised, double blind placebo controlled trial)		
Number of studies (number of participants)	n=1 (n=100)		
Countries and setting	Conducted in USA; Setting: single community Hospital		
Line of therapy	1st line		
Duration of study	Intervention + follow up (12 days and 30 days)		
Method of assessment of guideline condition	Adequate method of assessment/diagnosis		
Stratum	Adults		
Subgroup analysis within study	Not applicable		
Inclusion criteria	Patients of the surgeon author, aged 18 years or older, who were scheduled for a primary total knee arthroplasty (TKA) or a primary THA (primary total hip arthroplasty) with or without cement, were eligible for inclusion in the trial.		
Exclusion criteria	Revisions, bilateral joint arthroplasty procedures, known hypersensitivity to TXA or its ingredients, active intravascular clotting disorders, and acute subarachnoid haemorrhage.		
Recruitment/selection of patients	From January 2012 through July 2012, 50 patients undergoing TKA and 50 patients undergoing THA were randomised to receive either 2g TXA in 100 ml of normal saline or the equivalent volume of placebo in to the joint space prior to surgical closure.		
Age, gender and ethnicity		Placebo (n=25)	2 g TXA (n=25)
	Age	64.28±9.68	67.16±10.55
	% female	56%	44%
Further population details	There were no differences between the groups in age, gender, weight, height, BMI, ASA status, haemoglobin, platelet count, INR and predetermined pre-operative co-morbidities. Unless contraindicated all patients were placed on warfarin while in the hospital and then discharged on aspirin 325 mg		

	orally twice daily for 30 days.
Indirectness of population	No indirectness
Interventions	TXA: n= 50 2 g TXA in 100 ml of normal saline The treatment arm was prepared by removing 20 ml of normal saline from a 100 ml normal saline IV piggyback and adding 2 g/20 ml TXA to the normal saline piggyback to provide a total volume of 100 ml. Placebo: n=50 Equivalent volume of normal saline. The placebo arm was prepared by removing 20ml of normal saline from a 100ml normal saline IV piggyback and adding 20ml normal saline back in to the piggyback to provide a total volume of 100ml. Note: All surgeries were performed without the use of drains and maintenance fluid requirements were replaced with normal saline and each patient received 500 ml bolus of hydroxyethyl starch on post-operative day one per standard practice. Patients were considered for blood transfusion if they demonstrated symptomatic hypotension, or had a post-operative haemoglobin level less than 7 g/dl.
Funding	Not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : TRANEXAMIC ACID VERSUS PLACEBO

No. of patients requiring allogeneic transfusions
TXA: 7/50
Placebo: 10/50
Risk of bias: low; Indirectness of outcome: No indirectness

Length of hospital stay
No difference in average length of stay (p=0.647)
Risk of bias: low; Indirectness of outcome: No indirectness

Thromboembolic events (DVT/PE) TXA:0/50 Placebo: 0/50 Risk of bias: low; Indirectness of outcome: No indirectness Infections TXA: 0/50 Placebo: 0/50 Risk of bias: low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Infections, Number of patients needing transfusions, Number of units of allogeneic blood transfused / volume of allogeneic blood transfused (in ml), Serious adverse events (as defined by study)

Study	**McConnell 2011**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=66)
Countries and setting	Conducted in United Kingdom
Line of therapy	1st line
Duration of study	Intervention + follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable

Inclusion criteria	Eligible patients were approached and given information sheets at pre-operative assessment clinics. Patients were eligible if they were scheduled to undergo elective primary unilateral cemented hip arthroplasty.
Exclusion criteria	Patients were excluded if they were taking anti-coagulant medication or had a known coagulopathy, as such patients would have been predisposed to higher blood loss. Patients were also excluded if there were contraindications to giving the medications in the study: known allergy to the medications used, including allergy to aspirin, previous reaction to blood products, ethical/religious objection to receiving blood products, or previous thromboembolism.
Recruitment/selection of patients	Patients were recruited from June 2006 through May 2008.
Age, gender and ethnicity	Age - --: Not reported. Gender (M: F): TXA: 7/15; control:9/13. Ethnicity: Not stated
Further population details	Type of surgery: elective primary unilateral cemented hip arthroplasty
Extra comments	Each patient underwent a single joint replacement.
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Tranexamic acid. Tranexamic acid given as a single dose as an intravenous bolus at the start of the surgical procedure. Duration At the start of the surgery. Concurrent medication/care: None (n=22) Intervention 2: Placebo. Nothing (reported as not given TXA- no further details). Duration Not reported. Concurrent medication/care: None
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Bleeding at end of follow-up - Actual outcome for Adults: Total blood loss at During and after surgery; Group 1: mean 0.93 l (SD 0.35); n=22, Group 2: mean 1.2 l (SD 0.5); n=22; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up

Study	McConnell 2012
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=66)
Countries and setting	Conducted in United Kingdom; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were considered for inclusion if they were awaiting a primary cemented knee arthroplasty
Exclusion criteria	Those who were to undergo uncemented or revision arthroplasty were excluded. Other exclusion criteria were- previous thromboembolism, known coagulopathy or ongoing use of anticoagulant medication, known allergy to the medications used, previous reaction to blood products or ethical/religious objection to receiving blood products
Recruitment/selection of patients	The study was conducted at an elective arthroplasty unit in the UK during the period June 2006 to May 2008. . Patients were recruited at pre-operative assessment clinics
Age, gender and ethnicity	Age - --: Not stated. Gender (M:F): TXA: 10/12; control:15/7. Ethnicity: Not stated
Further population details	
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Tranexamic acid. Single 10 mg/kg bolus dose of tranexamic acid intravenously at induction of anaesthesia. Duration single dose before surgery. Concurrent medication/care: oral aspirin 150 mg- 35 day course (n=22) Intervention 2: Placebo. No treatment. Duration Not stated. Concurrent medication/care: None

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Number of patients needing transfusions at end of follow-up - Actual outcome for Adults: Number of patients needing transfusions at end of follow-up; Group 1: 0/22, Group 2: 0/22; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Bleeding at end of follow-up - Actual outcome for Adults: Total blood loss at end of follow-up; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up

Study	**Miller 1980**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=100)
Countries and setting	Conducted in United Kingdom; Setting: Surgery (Hospital)
Line of therapy	1st line
Duration of study	Follow up (post intervention)
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable

Inclusion criteria	Patients undergoing transurethral prostatectomy or endoscopic bladder tumour resection.
Exclusion criteria	Not reported
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Not reported. Gender (M: F): Male patients. Ethnicity: Not reported
Further population details	Type of surgery: transurethral prostatectomy
Indirectness of population	No indirectness
Interventions	(n=52) Intervention 1: Tranexamic acid. Tranexamic acid orally (Cyklokapron-KabiViturm) 1 g thrice daily for 3 weeks from the first post-operative day. Duration Post-operative period (up to 4 weeks). Concurrent medication/care: None Further details: routes of administration: Oral route (n=48) Placebo. No treatment was given to the control group (not placebo controlled). Duration Post-operative period. Concurrent medication/care: None
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS CONTROL GROUP Protocol outcome 1: Thrombosis at end of follow-up - Actual outcome for Adults: Deep vein thrombosis at Post-operative period; Group 1: 1/52, Group 2: 1/48; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 2: Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up - Actual outcome for Adults: Pulmonary embolism at Post-operative period; Group 1: 0/52, Group 2: 1/48; Risk of bias: Unclear; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Bleeding at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up

Study	Movafegh 2011
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in Iran; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Women aged 20-40 years with a singleton pregnancy at between 38 weeks +5 days and 40 weeks gestation, who were categorised as class 1 (normally healthy) according to the American Society of Anesthesiologists and were scheduled to undergo caesarean delivery by Pfannenstiel incision under spinal anaesthesia. The indications for caesarean delivery were malpresentation, contracted pelvis, and patient request.
Exclusion criteria	Previous history of caesarean delivery or intra-abdominal surgery, polyhydramniosis, macrosomia, pre-eclampsia or abnormal placenta, thrombophilia, anaemia, or coagulopathy, cardiovascular , renal, or liver disorders or contra-indication to any drug used in the study protocol.
Age, gender and ethnicity	Age - Mean (SD): TXA: 27 (3.4); Control: 27.6 (4.1). Gender (M: F): All women. Ethnicity: Not stated
Further population details	Type of surgery: caesarean delivery
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Tranexamic acid. 10 mg/kg of intravenous TXA in 200 ml of normal saline. Duration Drug and placebo were infused over 10 minutes, 20 minutes before beginning of spinal anaesthesia. Concurrent medication/care: None Comments: Intra-operative blood loss was recorded as the sum of the suction container blood and the difference between the weight of the dry and bloody gauze pads and operation sheets. Blood loss was recorded 2 hours after delivery using the weight of soaked pads and gauze before.

	(n=50) Intervention 2: Placebo. 200ml of normal saline. Duration Drug and placebo were infused over 10 minutes, 20 minutes before beginning of spinal anaesthesia. Concurrent medication/care: None
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Bleeding at end of follow-up - Actual outcome for Adults: Post-operative blood loss at 2 hours after delivery; Group 1: mean 67.1 ml (SD 6.5); n=50, Group 2: mean 141 ml (SD 33.9); n=50; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for Adults: Intra-operative blood loss at During surgery; Group 1: mean 262.5 (SD 39.6); n=50, Group 2: mean 404.7 (SD 94.4); n=50; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up.

Study	**Neilipovitz 2001**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=40)
Countries and setting	Conducted in Canada; Setting: Surgery (Hospital)
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children: Children from 9-18 years of age

Subgroup analysis within study	Not applicable
Inclusion criteria	Paediatric patients undergoing posterior spinal fusion for scoliosis
Exclusion criteria	Patients with a history of bleeding disorder, a low platelet count (<150), abnormal partial thromboplastin time or international ration test, body mass index >30kg/m2, previous thromboembolic event or a family history of thromboembolism.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): TXA group: 14.1(2.1); placebo group: 13.7(2.5). Gender (M: F): TXA group: 10:12; Placebo group: 13:5. Ethnicity: Caucasian
Further population details	Type of surgery: posterior spinal fusion
Extra comments	Paediatric patients undergoing posterior spinal fusion for scoliosis
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Tranexamic acid. Initial dose of 10mg/kg of Tranexamic acid (Cyclokapron 100 mg/ml, Pharmacia, Mississauga, Canada) administered over 15 minutes after final patient positioning; Maintenance induction of tranexamic acid in dose of 1mg/kg/hour was initiated upon completion of initial dose and was continued until skin closure. Duration Intra-operative. Concurrent medication/care: none (n=18) Intervention 2: Placebo. Initial dose of 10 mg/kg of placebo administered over 15 minutes after final patient positioning; Maintenance infusion of placebo in dose of 1 mg/kg/hour was initiated upon completion of initial dose and was continued until skin closure. Duration Intra-operative. Concurrent medication/care: none
Funding	Study funded by industry (Unrestricted grant from Pharmacia Pharmaceuticals)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up - Actual outcome for Children: Number of units transfused/volume in ml in children at end of follow up; Group 1: mean 1253 ml (SD 884); n=22, Group 2: mean 1784 ml (SD 733); n=18; Risk of bias: --; Indirectness of outcome: No indirectness	

Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome for Children: Number of patients needing transfusions at end of follow up; Group 1: 6/22, Group 2: 6/18; Risk of bias: Unclear; Indirectness of outcome: No indirectness Protocol outcome 3: Thrombosis at end of follow-up - Actual outcome for Children: Thrombotic complications at end of follow up; Group 1: 0/22, Group 2: 0/18; Risk of bias: --; Indirectness of outcome: No indirectness Protocol outcome 4: Bleeding at end of follow-up - Actual outcome for Children: Intra-operative blood loss at Intra-operative period; Group 1: mean 2453 ml (SD 1526); n=22, Group 2: mean 2703 ml (SD 1292); n=18; Risk of bias: --; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Length of hospital stay at end of follow-up

Study	**Oremus 2014**
Study type	RCT
Number of studies (number of participants)	n=1 (n=98)
Countries and setting	Conducted in Croatia; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up at 1 and 3 months post-operatively
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Adults (>18 years of age) scheduled for primary unilateral or bilateral total hip arthroplasty (THA) or total knee

	arthroplasty (TKA), written informed consent, American Society of Anaesthesiologist physical status I to III and osteoarthritis or rheumatoid arthritis as the underlying morbidity.
Exclusion criteria	Known hypersensitivity to TXA, history of coagulation abnormalities and thromboembolic disease or current abnormal coagulation test values, history of stroke or acute coronary syndromes within 3 months before surgery, renal failure (serum creatinine >250 micromoles/litre) or liver cirrhosis and chronic (on-going) anticoagulant therapy.
Recruitment/selection of patients	The study was conducted between August 2009 and December 2010
Age, gender and ethnicity	TXA (n=49) placebo (n=49) Men 41 (83.7) 37 (75.5) Age (years) 68.8±8.6 68.6±8.3
Further population details	TXA (n=49) placebo (n=49) Hb (g/dl) 14.99±1.33 15.19±1.38 Anaemic patients were prescribed daily oral elemental iron supplementation in a dose of 200 mg with the aim to reach Hb level above 12 g/dl for females and 13 g/dl for males until surgery.
Indirectness of population	No indirectness
Interventions	TXA +PCS (n=49) TXA intravenous injection (Cyklokapron injections 500 mg/5 ml). The individual dose was prepared by an anaesthesia technician not involved in perioperative patient care in a 10 ml syringe containing 1 g of TXA, immediately before surgery. PCS (n=49) 0.9% normal saline prepared in the same way as TXA. In the THA patients first drug administration (10 minute-IV bolus) was at the beginning of surgical field preparation (15 minutes before skin incision) and during cementing of the femoral component in TKA patients (15 minutes before tourniquet release). The second dose was administered 3 hours later as a 30 minute infusion after adding the study syringe content in to a container with 100 ml of 0.9% saline. In both the groups: Two drains were placed intra-articularly at the end of TKA whereas THA patients received one intra-articular and one sub-fascial drain. After skin closure, both drains were connected through a Y-connector to a commercially obtained autologous blood recovery and re-infusion system set to produce a constant negative suction pressure of 25 mm Hg. Shed blood was re-infused when at least 500 ml was collected at any time within the first 6 post-operative hours and/or if the collection chamber contained at least 250 ml of blood at the end of this period. Thereafter, the system was used as a standard closed drainage until 24 hours post-operatively when the drains were

	removed.
Funding	Not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON): PCS+TXA versus PCS No. of patients requiring allogeneic transfusions PCS+TXA: 3/49 PCS: 5/49 Risk of bias: High; Indirectness of outcome: No indirectness Thrombotic complications (PE, DVT) PCS+TXA: 0/49 PCS: 2/49 Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Length of stay (hospitalisation), Infections , Number of units of allogeneic blood transfused / volume of allogeneic blood transfused(in ml), Serious adverse events (as defined by study)

Study	**Perel 2013 (included studies- Hemsinli 2012, Moghaddam 2011, Pfizer 2011, Sadeghi 2007, Zufferey 2010)**
Study type	Systematic review
Number of studies (number of participants)	n=5 (n=372)
Countries and setting	Conducted Iran, Turkey, France and India ; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Randomised controlled trials Adult patients (over 18 years old) undergoing emergency or urgent surgery. The authors considered the surgery as 'emergency or urgent', if the surgeries were conducted within 48 hours of hospital admission, or if because the nature of the condition is implicitly understood that patients will require emergency surgery (e.g. long bone fracture, hip fracture or acute aortic dissection). Tranexamic acid compared with placebo or no tranexamic acid.
Exclusion criteria	Not stated
Recruitment/selection of patients	-
Age, gender and ethnicity	-
Further population details	Two trials involved patients with hip fracture, two trial involved patients with femur fracture, and one trial involved patients undergoing emergency coronary artery bypass graft. All of the trials compared tranexamic versus no tranexamic acid, one trial also included two more comparison arms – desmopressin or tranexamic plus desmopressin.
Indirectness of population	No indirectness
Interventions	Tranexamic acid compared with placebo or no tranexamic acid.
Funding	Cochrane Review Incentive Scheme, Department of Health, UK.

Study	**Rajesparan 2009**
Study type	RCT
Number of studies (number of participants)	n=1 (n=73)
Countries and setting	Conducted in UK; Setting: Hospital

Line of therapy	1st line		
Duration of study	Intervention + follow up		
Method of assessment of guideline condition	Adequate method of assessment/diagnosis		
Stratum	Adults		
Subgroup analysis within study	Not applicable		
Inclusion criteria	Patients undergoing total hip replacement (THR)		
Exclusion criteria	Not reported		
Recruitment/selection of patients	Not reported		
Age, gender and ethnicity		TXA (n=36)	Control (n=37)
	Age in years	67.5 (11)	67.7 (9.8)
	Male/female	13/23	13/24
Further population details		TXA (n=36)	Control (n=37)
	Osteoarthritis	35	36
	Rheumatoid arthritis	1	1
Indirectness of population	No indirectness		
Interventions	TXA: n=36 Standardised dose of 1 g of intravenous TXA before total hip replacement (conventional stemmed unilateral total hip replacement). Patients received a single dose of 1 g TXA intravenously before the skin incision. Control: n=37 Did not receive anything		
Funding	No funding received		

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : TRANEXAMIC ACID VERSUS PLACEBO No. of patients requiring allogeneic transfusions TXA:3/36 Placebo:10/37 Risk of bias: High; Indirectness of outcome: No indirectness Thrombotic complications TXA: 1/36 Placebo:2/37 Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Length of stay (hospitalisation), Infections , Number of units of allogeneic blood transfused / volume of allogeneic blood transfused(in ml), Serious adverse events (as defined by study)

Study	**Rannikko 2004**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=136)
Countries and setting	Conducted in Finland; Setting: Surgery (hospital)
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing transurethral resection of prostate (TURP) for obstructive urinary symptoms. All patients had clinical and laboratory evidence of benign prostatic hyperplasia

Exclusion criteria	Patients taking finasteride or with a history of prostatic cancer.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Median (range): Tranexamic acid: 71(67-76), Control: 68 (63-75). Gender (M:F): all male patients. Ethnicity: Caucasian
Further population details	Type of surgery: transurethral resection of prostate (TURP)
Indirectness of population	No indirectness
Interventions	(n=70) Intervention 1: Tranexamic acid. 2 g of tranexamic acid (Caprilon, Leiras, Finland) orally 3 times daily on the operative and first post-operative day. Duration Intra and post-operative period. Concurrent medication/care: Patients taking warfarin discontinued it 7 days before surgery and patients taking aspirin discontinued it 2 days before surgery. (n=66) Intervention 2: Placebo. Control group received no treatment. Duration Intra and post-operative period. Concurrent medication/care: None
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS CONTROL GROUP Protocol outcome 1: Number of patients needing transfusions at end of follow-up - Actual outcome for Adults: Number of patients transfused at Post-operative period; Group 1: 6/70, Group 2: 5/66; Risk of bias: Unclear; Indirectness of outcome: Protocol outcome 2: Bleeding at end of follow-up - Actual outcome for Adults: Intra-operative blood loss at Intra-operative period; Risk of bias: Unclear; Indirectness of outcome:	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up

Study	**Raviraj 2012**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=175)
Countries and setting	
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who underwent simultaneous bilateral cemented total knee replacement were included in the study
Exclusion criteria	The exclusion criteria were as follows- patients with bleeding or clotting disorders, those on pre-operative anti-coagulation therapy, abnormal coagulation profile, rheumatoid arthritis, renal disorders or insufficiency, sickle cell disease, patients allergic to LA/TXA.
Age, gender and ethnicity	Age - Mean (SD): TXA: 65 (9); control: 68 (9). Gender (M:F): TXA: 49/39; control: 48/39. Ethnicity: Not stated
Further population details	Type of surgery: bilateral cemented total knee replacement
Indirectness of population	No indirectness
Interventions	(n=88) Intervention 1: Tranexamic acid. TXA was administered as a bolus dose of 10 mg/kg, 10 minutes before the deflation of tourniquet on the first side, followed by a continued intravenous infusion of 10 mg/kg/h over the next 3 hours. Duration Before and during surgery. Concurrent medication/care: Post-operatively all patients received a total of 3 doses of cefuroxime 750 mg over 24 hours and prophylaxis for deep vein thrombosis was initiated with low molecular weight heparin at 8 hours post-surgery. (n=87) Intervention 2: Placebo. Placebo- Same volume as TXA was administered at the same rate and route. Duration Before and during surgery. Concurrent medication/care: Post-operatively all patients received a total of 3 doses of cefuroxime 750 mg over 24 hours and prophylaxis for deep vein thrombosis was initiated with low molecular weight heparin at 8 hours post-surgery.

Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Length of hospital stay at end of follow-up - Actual outcome for Adults: Length of hospital stay at end of follow-up; Group 1: mean 7 days (SD 2); n=88, Group 2: mean 7 days (SD 2); n=87; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome for Adults: Number of patients needing transfusions at end of follow-up; Group 1: 7/88, Group 2: 18/87; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Thrombosis at end of follow-up - Actual outcome for Adults: Deep vein thrombosis at end of follow-up; Group 1: 0/88, Group 2: 1/87; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Bleeding at end of follow-up - Actual outcome for Adults: Total blood loss at 24 hour after surgery; Group 1: mean 402 ml (SD 24.49); n=88, Group 2: mean 569.4 ml (SD 56.33); n=87; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up

Study	**Reid 1997**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=43)
Countries and setting	Conducted in USA; Setting: Surgery
Line of therapy	1st line

Duration of study	Follow up (post intervention): duration not clear
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children: Includes children from 6 months to 14 years of age
Subgroup analysis within study	Not applicable
Inclusion criteria	Children undergoing elective repeat cardiac surgery via strenotomy with cardiopulmonary bypass
Exclusion criteria	children with existing coagulopathy or pre-operative anticoagulation
Age, gender and ethnicity	Age - Mean (SD): In years: Tranexamic acid group: 3.2(2.2); Placebo group: 3.1(1.8). Gender (M:F): Not reported. Ethnicity: Not clear
Further population details	Type of surgery: cardiac surgery
Indirectness of population	Serious indirectness: Includes children less than 1 year of age although mean age >3 years
Interventions	(n=20) Intervention 1: Tranexamic acid. After induction of anaesthesia and before skin incision: Tranexamic acid 100 mg/kg diluted to a fixed volume of 20 ml with normal saline was administered. An infusion of tranexamic acid 10 mg/kg/hour was then started and continued until transport to ICU. Immediately upon initiation of cardiopulmonary bypass, a second bolus of tranexamic acid 100 mg/kg or normal saline was injected in to the pump reservoir. Duration Intra and post-operative. Concurrent medication/care: Heparin was injected into the atrium immediately prior to aortic cannulation (200 U/kg for children less than 30 kg and 300 U/kg for children more than 30 kg). (n=21) Intervention 2: Placebo. After induction of anaesthesia and before skin incision: Normal saline 100mg/kg administered over 15 minutes An infusion of normal saline 10 mg/kg/hour was then started and continued until transport to ICU. . Duration Intra and post-operative period. Concurrent medication/care: Heparin was injected into the atrium immediately prior to aortic cannulation (200 U/kg for children less than 30 kg and 300 U/kg for children more than 30 kg).
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO
Protocol outcome 1: Bleeding at end of follow-up
- Actual outcome for Children: Total blood loss at Intra and post- operative period; Risk of bias:; Indirectness of outcome: Serious indirectness

Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up

Study	**Reyes 2011**		
Study type	RCT (Patient randomised; Parallel)		
Number of studies (number of participants)	1 (n=63)		
Countries and setting	Conducted in Spain; Setting: hospital		
Line of therapy	1st line		
Duration of study	Intervention + follow up 30 days after the procedure.		
Method of assessment of guideline condition	Adequate method of assessment/diagnosis		
Stratum	Adults		
Subgroup analysis within study	Not applicable		
Inclusion criteria	Patients undergoing cardiac surgery with the use of cardiopulmonary bypass.		
Exclusion criteria	Patients over 80 years old, redo and emergency surgery, patients with aorta, endocarditis or peri-cardio disease, patients with combined procedures or requiring triple valve surgery, patients that do not accept the use of blood products, patients with a logistic EuroScore >10% and patients with a high risk of bleeding if she/he had two or more of the following conditions: Pre-operative creatinine >2.2mg/ml, liver insufficiency, severe lung disease, body surface area <1.6m^2, pre-operative haemoglobin levels <13 g/dl in males and <12 g/dl in females, platelet counts below 50,000/ml or any platelet dysfunction, patients with any coagulation disorders, intake of aspirin three days prior surgery or clopidogrel seven days prior surgery.		
Age, gender and ethnicity		Cell salvage (n=34)	Control group (n=29)
	Mean age (years)	65.5±12.1	63.7±12.7

	Female	10 (29.4%)	11 (37.9%)
Further population details		Cell salvage (n=34)	Control group (n=29)
	Diabetes mellitus	9 (26.5%)	8 (27.6%)
	Type of surgery: Cardiopulmonary bypass - 6 patients underwent CABG surgery, 55 patients underwent heart valve surgery, 1 patient had a left atrial mixoma and in 1 patient a haematoma in the left atria was removed.		
Indirectness of population	No indirectness		
Interventions	(n=34) Intervention 1: Cell salvage +Tranexamic acid (CS+TXA). Cell saving device was used the cell salvage group. The cell saving device was used all along the procedure. At the end of the surgery all remaining blood inside the circuits was recovered and concentrated by the cell saving device. All recovered blood was transfused to the patients using a 200 micron filter. Also in this group the cardiotomy suction was used when the patient was heparinized. This blood was re-infused to the patient continuously during the extracorporeal circulation. Tranexamic acid was used in the following dose: 2g at the beginning of surgery followed by a continuous perfusion of 15 mg/kg/h until the end of procedure plus two more grams during the extracorporeal circulation. (n=29) Intervention 2: Tranexamic acid. (TXA) Tranexamic acid was used in the following dose: 2g at the beginning of surgery followed by a continuous perfusion of 15 mg/kg/h until the end of procedure plus two more grams during the extracorporeal circulation. All blood in the surgical filed was aspirated only using the cardiotomy suction. In this group all blood aspirated before starting the heparine and after the protamine administration was lost. Transfusion protocol: A transfusion protocol was used in all patients during the surgical procedure and in the intensive care unit.		
Funding	Funding not stated		
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : CELL SALVAGE + TRANEXAMIC ACID VERSUS TRANEXAMIC ACID Mortality CS+TXA: 4/34 TXA: 0/29 Risk of bias: High; Indirectness of outcome: No indirectness			

Total length of stay (days) CS+TXA: 13.3±11.7 TXA: 3.6±6.6 Risk of bias: High; Indirectness of outcome: No indirectness Infection CS+TXA: 5/34 TXA: 4/29 Risk of bias: High; Indirectness of outcome: No indirectness Number of patients needing blood transfusion CS+TXA: 12/34 TXA: 13/29 Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Serious adverse events related to transfusion at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up

Study	**Sangasoo 2013**
Study type	RCT
Number of studies (number of participants)	n=1 (n=135)
Countries and setting	Conducted in Thailand ; Setting: Hospital
Line of therapy	1st line

Duration of study	Intervention + follow up			
Method of assessment of guideline condition	Adequate method of assessment/diagnosis			
Stratum	Adults			
Subgroup analysis within study	Not applicable			
Inclusion criteria	Patients diagnosed as primary knee osteoarthritis and underwent unilateral primary cemented conventional total knee replacement between January 2010 and January 2011.			
Exclusion criteria	No risk of abnormal bleeding tendency or bleeding disorder (normal coagulogram, serum creatinine <2.0 mg/dl, stop NSAIDs and anti-platelet drugs more than 7 days); no contra-indication for TXA use (no active intravascular clotting process, no acquired defective colour vision, no sub-arachnoid haemorrhage, no hypersensitivity to TXA, and no any history of serious adverse effects, thrombotic disorder and haematuria).			
Recruitment/selection of patients	Not stated			
Age, gender and ethnicity		TXA -250 (n=45)	TXA-500 (n=45)	Control (n=45)
	Age (years)	67.6 (8.7)	68.1 (6.2)	66.2 (7.3)
	Females	42 (93.3%)	40 (88.95)	43 (95.6%)
Further population details		TXA -250 (n=45)	TXA-500 (n=45)	Control (n=45)
	Pre-operative Hb (g/dl)	11.9 (1.0)	12.6 (1.3)	12.1 (1.1)
Indirectness of population	No indirectness			
Interventions	TXA 250 The solution contained 250mg (5 ml) of TXA TXA-500 The solution contained 500mg (10 ml) of TXA Control This group received 25 ml of physiologic saline. All of the solution in this study was prepared as total 25 ml volume in the same-size syringe, according to the allocation received, under sterile condition and behind the fluoroscopic scene. Due to a fixed concentration of TXA medication (250 mg/5ml), the dosage of TXA could be calculated from the volume of TXA used.			

	All of the prepared solution had the same appearance. This solution was injected to the knee joint via drain tube after fascia closure, in order to prevent leakage. Then the vacuum drain was connected to the drain tube and clamped for 2 hours.
Funding	Not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : TRANEXAMIC ACID VERSUS CONTROL No. of patients requiring allogeneic transfusions TXA:6/90 control:10/45 Risk of bias: High; Indirectness of outcome: No indirectness Thromboembolic events (DVT, PE) TXA: 3/90 control:4/45 Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Length of stay (hospitalisation), Infections , Number of units of allogeneic blood transfused / volume of allogeneic blood transfused(in ml), Serious adverse events (as defined by study)

Study	**Sankar 2012**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in India; Setting: Dental hospital
Line of therapy	1st line

Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	All patients ASA I aged 17-30 years scheduled for orthognathic surgery were included in the study. Subjects included had congenital or acquired skeletal deformities corrected using conventional orthognathic operations.
Exclusion criteria	Patients who had bone diseases, cleft lip and palate, craniofacial syndromes, patients requiring palatal expansion surgery, distraction osteogenesis, simultaneous rhinoplasty, TMJ surgery, bone graft or implant replacement and endoscopically assisted surgeries were excluded from the study.
Age, gender and ethnicity	Age - Mean (SD): TXA: 23.2 (4.3); control: 24.3 (3.7). Gender (M:F): TXA:8/17; control: 9/16. Ethnicity: Not stated
Further population details	Type of surgery: orthognathic surgery
Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: Tranexamic acid. TXA was administered intravenously as an initial bolus dosage of 10 mg/kg before the incision was made over a period of 20 min, followed by 1 mg/kg intra-operatively for every 1 hour until the end of the surgery. Duration Before and during surgery. Concurrent medication/care: Ampicillin 1 g, Metronidazole 500mg, dexamethasone 8 mg were given intravenously intra operatively. (n=25) Intervention 2: Placebo. Placebo was administered intravenously as an initial bolus dosage of 10 mg/kg before the incision was made over a period of 20 min, followed by 1mg/kg intra-operatively for every 1 hour until the end of the surgery. Duration Before and during surgery. Concurrent medication/care: None
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Number of patients needing transfusions at end of follow-up - Actual outcome for Adults: Number of patients needing transfusion at end of follow-up; Group 1: 0/25, Group 2: 0/25; Risk of bias: Low; Indirectness of outcome: No indirectness	

Protocol outcome 2: Drug related adverse events at end of follow-up - Actual outcome for Adults: Drug related adverse events at end of follow-up; Group 1: 0/25, Group 2: 0/25; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Thrombosis at end of follow-up - Actual outcome for Adults: Thromboembolic events at end of follow-up; Group 1: 0/25, Group 2: 0/25; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Bleeding at end of follow-up - Actual outcome for Adults: Total blood loss at Intra-operative and post-operative; Group 1: mean 166.1 ml (SD 65.49); n=25, Group 2: mean 256.4 ml (SD 77.8); n=25; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up.

Study	**Sethna 2005**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=44)
Countries and setting	Conducted in USA; Setting: Surgery
Line of therapy	1st line
Duration of study	Follow up (post intervention): Duration not clear
Method of assessment of guideline condition	--
Stratum	Children: Children aged 8-18 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Children and adolescents with American society of Anaesthesiologists (ASA) physical status of I-III who were scheduled

	for initial scoliosis correction.
Exclusion criteria	Patients with pre-existing renal and hepatic disorders; bleeding diathesis and abnormal prothrombin time, partial thromboplastin time or platelet counts; intake of acetylsalicylate within 2 weeks or non-steroidal anti-inflammatory drugs within 7 days before surgery.
Recruitment/selection of patients	Not reported
Age, gender and ethnicity	Age - Mean (SD): Tranexamic acid group: 13.6(1.8); Placebo group: 14(2). Gender (M:F): Tranexamic acid group: 17:6; Placebo group: 13:8. Ethnicity: Not stated
Further population details	Type of surgery: scoliosis correction
Indirectness of population	No indirectness
Interventions	(n=23) Intervention 1: Tranexamic acid. After induction of anaesthesia and before skin incision, patients received tranexamic acid solution 100 mg/kg (100 mg/ml concentration) over 15 minutes. An infusion of 10 mg/kg/hour was then initiated and continued until skin closure. Duration Intra-operative. Concurrent medication/care: None (n=21) Intervention 2: Placebo. After induction of anaesthesia and before skin incision patients received 1 ml/kg saline 0.9%.An infusion of 0.1 ml/kg/hour saline was then initiated and continued until skin closure. Duration Intra-operative. Concurrent medication/care: None
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO

Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up
- Actual outcome for Children: Amount of blood transfused at Intra-operative; Group 1: mean 615 ml (SD 460); n=23, Group 2: mean 940 ml (SD 718); n=21; Risk of bias: --; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of patients needing transfusions at end of follow-up
- Actual outcome for Children: Number of patients needing transfusions at Intra-operative; Group 1: 14/23, Group 2: 15/21; Risk of bias: --; Indirectness of outcome: No indirectness

Protocol outcome 3: Bleeding at end of follow-up
- Actual outcome for Children: Intra-operative blood loss at Intra-operative; Group 1: mean 1230 ml (SD 535); n=23, Group 2: mean 2085 ml (SD 1188); n=21; Risk of

bias: --; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Length of hospital stay at end of follow-up.

Study	**Shahid 2013**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=74)
Countries and setting	Conducted in Pakistan; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Full term primipara/multiparas (parity not more than two) with singleton pregnancy being delivered by LSCS were included in the study.
Exclusion criteria	Subjects having allergy to TXA, history of thromboembolic disorders, abnormal placentation, severe pre-eclampsia, multiple pregnancy, macrosomia, polyhydromnios and those requiring blood transfusion due to anaemia were also excluded from the study.
Age, gender and ethnicity	Age - Mean (SD): TXA: 24.18 (3.93); control: 24.89 (4.16). Gender (M: F): All women. Ethnicity: Not stated
Further population details	Type of surgery: caesarean surgery

Extra comments	Women undergoing lower segment caesarean section (LCSC).
Indirectness of population	No indirectness
Interventions	(n=38) Intervention 1: Tranexamic acid. Injection of TXA just before surgery (no more details). TXA injection was prepared by diluting 1g (10ml) TXA with 20 ml of 5% glucose.. Duration Just before surgery. Concurrent medication/care: None (n=36) Intervention 2: Placebo. Distilled water diluted with 20 ml of 5% glucose for IV injection. Duration Just before surgery. Concurrent medication/care: None
Funding	No funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO

Protocol outcome 1: Number of patients needing transfusions at end of follow-up
- Actual outcome for Adults: Number of patients needing transfusion at end of follow-up; Group 1: 3/36, Group 2: 12/36; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Thrombosis at end of follow-up
- Actual outcome for Adults: Deep vein thrombosis at end of follow-up; Group 1: 0/38, Group 2: 0/36; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Bleeding at end of follow-up
- Actual outcome for Adults: Intra-operative blood loss at During surgery; Group 1: mean 356.44 ml (SD 143.2); n=38, Group 2: mean 710.22 ml (SD 216.72); n=36; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for Adults: Post-operative blood loss at 2 hours post-partum; Group 1: mean 35.68 ml (SD 23.29); n=38, Group 2: mean 43.63 ml (SD 28.04); n=36; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up

Study	Shi 2013
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=552)
Countries and setting	
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Define
Exclusion criteria	Define
Age, gender and ethnicity	Age - Mean (SD): TXA: 60 (9.41); placebo: 59.6 (9.02). Gender (M:F): Define. Ethnicity: Not stated
Further population details	Type of surgery: Cardiac surgery (CABG).
Indirectness of population	No indirectness
Interventions	(n=285) Intervention 1: Tranexamic acid. 50 mg/ml of TXA. The medication was pumped intravenously with a bolus of 0.2 ml/kg after induction over 10 minutes followed by a maintenance dose of 0.2 ml/kg/hour throughout the surgery, fulfilling the dosage regimen of TXA as a bolus of 10mg/kg and a maintenance dose of 10 mg/kg/hour. Duration: Before and during surgery. Concurrent medication/care: All patients received sub-cutaneous low-molecular weight heparin within 24 hours pre-operatively. Patients on either Nitrates, BBlockers, ACE inhibitors, diuretics, statins, clopidogrel (n=285) Intervention 2: Placebo. 50mg/ml of saline. Duration Before and during surgery. Concurrent medication/care: All patients received sub-cutaneous low-molecular weight heparin within 24 hours pre-operatively. Patients on either Nitrates, BBlockers, ACE inhibitors, diuretics, statins, clopidogrel

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up - Actual outcome for Adults: Number of units transfused-plasma at end of follow-up; Group 1: mean 1.43 ml (SD 2.02); n=274, Group 2: mean 2.77 ml (SD 3.62); n=278; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Number of units transfused-RBC at end of follow-up; Group 1: mean 3.93 ml (SD 4.66); n=274, Group 2: mean 6.51 ml (SD 7.33); n=278; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Mortality (all causes) at 30 days - Actual outcome for Adults: Mortality- at discharge; Group 1: 2/274, Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Number of patients needing transfusions at end of follow-up - Actual outcome for Adults: Number of patients needing transfusions- RBC at end of follow-up; Group 1: 166/274, Group 2: 221/278; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Number of patients needing transfusions- plasma at end of follow-up; Group 1: 132/274, Group 2: 202/278; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Number of patients needing transfusions- RBC at end of follow-up; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Bleeding at end of follow-up - Actual outcome for Adults: Bleeding at end of follow-up; Group 1: mean 959 ml (SD 515); n=274, Group 2: mean 1237 ml (SD 691); n=278; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Length of hospital stay at end of follow-up

Study	**Shi 2013**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=120)
Countries and setting	Conducted in China; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Men and women aged 18 to 85 years undergoing primary and isolated on-pump CABG who received dual anti-platelet therapy (clopidogrel 75mg and aspirin 100 mg daily) with their last ingestion less than 7 days pre-operatively.
Exclusion criteria	Patients with previous cardiac surgery, haematocrit less than 33%, platelet count less than 100,000/ml, or allergy to TXA and those recruited in other studies.
Age, gender and ethnicity	Age - Mean (SD): 60.3 (8.41); 59.5 (9.96). Gender (M: F): male: TXA- 46; Control: 48. Ethnicity: Not stated
Further population details	Type of surgery: CABG
Extra comments	Patients undergoing primary and isolated on-pump CABG with their last dose of clopidogrel and aspirin less than 7 days pre-operatively.
Indirectness of population	No indirectness
Interventions	(n=60) Intervention 1: Tranexamic acid. TXA 50 mg/ml. The target volume was calculated by the body weight to fulfil the dosage of 15 mg/kg TXA. One target volume was infused IV before surgical incision, and a second one was administered after protamine neutralisation. Thus the dose in the study was 15 mg/kg before surgical incision and 15 mg/kg after protamine neutralization. Duration 15 minutes before incision. Concurrent medication/care: None reported Comments: The threshold for allogeneic erythrocyte transfusion was a Hb concentration of less than 60 g/litre during cardiopulmonary bypass and less than 80 g/litre post-operatively or less than 90 g/litre for elderly people (>70 years). Indication for FFP was excessive bleeding of greater than 2 ml/kg for 2 consecutive hours with a thromboelastography result implying clotting factors. Concentrated platelets were given at the discretion of the attending physician.

	(n=60) Intervention 2: Placebo. Saline solution. Duration 15 minutes before incision. Concurrent medication/care: None
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up - Actual outcome for Adults: No. of units transfused per patient- red blood cells at end of follow-up; Group 1: mean 4.84 units (SD 5.85); n=58, Group 2: mean 9.36 units (SD 11.41); n=59; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: No. of units transfused per patient- plasma at end of follow-up; Group 1: mean 1.71 units (SD 1.67); n=58, Group 2: mean 3.68 units (SD 5.28); n=59; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: No. of units transfused per patient- platelets at end of follow-up; Group 1: mean 0.28 (SD 1.84); n=58, Group 2: mean 0.44 (SD 1.88); n=59; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Mortality (all causes) at 30 days - Actual outcome for Adults: Mortality at 1 year; Group 1: 2/58, Group 2: 2/59; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Number of patients needing transfusions at end of follow-up - Actual outcome for Adults: No. of patients needing transfusion- red blood cells at end of follow-up; Group 1: 42/58, Group 2: 54/59; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: No. of patients needing transfusion- plasma at end of follow-up; Group 1: 34/58, Group 2: 50/59; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: No. of patients needing transfusion- platelets at end of follow-up; Group 1: 3/58, Group 2: 5/59; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Bleeding at end of follow-up - Actual outcome for Adults: Blood loss (ml) at end of follow-up; Group 1: mean 10691 ml (SD 565.5); n=58, Group 2: mean 14498 ml (SD 899.8); n=59; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Length of hospital stay at end of follow-up

Study	**Soosman 2014**		
Study type	RCT		
Number of studies (number of participants)	n= 1 (n=1759)		
Countries and setting	Conducted in The Netherlands; Setting: Hospitals		
Line of therapy	1st line		
Duration of study	Intervention + follow up		
Method of assessment of guideline condition	Adequate method of assessment/diagnosis		
Stratum	Adults		
Subgroup analysis within study	Not applicable		
Inclusion criteria	Adult patients (18 years or older) scheduled for elective primary or revision total hip or knee replacement surgery.		
Exclusion criteria	Patients were excluded if they had Hb less than 13 g/dl, untreated hypertension (diastolic blood pressure >95 mm Hg); a serious disorder of the coronary, peripheral, and/or carotid arteries; a recent MI or stroke (within 6 months); sickle cell anaemia; a malignancy in the surgical area, a contraindication for anti-coagulation prophylaxis, an infected wound bed, a revision of an infected prosthesis, which was being treated with local antibiotics, difficulty understanding the Dutch language, or were pregnant or refused homologous blood transfusions.		
Recruitment/selection of patients	After providing written informed consent, patients were enrolled between May 1, 2004 and October 1, 2008 from 4 hospitals in the Netherlands with the study closure after completed follow-up on October 1, 2009.		
Age, gender and ethnicity		Pre-operative Hb >13 g/dl	
		AUTO (n=1061)	Control (n=698)
	Females	694 (65)	410 (59)
	Age (years)	69 (10)	68 (10)
Further population details		AUTO (n=1061)	Control (n=698)
	High risk	40 (4)	23 (3)
Indirectness of population	No indirectness		

Interventions	Combined autologous group (AUTO): n= 1061 (ICS+PCS+PCS) Autologous blood re-infusion by cell saver or post-operative drain re-infusion device (DRAIN). Two different DRAIN devices were used for re-infusion of collected autologous blood up to 6 hours after surgery. The OrthoPAT cell saver was used for both intra-and post-operative collection and re-infusion of autologous blood, collected up to 6 hours after surgery. Control: n=698 All control patients received a low vacuum wound drain, of which the collected blood was discarded.
Funding	Not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISONS : ICS +PCS+PCS VERSUS CONTROL, ICS+PCS VERSUS CONTROL, PCS (DRAIN) VERSUS CONTROL

<u>ICS +PCS+PCS versus control</u>
Number of patients transfused
ICS +PCS+PCS: 75/1061
control: 57/698
Risk of bias: low; Indirectness of outcome: No indirectness

Number of units transfused
ICS +PCS+PCS : 0.19 (28)
control: 0.22 (24)
Risk of bias: low; Indirectness of outcome: No indirectness

Thrombotic events (DVT/PE)
ICS +PCS+PCS :4/1061
control: 4/698
Risk of bias: low; Indirectness of outcome: No indirectness

Length of hospital stay
ICS+PCS+PCS: 7.83 (days)
control: 7.38 (days)
No SD reported
Risk of bias: low; Indirectness of outcome: No indirectness

ICS+PCS vs. control
No. of patients requiring allogeneic transfusions
ICS+PCS: 23/321
Control: 54/658
Risk of bias: low; Indirectness of outcome: No indirectness

Units of allogeneic blood transfused
ICS+PCS: 0.25 ±0.5 (n=321)
control: 0.22 ±0.9 (n=658)
Risk of bias: low; Indirectness of outcome: No indirectness

PCS (DRAIN) vs. control
No. of patients requiring allogeneic transfusions
PCS: 33/321
control: 54/658
Risk of bias: low; Indirectness of outcome: No indirectness

Units of allogeneic blood transfused PCS: 0.13 ±0.7 (n=321) control: 0.22 ±0.9 (n=658) Risk of bias: low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Infections, Serious adverse events (as defined by study)

Study	**Soosman 2014A**
Study type	RCT (multicentre)
Number of studies (number of participants)	n=1 (n=344)
Countries and setting	Conducted in The Netherlands; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients 18 years or older, scheduled for primary or revision total hip or knee replacement surgery.
Exclusion criteria	Patients were excluded if they had untreated hypertension (diastolic blood pressure >95 mm Hg), a serious disorder of the coronary , peripheral and or carotid arteries, a recent MI or stroke (within 6 months), sickle cell anaemia, a malignancy in the surgical area, a contraindication for anti-coagulation prophylaxis, a known allergy to erythropoietin, an infected wound bleed, a revision of an infected prosthesis, which was being treated with local antibiotics, difficulty in understanding the Dutch language, or were pregnant or refused homologous blood transfusions.
Recruitment/selection of patients	The patients were enrolled between May 1, 2004 and October 1, 2008 from 4 hospitals with the study closure after completed follow-up on October 1, 2009.

Age, gender and ethnicity		AUTO (n=206)	Control (n=138)
	Females	177 (86)	121 (88)
	Age (years)	71 (12)	70 (11)
Further population details		AUTO (n=206)	Control (n=138)
	High risk	8 (4)	5 (4)
Indirectness of population	No indirectness		
Interventions	Combined autologous group (AUTO): n=206 (ICS+PCS+PCS) Cell saver (intra and post-operative autologous reinfusion device) that washed , filtered and re-infused the autologous shed blood (only in hip surgery) and a post-operative autologous reinfusion drainage system (DRAIN) that filtered and reinfused autologous unwashed shed blood (both and knee surgery) Control: n=138 No blood salvage device, although a low vacuum wound drain was placed but the collected blood was discarded. All patients were transfused according to a restrictive transfusion policy as advised in the Dutch transfusion guideline. The type of cell saver (OrthoPAT) was uniform for all patients		
Funding	Not stated		

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : ICS+PCS+PCS VERSUS CONTROL

Thrombotic events (DVT/PE)
ICS+PCS+PCS:1/206
control:0/138
Risk of bias: low; Indirectness of outcome: No indirectness

Number of patients transfused
ICS+PCS+PCS:60/206
control:32/138
Risk of bias: low; Indirectness of outcome: No indirectness

Number of units transfused ICS+PCS+PCS: 0.76 (23) control: 0.64 (19) Risk of bias: low; Indirectness of outcome: No indirectness Length of hospital stay ICS+PCS+PCS: 9.08 (days) control: 8.26 (days) No SD reported Risk of bias: low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Infections , Serious adverse events (as defined by study)

Study	**Thomassen 2014**
Study type	RCT (multi-centre, prospective, single-blinded controlled trial)
Number of studies (number of participants)	n= 1(n=575)
Countries and setting	Conducted in The Netherlands; Setting: Hospital (2 hospitals)
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients planned for primary total hip replacement (THR) or total knee replacement (TKR).

Exclusion criteria	Inability to give informed consent, patients with bleeding disorders, a religious objection to the concept of blood transfusion, and patients where bone grafting was expected during THR.			
Recruitment/selection of patients	All consecutive patients planned for primary total hip replacement (THR) or total knee replacement (TKR) between November 2010 and November 2012 were eligible for the study. The study population consisted of 322 THRs and 253 TKRs undertaken in 575 patients.			
Age, gender and ethnicity		Group A (n=190)	Group B (n=191)	Group C (n=194)
	Age (years)	68.9	69.5	68.2
	M/F	132/58	123/68	120/74
Further population details	Type of surgery: primary total hip replacement (THR) or total knee replacement (TKR). The 3 groups were comparable with regards to mean age; body mass Index (BMI) and American Society of Anaesthesiologists (ASA) classification. The 3 different surgical approaches used for THR (15 1 SL, 15 SPL and 16 AS), were equally divided between the transfusion sub-groups.			
Indirectness of population	No indirectness			
Interventions	Group A: patients with no wound drainage (n=190) Group B: patients who received autologous blood re-infusion from their drain after 6 hours at which stage this drain was removed. Group C: patients who received autologous blood reinfusion from their drain after 6 hours but drain removal after 24 hours. The re-infusion drains were used in groups B and C according to the manufacturer's instructions for post-operative autologous blood collection and re-infusion. The collected shed blood was returned to the patient in both re-infusion groups irrespective of their haemoglobin (Hb) level. Note: Erythropoietin was routinely used in one of the two hospitals in anaemic patients with a pre-operative Hb level below 13g/dl (n=17) Three subcutaneous injections (40,000 IU of erythropoietin alpha in each injection) were given weekly, beginning 3 weeks before surgery with iron supplementation. Patients who used anti-coagulation stopped these 7 to 10 days pre-operatively so that their INR was <1.8 before surgery. All patients received thrombo-prophylaxis with low-weight molecular heparin after surgery and continued until 6 weeks post-operatively.			

Funding	No funding received
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : PCS (Post-operative cell salvage) vs. standard treatment No. of patients requiring allogeneic transfusions PCS: 29/382 Standard Treatment: 12/190 Risk of bias: low; Indirectness of outcome: No indirectness Infection (Pneumonia) PCS: 4/382 Standard Treatment: 0/190 Risk of bias: low; Indirectness of outcome: No indirectness Deep vein thrombosis (DVT) PCS: 2/382 Standard Treatment: 1/190 Risk of bias: low; Indirectness of outcome: No indirectness Deep (THR/TKR) infection PCS: 7/382 Standard Treatment: 4/190 Risk of bias: low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Length of stay (hospitalisation), Infections , Number of units of allogeneic blood transfused / volume of allogeneic blood transfused(in ml), Thrombotic complications, Serious adverse events (as defined by study)

Study	**Verma 2014**

Study type	RCT
Number of studies (number of participants)	n=1 (n=175)
Countries and setting	Conducted in USA ; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients adolescent idiopathic scoliosis undergoing posterior spinal arthrodesis
Exclusion criteria	Not stated
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	TXA (n=36) / Control (n=47) Age: 15.30 (2.37) / 14.61 (1.89) M:F: 4:32 / 16:31
Further population details	Type of surgery: posterior spinal arthrodesis TXA (n=36) / Control (n=47) Estimated blood loss volume (ml): 3672 (949) / 4273 (1131)
Indirectness of population	No indirectness
Interventions	TXA: n=36 The loading dose was 10 mg/kg infused over 15 minutes, while the maintenance dose was 1 mg/kg/hour. Control: n=47 Saline
Funding	Not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : TRANEXAMIC ACID VERSUS PLACEBO
Length of stay (in days) TXA: 5.4±1.2, n=36 Placebo: 5.3±0.9, n=47 Risk of bias: low; Indirectness of outcome: No indirectness No. of patients requiring allogeneic transfusions: Combined data presented for autologous and allogeneic transfusions; not separate for allogeneic transfusions Risk of bias: high; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	All-cause mortality at 30 days, Quality of life, Infections, Number of units of allogeneic blood transfused / volume of allogeneic blood transfused (in ml), Thrombotic complications, Serious adverse events (as defined by study)

Study	Vermeijden 2015
Study type	RCT (Patient randomised; partially blinded)
Number of studies (number of participants)	1 (n=738) (Only 2 relevant comparisons CS, n=189; control, n=177)
Countries and setting	Conducted in The Netherlands ; Setting: Hospital

Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients scheduled for elective coronary artery bypass grafting (CPB), valve surgery, or combined procedures were included.
Exclusion criteria	Patients scheduled for off-pump surgery and patients with known coagulation disorders except after the use of aspirin, clopidogrel or low-molecular weight heparin were excluded.
Age, gender and ethnicity	Age - Mean (SD): CS - 66±9.5 ; control -66±9.7 Gender, male, n(%): CS- 134 (71); control- 127 (71)
Further population details	Pulmonary disease (%): CS: 11; control: 10 Myocardial Infarction (%): CS: 23; control: 27 Stroke (%): CS: 4; control: 6 Aspirin and clopidogrel were stopped according to local protocol.
Extra comments	Participants were recruited from January 2005 to January 2009. As a result of the implementation of new Dutch transfusion guidelines during the study period, tranexamic acid (2g) was used .
Indirectness of population	No indirectness

Interventions	(n=189) Intervention 1: Cell salvage. The centres used their own CS with standard washing program (CATS [Fresenius], Brat 5 [Haemonetics, Braintree, MA] or Dideco-electa [Sorin, Milan, Italy]. Suction pressure was minimised to prevent hemolysis. (n= 177) Intervention 2: Control. No cell salvage used. Extra comments: Based on Dutch transfusion guidelines, RBCs were transfused when the post-operative haemoglobin level was less than 5 mmol/L. Transfusion of RBCs during CPB was guided by clinical judgement of the attending anaesthesiologist and perfusionist. Transfusion of FFP occurred in cases of excessive bleeding (>150 Ml/h for 2 consecutive hours and prothrombin time >1.5 times normal).
Funding	The Netherlands Organisation for Health Research and Development funded this study
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CELL SALVAGE versus STANDARD TREATMENT Protocol outcome 1: Number of units transfused (red cells) - Group 1: (mean) units:3.8 ; n=189 , Group 2: (mean) units:3.4; n=49 ; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at the end of follow-up - Group 1: 98/189 , Group 2:108/177 ; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Length of hospital stay - Group 1: (mean± SD) days: 11.5±10.5 ; n= , Group 2: (mean± SD) days:11.8 ±9.6 ; n=; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Mortality (30 days) -Group 1: 1/189 , Group 2: 5/177 ; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; thrombotic complications at end of follow-up, Serious adverse events related to transfusion at End of follow-up

Study	Vijay 2013
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=90)
Countries and setting	Conducted in India; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	90 patients (ASA grade I/II between 18 and 80 years, weighing 40-100 kg) undergoing surgery for femoral fracture like open reduction internal fixation, hemiarthroplasty, total hip replacement was included.
Exclusion criteria	Patients with chronic diseases like rheumatoid arthritis, ischaemic heart disease, malignancy, history of any previous thromboembolic episodes, Hb <8g/dl were excluded from the study.
Age, gender and ethnicity	Age - Mean (SD): TXA: 48.8 (16.2); control: 49.3 (19.5). Gender (M:F): TXA: 10/35; control: 10/35. Ethnicity: Not stated
Further population details	Type of surgery: Orthopaedic surgery (Hip and femoral surgeries).
Indirectness of population	No indirectness
Interventions	(n=45) Intervention 1: Tranexamic acid. Patients received bolus intravenous injection of 500 mg TXA through 50 ml syringe during 10 minutes about 15 minutes before incision, followed by a continuous infusion of 1 mg/kg/hour dissolved in 1 litre of saline until the completion of surgery. Duration: Before and during surgery. Concurrent medication/care: None (n=45) Intervention 2: Placebo. Patients received physiological saline a bolus intravenous injection of 50 ml about 15 minutes before the surgery followed by a continuous infusion of 1 litre of saline until the surgery completed. Duration

	Before and during surgery. Concurrent medication/care: None reported
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Number of patients needing transfusions at end of follow-up - Actual outcome for Adults: Number of patients needing transfusion at end of follow-up; Group 1: 7/45, Group 2: 18/45; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Thrombosis at end of follow-up - Actual outcome for Adults: Thromboembolic events at end of follow-up; Group 1: 0/45, Group 2: 0/45; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Bleeding at end of follow-up - Actual outcome for Adults: Post-operative blood loss at After surgery on the day of the operation; Group 1: mean 39.3 ml (SD 10.1); n=45, Group 2: mean 91.1 ml (SD 17.6); n=45; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up

Study	**Wang 2012**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=231)
Countries and setting	Conducted in China; Setting: Hospital
Line of therapy	1st line

Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing OPCAB
Exclusion criteria	Known allergy to the study drug, history of bleeding disorders, pre-operative anaemia (Hb <10g/dl), chronic renal insufficiency (serum creatinine >2 mg/dl), active chronic hepatitis or cirrhosis, previous cardiac surgery, myocardial infarction <30 days and withdrawal of clopidogrel or aspirin <5 days before surgery.
Recruitment/selection of patients	From Feb 2009 to Dec 2009, consecutive patients scheduled for elective off-pump coronary artery bypass grafting (OPCAB) were enrolled in the study.
Age, gender and ethnicity	Age - Mean (SD): TXA- 60 (5); Placebo- 60 (8.5). Gender (M:F): Males: TXA- 93; placebo- 102. Ethnicity: NR
Further population details	Type of surgery: Cardiac surgery (Off pump coronary artery bypass grafting).
Indirectness of population	No indirectness
Interventions	(n=116) Intervention 1: Tranexamic acid. Tranexamic acid 1g was administered as a bolus injection 20 minutes before the incision and followed by a continuous infusion of 400 mg/h until the completion of the surgery. Duration Before surgery. Concurrent medication/care: All patients received pre-medication with IM morphine 0.2 mg/kg. A heparin dose of 150 IU/kg was administered to obtain an activated clotting time >300 seconds. All patients underwent intra-operative cell salvage with auto transfusion of washed salvaged red cells at the end of the operation. (n=115) Intervention 2: Placebo. The placebo consisted of an equivalent volume of saline solution. Duration Before surgery. Concurrent medication/care: All patients received pre-medication with IM morphine 0.2 mg/kg. A heparin dose of 150 IU/kg was administered to obtain an activated clotting time >300 seconds. All patients underwent intra-operative cell salvage with auto transfusion of washed salvaged red cells at the end of the operation.
Funding	No funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO	

Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up - Actual outcome for Adults: No. of units transfused- RBC (intra-operative) at end of hospital stay; Group 1: mean 0.12 unit (SD 0.55); n=116, Group 2: mean 0.1 unit (SD 0.64); n=115; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: No. of units transfused- RBC (post-operative) at end of hospital stay; Group 1: mean 0.91 units (SD 1.59); n=116, Group 2: mean 1.62 units (SD 2.57); n=115; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: No. of units transfused- FFP (intra-operative) at end of hospital stay; Group 1: mean 0.21 units (SD 0.89); n=116, Group 2: mean 0.1 units (SD 0.69); n=116; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: No. of units transfused- FFP (post-operative) at end of hospital stay; Group 1: mean 0.57 units (SD 1.39); n=116, Group 2: mean 1.43 units (SD 2.72); n=115; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Length of hospital stay at end of follow-up - Actual outcome for Adults: Length of hospital stay at end of hospital stay; Group 1: mean 7.6 days (SD 1.6); n=116, Group 2: mean 7.6 days (SD 1.1); n=115; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Mortality (all causes) at 30 days - Actual outcome for Adults: In-hospital deaths at end of hospital stay; Group 1: 0/116, Group 2: 0/115; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Number of patients needing transfusions at end of follow-up - Actual outcome for Adults: Number patients transfused- RBC at end of hospital stay; Group 1: 37/116, Group 2: 54/115; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Number patients transfused- FFP at end of hospital stay; Group 1: 20/116, Group 2: 34/115; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for Adults: Number patients transfused- platelets at end of hospital stay; Group 1: 0/116, Group 2: 0/115; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Bleeding at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery

Study	**Xu 2013**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=174)
Countries and setting	Conducted in China
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Women with a singleton pregnancy who were scheduled to undergo caesarean delivery by Pfannenstiel incision under spinal anaesthesia
Exclusion criteria	Age <18 years, informed consent was not obtained, severe medical and surgical complications involving the heart, liver or kidney, brain disease and blood disorders were present, allergic to tranexamic acid, multiple pregnancies, macrosomia or polyhydramnios occurred, known haemostatic abnormalities before pregnancy were present.
Recruitment/selection of patients	176 primipara with a singleton pregnancy who were scheduled to undergo caesarean delivery by Pfannenstiel incision under spinal anaesthesia were recruited for this study.
Age, gender and ethnicity	Age - Mean (SD): TXA: 27.1 (3.7); control group: 27.1 (4.1). Gender (M:F): All females. Ethnicity: Not stated
Further population details	Type of surgery: caesarean delivery
Indirectness of population	No indirectness
Interventions	(n=88) Intervention 1: Tranexamic acid. Patients received 10 mg/kg of intravenous TXA in 200 ml of normal saline.. Duration The study intervention drug and the placebo were infused over 10 and 20 minutes before beginning spinal anaesthesia. Concurrent medication/care: None Comments: Both in TXA and control groups, infusion of fresh frozen plasma would have taken place when blood loss exceeded 2500 ml, while the transfusion threshold of packed red blood cells was a Hb concentration of 8 g/dl. (n=86) Intervention 2: Placebo. Control patients received 200 ml of normal saline. Duration The study intervention drug and the placebo were infused over 10 and 20 minutes before beginning spinal anaesthesia.. Concurrent

	medication/care: None
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Drug related adverse events at end of follow-up - Actual outcome for Adults: Side effects of TXA (including DVT, renal failure, seizures, maternal death) at end of follow-up; Group 1: 2/88, Group 2: 2/86; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Thrombosis at end of follow-up - Actual outcome for Adults: Deep vein thrombosis at end of follow-up; Group 1: 2/88, Group 2: 2/86; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Bleeding at end of follow-up - Actual outcome for Adults: Total blood loss from the end of caesarean section to 2 hours post-partum at 2 hours post-partum; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Serious adverse events related to transfusion at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up

Study	Yang 2015
Study type	RCT (Patient randomised; double blind)
Number of studies (number of participants)	1 (n=80) (n= 40 TXA; n= 40 placebo)

Countries and setting	Conducted in China; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients >60 years old; diagnosed with osteoarthritis, traumatic arthritis or rheumatoid arthritis, and with a body mass index (BMI) <40 $kg/m^{2.}$
Exclusion criteria	Patients with haemorrhagic blood diseases; haemoglobin <90 g/L; with peripheral nerve vascular disease, cancer, history of thromboembolic disease; affected lower limb with a history of infection; and American Society of Anaesthesiologists (ASA) anaesthesia rating >3.
Age, gender and ethnicity	Age - Mean (SD): TXA:69±5 ; Placebo : 67±6 Gender (M: F): male: TXA – 12/40; Control: 10/40. Ethnicity: Not stated
Further population details	Type of surgery: Unilateral total knee arthroplasty. There were no statistically significant differences between the two groups regarding the pre-operative data, age ratio, gender ratio, BMI, surgical side, Hb level, Hct, FIB, PT, APTT and activity of the knee joint.
Extra comments	Elderly patients who underwent a primary unilateral TKA between January 2011 and October 2013 and for whom complete medical records were available were selected for inclusion in the study.
Indirectness of population	No indirectness

Interventions	(n=40) Intervention 1: Tranexamic acid. Patients received an injection of TXA (500 mg/20 ml) in to the knee joint cavity after completion of fascial closure in order to prevent leakage. (n= 40) Intervention 2: Placebo. Patients received normal saline (same quantity as TXA) Additional comments: A dose of 0.6 ml low-molecular weight heparin calcium was administered subcutaneously to all of the patients at 12 h post-surgery and was repeated daily until discharge. The patients were all encouraged to perform a mechanical ankle pumping exercises to prevent deep vein thrombosis as soon as they were able. The patients were also encouraged to exercise the legs by walking with the aid of a crutch from 2 days post-surgery. Patients received blood transfusions according to the following protocol: (1) patients with Hb levels less than 70 g/L received a homologous blood transfusion until the level reached or exceeded 80 g/L; (2) patients with Hb levels between 70-100 g/L received a transfusion determined by the specific circumstances of the patients.
Funding	Not reported

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID versus PLACEBO

Protocol outcome 1: Number of units transfused
- Group 1: (mean) units: 10 ; n= 40, Group 2: 21; n= 40; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of patients needing transfusions
- Group 1: 10/40 , Group 2:19/40; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Thrombotic events (Pulmonary embolism/Deep vein thrombosis) at end of follow-up
- Group 1:0/40, Group 2: 0/40; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at End of follow-up ;mortality at end of follow-up; Infection at the end of follow-up; Serious adverse events related to transfusion at End of follow-up; Length of hospital stay at End of follow-up

Study	Yue 2015
Study type	RCT (Patient randomised; double blind)
Number of studies (number of participants)	1 (n=101) (n= 52 TXA; n= 49 placebo)
Countries and setting	Conducted in China ; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients undergoing primary unilateral total hip arthroplasty (THA) for osteoarthritis (OA) or osteonecrosis of the femoral head (ONFH).
Exclusion criteria	Patients who were receiving anticoagulant therapy, patients with a history of haemophilia, deep vein thrombosis, pulmonary embolism or ischaemic heart disease and patients who were allergic to TXA.
Age, gender and ethnicity	Age - Mean (SD): TXA: 60.9±13.2 ; Placebo : 63.7±10.0 Gender (M: F): male: TXA – 21/52; Control: 18/49. Ethnicity: Not stated
Further population details	Type of surgery: Primary Total Hip Arthroplasty

Extra comments	Pre-operative Hb (g/l): TXA: 134.27±9.26 Control: 135.47±11.16
Indirectness of population	No indirectness
Interventions	(n=52) Intervention 1: Topical Tranexamic acid (TXA). 3 g TXA in 150 ml saline was used at three points during the whole procedure of THA. First after the acetabular preparation, a gauze was used which was full of 50 ml of the TXA solution to soak the acetabulum for three minutes, a cementless acetabular component was then impacted. Then after femoral canal broach preparation, gauze with the same concentration of TXA was inserted in the femoral canal for three minutes, and then the cementless femoral stem was impacted. At last, the remaining 50 ml TXA fluid was injected to the hip joint after fascia closure. A drain was used and clamped for 30 minutes. (n= 49) Intervention 2: Control. In the control group, the same method used in the TXA group was used with the same dose of saline and clamped for 30 minutes. The drainage was removed the next morning after the operation. Additional comments: All patients were given chemical thromboprophylaxis by low molecular weight heparin combined with mechanical thromboprophylaxis by a leg pump.
Funding	Not reported

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID versus CONTROL

Protocol outcome 1: Number of units transfused (red cells)
- Group 1: (mean) units:5.5 ; n=52 , Group 2: 24.5 (mean) units:; n=49 ; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of patients needing transfusions at the end of follow-up
- Group 1: 3/52, Group 2:11/49; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Length of hospital stay - Group 1: (mean± SD) days: 5.1±0.5 ; n=52 , Group 2: (mean± SD) days: 4.9±0.7; n=49 ; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Thrombotic events (Pulmonary embolism/deep vein thrombosis) at end of follow-up -Group 1: 1/52 , Group 2: 0/49 ; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Serious adverse events related to transfusion at End of follow-up

Study	**Zonis 1996**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=88)
Countries and setting	Conducted in Canada; Setting: Pediatric hospital (surgery)
Line of therapy	1st line
Duration of study	Follow up (post intervention):
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children: Age range from 1 day to 14 years
Subgroup analysis within study	Not applicable
Inclusion criteria	Children undergoing cardiopulmonary bypass surgery
Exclusion criteria	History of haematuria, Renal failure, Previous thrombotic episodes, or past bleeding complications
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Age in months-Tranexamic acid: 62.8(58.1); Placebo: 52.6 (51.2). Gender (M: F): Tranexamic acid:

	19:21; Placebo: 21:21. Ethnicity: Not reported
Further population details	Type of surgery: cardiopulmonary bypass surgery
Indirectness of population	Serious indirectness: Includes children less than 1 year of age; mean age in both groups >5 years
Interventions	(n=40) Intervention 1: Tranexamic acid. Single intravenous dose of 50mg/kg of tranexamic acid (Cyclokapron, Kabi Pharmacia, Canada). Duration Intra-operative. Concurrent medication/care: None (n=42) Intervention 2: Placebo. Single intravenous dose of 50mg/kg saline given before first skin incision. Duration Intra-operative. Concurrent medication/care: None
Funding	Study funded by industry (Grant from Kabi pharmacia, Misissauga, Ontario, Canada.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: TRANEXAMIC ACID VERSUS PLACEBO Protocol outcome 1: Bleeding at end of follow-up - Actual outcome for Children: Post -operative blood loss at 24 hours post-operatively; Group 1: mean 21.2 ml/kg (SD 12); n=40, Group 2: mean 27.2 ml/kg (SD 20.3); n=42; Risk of bias: Low; Indirectness of outcome:	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Mortality (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Serious adverse events related to transfusion at end of follow-up; Drug related adverse events at end of follow-up; Thrombosis at end of follow-up; Other thrombosis (including MI, stroke, pulmonary embolism, arterial embolism) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up

H.3 Red blood cells

Study	**Carson 2012[22]**
Study type	Systematic review

Number of studies (number of participants)	19 (n=6264)
Countries and setting	Conducted in Canada, Netherlands, United Kingdom, USA; Setting: Surgery, Trauma, critical care, chemotherapy
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Systematic review - pre-specified in protocol
Inclusion criteria	Surgical or medical patients, involving adults and children. The intervention considered was the use of transfusion thresholds
Exclusion criteria	Neonates. No relevant interventions and comparisons specified in the protocol.
Age, gender and ethnicity	Age - Other: Adults and children. No infants. Gender (M:F): Define. Ethnicity: Mixed from various trials
Further population details	1. Acute Coronary syndrome: 2. Co-existing ischaemic heart disease: 3. Congenital cardiac disease: 4. Gender: 5. Neurological disease: 6. Stroke: 7. Traumatic brain injury: Traumatic brain injury
Indirectness of population	No indirectness
Interventions	(n=3066) Intervention 1: High (liberal) haemoglobin thresholds for transfusion (as defined by the trial). The liberal transfusion triggers varied: 100% of 'normal red cell volume' (Topley 1956), two units of blood (immediately in one trial (Blair 1986), post-operatively in another (Lotke 1999)) irrespective of clinical state; transfusion sufficient to maintain haemoglobin levels at or above 12.0 g/dl (Webert 2008), 10.0 g/dl (Bush 1997; Carson 1998; Carson 2011; Foss2009;Grover 2005;Hebert 1995;Hebert 1999);Hajjar 2010, 9.5 g/dl (Lacroix 2007) and 9.0 g/dl (Bracey 1999; Colomo 2008; Zygun 2009).Two trials specified the liberal triggers as haematocrit levels of 32% (Johnson 1992) and 40%(Fortune 1987). One trial compared a new uniform, restrictive transfusion policy with more liberal standard care (So-Osman 2010). Duration Variation in studies. Concurrent medication/care: Various depending on the study Further details: 1. Critical care: In critical care 2. Patients receiving radiotherapy: Patients receiving radiotherapy 3. Patients undergoing chemotherapy and stem-cell transplants.: Patients undergoing chemotherapy and stem-cell transplants. 4. Peri-operative surgical patients: Peri-operative surgical patients (n=3059) Intervention 2: Low (restrictive) haemoglobin thresholds for transfusion (as defined by the trial). the restrictive

	transfusion strategies varied from 7.0 to 9.0 g/dl, with two further trials specifying haematocrit values of 25% or 30% (equivalent to haemoglobin levels of around 8.0 and 10.0 g/dl respectively).. Duration Variation in studies. Concurrent medication/care: Various depending on the study Further details: 1. Critical care: In critical care 2. Patients receiving radiotherapy: Patients receiving radiotherapy 3. Patients undergoing chemotherapy and stem-cell transplants. Patients undergoing chemotherapy and stem-cell transplants. 4. Peri-operative surgical patients: Peri-operative surgical patients
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW (RESTRICTIVE) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) VERSUS HIGH (LIBERAL) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL)

Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up
- Actual outcome for adults: Number of units transfused at end of follow-up; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Length of hospital stay at end of follow-up
- Actual outcome for adults: Length of hospital stay at end of follow-up; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: All-cause mortality at 30 days (all causes) at 30 days
- Actual outcome for adults: Mortality at 30 days; Group 1: 171/2495, Group 2: 199/2484; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery
- Actual outcome for adults: Pneumonia at end of follow-up; Group 1: 147/1849, Group 2: 160/1846; Risk of bias: High; Indirectness of outcome: No indirectness
- Actual outcome for adults: Infections at end of follow-up; Group 1: 180/2149, Group 2: 223/2157; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 5: Number of patients needing transfusions at end of follow-up
- Actual outcome for adults: Number of patients needing transfusion at end of follow-up; Group 1: 1416/3059, Group 2: 2575/3066; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 6: New cardiac event (Myocardial infarction, Cardiac failure) at end of follow-up
- Actual outcome for adults: Myocardial infarction at end of follow-up; Group 1: 45/1940, Group 2: 39/1944; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at end of follow-up; Acute and delayed serious adverse events as reported in study (TACO and TRALI, iron overload at end of follow-up

Study	Carson 2013[21]
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=110)
Countries and setting	Conducted in United Kingdom; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention+follow-up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients enrolled from 8 US hospitals from March 15, 2010 to May 8, 2012 who were: 1) greater than 18 years of age 2) had either S segment elevation myocardial infarction/Non S segment elevation myocardial infarction/unstable angina/stable coronary artery disease undergoing a cardiac catheterisation and had a haemoglobin concentration less than 10 g/dl at the time of random allocation.
Exclusion criteria	Patients who has active bleeding from cardiac catheterisation puncture site, including retroperitoneal, judged to be uncontrolled or needing surgical repair or resulting in haemodynamic instability at any time during the index admission; symptoms of anaemia at the time of randomisation; or other health concerns (that is, acute psychiatric illness) that would interfere with the reporting of symptoms and adherence to treatment protocols.
Recruitment/selection of patients	A total of 1920 patients with a Hb concentration less than 11g/dl were screened. The mean Hb concentration was between 1.3 and 1.8g/dl higher in the liberal transfusion group than restrictive transfusion group (all p<0.001).
Age, gender and ethnicity	Age - Mean (SD): liberal -67.3 (13.6); restrictive- 74.3 (11.1). Gender (M:F): 55/55. Ethnicity: Not stated
Further population details	1. Acute Coronary syndrome: Acute coronary syndrome (ST segment elevation MI, Non ST segment elevation MI). 2. Co-existing ischaemic heart disease: Co-existing ischaemic heart disease (stable coronary artery disease undergoing catheterisation). 3. Congenital cardiac disease: 4. Gender: 5. Neurological disease: 6. Stroke: 7. Traumatic brain injury:
Extra comments	Prior PCI- 41.8%, Prior CABG- 30.9%, Prior MI- 27.3%, Cerebrovascular accident- 8.2%, Bleeding- 13.6%, Congestive heart failure- 30%, Hypertension- 83.6%, Diabetes mellitus- 57.3%. The most common reason for exclusion were Hb <10g/dl

	(n=644), patient declined (n=198), patient was unable to provide consent (n=144) or severe illness (n=139)
Indirectness of population	No indirectness
Interventions	(n=55) Intervention 1: High (liberal) haemoglobin thresholds for transfusion (as defined by the trial). Patients received one unit of packed red blood cells following randomisation and then received enough blood to raise the Hb concentration to 10 g/dl or above any time the Hb concentration was detected to be below 10 g/dl during the hospitalisation for up to 30 days. Duration Up to 30 days after hospitalisation. Concurrent medication/care: Aspirin, Clopidogrel, Warfarin, Heparin, Statins. Angiogram in the past year -94.5% Further details: 1. Critical care: 2. Patients receiving radiotherapy. 3. Patients undergoing chemotherapy and stem-cell transplants. 4. Peri-operative surgical patients: (n=55) Intervention 2: Low (restrictive) haemoglobin thresholds for transfusion (as defined by the trial). Patients permitted to receive a transfusion if they developed symptoms related to anaemia. A blood transfusion was also permitted but not required, in the absence of symptoms if the haemoglobin concentration fell below 8 g/dl. There was no lower threshold for which blood was required in the restrictive group. Blood was to be administered one unit at a time and the presence of symptoms reassessed. Only enough blood was given to relieve symptoms or to increase the Hb concentration above 8 g/dl. Symptoms of anaemia that were indications for transfusion included definite angina requiring treatment with sublingual nitroglycerin or equivalent therapy and unexplained tachycardia or hypotension. Leukoreduction was not required. . Duration Up to 30 days after hospitalisation. Concurrent medication/care: Aspirin, Clopidogrel, Warfarin, Heparin, Statins. Angiogram in the past year -94.5% Further details: 1. Critical care: 2. Patients receiving radiotherapy. 3. Patients undergoing chemotherapy and stem-cell transplants. 4. Peri-operative surgical patients:
Funding	Academic or government funding (National Heart Lung and Blood Institute)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW (RESTRICTIVE) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) VERSUS HIGH (LIBERAL) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL)

Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up
- Actual outcome for adults: Number of units transfused at 6 months; Group 1: mean 0.49 (SD 1.03); n=55, Group 2: mean 1.58 (SD 1.13); n=55; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 30 days (all causes) at 30 days
- Actual outcome for adults: Mortality at 30 days at 30 days; Group 1: 7/54, Group 2: 1/54; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery - Actual outcome for adults: Pneumonia and blood stream infection at 6 months; Group 1: 2/54, Group 2: 0/55; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Acute and delayed serious adverse events as reported in study (TACO and TRALI, iron overload at end of follow-up - Actual outcome for adults: stroke at 6 months; Group 1: 0/54, Group 2: 1/55; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for adults: DVT or pulmonary embolism at 6 months; Group 1: 0/54, Group 2: 1/55; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: New cardiac event (Myocardial infarction, Cardiac failure) at end of follow-up - Actual outcome for adults: Myocardial infarction at 6 months; Group 1: 7/54, Group 2: 5/55; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for adults: Congestive heart failure at 6 months; Group 1: 7/54, Group 2: 2/55; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Number of patients needing transfusions at end of follow-up; Length of hospital stay at end of follow-up

Study	**Cholette 2011[27]**
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=60)
Countries and setting	Conducted in USA; Setting: Paediatric cardiac intensive care unit in a teaching hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children
Subgroup analysis within study	Not applicable
Inclusion criteria	Infants and children presenting to the University of Rochester Medical centre for elective partial or total cavopulmonary connection were eligible.

Exclusion criteria	Children were excluded only if consent could not be obtained.
Recruitment/selection of patients	Subjects were enrolled at their pre-anaesthesia visit.
Age, gender and ethnicity	Age - Mean (SD): Restrictive: 27 (23) months; Liberal: 32.5 (27) months. Gender (M:F): Restrictive:17% males; Liberal:17% males . Ethnicity: Not stated
Further population details	Type of surgery: cardiac surgery
Indirectness of population	No indirectness
Interventions	(n=30) Intervention 1: High (liberal) haemoglobin thresholds for transfusion (as defined by the trial). The liberal transfusion group required 10ml/kg of RBCs for any Hb of <13g/dl regardless of whether there was a clinical indication for transfusion. Duration The transfusion strategy was initiated on post-operative admission to the paediatric cardiac intensive care unit and continued until 48 hours from the time of admission after which RBC transfusions were utilised. . Concurrent medication/care: All subjects received aspirin daily beginning on the first post-operative day. In addition, subjects having Fontan procedures were begun on warfarin once patients were tolerating oral medications. Further details: Peri-operative surgical patients (Cardiac surgery. Cavopulmonary connection was achieved with a BDG or Fontan procedure.). (n=30) Intervention 2: Low (restrictive) haemoglobin thresholds for transfusion (as defined by the trial). The restrictive transfusion group required 10ml/kg of RBCs for any Hb of <9 g/dl accompanied by clinical findings suggestive of symptomatic anaemia (i.e. tachycardia and /or hypotension unresponsive to crystalloid or colloid infusion; poor perfusion and /or worsening oxygenation). Duration: The transfusion strategy was initiated on post-operative admission to the paediatric cardiac intensive care unit and continued until 48 hours from the time of admission after which RBC transfusions were utilised. Concurrent medication/care: All subjects received aspirin daily beginning on the first post-operative day. In addition, subjects having Fontan procedures were begun on warfarin once patients were tolerating oral medications. Further details:. Peri-operative surgical patients (cardiac surgery). Comments: Transfusion of fresh-frozen plasma, platelets and /or cryoprecipitate was performed as clinically indicated for both groups.
Funding	Academic or government funding (University of Rochester Strong Childrens Research Center Research Development Award)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW (RESTRICTIVE) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) VERSUS HIGH (LIBERAL) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up - Actual outcome for Children: Number of units transfused at end of follow-up; Group 1: mean 0.43 units (SD 0.6); n=30, Group 2: mean 2.1 units (SD 1.2); n=30; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Length of hospital stay at end of follow-up - Actual outcome for Children: Length of hospital stay at end of follow-up; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: All-cause mortality at 30 days (all causes) at 30 days - Actual outcome for Children: Mortality at end of follow-up; Group 1: 0/30, Group 2: 1/30; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Number of patients needing transfusions at end of follow-up - Actual outcome for Children: Number of patients needing transfusion at end of follow-up; Group 1: 11/30, Group 2: 29/30; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcomes not reported by the study	Quality of life at end of follow-up; Acute and delayed serious adverse events as reported in study (TACO and TRALI, iron overload at end of follow-up; New cardiac event (Myocardial infarction, Cardiac failure) at end of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery

Study	**CRIT trial trial: Cooper 2011[32]**
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=45)
Countries and setting	Conducted in USA; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients admitted to the Washington Hospital Centre, Washington DC VA Medical centre, or Durham VA medical centre with Acute myocardial infarction (AMI) from May 2003 through October 2009 were considered for enrolment. AMI was defined as ischemic type chest discomfort lasting >30 minutes and associated with a creatinine kinase-MB or cardiac troponin level above the upper limit of normal. Patients were included whom the haematocrit was <30% within 72 hours of symptoms onset
Exclusion criteria	Patients were excluded for following reasons 1) non coronary cause for clinical syndrome 2) active bleeding, defined as overt blood loss accompanied by a decrease in haematocrit of >5% in the preceding 12 hours 3) inability or unwillingness to receive RBC transfusion 4) RBC transfusion within 7 days of enrolment 5) previous severe transfusion reaction 6) imminent death 7) decision to provide limited or comfort care 8) age 9) pregnancy 10) participation in another clinical trial in which RBC transfusion was a requirement or a component of a primary or secondary endpoint 11) previous participation in the present study.
Age, gender and ethnicity	Age - Mean (SD): Liberal: 76.4 (13.5); Conservative: 70.3 (14.3). Gender (M:F): Liberal: 48%/52%; Conservative: 54%/46%. Ethnicity: Liberal: 76% white; Conservation: 54% white
Further population details	-
Extra comments	Hypertension requiring drug treatment: liberal 91%; conservative 75%. Diabetes mellitus: liberal 76%, conservative 63%.There were 18 patients with S segment elevation MI and 27 patients with non-S segment elevation MI. PCI had been performed in 25 patients before enrolment.
Indirectness of population	No indirectness
Interventions	(n=21) Intervention 1: High (liberal) haemoglobin thresholds for transfusion (as defined by the trial). RBC transfusion when their haematocrit decreased <30% with the goal of maintaining a haematocrit from 30% to 33%.. Duration Not stated. Concurrent medication/care: All patients were receiving antiplatelet therapy Comments: In the 2 groups leukocyte depleted packed RBCs were transfused 1 U at a time and haematocrit was measured again 1 hour later. (n=24) Intervention 2: Low (restrictive) haemoglobin thresholds for transfusion (as defined by the trial). RBC transfusion when their haematocrit decreased <24% with the goal of maintaining a haematocrit from 24 to 27%. Duration: Not

	stated . Concurrent medication/care: Nearly all patients were receiving dual antiplatelet therapy.
Funding	Academic or government funding (Cardiovascular Research Institute)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW (RESTRICTIVE) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) VERSUS HIGH (LIBERAL) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up - Actual outcome for adults: Number of units transfused at 30 days; Group 1: mean 1.6 (SD 2); n=24, Group 2: mean 2.5 (SD 1.3); n=21; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Length of hospital stay at end of follow-up - Actual outcome for adults: Length of hospital stay at 30 days; Group 1: mean 10.4 days (SD 7.2); n=24, Group 2: mean 8.5 days (SD 5.6); n=21; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: All-cause mortality at 30 days (all causes) at 30 days - Actual outcome for adults: Mortality at 30 days at 30 days; Group 1: 2/24, Group 2: 1/21; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Number of patients needing transfusions at end of follow-up; Acute and delayed serious adverse events as reported in study (TACO and TRALI, iron overload at end of follow-up; New cardiac event (Myocardial infarction, Cardiac failure) at end of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery

Study	**De Gast-Bakker 2013[45]**
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=107)
Countries and setting	Conducted in Netherlands; Setting: Paediatric ICU
Line of therapy	1st line

Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children
Subgroup analysis within study	Not applicable
Inclusion criteria	Elective surgery for a congenital heart defect; patients between 6 weeks and 6 years of age and peripheral oxygen saturation above 95% on admission
Exclusion criteria	Not stated
Recruitment/selection of patients	Between April 2009 and January 2012, 162 eligible patients were scheduled for elective surgery for a non-cyanotic congenital heart defect
Age, gender and ethnicity	Age - Mean (range): group A - 7.3 (3.0-29.7) months; group B- 9.5 (3.6-30.4) months. Gender (M:F): 31/23. Ethnicity: Not stated
Further population details	-
Extra comments	Patients with non-cyanotic heart defects between 6 weeks and 6 years of age.
Indirectness of population	No indirectness
Interventions	(n=54) Intervention 1: High (liberal) haemoglobin thresholds for transfusion (as defined by the trial). Patients received an RBC transfusion if their Hb concentration dropped below 10.8 g/dl. When a threshold was reached each patient was to receive an RBC transfusion of 10 ml/kg. Duration: The transfusion policy was adhered from induction of anaesthesia to hospital discharge. Concurrent medication/care: None Comments: RBC units were always leukocyte depleted. (n=53) Intervention 2: Low (restrictive) haemoglobin thresholds for transfusion (as defined by the trial). Patients received an RBC transfusion if their Hb concentration was 8 g/dl or less. When a threshold was reached each patient was to receive an RBC transfusion of 10 ml/kg. Duration: The transfusion policy was adhered from induction of anaesthesia to hospital discharge. Concurrent medication/care: None Comments: RBC units were always leukocyte depleted.

Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW (RESTRICTIVE) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) VERSUS HIGH (LIBERAL) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up - Actual outcome for Children: Total RBC (ml/patient) at end of follow-up; Group 1: mean 186 (SD 70); n=53, Group 2: mean 259 (SD 90); n=54; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Length of hospital stay at end of follow-up - Actual outcome for Children: Length of hospital stay at end of follow-up; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Acute and delayed serious adverse events as reported in study (TACO and TRALI, iron overload at end of follow-up; New cardiac event (Myocardial infarction, Cardiac failure) at end of follow-up; All-cause mortality at 30 days (all causes) at 30 days

Study	**TRISS trial trial: Holst 2014[73]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=1005)
Countries and setting	Conducted in Denmark, Finland, Norway, Sweden; Setting: Intensive care Units (ICU)
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Low threshold: 272 (54.2); Higher threshold: 259 (52.2)
Stratum	Adults
Subgroup analysis within study	Not applicable

Inclusion criteria	Patients 18 years of age or older who were in the ICU, fulfilled the criteria for septic shock, and had a blood concentration of haemoglobin of 9 g per decilitre or less as measured by means of valid point of care testing.
Exclusion criteria	Patients were excluded if they had undergone randomisation in this study previously, if there were medical reasons, if they had received a blood transfusion during the current intensive care unit (ICU) admissions, if there was a documented wish not to receive a transfusion, or if informed consent could not be obtained.
Recruitment/selection of patients	Patients in 32 general ICUs in Denmark, Sweden, Norway and Finland underwent screening between December 3, 2011 and December 26, 2013.
Age, gender and ethnicity	Age - Median (IQR): Low threshold: 67 (57-73); Higher threshold: 67 (58-75). Gender (M:F): Male- no (%). Ethnicity: Not stated
Further population details	-
Extra comments	Chronic cardiovascular disease- no (%): low threshold: 75 (14.9) ; high threshold: 66 (13.3) ; Chronic lung disease- no (%): low threshold: 111 (22.1); high threshold: 102 (20.6); Hematologic cancer- no (%): low threshold: 39 (7.8) ; high threshold: 36 (7.3).
Indirectness of population	No indirectness
Interventions	(n=502) Intervention 1: Low (restrictive) haemoglobin thresholds for transfusion (as defined by the trial). Enrolled patients were given single units of cross-matched, prestorage leukoreduced red cells suspended in a saline-adenine-glucose-mannitol solution when the blood concentration of haemoglobin had decreased to the assigned transfusion threshold of ≤7 g per decilitre. Duration single unit. Concurrent medication/care: Not stated Comments: Haemoglobin concentrations were reassessed within 3 hours after termination of the transfusion or before the initiation of another transfusion. The intervention period was the entire ICU stay, to a maximum of 90 days after randomisation. (n=496) Intervention 2: High (liberal) haemoglobin thresholds for transfusion (as defined by the trial). Enrolled patients were given single units of cross-matched, prestorage leukoreduced red cells suspended in a saline-adenine-glucose-mannitol solution when the blood concentration of haemoglobin had decreased to the assigned transfusion threshold of ≤ 9 g per decilitre.. Duration single unit. Concurrent medication/care: Not stated Comments: Haemoglobin concentrations were reassessed within 3 hours after termination of the transfusion or before the initiation of another transfusion. The intervention period was the entire ICU stay, to a maximum of 90 days after randomisation.

Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW (RESTRICTIVE) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) versus HIGH (LIBERAL) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) Protocol outcome 1: All-cause mortality at 30 days (all causes) at 30 days - Actual outcome for Adults: Mortality (all causes- 30 days) at End of follow-up ; Group 1: 168/502, Group 2: 175/496; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at End of follow-up - Actual outcome for Adults: Number of patients needing transfusion at End of follow-up ; Group 1: 326/502, Group 2: 490/496; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Acute and delayed serious adverse events as reported in study (TACO and TRALI, iron overload at End of follow-up - Actual outcome for Adults: Serious adverse events at End of follow-up ; Group 1: 0/488, Group 2: 1/489; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: New cardiac event (Myocardial infarction, Cardiac failure) at End of follow-up - Actual outcome for Adults: New cardiac events (MI) at End of follow-up ; Group 1: 13/488, Group 2: 6/489; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Length of hospital stay at End of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at End of follow-up

Study	**Markatou 2012[99]**

Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=58)
Countries and setting	Conducted in Greece; Setting: University Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis: Restrictive: 58.2 (11.7); liberal: 63.4 (11.3)
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult patients, American Society of Anesthesiologists (ASA) distribution I-III, scheduled for elective upper major abdominal surgery.
Exclusion criteria	History of bleeding diathesis associated with thrombocytopenia, hereditary haemostatic defects such as haemophilias or chronic anti-coagulant administration, refusal of transfusions for religious reasons, ischaemic heart disease (unstable angina or myocardial infarction within the last 6 months) and pre-existing infectious or autoimmune diseases as well use of corticosteroids or immunosuppressive drugs within the last 6 months.
Age, gender and ethnicity	Age - Mean (SD): Gender (M:F): Restrictive: 13/12; liberal: 16/11. Ethnicity: Not stated
Further population details	-
Extra comments	Pre-opeartive Hb level: Restrictive- 13.1 (1.97); liberal: 13.1 (1.40)
Indirectness of population	No indirectness

Interventions	(n=25) Intervention 1: Low (restrictive) haemoglobin thresholds for transfusion (as defined by the trial). Pre-operatively patients to receive blood transfusion intra- and post-operatively if haemoglobin was below 7.7 gdL. The post-operative target haemoglobin values were between 7.7 gdL and 9.9gdl. Duration Intra-and post-operative. Concurrent medication/care: Not stated Further details: Peri-operative surgical patients (Major abdominal surgery). (n=27) Intervention 2: High (liberal) haemoglobin thresholds for transfusion (as defined by the trial). Pre-operatively patients to receive blood transfusion intra- and post-operatively if haemoglobin was below Hb 9.9 gdL . The post-operative target haemoglobin values were above for the Hb 9.9 gdL. Duration Intra-and post-operative. Concurrent medication/care: Not stated Further details: Peri-operative surgical patients (Major abdominal surgery). Comments: Transfusions were administered one unit at a time and the length of storage of each unit transfused were recorded.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW (RESTRICTIVE) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) versus HIGH (LIBERAL) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) Protocol outcome 1: All-cause mortality at 30 days (all causes) at 30 days - Actual outcome for Adults: All-cause mortality 30 days at End of follow-up; Group 1: 0/25, Group 2: 2/27; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) at Within 30 days of surgery - Actual outcome for Adults: Pulmonary complications at End of follow-up; Group 1: 3/25, Group 2: 10/27; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Number of patients needing transfusions at End of follow-up - Actual outcome for Adults: Number of patients needing transfusion at End of follow-up; Group 1: 9/25, Group 2: 19/27; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at End of follow-up; Length of hospital stay at End of follow-up; Acute and delayed serious adverse events

	as reported in study (TACO and TRALI, iron overload at End of follow-up; New cardiac event (Myocardial infarction, Cardiac failure) at End of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at End of follow-up

Study	**Nielsen 2012[117]**
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=48)
Countries and setting	Conducted in Denmark; Setting: Hospital
Line of therapy	1st line
Duration of study	--:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients at least 18 years of age and scheduled for elective spinal fusion with instrumentation.
Exclusion criteria	Disseminated cancer, prior stroke or cardiac disease with functional impairment (NYHA class II or above)
Recruitment/selection of patients	Recruitment took place the day before surgery in the ward. If more than one patient was scheduled for surgery on the same day the patient with the largest anticipated intra-operative blood loss was asked first.

Age, gender and ethnicity	Age - Median (range): Restrictive: 63 (34-78); Liberal: 58 (34-68). Gender (M:F): Restrictive: 7/18; Liberal: 10/13. Ethnicity: Not stated
Further population details	Type of surgery: Spinal
Indirectness of population	--
Interventions	(n=23) Intervention 1: High (liberal) haemoglobin thresholds for transfusion (as defined by the trial). Receiving transfusion of RBCs at a Hb concentration of 8.9 g/dl. Duration: Not stated. Concurrent medication/care: Not reported. Further details: Peri-operative surgical patients (Patients undergoing major spinal surgery). Comments: other blood products were given according to the hospitals stand ad procedure. In case of massive bleeding the protocol was abandoned and a balanced transfusion strategy was used giving 5 units of packed RBCs parallel with 5 units of fresh frozen plasma and 2 units of platelets. Further transfusion was guided by thromboelastography. Cell Salvage was used if recommended by the surgeon. Cell salvaged blood was infused continuously throughout surgery. (n=25) Intervention 2: Low (restrictive) haemoglobin thresholds for transfusion (as defined by the trial). Receiving transfusion of RBCs at a Hb concentration of 7.3gdl. Duration Not stated. Concurrent medication/care: Not stated Further details: Peri-operative surgical patients (Patients undergoing major spinal surgery). Comments: other blood products were given according to the hospitals stand ad procedure. In case of massive bleeding the protocol was abandoned and a balanced transfusion strategy was used giving 5 units of packed RBCs parallel with 5 units of fresh frozen plasma and 2 units of platelets. Further transfusion was guided by thromboelastography.
Funding	Academic or government funding (TrygFonden foundation, The Strategic Research Council, Denmark)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW (RESTRICTIVE) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) VERSUS HIGH (LIBERAL) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) Protocol outcome 1: Acute and delayed serious adverse events as reported in study (TACO and TRALI, iron overload at end of follow-up - Actual outcome for adults: Acute and delayed adverse events at During and 30 days after surgery; Group 1: 0/25, Group 2: 0/23; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; All-cause mortality at 30 days (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery; Number of patients needing transfusions at end of follow-up; New cardiac event (Myocardial infarction, Cardiac failure) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and

	cryoprecipitate)/volume in ml in children at end of follow-up

Study	**Pinheiro de Almeida 2015[126]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=198)
Countries and setting	Conducted in Brazil; Setting: Intensive care unit of a tertiary oncology hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	All adult patients who had a major surgical procedure for abdominal cancer and required post-operative care in the ICU because of physiological instability and had an expected ICU stay of more than 24h were included.
Exclusion criteria	All patients with any of the following characteristics: age less than 18 years, haematological malignancy, a Karnofsky score less than 50, pre-existing anaemia (defined as a pre-operative haemoglobin concentration <9g/dl), pre-existing thrombocytopenia (defined as a platelet count <50,000/mm3), pre-existing coagulopathy (defined as a prothrombin >14.8 s) or anticoagulation therapy, active or uncontrolled bleeding, expected death within 24h of ICU admission, end-stage renal failure requiring renal replacement therapy, pregnancy, a do-not resuscitate order, inability to receive transfusion of blood components or refusal to participate in the study.
Recruitment/selection of patients	All patients were assessed for eligibility at the time of ICU admission by a member of the medical staff.
Age, gender and ethnicity	Age - Mean (SD): Restrictive: 64 (12); Liberal: 64 (14). Gender (M:F): Restrictive: 55% males; Liberal: 55% males. Ethnicity: Not stated
Further population details	Patients in critical care
Extra comments	Patients enrolled in the study were admitted to the intensive care unit (ICU) of atertiary oncology university hospital in

	Sao Paulo, Brazil between January 2012 and July 2012.
Indirectness of population	No indirectness
Interventions	(n=101) Intervention 1: Low (restrictive) haemoglobin thresholds for transfusion (as defined by the trial). The patients in the restrictive erythrocyte transfusion strategy group received one erythrocyte unit each time their haemoglobin concentration decreased to less than 7 g/dl , during their ICU stay. Physicians were instructed to administer transfusions 1 unit at a time and to measure haemoglobin concentration after each transfusion unit. No further units were given if the goal haemoglobin concentration was obtained (7 g/dl for the restrictive strategy). Duration During ICU stay. Concurrent medication/care: Not stated Comments: Haemoglobin levels were measured in all patients at least twice a day while patients were in the ICU. (n=97) Intervention 2: High (liberal) haemoglobin thresholds for transfusion (as defined by the trial). The patients in the liberal erythrocyte transfusion strategy groups received one erythrocyte unit each time their haemoglobin concentration decreased to less than 9 g/dl, during their ICU stay. Physicians were instructed to administer transfusions 1 unit at a time and to measure haemoglobin concentration after each transfusion unit. No further units were given if the goal haemoglobin concentration was obtained (9g/dl for the liberal strategy). Duration During ICU stay. Concurrent medication/care: Not stated
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW (RESTRICTIVE) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) VERSUS HIGH (LIBERAL) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL)

Protocol outcome 1: All-cause mortality at 30 days (all causes) at 30 days
- Actual outcome for Adults: Mortality at 30 days at end of follow-up; Group 1: 23/101, Group 2: 8/97; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Number of patients needing transfusions at end of follow-up
- Actual outcome for Adults: Number of patients needing transfusion at end of follow-up; Group 1: 47/101, Group 2: 32/97; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: New cardiac event (Myocardial infarction, Cardiac failure) at end of follow-up
- Actual outcome for Adults: Myocardial Infarction at end of follow-up; Group 1: 1/101, Group 2: 0/97; Risk of bias: Low; Indirectness of outcome: No indirectness

- Actual outcome for Adults: Congestive Heart Failure at end of follow-up; Group 1: 5/101, Group 2: 2/97; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery; Acute and delayed serious adverse events as reported in study (TACO and TRALI, iron overload at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up

Study	**Shehata 2012[149]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=50)
Countries and setting	Conducted in Canada; Setting: University affiliated tertiary care centre
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible participants were adult patients undergoing cardiac surgery with a CARE score (a score for cardiac surgery patients used to predict morbidity and mortality) of 3 or 4 or patients of advanced age defined as greater than or equal to 80 years on the day of screening were included.
Exclusion criteria	Patients were excluded if they refused participation, were unable to receive or refused blood products or were involved in the autologous predonation program
Age, gender and ethnicity	Age - Mean (SD): restrictive- 67.2 (11.2) years; liberal - 68.8 (9.2) years. Gender (M: F): restrictive: 17:8; liberal - 20:5. Ethnicity: Not stated
Further population details	-

Indirectness of population	No indirectness
Interventions	(n=25) Intervention 1: High (liberal) haemoglobin thresholds for transfusion (as defined by the trial). Patients received RBC transfusions if their Hb concentration was 95 g/dl or less during and less than 100 g/dl after bypass surgery.. Duration During and after bypass surgery. Concurrent medication/care: 72% of the patients in the restrictive group and 68% of patients in the liberal group were using anti-platelet medications before surgery. Comments: When the threshold was reached each group was to receive 1 unit of RBCs administered at a time followed by determination of the Hb concentration. Patients who had rapid blood loss were transfused at the discretion of the attending physicians. (n=25) Intervention 2: Low (restrictive) haemoglobin thresholds for transfusion (as defined by the trial). Patients received RBC transfusions if their Hb was 70g/litre or less during bypass surgery and 75 g/litre or less post-operatively after bypass. Duration During and after surgery. Concurrent medication/care: 72% of the patients in the restrictive group and 68% of patients in the liberal group were using anti-platelet medications before surgery. Comments: When the threshold was reached each group was to receive 1 unit of RBCs administered at a time followed by determination of the Hb concentration. Patients who had rapid blood loss were transfused at the discretion of the attending physicians.
Funding	Academic or government funding (Canadian Blood services)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW (RESTRICTIVE) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) VERSUS HIGH (LIBERAL) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL)

Protocol outcome 1: Length of hospital stay at end of follow-up
- Actual outcome for adults: Length of hospital stay at end of follow-up; Group 1: mean 9 (SD 12); n=25, Group 2: mean 7 (SD 4); n=25; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 30 days (all causes) at 30 days
- Actual outcome for adults: Mortality at In-hospital; Group 1: 4/25, Group 2: 1/25; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery
- Actual outcome for adults: Pneumonia at end of follow-up; Group 1: 4/25, Group 2: 0/25; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Number of patients needing transfusions at end of follow-up - Actual outcome for adults: Number of patients transfused at During and after surgery; Group 1: 20/25, Group 2: 36/25; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Acute and delayed serious adverse events as reported in study (TACO and TRALI, iron overload at end of follow-up - Actual outcome for adults: Transfusion reaction at end of follow-up; Group 1: 0/25, Group 2: 0/25; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for adults: pulmonary embolism/DVT at end of follow-up; Group 1: 1/25, Group 2: 0/25; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for adults: stroke at end of follow-up; Group 1: 3/25, Group 2: 0/25; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 6: New cardiac event (Myocardial infarction, Cardiac failure) at end of follow-up - Actual outcome for adults: Post-op Myocardial infarction at end of follow-up; Group 1: 1/25, Group 2: 0/25; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up

Study	**TRIPICU study trial: Karam 2011[76]**
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=137)
Countries and setting	Conducted in Canada; Setting: Paediatric critical care units
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children
Subgroup analysis within study	Sys review – pre-specified in protocol
Inclusion criteria	Stabilised critically ill children from 19 tertiary paediatric intensive care units from 4 countries. The condition of patients was considered stable if the mean systemic arterial pressure was not <2SD below the normal mean for age and if

	cardiovascular support had not been increased for at least 2 hours before enrolment. Once stabilised, children aged between 3 days and 14 years with at least one Hb concentration <9.5 g/dl within the first 7 days after PICU admission, were considered for inclusion.
Exclusion criteria	Patients expected to stay <24 hours in PICU, without physicians approval, were <3 days or <14 years of age, were unstable thermodynamically, had acute blood loss, weighed <3 kg, had cardiovascular problems, were never discharged from NICU, had haemolytic anaemia, were enrolled in another study, were excluded for another reason.
Recruitment/selection of patients	There were 137 septic patients enrolled from 19 sites and 4 countries in the septic patients sub-group, representing 21.5% of all TRIPICU patients.
Age, gender and ethnicity	Age - Mean (SD): Restrictive: 29.4 (39.6) months; Liberal: 32.9 (43.2) months. Gender (M: F): Restrictive: male 59%; Liberal 57%. Ethnicity: Not stated
Further population details	-
Extra comments	Both groups were similar with regard to demographic data, severity and proportion requiring mechanical ventilation. There were fewer patients with septic shock in the restrictive compared with the liberal group (13 vs. 21)
Indirectness of population	No indirectness
Interventions	(n=68) Intervention 1: High (liberal) haemoglobin thresholds for transfusion (as defined by the trial). Transfusion Threshold was 9.5 g/dl with a target range of 11 to 12 g/dl. Only pre-storage leukocyte reduced allogeneic RBC units were used. Duration Transfusion strategies were applied until intensive care unit discharge, 28 days after randomisation, or until the time of death, whichever came first. Concurrent medication/care: Patients on vasoactive drugs: restrictive (46%); liberal (54%) Further details: 1. Critical care: In critical care (PICU -patients with sepsis). Comments: Temporary suspension from the transfusion strategy protocol was allowed during active blood loss, emergency surgery, severe hypoxia, or hemodynamic instability. (n=69) Intervention 2: Low (restrictive) haemoglobin thresholds for transfusion (as defined by the trial). Transfusion threshold was Hb of 7g/dl with a target range of 11 to 12 g/dl.. Duration Transfusion strategies were applied until intensive care unit discharge, 28 days after randomisation, or until the time of death, whichever came first. . Concurrent medication/care: Patients on vasoactive drugs: restrictive (46%); liberal (54%) Further details: 1. Critical care: In critical care (PICU). Comments: Temporary suspension from the transfusion strategy protocol was allowed during active blood loss, emergency surgery, severe hypoxia, or hemodynamic instability.

Funding	Academic or government funding (Canadian Institutes of Health Research)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW (RESTRICTIVE) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) VERSUS HIGH (LIBERAL) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) Protocol outcome 1: Length of hospital stay at end of follow-up - Actual outcome for Children: Length of stay in PICU at end of follow-up; Group 1: mean 7.5 (SD 6.3); n=69, Group 2: mean 7.1 (SD 6.2); n=68; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: All-cause mortality at 30 days (all causes) at 30 days - Actual outcome for Children: Mortality at 28 days; Group 1: 7/69, Group 2: 2/68; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Number of patients needing transfusions at end of follow-up - Actual outcome for Children: Number of patients needing transfusion at end of follow-up; Group 1: 30/69, Group 2: 59/68; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery; Acute and delayed serious adverse events as reported in study (TACO and TRALI, iron overload at end of follow-up; New cardiac event (Myocardial infarction, Cardiac failure) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up

Study	**Villanueva 2013[178]**
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=921)
Countries and setting	Conducted in Spain; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:

Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients older than 18 years of age who had haematemesis (or bloody nasogastric aspirate), melena, or both, as confirmed by the hospital staff, were considered for inclusion.
Exclusion criteria	Patients were excluded if they declined to undergo a blood transfusion. Additional exclusion criteria were massive exsanguinating bleeding; an acute coronary syndrome, symptomatic peripheral vasculopathy, stroke, transient ischemic attack, or transfusion within the previous 90 days, a recent history of trauma or surgery, lower gastrointestinal bleeding, a previous decision on the part of the attending physician that the patient should avoid specific medical therapy, and a clinical Rockall score of 0 with a Hb level higher than 12 g/dl.
Recruitment/selection of patients	From June 2003 through December 2009, the study consecutively enrolled patients with gastrointestinal bleeding who were admitted to Hospital de la Santa Creu I Sant Pau in Barcelona.
Age, gender and ethnicity	Age - --: Not reported. Gender (M:F): Not reported . Ethnicity: Not stated
Further population details	-
Extra comments	Baseline characteristics were similar in the 2 groups.
Indirectness of population	No indirectness
Interventions	(n=445) Intervention 1: High (liberal) haemoglobin thresholds for transfusion (as defined by the trial). The Hb threshold for transfusion was 9g/dl with a target range for the post-transfusion Hb level of 9 to 11 g/dl. In both the groups, 1 unit of red cells was transfused initially, the Hb was assessed after the transfusion, and an additional unit was transfused if the Hb level was below the threshold value. Only pre-storage leukocyte reduced units of packed red cells were used for transfusion. The volume of a unit ranged from 250 to 320 ml with a haematocrit of approximately 60%. Duration The transfusion protocol was applied until the patients discharge from the hospital or death. Concurrent medication/care: Patients with peptic ulcer received a continuous intravenous infusion of omeprazole (80mg per 10 hour period after an initial bolus of 80 mg) for the first 72 hours, followed by oral administration of omeprazole. Comments: The protocol allowed for a transfusion to be administered any time symptoms or signs related to anaemia developed, massive bleeding occurred during follow-up or surgical intervention was required.

	(n=444) Intervention 2: Low (restrictive) haemoglobin thresholds for transfusion (as defined by the trial). The Hb threshold for transfusion was 7g/dl with a target range for the post-transfusion Hb level of 7 to 9 g/dl. Duration The transfusion protocol was applied until the patients discharge from the hospital or death.. Concurrent medication/care: Patients with peptic ulcer received a continuous intravenous infusion of omeprazole (80mg per 10 hour period after an initial bolus of 80 mg) for the first 72 hours, followed by oral administration of omeprazole. Comments: The protocol allowed for a transfusion to be administered any time symptoms or signs related to anaemia developed, massive bleeding occurred during follow-up or surgical intervention was required.
Funding	Academic or government funding (Fundacio Investigacio Sant Pau)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW (RESTRICTIVE) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) VERSUS HIGH (LIBERAL) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up - Actual outcome for adults: Number of units transfused at 45 days; Group 1: mean 1.5 (SD 2.3); n=444, Group 2: mean 3.7 (SD 3.8); n=445; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Length of hospital stay at end of follow-up - Actual outcome for adults: Length of hospital stay at 45 days; Group 1: mean 9.6 days (SD 8.7); n=444, Group 2: mean 11.5 days (SD 12.8); n=445; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: All-cause mortality at 30 days (all causes) at 30 days - Actual outcome for adults: All-cause mortality at 45 days at 45 days; Group 1: 23/444, Group 2: 41/445; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Number of patients needing transfusions at end of follow-up - Actual outcome for adults: Number of patients needing transfusion at 45 days; Group 1: 219/444, Group 2: 384/445; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 5: Acute and delayed serious adverse events as reported in study (TACO and TRALI, iron overload at end of follow-up - Actual outcome for adults: Any adverse event at 45 days; Group 1: 179/444, Group 2: 214/445; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; New cardiac event (Myocardial infarction, Cardiac failure) at end of follow-up;

	Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery

Study	**Walsh 2013[180]**
Study type	RCT (patient randomised; parallel)
Number of studies (number of participants)	1 (n=100)
Countries and setting	Conducted in United Kingdom; Setting: ICU
Line of therapy	1st line
Duration of study	--:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients who fulfilled all of the following: 1) had already required mechanical ventilation via endotracheal tube or tracheostomy tube >96 hours 2) were expected to require >24 hours of further mechanical ventilation when assessed 3) aged >55 years 4) and had a Hb value of <90 g/litre at the time of assessment.
Exclusion criteria	Patients with active bleeding at the time of screening, traumatic brain injury and /or intracranial haemorrhage not expected to survive for 48 hours when assessed, objection to receiving RBC transfusions, concurrent treatment with erythropoietin or similar agents, follow-up that was not feasible, and enrolment in another trial with similar endpoints.
Recruitment/selection of patients	Recruitment took place between August 2009 and Dec 2010. 6 participating ICUs.
Age, gender and ethnicity	Age - Mean (SD): Restrictive- 67(7) years; Liberal- 68 (8) years. Gender (M:F): restrictive- 36 males; liberal- 24 males. Ethnicity: Not stated
Further population details	-
Indirectness of population	No indirectness
Interventions	(n=51) Intervention 1: High (liberal) haemoglobin thresholds for transfusion (as defined by the trial). Patients received single unit RBC transfusion with a transfusion trigger of less than or equal to 90 g/litre and a target of 91-110 g/litre

	during intervention. Duration 14 days from randomisation or until discharge from the ICU. Concurrent medication/care: none reported (n=49) Intervention 2: Low (restrictive) haemoglobin thresholds for transfusion (as defined by the trial). Patients received single unit RBC transfusion with a transfusion trigger of less than or equal to 70g/dl and a target Hb concentration of 71-90g/litre during the intervention period. Duration 14 days from randomisation or until discharge from the ICU. Concurrent medication/care: none reported
Funding	Academic or government funding (Chief Scientists office, Scotland; the Scottish National Blood transfusion Service; the NHS Lothian Academic Health Science Centre; and the Transfusion Medicine Education and Research Foundation.)
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW (RESTRICTIVE) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) VERSUS HIGH (LIBERAL) HAEMOGLOBIN THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) Protocol outcome 1: Quality of life at end of follow-up - Actual outcome for adults: Quality of life- SF-12-Physical function score at 180 days; Group 1: mean 13 median (first quartile values) (SD 7); n=49, Group 2: mean 10 median (first quartile values) (SD 5); n=51; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for adults: Quality of life- S-12 Mental component score at 180 days; Group 1: mean 51 median first quartile values (SD 31); n=49, Group 2: mean 34 median first quartile values (SD 39); n=51; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Length of hospital stay at end of follow-up - Actual outcome for adults: Length of hospital stay at 180 days; Group 1: mean 34 (SD 13); n=49, Group 2: mean 31 (SD 19); n=51; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: All-cause mortality at 30 days (all causes) at 30 days - Actual outcome for adults: Mortality at 30 days; Group 1: 12/49, Group 2: 16/51; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Acute and delayed serious adverse events as reported in study (TACO and TRALI, iron overload at end of follow-up - Actual outcome for adults: Adverse events (acute coronary syndrome, thrombotic events) at 180 days; Group 1: 8/49, Group 2: 5/51; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery;

	Number of patients needing transfusions at end of follow-up; New cardiac event (Myocardial infarction, Cardiac failure) at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up

H.4 Platelets

H.4.1 Platelet thresholds and targets

Study	**Diedrich 2005[47]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=166)
Countries and setting	Conducted in Sweden; Setting: University Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults who are haematology patients –non-bleeding patients
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Patients undergoing allogeneic hematopoietic progenitor cell transplantation (HPCT)
Exclusion criteria	Patients with a known bleeding disorder or coagulopathy were excluded.
Recruitment/selection of patients	Patients undergoing allogeneic hematopoietic progenitor cell transplantation (HPCT) at Huddinge University Hospital were randomised after stratification for type of donor (related vs. unrelated), origin of HPCs (marrow vs. peripheral blood progenitor cells) and age (children< 18 years vs. adults), to receive prophylactic PLT transfusions when their morning PLT counts decreased below $10x10^9$ per litre or $30x10^9$ per litre. For an operation or a biopsy, a PLT level of more than $50x10^9$ per litre was aimed at. RBCs were transfused when Hb count decreased below 80g per litre.
Age, gender and ethnicity	Age - Mean (range): Group T10: Adults: 33 (2-62); Group T30: adults: 34 (1-63); Group T10 children <18 years: 25 (32);

	Group T30: children <18 years: 26 (30). Gender (M:F): Group T10:48/31; Group T30: 56/31. Ethnicity: Not stated
Further population details	-
Extra comments	From September 1996 to September 2001, a total of 166 patients were included. The two groups had no significant differences regarding patient and donor characteristics.
Indirectness of population	No indirectness
Interventions	(n=79) Intervention 1: Low platelet thresholds for transfusion (as defined by the trial). Patients to receive prophylactic PLT transfusions when their morning PLT counts decreased below $10x10^9$ per litre (Group T10). Platelet dose (mean ± S.D.): (buffy coat) approximately $410x10^9 \pm 20x10^9$; (apheresis) approximately $380x10^9 \pm 20x10^9$. Platelet type: pooled random donor platelets (buffy coat) 85% of platelet transfusions given; apheresis 15% of platelet transfusions given. All were ABO matched, irradiated and leuco depleted. Duration: Not specified. Concurrent medication/care: Patients on cyclosporine, cyclosporine plus methotextrate or prednisolone or mycofenolate mofetil Comments: For operation or biopsy a PLT level of more than $50x10^9$ per litre was aimed for. RBCs were transfused when Hb count decreased below 80 g per litre. (n=87) Intervention 2: High platelet thresholds for transfusion (as defined by the trial). Patients to receive prophylactic PLT transfusions when their morning PLT counts decreased below $30x10^9$ per litre (Group T30). Platelet dose (mean ± S.D.): (buffy coat) approximately $410x10^9 \pm 20x10^9$; (apheresis) approximately $380x10^9 \pm 20x10^9$. Platelet type: pooled random donor platelets (buffy coat) 85% of platelet transfusions given; apheresis 15% of platelet transfusions given. All were ABO matched, irradiated and leuco depleted. Duration: Not specified. Concurrent medication/care: Patients on cyclosporine, cyclosporine plus methotextrate or prednisolone or mycofenolate mofetil.
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW PLATELET THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) VERSUS HIGH PLATELET THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL)

Protocol outcome 1: All-cause mortality at 30 days (all causes) at 30 days
- Actual outcome for adults who are haematology patients -presence of bleeding: Transfusion related mortality at 3 years; Group 1: 29/79, Group 2: 28/87; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery
- Actual outcome for adults who are haematology patients -presence of bleeding: Bacteraemia at end of follow-up; Group 1: 31/79, Group 2: 30/87; Risk of bias: High;

Indirectness of outcome: No indirectness Protocol outcome 3: Bleeding: Occurrence of bleeding (prophylactic platelet transfusions); Cessation of bleeding (therapeutic platelet transfusions)- Bleeding reported as WHO grade 2 and above or equivalent at end of follow-up - Actual outcome for adults who are haematology patients -presence of bleeding: Bleeding at end of follow-up; Group 1: 14/79, Group 2: 13/87; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Number of patients needing transfusions at end of follow-up; Serious adverse events as reported in study at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up

Study	**Heckman 1997[67]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=78)
Countries and setting	Conducted in USA; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults who are haematology patients - non-bleeding patients
Subgroup analysis within study	Not applicable
Inclusion criteria	1) Unequivocal diagnosis of acute leukaemia including the following: acute myeloblastic leukaemia, acute lymphoblastic leukaemia in relapse or acute undifferentiated leukaemia, or myelodysplastic syndrome transformed to acute leukaemia. 2) Age greater than 17 years. 3) Patient undergoing initial induction or re-induction chemotherapy after relapse.
Exclusion criteria	Uncontrolled infection at randomisation, history of bleeding diathesis, disseminated intravascular coagulation at randomisation, defined as evidence of depletion of clotting factors plus elevated fibrin degradation products titre, acute promyelocytic leukaemia, concomitant malignancy or AIDS diagnosis or history of platelet refractory status

	requiring HLA-matched platelet transfusion during a previous induction chemotherapy.
Age, gender and ethnicity	Age - Mean (range): <10,000: 52 (20-79); <20,000: 51 (19-82). Gender (M:F): <10,000: 23/14; <20,000:27/14. Ethnicity: Not stated
Further population details	-
Indirectness of population	No indirectness
Interventions	(n=37) Intervention 1: Low platelet thresholds for transfusion (as defined by the trial). Patients received platelet transfusions when platelet count <10,000 microlitres. Platelets were to be given at a rate of one prophylactic apheresis unit per day regardless of the response of as assigned above and based on a morning platelet count. All platelet and RBC units were leukoreduced by filtration at the bedside until November 1993, after which pre-storage leukofiltration was performed in the blood bank. Duration: Until the patient obtained a satisfactory post-transfusion corrected count increment (CCI)[CCI=post transfusion platelet count – pre-transfusion count x body surface area/number of platelets transfused expressed $x10^{11}$]. Concurrent medication/care: Patients were treated with one of three chemotherapy regimens: Cytarabine 200 mg/m^2 continuous infusion for 7 days plus daunorubicin 45 mg/m^2 for 3 days, high dose cytarabine 2 to 3 g/m^2 every 12 hours for 12 doses, or mitoxantrone 12 mg/m^2 for 3 days plus etoposide 150 mg/m^2 continuous infusion for 5 days. Transfusion pre-medications of acetaminophen 650 mg and diphenhydramine 25 to 50 mg were routinely administered. Further details:. Type of treatment: Chemotherapy Comments: If a patient failed to obtain satisfactory increment after three consecutive platelet transfusions defined as post-transfusion corrected count (CCI) at 1 hour of less than 7000 per m^2 body surface area per each 10^{11} platelets transfused, then HLA matched platelets were used. If three or more of these consecutive HLA matched transfusion failed to result in significant CCI, and if the result of platelet antibody studies were negative (RBC adherence and microlymphocytotoxicity), then random platelets were again used. Two further random apheresis platelet transfusions were given and if no response was documented, the patient was removed from the study. Therapeutic platelets were given for serious or life threatening bleeding and for procedures at the discretion of the treating physician. (n=41) Intervention 2: High platelet thresholds for transfusion (as defined by the trial). Patients received platelet transfusions when platelet count <20,000 microlitres. Platelets were to be given at a rate of one prophylactic apheresis unit per day regardless of the response of as assigned above and based on a morning platelet count. All platelet and RBC units were leukoreduced by filtration at the bedside until November 1993, after which pre-storage leukofiltration was performed in the blood bank. Duration: Until the patient obtained a satisfactory post-transfusion corrected count increment (CCI)(CCI=post transfusion platelet count – pre-transfusion count x body surface area/number of platelets transfused expressed $x10^{11}$). Concurrent medication/care: Patients were treated with one of

	three chemotherapy regimens: Cytarabine 200mg/m^2 continuous infusion for 7 days plus daunorubicin 45 mg/m^2 for 3 days, high dose cytarabine 2 to 3 g/m^2 every 12 hours for 12 doses, or mitoxantrone 12 mg/m^2 for 3 days plus etoposide 150 mg/m^2 continuous infusion for 5 days. Transfusion pre-medications of acetaminophen 650 mg and diphenhydramine 25 to 50 mg were routinely administered. Further details: Type of treatment: Chemotherapy Comments: If a patient failed to obtain satisfactory increment after three consecutive platelet transfusions defined as post-transfusion corrected count (CCI) at 1 hour of less than 7000 per m^2 body surface area per each 10^{11} platelets transfused, then HLA matched platelets were used. If three or more of these consecutive HLA matched transfusion failed to result in significant CCI, and if the result of platelet antibody studies were negative (RBC adherence and microlymphocytotoxicity), then random platelets were again used. Two further random apheresis platelet transfusions were given and if no response was documented, the patient was removed from the study. Therapeutic platelets were given for serious or life threatening bleeding and for procedures at the discretion of the treating physician.
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW PLATELET THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) VERSUS HIGH PLATELET THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL)

Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up
- Actual outcome for adults who are haematology patients -presence of bleeding: Number of platelet units transfused per patient at end of follow-up ; Group 1: mean 8.4 (SD 5.3); n=37, Group 2: mean 11.4 (SD 7.1); n=41; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 2: All-cause mortality at 30 days (all causes) at 30 days
- Actual outcome for adults who are haematology patients -presence of bleeding: All-cause mortality at end of follow-up ; Group 1: 25/37, Group 2: 29/41; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Serious adverse events as reported in study at end of follow-up
- Actual outcome for adults who are haematology patients -presence of bleeding: Transfusion reaction at end of follow-up ; Group 1: 0/37, Group 2: 8/41; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 4: Bleeding: Occurrence of bleeding (prophylactic platelet transfusions); Cessation of bleeding (therapeutic platelet transfusions)-Bleeding reported as WHO grade 2 and above or equivalent at end of follow-up
- Actual outcome for adults who are haematology patients -presence of bleeding: Number of patients with bleeding events at end of follow-up ; Group 1: 17/37, Group 2: 7/41; Risk of bias: High; Indirectness of outcome: No indirectness

Study	Murphy 1982[113]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=56)
Countries and setting	Conducted in USA
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Children who are haematology patients- non-bleeding patients
Subgroup analysis within study	Not applicable
Inclusion criteria	From July 1, 1972 to January 1976, 56 previously untreated children with acute leukaemia cared for at the Children's Hospital of Philadelphia were randomised to receive one of two regimens of platelet transfusion therapy. All patients were followed until July 1, 1976, at which point analysis begun.
Exclusion criteria	No details reported
Age, gender and ethnicity	Age - --: Children - specific age group not reported. Gender (M:F): Not reported. Ethnicity: Not stated
Further population details	-
Extra comments	Mean platelet counts at entry in the prophylactic and therapeutic groups were 59,000 per mm and 94,000 per mm, respectively; this difference was not statistically significant.
Indirectness of population	No indirectness
Interventions	(n=35) Intervention 1: Prophylactic transfusion. Patients were given 4 units per m^2 of random donor platelets whenever the platelet count fell below 20,000 per mm^3, irrespective of clinical events. The goal in this group was to maintain the platelet count above this level for the maximum period of time during the patient's course. Duration: 4 years. Concurrent medication/care: Not reported Comments: At entry, 3 patients in the prophylactic group and 1 patient in the therapeutic group were having significant bleeding. (n=21) Intervention 2: No prophylactic transfusion. Patients were not given platelets for thrombocytopenia per se but

	only when thrombocytopenia was accompanied by one of the following five clinical indications: epistaxis not controlled by initial packing, gross gastrointestinal bleeding, gross genitourinary tract bleeding, any central nervous system bleeding, or any bleeding episode. Duration: 4 years. Concurrent medication/care: Not reported
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROPHYLACTIC TRANSFUSION VERSUS THERAPEUTIC TRANSFUSION Protocol outcome 1: All-cause mortality at 30 days (all causes) at 30 days - Actual outcome for children who are haematology patients- absence of bleeding: Mortality (All cause) at 4 years; Group 1: 12/35, Group 2: 7/21; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for children who are haematology patients- absence of bleeding: Mortality from bleeding at 4 years; Group 1: 1/35, Group 2: 2/21; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Bleeding; Occurrence of bleeding (prophylactic platelet transfusions); Cessation of bleeding (therapeutic platelet transfusions)-Bleeding reported as WHO grade 2 and above or equivalent at end of follow-up - Actual outcome for children who are haematology patients- absence of bleeding: Number of patients with major bleeding episodes at 4 years; Group 1: 10/35, Group 2: 11/21; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Serious adverse events as reported in study at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up.

Study	**Platelet Trigger Trial: Rebulla 1997[133]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=255)
Countries and setting	Conducted in Italy; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	Adults who are haematology patients - non-bleeding patients
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with acute myeloid leukaemia (AML); adolescents and adults (aged 16-70 years); admitted to hospital for 1st course of induction chemotherapy
Exclusion criteria	Patients diagnosed with promyelocytic leukaemia or secondary AML; patients who had received a blood transfusion prior to diagnosis of AML
Age, gender and ethnicity	Age - Median (range): Threshold 10,000group: 51 (16-70); Threshold 20,000group: 49 (17-70). Gender (M:F): Male %: Threshold 10,000 group: 53%; Threshold 20,000group: 52%. Ethnicity: Not stated
Further population details	-
Indirectness of population	No indirectness
Interventions	(n=144) Intervention 1: Low platelet thresholds for transfusion (as defined by the trial). Transfusion platelets prophylactically when the platelet count falls below 10,000 per cubic millimetre or was 10,000 to 20,000 cubic millimetres when the body temperature exceeded 38°C, in the presence of fresh minor or major bleeding or if invasive procedures were necessary. Platelet concentrates were prepared by the platelet rich plasma method, the buffy coat method, or apheresis and were stored at 20 to 24°C for a maximum of 5 days. Each transfusion involved 1 unit of platelet rich plasma or buffy coat concentrate per 10 kg of body weight or 1 apheresis concentrate. Duration: Not stated. Concurrent medication/care: Patients received standard antibiotic and supportive care. A standard protocol was used for remission-induction chemotherapy. It consisted of cytarabine (an intravenous bolus of 25 mg per square metre of body surface area followed by a continuous intravenous infusion of 100 mg per square metre intravenously from day 1 to day 5 and idarubicin (10 mg per square metre intravenously on days 1, 3 and 5) or mitoxantrone (12 mg per square metre intravenously on days 1, 3 and 5) or daunorubicin (50 mg per square metre intravenously on days 1, 3 and 5). Type of treatment: Chemotherapy (Patients undergoing induction chemotherapy for acute myeloid leukaemia). Comments: Red cells were administered when the Hb level below 80g per litre. Acetaminophen was used as antipyretic agent. Aspirin and NSAIDs with effect on platelet function were not used. (n=132) Intervention 2: High platelet thresholds for transfusion (as defined by the trial). Transfusion of platelets prophylactically when the platelet count falls below 20,000 per cubic millimetre. Platelet concentrates were prepared by the platelet rich plasma method, the buffy coat method, or apheresis and were stored at 20 to 24°C for a maximum of 5 days. Each transfusion involved 1 unit of platelet rich plasma or buffy coat concentrate per 10 kg of body weight or 1 apheresis concentrate. Duration: Not stated. Concurrent medication/care: Patients received standard antibiotic and supportive care. A standard protocol was used for remission-induction chemotherapy. It consisted of cytarabine

	(an intravenous bolus of 25 mg per square metre of body surface area followed by a continuous intravenous infusion of 100 mg per square metre intravenously from day 1 to day 5 and idarubicin (10 mg per square metre intravenously on days 1, 3 and 5) or mitoxantrone (12 mg per square metre intravenously on days 1, 3 and 5) or daunorubicin (50 mg per square metre intravenously on days 1, 3 and 5). Type of treatment: Chemotherapy (Patients undergoing induction chemotherapy for acute myeloid leukaemia). Comments: Red cells were administered when the Hb level below 80 g per litre. Acetaminophen was used as antipyretic agent. Aspirin and NSAIDS with effect on platelet function were not used.
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW PLATELET THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) VERSUS HIGH PLATELET THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) Protocol outcome 1: All-cause mortality at 30 days (all causes) at 30 days - Actual outcome for adults who are haematology patients -presence of bleeding: Mortality (all causes) at end of follow-up; Group 1: 18/135, Group 2: 9/120; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Bleeding o Occurrence of bleeding (prophylactic platelet transfusions)o Cessation of bleeding (therapeutic platelet transfusions)-Bleeding reported as WHO grade 2 and above or equivalent'. at end of follow-up - Actual outcome for adults who are haematology patients -presence of bleeding: Number of major bleeding episodes at end of follow-up; Group 1: 39/135, Group 2: 33/120; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for adults who are haematology patients -presence of bleeding: Number of patients with major bleeding episodes at end of follow-up; Group 1: 29/135, Group 2: 24/120; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Serious adverse events as reported in study at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and Cryoprecipitate)/volume in ml in children at end of follow-up

Study (subsidiary papers)	**Trial of Prophylactic Platelets (TOPPS) trial: Stanworth 2013[163] (Stanworth 2010[162])**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=600)
Countries and setting	Conducted in Australia, United Kingdom; Setting: Hospital

Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults who are haematology patients - non-bleeding patients
Subgroup analysis within study	Not applicable
Inclusion criteria	Eligible patients were persons 16 years of age or older who were undergoing or about to undergo chemotherapy or stem cell transplantation to treat a hematologic cancer and who had or were expected to have thrombocytopenia (platelet count <50x10^9 per litre) for at least 5 days.
Exclusion criteria	Exclusion criteria were a previous bleeding episode of WHO grade 2 during the current admission, an inherited haemostatic or thrombotic disorder, a requirement for therapeutic doses of anticoagulant agents, a diagnosis of acute promyelocytic leukaemia, known HLA antibodies or prior randomisation in this trial
Age, gender and ethnicity	Age - Mean (SD): No prophylaxis: 55.7 (10.4); Prophylaxis: 55.3 (11.2). Gender (M:F): Females: no prophylaxis- 34%; Prophylaxis- 36%. Ethnicity: Not stated
Further population details	-
Indirectness of population	No indirectness
Interventions	(n=301) Intervention 1: Prophylactic transfusion. Prophylactic transfusion if the platelet count was less than 10x10^9 per litre. A single adult dose was given on the same day that the platelet count was recorded to be less than 10x10^9 per litre. The type of platelet component was not specified. All platelet components were leukoreduced, platelets were collected by means of apheresis in approximately 80% of cases, and common hospital practice was to transfuse platelets that were ABO and RhD identical. Duration Not stated. Concurrent medication/care: Not specified Comments: In both trial groups, platelet transfusions were given therapeutically for bleeding, given before invasive procedures, or given at the clinician's discretion. Therapeutic platelet transfusions for bleeding episodes of WHO grade 2 were given according to standard practice, followed by prophylactic platelet transfusions per protocol, if indicated. Patients who had bleeding of WHO grade 3 or 4 during the study received platelet transfusions at the clinicians discretion; these patients no longer received treatment according to the trial protocol, but assessment continued for 30 days after randomisation. (n=299) Intervention 2: No prophylactic transfusion. No prophylaxis if the platelet count was less than 10x10^9 per litre. Duration NA. Concurrent medication/care: Not specified. Comments: In both trial groups, platelet transfusions were given therapeutically for bleeding, given before invasive

	procedures, or given at the clinician's discretion. Therapeutic platelet transfusions for bleeding episodes of WHO grade 2 were given according to standard practice, followed by prophylactic platelet transfusions per protocol, if indicated. Patients who had bleeding of WHO grade 3 or 4 during the study received platelet transfusions at the clinicians discretion; these patients no longer received treatment according to the trial protocol, but assessment continued for 30 days after randomisation.
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROPHYLACTIC TRANSFUSION VERSUS THERAPEUTIC TRANSFUSION Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up - Actual outcome for adults who are haematology patients -presence of bleeding: Number of units transfused/patient- platelets at end of follow-up; Group 1: mean 1.9 (SD 3.3); n=300, Group 2: mean 3.2 (SD 3.6); n=298; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Number of patients needing transfusions at end of follow-up - Actual outcome for adults who are haematology patients -presence of bleeding: Number of patients needing platelet transfusions at end of follow-up; Group 1: 176/300, Group 2: 266/298; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Serious adverse events as reported in study at end of follow-up - Actual outcome for adults who are haematology patients -presence of bleeding: Serious adverse events at end of follow-up; Group 1: 18/300, Group 2: 20/298; Risk of bias: High; Indirectness of outcome: No indirectness - Actual outcome for adults who are haematology patients -presence of bleeding: Transfusion related serious adverse event at end of follow-up; Group 1: 1/300, Group 2: 0/298; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 4: Bleeding o Occurrence of bleeding (prophylactic platelet transfusions)o Cessation of bleeding (therapeutic platelet transfusions)-Bleeding reported as WHO grade 2 and above or equivalent'. at end of follow-up - Actual outcome for adults who are haematology patients -presence of bleeding: Number of patients with bleeding events at end of follow-up; Group 1: 151/300, Group 2: 128/298; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; All-cause mortality at 30 days (all causes) at 30 days; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery; Length of hospital stay at end of follow-up

Study	**Wandt 2012[182]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=197)
Countries and setting	Conducted in Germany; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults who are haematology patients - non-bleeding patients
Subgroup analysis within study	Not applicable
Inclusion criteria	A multicentre, open-label, randomised parallel-group trial at eight haematology centres in Germany between Feb 1, 2005, and May 31, 2010. Centres had to have a 24 hour medical and transfusion service providing platelet transfusions within 4 h. Patients were allocated to two groups: group A for those with all subtypes of acute myeloid leukaemia (patients with promyelocytic leukaemia could be included only after reaching complete remission) and group B for those who had undergone autologous peripheral blood stem-cell trans plantation. Eligible participants in group A were aged 16–80 years and receiving induction and consolidation chemotherapy of standard dose intensity. These patients could follow the protocol during induction and consolidation. Eligible participants in group B were aged 16–68 years and receiving the standard intensity of a high-dose chemotherapy regimen.
Exclusion criteria	Excluded patients who were refractory to platelet transfusions or who had previous major bleeding or plasmatic coagulopathy. Additionally, from group B, patients with pulmonary or cerebral lesions were excluded. All participants were hospital inpatients during the study.
Age, gender and ethnicity	Age - --: . Gender (M:F): Define. Ethnicity: Not stated
Further population details	-
Indirectness of population	No indirectness
Interventions	(n=194) Intervention 1: Prophylactic transfusion. Patients in the group assigned the prophylactic platelet transfusion strategy with no signs of clinically relevant bleeding were transfused prophylactically with one platelet unit when the morning platelet count was 10×10^9 per litre or lower. For platelet transfusions, both single-donor apheresis platelets and pooled platelet concentrates were accepted. In Germany, apheresis units are standardised to contain 200–400×10^9 platelets; pooled concentrates in Germany produced from four to six buff y coats from random donors contain a similar amount (at least 200×10^9, range 240–360×10^9). All platelet products were provided leukoreduced to less than 1×10^6 leucocytes per unit. Duration: Not specified. Concurrent medication/care: Patients were receiving-Group A- induction and consolidation chemotherapy of standard dose intensity and Group B-Standard intensity of a

	high dose chemotherapy regimen. Further details:. Type of treatment: Chemotherapy Comments: A prophylactic platelet transfusion at platelet counts of 10×10^9 per litre or lower was recommended when sepsis or infections with an increased bleeding risk, such as invasive fungal infection or plasmatic coagulopathy (for example, disseminated intravascular coagulation or hyperfibrinolysis), were present. (n=197) Intervention 2: No prophylactic transfusion. Those in a stable clinical state in the therapeutic group were given platelet transfusions only when clinically relevant bleeding occurred, defined as bleeds of grade 2 or higher according to modified WHO criteria. If bleeding continued despite one platelet transfusion, further transfusions were given according to the decision of the treating physician. For platelet transfusions, both single-donor apheresis platelets and pooled platelet concentrates were accepted. In Germany, apheresis units are standardised to contain $200–400\times10^9$ platelets; pooled concentrates in Germany produced from four to six buffy coats from random donors contain a similar amount (at least 200×10^9, range $240–360\times10^9$). All platelet products were provided leukoreduced to less than 1×10^6 leucocytes per unit. Duration: Not specified. Concurrent medication/care: Patients were receiving-Group A- induction and consolidation chemotherapy of standard dose intensity and Group B-Standard intensity of a high dose chemotherapy regimen.
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: PROPHYLACTIC TRANSFUSION VERSUS THERAPEUTIC TRANSFUSION Protocol outcome 1: All-cause mortality at 30 days (all causes) at 30 days - Actual outcome for adults who are haematology patients -absence of bleeding: All-cause mortality at end of follow-up; Group 1: 10/194, Group 2: 2/197; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Serious adverse events as reported in study at end of follow-up - Actual outcome for adults who are haematology patients -absence of bleeding: Side effects of transfusion at end of follow-up; Group 1: 25/194, Group 2: 27/27; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Bleeding: Occurrence of bleeding (prophylactic platelet transfusions); Cessation of bleeding (therapeutic platelet transfusions)-Bleeding reported as WHO grade 2 and above or equivalent'. at end of follow-up - Actual outcome for adults who are haematology patients -absence of bleeding: Number of patients with bleeding events at end of follow-up ; Group 1: 65/194, Group 2: 127/197; Risk of bias: Low; Indirectness of outcome: No indirectness - Actual outcome for adults who are haematology patients -absence of bleeding: Number of patients with major bleeding events at end of follow-up; Group 1: 7/194, Group 2: 21/197; Risk of bias: Low; Indirectness of outcome: No indirectness	

Protocol outcomes not reported by the study	Quality of life at end of follow-up; Length of hospital stay at end of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up

Study	**Zumberg 2002[195]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=159)
Countries and setting	Conducted in USA; Setting: Hospital
Line of therapy	1st line
Duration of study	Intervention + follow up:
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults who are haematology patients - non-bleeding patients
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Patients older than 2 years who underwent an allogeneic, matched unrelated donor (MUD),syngeneic, or autologous bone marrow transplant (BMT)
Exclusion criteria	Patients with any of the following indications were ineligible for the study: known bleeding disorder or coagulopathy, concurrent need for anticoagulation, history of acute haemorrhage within 1 week of enrolment or within 1 week of a fall in the platelet count to below $50x10^9$/litre, history of prior bladder irradiation if the use of cyclophosphamide was planned, or platelet alloimmunisation.
Recruitment/selection of patients	Between July 1997 and December 1999, patients older than 2 years who underwent an allogeneic, matched unrelated donor (MUD), syngeneic, or autologous bone marrow transplant (BMT) were included in the study.
Age, gender and ethnicity	Age - Median (range): Group 1: 44 (8-70); Group 2 : 47 (3-69). Gender (M:F): Group 1: 44/34; Group 2: 39/42. Ethnicity: Not stated
Further population details	-
Indirectness of population	No indirectness
Interventions	(n=78) Intervention 1: Low platelet thresholds for transfusion (as defined by the trial). 10 K trigger group: Patients to

	receive prophylactic platelet transfusions if their morning platelet counts fell below $10x10^9$/litre. All platelet products were leukocyte depleted and irradiated. The dose of platelets administered in adults and children with an ideal body weight >50 kg was 1 unit of apheresis platelet concentrates. In children with an ideal body weight <50 kg the dose of single donor apheresis platelets was 0.5 units/m^2. Duration: A post-transfusion platelet count was obtained 30 to 90 minutes after each transfusion. If the platelet transfusion threshold was attained after transfusion, no further routine platelet transfusions were prescribed that day. If the post-transfusion platelet count did not reach the platelet trigger value, then action proceeded based on a predetermined algorithm. Concurrent medication/care: All patients received antibiotics and supportive care based on the standardised supportive care guideline. cyclophosphamide and/or total body irradiation. Further details: Type of treatment: Allogeneic transplant Comments: The presence of an acute bleeding event, recent major or minor bleeding, planned procedures such as central line placement or biopsies or worsening of a patients clinical condition were reasons for the transfusion of platelets at levels above the assigned trigger value. (n=81) Intervention 2: High platelet thresholds for transfusion (as defined by the trial). 20 K trigger group: Patients to receive prophylactic platelet transfusions if their morning platelet counts fell below $20x10^9$/litre. All platelet products were leukocyte depleted and irradiated. The dose of platelets administered in adults and children with an ideal body weight >50 kg was 1 unit of apheresis platelet concentrates. In children with an ideal body weight <50 kg the dose of single donor apheresis platelets was 0.5 units/m^2. Duration: A post-transfusion platelet count was obtained 30 to 90 minutes after each transfusion. If the platelet transfusion threshold was attained after transfusion, no further routine platelet transfusions were prescribed that day. If the post-transfusion platelet count did not reach the platelet trigger value, then action proceeded based on a predetermined algorithm. Concurrent medication/care: All patients received antibiotics and supportive care based on the standardised supportive care guideline, cyclophosphamide and/or total body irradiation. Further details:. Type of treatment: Allogeneic transplant Comments: The presence of an acute bleeding event, recent major or minor bleeding, planned procedures such as central line placement or biopsies or worsening of a patients clinical condition were reasons for the transfusion of platelets at levels above the assigned trigger value.
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW PLATELET THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) VERSUS HIGH PLATELET THRESHOLDS FOR TRANSFUSION (AS DEFINED BY THE TRIAL) Protocol outcome 1: Number of units transfused (all blood components- red cells, platelets, FFP and cryoprecipitate)/volume in ml in children at end of follow-up - Actual outcome for adults who are haematology patients -presence of bleeding: Number of units of platelet transfused at end of follow-up; Group 1: mean 10.4 (SD	

17); n=78, Group 2: mean 10.2 (SD 11); n=81; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: All-cause mortality at 30 days (all causes) at 30 days - Actual outcome for adults who are haematology patients -presence of bleeding: All-cause mortality at end of follow-up; Group 1: 10/78, Group 2: 5/81; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 3: Bleeding: Occurrence of bleeding (prophylactic platelet transfusions); Cessation of bleeding (therapeutic platelet transfusions)-Bleeding reported as WHO grade 2 and above or equivalent at end of follow-up. - Actual outcome for adults who are haematology patients -presence of bleeding: Bleeding (major and minor) at end of follow-up; Group 1: 74/78, Group 2: 79/81; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at end of follow-up; Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteraemia) within 30 days of surgery; Number of patients needing transfusions at end of follow-up; Serious adverse events as reported in study at end of follow-up; Length of hospital stay at end of follow-up.

H.4.2 Platelet dose

Study	**SToP- Standard and low dose strategies for transfusion of platelets trial: Heddle 2009[69]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	Not applicable (n=129)
Countries and setting	Conducted in Canada, Multiple countries, Norway, USA; Setting: Multi-centre international study conducted in academic teaching hospitals.
Line of therapy	1st line
Duration of study	Intervention + follow up: 30 days of follow up or day of last platelet transfusion before marrow recovery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adult haematology patients who are not bleeding: The patients were stratified into transplant patients (bone marrow/stem cell transplant) or non-transplant patients.
Subgroup analysis within study	Stratified then randomised
Inclusion criteria	Hypoproliferative thrombocytopenia where the platelet count is expected to be less than 10 x 10^9 per litre for a minimum of 10 days; receiving treatment as an inpatients and weight between 40 and 100 kg; age >17 years

Exclusion criteria	diagnosis of acute promyelocytic leukaemia, history of current diagnosis of immune thrombocytopenia, thrombotic thrombocytopenic purpura or haemolytic uremic syndrome, evidence of WHO grade 2 bleeding or greater at the time of study assessment, indication for bedside leukoreduced platelet components' pregnancy.
Age, gender and ethnicity	Age - Other: Mean age- 17 years. Gender (M:F): Define. Ethnicity: Caucasian
Further population details	Type of treatment: Allogeneic transplant (12 transplant patients (60%) had an allogeneic transplant; remaining 40% had an autologous transplant.).
Indirectness of population	No indirectness
Interventions	(n=58) Intervention 1: Low dose - Low dose was defined as $1.1x10^{11}$ platelets per square metre of body surface area per transfusion or administration of 3 platelet units.. Platelets given in a range of $1.5\text{-}3x10^{11}$ platelets /product in the low dose arm; Apheresis platelets and whole blood derived platelets used; Prophylactic platelet transfusion was administered at a threshold of $10x10^{9}$/litre; higher triggers were used in some cases (sepsis) at discretion of treating physician. Duration Platelet transfusion with a 30 day follow up period. Concurrent medication/care: None reported (n=61) Intervention 2: Medium dose - Medium dose was defined as $2.2x10^{11}$ platelets per square metre of body surface area per transfusion or, 5 platelet units, or, $0.5x10^{11}$/10 kg. Platelets administered in the range of $3\text{-}6x10^{11}$ platelets/product; Apheresis and whole blood derived platelets were used; Prophylactic transfusions were given at thresholds of $10x10^{9}$/litre and at higher triggers in some cases (sepsis) at the discretion of the treating physician.. Duration Platelet transfusion with 30 days of follow up. Concurrent medication/care: None reported
Funding	Academic or government funding (Canadian Blood Services)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW DOSE VERSUS MEDIUM DOSE

Protocol outcome 1: All-cause mortality at 30 days
- Actual outcome for Adult haematology patients who are not bleeding: All-cause mortality at 30 days; Group 1: 1/58, Group 2: 1/61; Risk of bias:High; Indirectness of outcome:

Protocol outcome 2: Bleeding at end of follow up
- Actual outcome for Adult haematology patients who are not bleeding: Bleeding (WHO grade 2 and above) at end of follow up; Group 1: 30/58, Group 2: 30/61; Risk of bias: High; Indirectness of outcome: No indirectness

Protocol outcome 3: Number of patients needing platelet transfusions at end of follow up
- Actual outcome for Adult haematology patients who are not bleeding: Mean number of platelet transfusion episodes at During period of thrombocytopenia; Group 1:

mean 9.5 (SD 7.8); n=58, Group 2: mean 5.3 (SD 3.3); n=61; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at Define; Infections, for example, pneumonia at end of follow up; Serious adverse events as defined by study at end of follow up; Number of units of platelets transfused at end of follow up; Length of stay (hospitalisation) at end of follow up

Study	**PROBE study trial: Sensebe 2005[146]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=101)
Countries and setting	Conducted in France
Line of therapy	1st line
Duration of study	Intervention + follow up: Follow up was till discharge or death of patients or till the patients had a stable platelet count more than $25x10^9$/litre.
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adult haematology patients who are not bleeding
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients with thrombocytopenia who had not undergone transfusion; had acute leukaemia (excluding AML3); undergoing first line treatment or autologous haematopoietic stem cell transplantation without criteria impairing platelet efficiency.
Exclusion criteria	Patients with AML3; had criteria impairing platelet efficiency.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Mean (SD): Medium dose: 50 (9); High dose: 49 (11). Gender (M:F): Define. Ethnicity: Not reported
Further population details	Type of treatment: Mixed group including autologous transplants
Indirectness of population	No indirectness
Interventions	(n=48) Intervention 1: High dose - High dose was defined as $4.4x10^{11}$ platelets per square metre of body surface area per transfusion or, $1.0x10^{11}$/10 kg. High dose was defined as double dose of platelets in this study ($1x10^{11}$/10 kg). Duration

	Platelet infusion with follow up until discharge or death. Concurrent medication/care: None reported (n=48) Intervention 2: Medium dose - Medium dose was defined as $2.2x10^{11}$ platelets per square metre of body surface area per transfusion or, 5 platelet units, or, $0.5x10^{11}$/10 kg. Medium dose was defined as a single dose in this study ($0.5x10^{11}$/10 kg). Duration Platelet infusion with follow up till discharge or death. Concurrent medication/care: None reported
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH DOSE VERSUS MEDIUM DOSE Protocol outcome 1: All-cause mortality at 30 days - Actual outcome for Adult haematology patients who are not bleeding: Mortality at Time not reported; Group 1: 0/48, Group 2: 0/48; Risk of bias: High; Indirectness of outcome: No indirectness Protocol outcome 2: Bleeding at end of follow up - Actual outcome for Adult haematology patients who are not bleeding: Number of patients with bleeding (WHO grade 2 and above) at From time of platelet infusion till discharge or death; Group 1: 3/48, Group 2: 2/48; Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at Define; Infection, for example, pneumonia at end of follow up; Serious adverse events as defined by study at end of follow up; Number of patients needing platelet transfusions at end of follow up; Number of units of platelets transfused at end of follow up; Length of stay (hospitalisation) at end of follow up

Study	**Platelet dose trial (PLADO) trial: Slichter 2010[155,156]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=1351)
Countries and setting	Conducted in USA; Setting: Multicentre study across 26 hospitals in the USA.
Line of therapy	1st line
Duration of study	Intervention + follow up: 30 days after first platelet transfusion
Method of assessment of guideline condition	Adequate method of assessment/diagnosis

Stratum	Overall: Study population includes adult and children haematology patients who are receiving prophylactic platelet transfusions
Subgroup analysis within study	Stratified then randomised: Patients were stratified based into four treatment groups- allogeneic haematopoietic stem cell transplantation, autologous or syngeneic haematopoietic stem cell transplantation, chemotherapy for haematologic cancer or chemotherapy for solid tumour.
Inclusion criteria	In patients of any age undergoing haematopoietic stem cell transplantation or chemotherapy for haematologic cancers or solid tumours and expected to have platelet counts of 10,000 per cubic mm or lower for 5 days or more; weight of 10 to 135 kg; PTT 1.3 times higher than upper limit of normal range or less, no previous platelet transfusions for thrombocytopenia during the current period of hospitalisation.
Exclusion criteria	Bleeding of WHO grade 2 or higher before or at time of assessment, performance of bedside platelet leukoreduction, platelet refractoriness within the past 30 days according to local criteria, a panel reactive HLA antibody level of 20% or more, acute promyelocytic leukaemia, idiopathic or thrombotic thrombocytopenic purpura or haemolytic uremic syndrome, planned prophylactic platelet transfusion of platelets at platelet counts of more than 10,000 per cubic mm, major surgery within the previous two weeks, use of drugs intended to affect platelet number or function, pregnancy, previous enrolment in this study.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Median (IQR): Low dose: 47 (37-57), Medium dose: 50(34-58), 51 (32-62). Gender (M:F): Define. Ethnicity: Not reported
Further population details	Type of treatment: Mixed group-Study included patients from all three subgroups- autologous transplant, allogeneic transplant and chemotherapy
Indirectness of population	No indirectness
Interventions	(n=417) Intervention 1: Low dose - Low dose was defined as $1.1x10^{11}$ platelets per square metre of body surface area per transfusion or administration of 3 platelet units.. Platelets administered in dose of $1.1x10^{11}$ per square metre of body surface area per transfusion.Duration Platelet infusion with 30 day follow up . Concurrent medication/care: None reported (n=423) Intervention 2: Medium dose - Medium dose was defined as $2.2x10^{11}$ platelets per square metre of body surface area per transfusion or, 5 platelet units, or, $0.5x10^{11}$/10 kg.. Platelets administered in dose of $2.2x10^{11}$ per square metre of body surface are per transfusion. Duration Platelet infusion with 30 day follow up. Concurrent medication/care: None reported.

	(n=432) Intervention 3: High dose - High dose was defined as $4.4x10^{11}$ platelets per square metre of body surface area per transfusion or, $1.0x10^{11}$/10 kg. Platelets administered in dose of $4.4x10^{11}$ per square metre of body surface area per transfusion. Duration Platelet infusion with 30 day follow up. Concurrent medication/care: None reported
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH DOSE VERSUS MEDIUM DOSE ; LOW DOSE VERSUS HIGH DOSE; LOW DOSE VERSUS MEDIUM DOSE

LOW DOSE VERSUS MEDIUM DOSE

Protocol outcome 1: All-cause mortality at 30 days
- Actual outcome for Adult haematology patients who are not bleeding: Mortality at Time not reported; Group 1: 9/417, Group 2: 4/423; Risk of bias:Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Bleeding at end of follow up
- Actual outcome for Adult haematology patients who are not bleeding: Number of patients with bleeding (WHO grade 2 and above) at From time of platelet infusion till discharge or death; Group 1: 296/417, Group 2: 292/423; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 3: Infection
- Actual outcome for Adult haematology patients who are not bleeding: : Infection; Group 1: 5/417, Group 2: 5/423; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 4: Serious adverse events
- Actual outcome for Adult haematology patients who are not bleeding: serious adverse events; Group 1: 35/417, Group 2: 27/423; Risk of bias: Low; Indirectness of outcome: No indirectness

HIGH DOSE VERSUS MEDIUM DOSE

Protocol outcome 1: All-cause mortality at 30 days
- Actual outcome for Adult haematology patients who are not bleeding: Mortality at Time not reported; Group 1: 7/432, Group 2: 5/423; Risk of bias: Low; Indirectness of outcome: No indirectness

Protocol outcome 2: Bleeding at end of follow up

- Actual outcome for Adult haematology patients who are not bleeding: Number of patients with bleeding (WHO grade 2 and above) at From time of platelet infusion till discharge or death; Group 1: 302/432, Group 2: 292/423; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Infection - Actual outcome for Adult haematology patients who are not bleeding: : Infection; Group 1: 7/432, Group 2: 5/423; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Serious adverse events - Actual outcome for Adult haematology patients who are not bleeding: serious adverse events; Group 1: 36/432, Group 2: 27/423; Risk of bias: Low; Indirectness of outcome: No indirectness LOW DOSE VERSUS HIGH DOSE Protocol outcome 1: All-cause mortality at 30 days - Actual outcome for Adult haematology patients who are not bleeding: Mortality at Time not reported; Group 1: 9/417, Group 2: 7/432; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 2: Bleeding at end of follow up - Actual outcome for Adult haematology patients who are not bleeding: Number of patients with bleeding (WHO grade 2 and above) at From time of platelet infusion till discharge or death; Group 1: 71/417, Group 2: 70/432; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 3: Infection - Actual outcome for Adult haematology patients who are not bleeding: : Infection; Group 1: 5/417, Group 2: 7/432; Risk of bias: Low; Indirectness of outcome: No indirectness Protocol outcome 4: Serious adverse events - Actual outcome for Adult haematology patients who are not bleeding: serious adverse events; Group 1: 35/417, Group 2: 36/432; Risk of bias: Low; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at Define; Infections, for example, pneumonia at end of follow up; All-cause mortality at 30 days; Bleeding at end of follow up; Serious adverse events as defined by study at end of follow up; Number of patients needing platelet transfusions at end of follow up; Number of units of platelets transfused at end of follow up; Length of stay (hospitalisation) at end of follow up.

Study	Tinmouth 2004[170]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	(n=111)
Countries and setting	Conducted in Canada
Line of therapy	1st line
Duration of study	Intervention + follow up: 30 days
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adult haematology patients who are not bleeding
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients older than 16 years of age; undergoing autologous peripheral blood progenitor cell transplantation or induction chemotherapy for acute myelogenous leukaemia or acute lymphoblastic leukaemia.
Exclusion criteria	Patients with acute promyelocytic leukaemia, active bleeding, abnormal coagulation tests, prior history of bleeding diathesis, immune thrombocytopenic purpura, refractory to platelet transfusions, receiving anticoagulants, anti fibrinolytic agents or anti-platelet agents, or desmopressin acetate.
Recruitment/selection of patients	Consecutive patients
Age, gender and ethnicity	Age - Median (range): Low dose: 55.6 (26-80), Medium dose: 54.6 (22-82). Gender (M:F): Define. Ethnicity: Not reported
Further population details	Type of treatment: Mixed group- autologous transplant and chemotherapy.
Indirectness of population	No indirectness
Interventions	(n=56) Intervention 1: Low dose - Low dose was defined as 1.1 x 10^{11} platelets per square metre of body surface area per transfusion or administration of 3 platelet units.. Platelet transfusion of 3 platelet units. Duration Platelet infusion with 30 day follow up. Concurrent medication/care: None reported (n=55) Intervention 2: Medium dose - Medium dose was defined as 2.2 x 10^{11} platelets per square metre of body surface area per transfusion or, 5 platelet units, or, 0.5 x 10^{11}/10 kg.. Platelet transfusion of 5 platelet units. Duration platelet transfusions with 30 day follow up. Concurrent medication/care: None reported

Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: LOW DOSE VERSUS MEDIUM DOSE Protocol outcome 1: All-cause mortality at 30 days - Actual outcome for Adult haematology patients who are not bleeding: Mortality (data from Estcourt 2012) at 30 days; Group 1: 0/56, Group 2: 0/55 ; Risk of bias:High; Indirectness of outcome: No indirectness Protocol outcome 2: Bleeding at end of follow up - Actual outcome for Adult haematology patients who are not bleeding: No. of patients with major bleeding (WHO grade 2 or higher) at 30 days; Group 1: 6/56, Group 2: 4/55;Risk of bias: High; Indirectness of outcome: No indirectness	
Protocol outcomes not reported by the study	Quality of life at Define; Infections, for example, pneumonia at end of follow up; Serious adverse events as defined by study at end of follow up; Number of patients needing platelet transfusions at end of follow up; Number of units of platelets transfused at end of follow up; Length of stay (hospitalisation) at end of follow up

H.5 Fresh frozen plasma

H.5.1 Fresh frozen plasma thresholds and targets

Study	**Doussau 2014[50]**
Study type	Prospective cohort study
Number of studies (number of participants)	n=967 (n=562 transfused with FFP and n=405 not transfused with FFP)
Countries and setting	Recruited from 15 French centres
Line of therapy	First-line
Duration of study	February 2004 to January 2006
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults

Subgroup analysis within study	Not applicable
Inclusion criteria	All adult patients undergoing on-pump cardiac surgery and exhibiting peri-operative excessive bleeding complications until 48 hours after surgery were eligible unless they had been transfused before the onset of excessive bleeding.
Exclusion criteria	Patients who received a preventive FFP transfusion were excluded. Also patients exposed to congenital heart procedures or off-pump cardiac surgery or patients who experienced excessive bleeding before surgery were excluded.
Recruitment/selection of patients	The study recruited patients from 15 French cardiac surgery centres.
Age, gender and ethnicity	Age (years): 67 (13) years Females: 33%
Further population details	Type of surgery: CABG, mitral valve, aortic valve, thoracic aorta, cardiac transplantation. Most patients underwent aortic valve surgery (47.5%) or CBAG (45%).
Indirectness of population	No indirectness
Interventions	Therapeutic FFP transfusion vs. no FFP transfusion during the peri-operative period
Funding	Not stated
Outcomes	Mortality (30 days), Number of FFP transfusions, adverse events

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FFP VERSUS NO FFP

Results (numbers analysed) and risk of bias for comparison: A total of 562 of the 967 patients were per-operatively transfused with FFP (58.1%).

Among 590 patients included for intra-operative excessive bleeding, 220 (37.3%) were transfused with FFP during the intervention, 59 (10%) during the post-operative period only and 97 ((16.4%) both intra and post-operatively.

The median dose was 11.3 mL/kg (interquartile range, 7.6-19.5).

Adverse events with a possible link to FFP transfusion were reported in 4 patients.

The 30 day mortality was high 15.7% (95% CI, 13% to 7.9%) in patients transfused with FFP and 5.2% (95% CI, 3.4% to 7.9%) in those who did not receive FFP transfusion.

Other factors significantly associated with 30 day mortality in the univariate analysis were intra-operative haemorrhage (vs. post-haemorrhage), acquired coagulation diseases, pre-operative low PT, high APTT ratio and low Hb, cardiac transplantation, high Euroscore, long duration of surgery, RBC and platelet transfusion dose, plasma derived products use, and high volume of cell salvage blood transfused. After fitting a model adjusted for all factors assumed to be potential confounders, there was no association between FFP transfusion and 30 day mortality.

Risk of bias: High
Protocol outcomes not reported by the study Quality of life at end of follow-up, Infections (for example, pneumonia), Number of patients needing red cell transfusions , Number or volume of red cells transfused and Length of stay (hospitalisation), Correction of abnormal coagulation test

Study	**Karam 2013[75]**
Study type	Systematic review
Number of studies (number of participants)	No RCTs were identified that evaluated plasma transfusion strategies according to predetermined coagulation test thresholds. One excluded study: One protocol for an RCT on plasma transfusion strategies by Müller 2011et al was identified. The study authors described a non-inferiority randomised trial in critically ill adults with abnormal coagulation tests (INR 1.5 to 3.0) requiring an invasive procedure. In the control group, a prophylactic plasma transfusion was administered before the invasive procedure was performed, whereas the plasma transfusion was not included in the intervention group. The study authors planned to enrol 200 participants per treatment arm (400 participants in total). Although this study randomly assigned two plasma transfusion strategies (prophylactic plasma transfusion vs. no plasma transfusion), it did not randomly assign two strategies based on coagulation test results.
Countries and setting	NA
Line of therapy	First-line
Duration of study	NA
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	All critically ill patients of all ages (neonates, children and adults) requiring plasma transfusion.

Subgroup analysis within study	Not applicable
Inclusion criteria	Randomised clinical trials that assessed the effects of two plasma transfusion strategies, using a restrictive and a liberal threshold of at least one coagulation test, in critically ill participants. All randomised clinical trials were considered for inclusion (irrespective of language, blinding, publication status or sample size) if two thresholds (restrictive and liberal) and at least one coagulation test (international normalised ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen or thromboelastography) were compared
Exclusion criteria	Trials on plasmapheresis and plasma exchanges were not included
Recruitment/selection of patients	Not applicable
Age, gender and ethnicity	Age - --: NA. Gender NA
Further population details	NA
Indirectness of population	Critically ill patients
Interventions	The intervention in the experimental group to follow a protocol with one defined threshold required for plasma transfusion. The intervention in the control group to consist of another threshold or standard treatment By definition, “liberal” a transfusion strategy was based on a threshold allowing for more transfusions, and “restrictive” a transfusion strategy based on a threshold allowing for fewer transfusions.
Outcomes	Primary outcomes • All-cause mortality, at the end of the follow-up period in each trial. Secondary outcomes: • Nosocomial infections. • Multiple-organ dysfunction (new or progressive). • Volume of blood lost. • Transfusion of RBCs and platelets. • Transfusion reactions.
Funding	Not stated
RESULTS	

No studies were included in this review

Study	**Matsumoto 2007[101]**
Study type	RCT
Number of studies (number of participants)	n=43 (n=23 FFP; n=20 No FFP)
Countries and setting	Japan
Line of therapy	First-line
Duration of study	Not stated
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients at high risk for developing hepatic veno occlusive disease (VOD) after allogeneic SCT (stem cell transplantation) and fulfilled one of the following criteria: intensified conditioning regime, liver dysfunction and received intensified chemotherapy until just before SCT because of poor situation of the underlying disease.
Exclusion criteria	Not stated
Recruitment/selection of patients	Patients at high risk for developing hepatic veno occlusive disease (VOD) after allogeneic SCT (stem cell transplantation).
Age, gender and ethnicity	Adults and children included
Further population details	Patients were divided in to a child group (18 year old or under) and an adult group from (over 18 year old).
Indirectness of population	No indirectness
Interventions	FFP vs. no FFP FFP was induced twice a week during the conditioning regimen and until day 28 after SCT in patient in the FFP group. The volume of FFP infused was based upon body weight and determined as follows: 1 unit (80 mL) for patients under

	10kg, 2 units for 10-20 kg, 3 units
Funding	Research grants from the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare of Japan.
Outcomes	No relevant outcomes reported
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : FFP VERSUS NO FFP No relevant outcomes reported Risk of bias: High	

Study	**Noddeland 2002[119]**
Study type	Prospective parallel group randomised controlled trial
Number of studies (number of participants)	n=84
Countries and setting	Norway
Line of therapy	First-line
Duration of study	Till first and 2nd day of surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Only adult patients scheduled for elective open heart surgery were included after having given their consent after detailed written and oral information.
Exclusion criteria	Unstable angina pectoris, hypersensitivity to blood products, exposure to viral hepatitis during the past 6 months, suspected drug abuse, participation in other clinical studies or pregnancy.
Recruitment/selection of patients	Adult patients scheduled for elective open heart surgery.

Age, gender and ethnicity	Age: mean ±SD Group 1 : Uniplas (blood groups A,B or AB): 71±10.1 Group 2: Uniplas (blood group O):69.9±5.1 Group 3: Octaplas:67.6±12.5 Group 4: control (No FFP. All ABO blood groups):65.2±10.5
Further population details	-
Indirectness of population	No indirectness
Interventions	Therapeutic FFP transfusion vs. no FFP transfusion. If plasma transfusion was indicated during operation or over the two following days, patients were randomised to receive Uniplas or Octaplas. Group 1 (n=25): Uniplas (blood groups A,B or AB) Group 2 (n=11): Uniplas (blood group O) Group 3 (n=19): Octaplas Group 4 (n=29): control (No FFP. All ABO blood groups)
Funding	Not stated
Outcomes	Activated clotting time (ACTT) Activated partial thromboplastin time (APTT) Number of patients needing RBC transfusion Number of units (RBC) transfused Post-operative bleeding rates from chest
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: FFP VERSUS NO FFP Results and risk of bias for comparison: **No. of patients needing RBC transfusion** Group 1 (n=25): Uniplas (blood groups A,B or AB) :22 Group 2 (n=11): Uniplas (blood group O) :6 Group 3 (n=19): Octaplas : 13	

Group 4 (n=29): control (all ABO blood groups): 14

No. of units (RBC) transfused (median , range)
Group 1 (n=25): Uniplas (blood groups A,B or AB): 4 (1-14)
Group 2 (n=11): Uniplas (blood group O): 5 (1-15)
Group 3 (n=19): Octaplas :4 (2-7)
Group 4 (n=29): control (all ABO blood groups): 2 (1-5)

Post-operative bleeding rates from chest drainage
(mean ±SD) mL
Group 1 (n=25): Uniplas (blood groups A,B or AB): 854±544
Group 2 (n=11): Uniplas (blood group O): 946±943
Group 3 (n=19): Octaplas : 993±693
Group 4 (n=29): control (all ABO blood groups): 625±181

Activated partial thromboplastin time (APTT)-baseline [mean ±SD] seconds
Group 1 (n=25) Uniplas (blood groups A,B or AB): 31.68±5.52
Group 2 (n=11) Uniplas (blood group O): 32.11±4.51
Group 3 (n=19) Octaplas :28.38±8.15
Group 4 (n=29): control (all ABO blood groups): 37.19±30.20

Activated partial thromboplastin time (APTT)-After surgery [mean ±SD] seconds
Group 1 (n=25) Uniplas (blood groups A,B or AB): 46.50±21.03
Group 2 (n=11) Uniplas (blood group O): 41.11±9.48
Group 3 (n=19) Octaplas :36.88±5.28
Group 4 (n=29) control (all ABO blood groups): 37.69±5.06

Activated clotting time (ACTT) – Baseline [mean ±SD] seconds
Group 1 (n=25) Uniplas (blood groups A,B or AB): 136±14.90
Group 2 (n=11) Uniplas (blood group O):135.67±9.77

Group 3 (n=19) Octaplas: 135.13±11.64 Group 4 (n=29) control (all ABO blood groups): 132.27±16.83 **Activated clotting time (ACTT) – After surgery [mean ±SD] seconds** Group 1 (n=25) Uniplas (blood groups A,B or AB): 121.70±12.03 Group 2 (n=11) Uniplas (blood group O):113.50±10.97 Group 3 (n=19) Octaplas : 111.40±11.03 Group 4 (n=29) control (all ABO blood groups): 115.65±11.27 Risk of bias: High	
Protocol outcomes not reported by the study Bleeding, All-cause mortality at 30 days , Quality of life at end of follow-up, Infections (for example, pneumonia) , Serious adverse events (as defined by study) , Adverse events related to the transfusion , Number of patients needing red cell transfusions , Number or volume of red cells transfused and Length of stay (hospitalisation)	

Table 1: Stanworth 2011, Walsh 2010 (Intensive Care Study of Coagulopathy (ISOC study)[161,181]

Study	**Stanworth 2011, Walsh 2010 (Intensive Care Study of Coagulopathy (ISOC study)[161,181]**
Study type	Prospective multiple centre observational cohort study
Number of studies (number of participants)	1 (n= 1923)
Countries and setting	Conducted in UK; Setting: 29 adult intensive care units. The ICUs were in 19 tertiary hospitals and 10 regional hospitals and included 2 ICUs with specialist liver units and 5 ICUs admitting patients requiring neurointensive care.
Line of therapy	First-line
Duration of study	8 weeks
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults

Subgroup analysis within study	Not applicable
Inclusion criteria	Inclusion of all patients sequentially admitted to 29 adult UK general ICUs over 8 weeks. ICUs were mixed general units and did not include specialist cardiac centres.
Exclusion criteria	Exclusions were ICU readmissions during the same hospital stay, transfer from other ICUs and patients with short life expectancy (under 4 hours). Specialist medical and surgical cardiac ICUs were excluded.
Recruitment/selection of patients	All patients admitted to general adult ICUs were screened. There were 2386 admissions during the study period. Of these, 1990 admissions were eligible for data collection. The 396 exclusions comprised 138 re-admissions, 96 locally agreed exclusions, 83 transfers from other ICUs, 70 patients where admission was expected to be <4 hours, 67 did not have adequately complete data for analysis. Data were collected prospectively from patient records for the 24 hours prior to admission and every subsequent day in the ICU until discharge.
Age, gender and ethnicity	Age – (mean –SD) 58.3 (18.8). Male, no %- 1087 (57):
Further population details	Type of admission – no (%) Medical- 875 (46) Surgical- 908 (47) Trauma- 138 (7) Blood transfusion during initial treatment period 0 units- 1378 1-4 units- 332 5-8 units- 113 >8 units- 100
Indirectness of population	No indirectness
Interventions	INR ≤1.5 INR 1.6 to 2.5 INR 2.6 to 3.5 INR 3.6 to 5.0 INR >5

Funding	Funded by research grants from the National Health Service Blood and Transplant and Scottish National Blood transfusion service and the Transfusion medicine education and Research Foundation.
Outcomes	Pre transfusion INR Post-transfusion INR Dose of FFP Use of FFP

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : FFP TRANSFUSION AT DIFFERENT INR LEVELS

Results (numbers analysed) and risk of bias for comparison:

Of 1923 admissions, 12.7% (244 patients) received FFP. These patients received 404 FFP treatment episodes comprising 1.212 units of FFP (or an average 5 U of FFP/transfused patient).

Overall a median of 803 mL were administered per episode.

Reasons for FFP transfusion were bleeding (48%), prophylaxis for a procedure (15%), and prophylaxis without planned procedure (36%), 6 treatments were given for other reasons (1.5%).

Clinically significant haemorrhage was recorded on the day of FFP transfusion for 47% of FFP transfusion episodes.

INR values preceding FFP treatment during ICU stay and clinically significant haemorrhage on same day as FFP transfusion:

INR <1.5 (n=126); haemorrhage, n=72

INR 1.6 to 2.5 (n=187); haemorrhage, n=92

INR 2.6 to 3.5 (n=30); haemorrhage, n=10

INR 3.6 to 5.0 (n=14); haemorrhage, n=2

INR >5 (n=2); haemorrhage, n=3

The median reductions in INR were greater when the pre- FFP transfusion values were higher (median change -0.1, -0.4, -1.0 and -2.5 for pre-transfusion INRs in the ranges 1 to <1.5, 1.6 to 2.5, 2.6 to 3.5 and >3.5 respectively)

Median length of hospital stay:

overall: 2.0 (0.8, 5.5)

Admissions with INR >1.5: 3.0 (1.1, 8.1)

admissions with normal INR test: 1.8 (0.8, 4.3)

ICU mortality was higher for patients with PT prolongation than those without (35% vs. 12%) PT prolongation defined as INR >1.5 Risk of bias: High
Protocol outcomes not reported by the study Quality of life at end of follow-up, Infections (for example, pneumonia) , Serious adverse events (as defined by study) , Adverse events related to the transfusion , Number of patients needing red cell transfusions , Number or volume of red cells transfused and Length of stay (hospitalisation),

Study	**Trimble 1964**[172]
Study type	RCT
Number of studies (number of participants)	n=53
Countries and setting	Canada
Line of therapy	First-line
Duration of study	24 hours after surgery
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	53 consecutive patients with a variety of congenital and acquired heart defects were included in the study. Each had an open heart operation with the use of a large –disc oxygenator.
Exclusion criteria	Not stated
Recruitment/selection of patients	Patients undergoing open-heart surgery Included both adults and children

Age, gender and ethnicity	Not specified. Adults and children
Further population details	-
Indirectness of population	No indirectness
Interventions	Prophylactic FFP vs. No FFP FFP I unit (250 cc) and 2 units (500 cc) for adults was administered.
Funding	
Outcomes	Post-operative bleeding (chest drainage in first 24 hours)

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : PROPHYLACTIC FFP VERSUS NO FFP

Results (numbers analysed) and risk of bias for comparison:

- Chest drainage first 24 hours (cc) in Children (under 15 years of age) [mean, range]
- Prophylactic FFP (n=6): 120 (25 to 335)
- No FFP (n=7): 135 (10 to 335)
- Chest drainage first 24 hours (cc) in adults [mean, range]
- Prophylactic FFP (n=15): 400 (90 to 900)
- No FFP: 500 (75 to 3,700)

Risk of bias: High

Protocol outcomes not reported by the study

All-cause mortality at 30 days , Quality of life at end of follow-up, Infections (for example, pneumonia) , Serious adverse events (as defined by study) , Adverse events related to the transfusion , Number of patients needing red cell transfusions , Number or volume of red cells transfused and Length of stay (hospitalisation), Correction of abnormal coagulation test

H.5.2 Fresh frozen plasma

Study	Chowdhury 2004[28]
Study type	Retrospective cohort study
Number of studies (number of participants)	1 (n= 22)
Countries and setting	Conducted in UK; Setting: Hospital
Line of therapy	1st line
Duration of study	Not stated
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients in ICU who are bleeding or about to undergo an invasive procedure.
Exclusion criteria	Not stated
Recruitment/selection of patients	A consecutive cohort of patients who received FFP on the ICU at the University Hospital of Wales. Patients with either PT or an aPTT ratio greater than 1.5 were given FFP, either to arrest bleeding or before invasive procedures, according to routine protocols of the ICU.
Age, gender and ethnicity	Age - --: Not reported, Gender (M:F): Not reported. Ethnicity: Not stated
Further population details	Not reported
Indirectness of population	No indirectness
Interventions	Group 1: (n=10) The median dose of FFP infused was 1.0 litres (range 0.5 to 1.5 litres). The median volume of FFP given according to body weight was 12.2 ml/kg (range 5.6-22.1 ml/kg) Group 2: (n=12). The second group was infused with FFP with the aim of giving 30 ml/kg. The median volume of FFP infused was 2.5 litres (range 1.25 to 4 litres). The median volume of FFP given according to body weight was 33.5 ml/kg (range 18-51 ml/kg)

Funding	Not stated
Outcomes	Prothrombin time (PT), activated partial thromboplastin time (aPTT) before and after FFP infusion.

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : FFP VERSUS NO FFP

Retrospective analysis of the individual coagulation factor levels of patients (using the threshold of 30 IU/dl and 1 g/litres for fibrinogen) showed that 10 of the 22 patients had not required FFP replacement (9 patients had no coagulation factor levels below 30 IU/dl and one patient had only a decreased level of factor XII). Of these 10 patients, 5 were in group 1 and 5 in group 2 and the range of their PT and aPTT showed significant overlap with those that, in retrospect, had required FFP. Thus in this cohort, coagulation screens poorly predicted the levels of coagulation factors.

	All patients (median-range)	FFP not required (median-range)	FFP required (median-range)
PT ratio	1.8 (1.4 -20)	1.6 (1.4-1.9)	2.2 (1.5-20)
aPTT ratio	1.8 (1.1-10)	1.4 (1.1 -2.8)	2.2 (1.2-10)

The median PT, aPTT and coagulation factor levels before and after infusion of FFP.

	Group 1 (pre)	Group 1 (post)	Group 2(pre)	Group 2 (post)
PT (s)	22.8 (17-222)	19 (15-36)	24 (17-44)	16 (14-20)
APTT (s)	46.4 (30-223)	37 (30-158)	41 (28-198)	30* (24-45)

*significant difference when comparing groups 1 and 2 post-transfusion ($p<0.05$)

The coagulation factor levels were not statistically different between the two groups before the infusion.

In group 1, only 1 of the 5 patients who had had decreased coagulation factor levels before FFP had all coagulation factor levels before FFP had all coagulation factor levels above 30 IU/dl following infusion of 12.2 ml/kg FFP. In group 2, all 7 of the patients who had had low coagulation factor levels before FFP had levels above 30 IU/dl post-FFP (33 ml/kg). The median increment for group 2 for the individual coagulation factors was between 17 and 44 IU/dl.

Risk of bias: high

H.6 Cryoprecipitate

Study	Holcomb 2013 – Prospective Observational Multicentre Major Trauma Transfusion (PROMMT) study[72]
Study type	Prospective cohort study
Number of studies (number of participants)	n=1245
Countries and setting	USA
Line of therapy	First-line
Duration of study	July 2009 to October 2010
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Adult trauma patients
Exclusion criteria	Not stated
Recruitment/selection of patients	The study enrolled 1,245 adult trauma patients from 10 US Level 1 trauma centres during July 2009 to October 2010.
Age, gender and ethnicity	Age (median IQR): No cryoprecipitate -38 (25-54); cryoprecipitate- 38 (23-54) Male (No., %: No cryoprecipitate- 646 (73%); cryoprecipitate- 273 (76%) Race (white) (No., %): No cryoprecipitate- 561 (64%); cryoprecipitate- 275 (77%)
Further population details	Fibrinogen level (at baseline) <100 mg/dl: No cryoprecipitate- 12 (5%); cryoprecipitate- 20 (10%) <150 mg/dl: No cryoprecipitate- 38 (17%); cryoprecipitate- 58 (30%) Patients receiving cryoprecipitate had higher Injury Severity Score (ISS) and higher head, abdomen, and External Abbreviated Injury Scale (AIS) scores compared with patients who did not receive cryoprecipitate. Patients receiving cryoprecipitate were also more likely to have pelvic bleeding. Patients receiving cryoprecipitate had significantly higher admission heart rates, base deficit, INR, and lactate as well as significantly lower admission Glasgow Coma Scale (GCS) score, platelet count, thromboelastography maximal amplitude and α haemoglobin and haematocrit.

Indirectness of population	No indirectness
Interventions	Cryoprecipitate
Funding	Not stated
Outcomes	Mortality (30 days) Number of units (RBC) transfused

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : CRYOPRECIPITATE VERSUS NO CRYOPRECIPITATE
Mortality (30 days)
No cryoprecipitate (n=879): 163 (19%)
Cryoprecipitate (n=359) 95 (26%)

RBC units transfused (median, IQR)
No cryoprecipitate (n=879): 4 (2-7)
Cryoprecipitate (n=359) :7 (4-17)
p<0.001

Multivariate predictors of cryoprecipitate use:
Admission <100 mg/dl: OR (95% CI) – 3.8 (1.6 to 8.9), P=0.003
Characteristics of coagulopathic patients (INR> 1.3)
Mortality (30 days)
No cryoprecipitate (n=291): 82 (28%)
Cryoprecipitate (n=158) 60 (38%)

RBC units transfused (median, IQR)
No cryoprecipitate (n=291): 5 (3-9)
Cryoprecipitate (n=158) :11 (5-24)
p<0.001

Risk of bias: high

H.7 PCC

H.7.1 PCC thresholds

None

H.7.2 PCC targets

None

H.7.3 PCC doses

Study	Kerebel 2013[80]
Study type	Multi-centre RCT, open label study
Number of studies (number of participants)	n=1 (n=59)
Countries and setting	France (22 centres); setting: hospitals
Line of therapy	1st line
Duration of study	November 2008 to April 2011
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Adults
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients were eligible for inclusion if they had an objectively diagnosed oral anticoagulant therapy (OAT) associated cerebral haemorrhage (CT or MRI). Other inclusion criteria were age >18 years and written informed consent.
Exclusion criteria	Exclusion criteria were deep coma on admission (Glasgow coma scale 3 to 5), generalised seizure, acute sepsis, crush injury or disseminated intravascular coagulation, high risk of thrombosis, concomitant disability, patients having received vitamin K prior to admission to the investigational centre, known allergy to vitamin K, hypersensitivity to the active substances of 4-factor PCC (human coagulation factors II, VII, IX and X) or to any of its excipients (heparin and sodium citrate), known allergy to heparin or history of heparin induced thrombocytopenia, participation in another clinical study currently or during the past three months, pregnancy or breast feeding.

Recruitment/selection of patients	Between November 2008 and April 2011, 59 patients were included and randomised. Almost all patients were (n=53) were admitted in intensive care units, one in a neurology unit and one in a neurosurgery unit.		
Age, gender and ethnicity		25 IU/KG (n=29)	40 IU/KG (n=30)
	Age (mean, SD):	77.7 (9.4)	75.2 (11.1)
	Male (No., %):	19 (65.5)	23 (76.7)
	INR:	2.9±1.1	3.2±1.9
Further population details	All patients were treated with vitamin K antagonist: 85% were under oral anticoagulant with fluindione, 12% with warfarin sodium and 3% with acenoumarol.		
Indirectness of population	No indirectness		
Interventions	25 IU /kg body weight of 4-factor PCC (low dose) (octaplex) 40 IU /kg body weight of 4-factor PCC (high dose) (octaplex) Note: The study treatment is a human plasma-derived concentrate that contains vitamin K dependent clotting factors II, VII, IX and x as well as protein C and S. The product also contained heparin and citrate added during the manufacturing process. The treatment was administered immediately in an emergency setting after randomisation and usually before any INR results were available. All patients were treated concomitantly with IV infusion of 5 mg vitamin K. A PCC rescue dose was administered if the targeted INR (<1.5) was not reached, 10 minutes after the end of the infusion. An additional infusion of 4-factor PCC was allowed at intervals of 6 hours after the administration of the first dose, if the INR remained >2.		
Funding	Octapharma Pharmazeutica		
Outcomes	Adverse events Thromboembolic events Mortality Mean INR at 10 minutes after the end of 4-factor PCC infusion in each group. Changes in INR, PT, coagulation factors.		

	Follow-up: 30 days after the infusion

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : PCC LOW DOSE VERSUS PCC HIGH DOSE

	25 IU/kg (n=29)	40 IU/kg (n=30)
Mortality, n (%)	4 (13.)	6 (20); p=0.731
Patients with at least one adverse event, n (%)	24 (82.8)	25 (83.3)
Patients with at least one serious adverse event, n (%)	11 (37.9)	12 (40)
Patients with at least one thrombotic event, n (%)	2 (6.9)	2 (6.7)

At 10 minutes after 4-factor PCC infusion, median INR was significantly reduced to 1.2 (range 1 to 1.5), declining to <1.5 in all patients in both groups.

A target INR, defined as INR <1.2 was achieved in 44.5% of the 25 IU/kg group and in 76% of the 40 IU/kg group.

Significant differences were found between dose groups for PT (P=0.038) at 10 minutes after infusion. A dose of 40 IU/kg tended to be more effective in normalising PT and coagulation factors than a 25 IU/kg dose.

Risk of bias: High

Protocol outcomes not reported by the study:

Occurrence of bleeding (WHO grade 2 and above or equivalent), Cessation of bleeding in bleeding patients, Quality of life , Infections (for example, pneumonia), Number of patients needing red cell transfusions, Number or volume of red cells transfused, Length of stay (hospitalisation)

Study	**Khorsand 2012[82]**
Study type	Observation two cohort study
Number of studies (number of participants)	n=1 (n=240)
Countries and setting	The Netherlands; setting: hospital
Line of therapy	1st line

Duration of study	November 2007 to July 2010		
Method of assessment of guideline condition	Adequate method of assessment/diagnosis		
Stratum	Adults		
Subgroup analysis within study	Not applicable		
Inclusion criteria	Patients were eligible for inclusion if reversal of vitamin K antagonist (VKA) treatment with Prothrombin Complex Concentrate (PCC) was indicated for major or clinically relevant, non-intracranial bleeding.		
Exclusion criteria	Patients with an indication for PCC because of intracranial bleeding event, an urgent invasive procedure, and patients not using VKA treated with PCC were excluded.		
Recruitment/selection of patients	Not stated		
Age, gender and ethnicity		Fixed dose (n=101)	Variable dose (n=139)
	Age (median IQR):	77 (37-95)	79 (23-98)
	Male (No., %):	50 (50%)	71 (51%)
	Concomitant other antithrombotic agents, n(%):	22 (22%)	34 (24%)
	History of bleeding, n (%):	26 (26%)	46 (33%)
	Baseline INR, median (range):	5.1 (1.54->7.6)	5.9 (1.80->7.6)
Further population details	Both cohorts were comparable with regard to age, gender, weight, relevant co-medication and the indication for VKA treatment. In both cohorts, the VKA phenprocoumon was the most commonly used (88% VS. 84% of patients in the fixed dose and the variable dose cohort, respectively).		
Indirectness of population	No indirectness		
Interventions	Fixed dose PCC (1040 IU) vs. Variable dose PCC regime Variable dosing regimen - median PCC dosage per patient was 1,560 IU FIX (range 520-3120) (Cofact) *variable dose regime based on patient body weight, baseline INR, and target INR. In case of a high INR after treatment, deterioration in patient condition, or an on-going bleeding event- all patients received 10 mg vitamin k intravenously along with PCC infusion. Cofact used as PCC. This factor contains factors II, VII, IX and X. Cofact does not contain either activated factors or		

	heparin. Note: Dosage used in the fixed dose cohort was 1040 IU F IX and non-adherence to this dosage occurred in 32 (32%) patients. Of these 29 patients had a lower dose than the fixed dose, with a median of 520 IE and 3 patients received a higher dose (n=1, 1300 IE; n=2, 1560 IE)
Funding	Sanquin BV
Outcomes	Number of patients reaching the target INR rate (INR <2.0) at 15 minutes after PCC treatment. Mortality Stopping of visual bleeding Further PCC or blood transfusion Bleeding complications Deep vein thrombosis (DVT) Pulmonary embolism (PE) Myocardial infarction (MI) Ischaemic cerebrovascular events Follow-up: 10 days

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : FIXED DOSE PCC VERSUS VARIABLE DOSE PCC

In the fixed dose cohort, median INR declined from 5.1 at baseline to 1.5; in the variable dose cohort, from INR 5.9 to 1.4 after PCC treatment

	Fixed dose (n=101)	Variable dose (n=139)
Target INR reached, n (%)	88 (91.7%)	124 (94.7%)
PCC dosage , median (range)	1040 (260-1560)	1560 (520-3120); p<0.001
INR after PCC , median (range)	1.48 (1-2.94)	1.40 (0.9 -3.40); p=0.018
DVT, (n)	0	1
Mortality from thromboembolic complication	1	1
All-cause mortality	14	36
Fatal bleeding events	2/14	8/36

Risk of bias: High

Protocol outcomes not reported by the study:
Quality of life , Infections (for example, pneumonia), Serious adverse events (as defined by study), Adverse events related to the transfusion, Number of patients needing red cell transfusions, Number or volume of red cells transfused, Length of stay (hospitalisation)

Study	**Vannart 2006[177]**		
Study type	Open, prospective RCT		
Number of studies (number of participants)	n=1 (n=93)		
Countries and setting	Netherlands; setting: hospital		
Line of therapy	1st line		
Duration of study	October 1998 to march 2000		
Method of assessment of guideline condition	Adequate method of assessment/diagnosis		
Stratum	Adults		
Subgroup analysis within study	Not applicable		
Inclusion criteria	Patients were eligible if they were on OAT (oral anticoagulant therapy) (either acenocoumarol or phenprocoumon), had an INR >2.2, had a bleeding or indication for an urgent intervention, were >18 years and weighed <100 kg.		
Exclusion criteria	Hepatic insufficiency, anaemic anaphylactic reaction after administration of a blood product, disseminated intravascular coagulation, active thrombosis/pulmonary embolism, artificial heart valve, pregnancy and breast feeding.		
Recruitment/selection of patients	Between October 1998 and March 2000, 93 patients with an indication for acute reversal of OAT (oral anticoagulant therapy) were studied in Denventer Hospital		
Age, gender and ethnicity		Standard dose (500 IU FIX) (n=47)	Individualised dosing regimen (n=46)
	Age (years):	75 (8.7)	71.1 (11.8)
	Male (No., %):	21 (45%)	29 (63%)
	Weight in (kg)	70.8	72.5
Further population details		Standard dose (500 IU FIX) (n=47)	Individualised dosing regimen (n=46)
	Bleed	15 (31.9%)	22 (47.8%)

	Urgent interventions	32	24
	Target INR <2.1	15	13
	Target INR <1.5	32	33
Indirectness of population	No indirectness		
Interventions	Single dose of 20 ml of PCC (corresponding with a dose of 500 IU FIX or about 7IU FIX/kg) (n=47)(standard dose) Dose taking in to account the target INR* and the body weight of the patient (individualised dosing regimen)(n=46) Target INR- 1.5 was set for major bleeding e.g. in the digestive tract or the CNS and urgent surgical interventions. Target INR 2.1 was set for small urgent interventions, and for minor bleedings such as epistaxis or haematuria.		
Funding	Not stated		
Outcomes	Target INR at 15 minutes after the first dosage of PCC Serious adverse events		

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON : STANDARD DOSE PCC VERSUS INDIVIDUALISED DOSING REGIMEN FOR PCC

	Standard dose (500 IU FIX) (n=47)	Individualised dosing regimen (n=46)
Target INR at 15 minutes after the first dosage of PCC, n (%)	20 (42.6%)	41 (89%)
Serious adverse events	2	2

APTT was increased in nearly all patients before and normalised after the administration of Cofact.

Risk of bias: High

Protocol outcomes not reported by the study:

Occurrence of bleeding (WHO grade 2 and above or equivalent), Cessation of bleeding in bleeding patients, all-cause mortality at 30 days, Quality of life , Infections (for example, pneumonia), Serious adverse events (as defined by study), Adverse events related to the transfusion, Number of patients needing red cell transfusions, Number or volume of red cells transfused, Length of stay (hospitalisation)

H.8 Monitoring for acute reactions

None

H.9 Electronic decision support

Study	Adams et al., 2011[3]				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Adams et al., 2011[3] Study design: Retrospective cohort study. Before and after study Aim of study: to evaluate the effectiveness of timely provision of evidence based recommendations thorough computerised physician order entry system and alerts in reducing the red blood cell transfusions in children. Comparison:	Patient group: Children Inclusion criteria: Children aged between 1 month and 18 years for which a red blood cell transfusion (RBCT) prescription was written (including both stable, critically ill children and non-critically ill children). Exclusion criteria: Patients on haematology/oncology wards, cardiac wards and the NICU. Group 1 – Computerised physician order entry	Group 1 Intervention: Computerised physician order entry system (CPOE) alert. Alert generated before RBCT prescription order completion if the patient was normotensive for >6h before order and Hb level >7 g/dl. No alert was generated for patients if hypotensive or Hb level<7 g/dl Group 2 Control: no alert generated by the CPOE if	Proportion of inappropriate transfusions	Not reported	Funding: Not mentioned. No relevant financial disclosure to report Limitations: • non-randomised retrospective observational study • matched controls not used • groups not comparable at baseline (difference in pre-transfusion haemoglobin levels) • no mention of whether non-electronic decision support systems were used (e.g. checklists)
			Proportion of patients transfused (rate of RBCTs per patient day):	Group 1: 0.050 (0.019) 95% CI 0.038-0.062) Group 2: 0.076 (0.035) 95% CI 0.053-0.098) Acute care wards: Group 1: 0.017 (0.007) 95% CI 0.01-0.02 Group 2: 0.033 (0.01) 95% CI 0.02-0.04 RR: 0.66 (95% CI 0.57-0.78) PICU: Group 1: 0.14 (0.04) 95% CI 0.11-0.17 Group 2: 0.2 (0.11) 95% CI	

Electronic decision support system (computerised alert generated for blood ordering)vs. Control (no alert generated by ordering system) Setting: Paediatric intensive care unit (PICU) and acute care wards (quaternary care, Children's Hospital, California, US). Duration of follow-up: Control period between February 1, 2008, and January 31, 2009. Intervention period between February 1, 2009, and January 31, 2010. Follow up: inpatient stay	system (CPOE) alert n=3492 Age in years (mean SD): 7.18 (6.2) Female: 1694 (48.5%) Drop outs: Not reported Group 2 - Control (no alert generated) n=3294 Age in years (mean SD): 7.16 (6.1) Female: 1505 (45.7%) Drop outs: Not reported Age, gender and race not statistically different between groups. There was a significant difference in the patients admitted for diseases of the circulatory system; ear, nose, mouth and throat; respiratory system; and endocrine, nutritional and metabolic disorders.	parameters outside thresholds. Historical control group.		0.13-0.27 RR: 0.81 (95% CI 0.74-0.89)	• no mention of clinician adherence to decision support; no details of percentage of clinician who complied with decision support system • no follow-up after discharge Additional outcomes: • Diagnostic categories of patients during control and intervention periods • Case-mix index (based on centre medicare cost weights) assessed to determine severity of illness during control and intervention periods Notes:-
			Number of units transfused	Not reported	
			Hospital length of stay (days, mean SD)	Group 1: 8.07 (23.4) Group 2: 9.73 (24.3) (P=0.002 as reported in paper) Acute care wards Group 1: 6.8 (22.4) Group 2: 7.9 (21.7) (P=0.06 as reported in paper) PICU Group 1: 11.5 (25.8) Group 2: 16.4 (31.3) (P=0.0002 as reported in paper)	
			Quality of life	Not reported	
			Mortality (represented as rate per patient)	Group 1: 0.016 (0.03) Group 2: 0.023 (0.04)	
			Pre-transfusion haemoglobin levels (mean SD). Subgrouped into ICU and acute care wards	Acute care wards Group 1: 7.1(0.07) g/dl Group 2: 7.5 (0.04) g/dl (P<0.0001 as reported in paper) PICU	

				Group 1: 8.7 (0.07) g/dl Group 2: 9.83 (0.09) g/dl (P<0.0001 as reported in paper)	

Abbreviations: SD: Standard deviation; RBCT: Red blood cell transfusion; CPOE : Computerised physician order entry ; ICU: Intensive Carer Unit; PICU: Paediatric Intensive Care Unit, Hb: Haemoglobin

Study	**Chang et al., 2011[25]**				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Chang et al., 2011[25] Study design: Retrospective cohort study. Electronic decision support blood order system and review of clinical hospital information system in same cohort of patients to determine proportion of inappropriate transfusions Aim of study: To investigate physician compliance and appropriateness of fresh frozen plasma (FFP) use by using a computerised transfusion decision support system (CTDSS).	Patient group: All transfusion episodes within study period reviewed retrospectively. Inpatients Inclusion criteria: • All fresh frozen plasma transfusion episodes between January 2008 and December 2008 • Indications for use of FFP included pre-defined criteria laid down by the transfusion committee. Exclusion criteria: • Episodes of transfusion for these indications were excluded: • Transfusions for plasma exchange	Computerised transfusion decision support system (CTDSS) used. Physician selects indication for fresh frozen plasma (FFP) transfusion before completing order. Criteria for FFP transfusion were pre-defined by the committee. An appropriate transfusion order was defined as a blood product ordered with an indication that satisfies the criteria. Each FFP request was classified as 'indicated', 'not indicated', and	Proportion of inappropriate transfusions	6779/9931 transfusion episodes evaluated (68.5%) Inappropriate transfusion episodes include: 5492 episodes (55.3%) classified as not indicated as did not meet transfusion criteria 1307 episodes (13.2%) classified as unknown indication because there were not sufficient results to make a decision regarding transfusion)	Funding: Not reported Limitations: Non-randomised study with no control group Additional outcomes: • Pre- and post-transfusion INR and aPTT ratio, used to calculate therapeutic efficacy of transfusion. • Adherence (11.8% of transfusions performed without choosing an indication when ordering and 34.7% selected indication of abnormal coagulation test results although patients showed normal coagulation,
			Proportion of patients transfused.	Not reported	
			Number of units transfused	Not reported	
			Hospital length of stay	Not reported	

Comparison: Clinical hospital information system review (appropriateness of transfusion according to local guidelines) Setting: Medical University Hospital, Taiwan Duration of follow-up: 1 year retrospective review (January 2008 and December 2008)	• Massive transfusion with blood volume exceeding 1 total blood volume • Emergency heart surgery or operations without aPPT or PT tests • n=10,926 transfusion episodes (9931 transfusion episodes after applying exclusion criteria)	'unknown indication'.	Quality of life	Not reported	results not shown) Notes: Assessment of appropriateness of transfusion by reviewing clinical hospital information system could be limited by incomplete documentation
			Mortality	Not reported	
			Pre-transfusion haemoglobin levels/platelet count/coagulation result	Not reported	

Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Chen 2015 Study design: Retrospective review Aim of study: To understand why providers order blood	Patient group: Inpatient healthcare providers Inclusion criteria: Not stated Exclusion criteria: Not stated	Provider –best alert practice (BPA) interaction data were collected from January 2011 to August 2012 from the hospital electronic medical record. When an order for red blood cell transfusion is attempted, the EMR	Proportion of inappropriate transfusions	Not reported	Funding: Not reported Limitations: -Does not entirely meet the protocol criteria -No pre-defined inclusion/exclusion criteria reported.
			Proportion of patients transfused.	Not reported	
			Number of units transfused (mean±SD)	Not reported	
			Hospital length of stay (mean±SD) days	Not reported	
			Quality of life	Not reported	

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
transfusions outside of recommended guidelines despite interruptive alerts. Comparison: Not applicable Setting: Tertiary Care Hospital Duration of follow-up: 8 months after the implementation period.		(Electronic Medical Record) systems evaluate the patient chart for specific criteria based on previously published guidelines. Specifically the BPA reviews the last recorded Hgb value and trigger if the Hgb is >8, or if Hgb is >7 and there is no concurrent EMR problem list entry related to acute coronary syndrome or acute haemorrhage. Once the blood transfusion BPA triggers, the ordering provider is presented with an interruptive prompt reminding them of best practice guidelines and the 3 most recent Hgb values for the patient. Then the provider may either abort the transfusion or override the BPA and proceed. Overrides require the provider to select a reason from a pre-defined list of institutionally accepted	Mortality (30 days) Pre-transfusion haemoglobin levels for all patients , g/dl Non-protocol outcomes: • The ordering provider proceeded to override the BPA and continued with transfusion in 98% of cases (10,442/10, 642) • Resident physicians were the primary ordering provider group, accounting for approximately 55% (5863/10,642) of BPA interactions, followed by registered nurses, fellows, and attending physicians.	Not reported Not reported	Notes: No protocol outcomes reported.

Study details	Patients	Interventions	Outcome measures	Effect size	Comments
		transfusion indications including 'acute bleeding', 'acute coronary syndrome' and Hgb <8, and 'post-operative cardio thoracic surgery and Hgb>8'. If none of the pre-defined override reasons are selected, the provider selects 'other', with the option of a free-text comment to elaborate their rationale.	• Acute bleeding was the most common structured response (34%) • The majority of BPA overrides used the general purpose 'other' structured response option accounting for 56% (5886/10,442) of override responses, of which 37% (2185/5886) entered a free text comment elaborating the override reason. With 3701 'non responders', the overall response rate was 65%.		

Study	Fernandez Perez et al., 2007[58]				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Fernandez Perez et al., 2007[58] Study design: Retrospective cohort study. Before and after study in 2 separate group of patients. Aim of study: To evaluate if implementation of a computerised physician order entry decision support system for critically ill patients decreases the rate and cost for RBC transfusions. Comparison: Placebo: no decision support on ordering system Setting: Three multidisciplinary ICUs (medical, surgery and mixed), Minnesota, US Duration of follow-up:	Patient group: Critically ill patients (Adults) Inclusion criteria: Consecutive critically ill patients with anaemia (Hct<30%) from three ICUs (medical, surgery and mixed) Exclusion criteria: - Patients with admitting diagnosis of bleeding - Patients undergoing massive transfusion (>10units) Group 1 – Before decision support n=1100 Age in years (median and IQR): 65 (53-75) Female: 539 (49%) Drop outs: Not reported Group 2 – After decision support n=1100 Age in years (median and	Group 1-Before decision support Control – before introduction of decision support (existing transfusion electronic order system) Group 2- After decision support Decision support for RBC transfusion. Decision support algorithm justified RBC transfusion if Hb >7 g/dl in the presence of active bleeding, ischaemia or early septic shock. No other thresholds mentioned	Proportion of inappropriate transfusions	Not reported	Funding: Not mentioned Limitations: • No mention of whether non-electronic decision support systems were used (e.g. checklists) • No mention of blinding • No mention of clinician adherence to decision support • No follow-up after discharge Additional outcomes: • Cost of RBC transfusions • APACHE III score (acute physiology and chronic health evaluation) • APACHE III predicted mortality • ICU length of stay • ICU mortality Notes: • No mention of statistical methods
			Proportion of patients transfused.	Group 1: 53% Group 2: 48% P = 0.013 (as reported in paper)	
			Number of units transfused (mean no. per patient)	Group 1: 1.5 (1.9) Group 2: 1.3 (1.8) P = 0.045 (as reported in paper)	
			Hospital length of stay (days, median IQR)	Group 1: 9.3 (6-17) Group 2: 9.5 (5-17)	
			Quality of life	Not reported	
			Mortality (Hospital mortality)	Group 1: 108 (9.8%) Group 2: 139 (12.6%)	
			Pre-transfusion HAEMATOCRIT % median IQR (Pre-transfusion value for transfused patients but lowest value during ICU stay for non-transfused)	Group 1: 26.5 (24-28) Group 2: 26.6 (24-28)	

Control period between May 2003 and April 2004. Intervention period between January 2005 and December 2005. Follow up: inpatient stay	IQR): 65 (54-76) Female: 524 (48%) Drop outs: Not reported				used • Age, haematocrit%, ICU length of stay and hospital length of stay all reported as median (IQR). • Same study as Rana et al., 2006 paper (see below). The 1 year control and intervention periods include the 3 month control and intervention periods reported in the other paper. Same ICU wards at Mayo Clinic Rochester Hospitals, Minnesota, US

Study	**Goodnough et al., 2014[65]**				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Goodnough et al.;2014[65] Study design: Before and after implementation study Aim of study: To evaluate the effect of a computerised decision support system intervention	Patient group: Stable medical and surgical (post-operative) adults receiving blood transfusions	Group 1 Intervention - decision support (DS) on the computerised physician order entry (CPOE) for blood transfusions. Decision support was based on local evidence-based guidelines for the transfusion of RBCs,	Proportion of inappropriate transfusions (retrospective medical chart review for orders that do not satisfy the guidelines (disagree with DS) and orders incorrectly evaluated as DS-agree as estimated from random sample chart review of DS-agree orders)	Not reported	Funding: Not reported Limitations: Non- randomised before and after study Additional outcomes: -

Setting: Academic medical centre, tertiary care hospital, Stanford, California, US Duration of follow-up: • Phase 1: 1 year baseline; new set of evidence based guidelines educational program preceded the intervention, new guidelines disseminated to physicians • Phase 2: Followed by post-educational phase and 6 months intervention phase. • Phase 3: Follow up phase for more than 3 years after intervention to study sustainability and impact of intervention phase		platelets and FFP (Phase 2 and 3) Group 2 Control group where CPOE and DS was not used for ordering blood for transfusions.	Proportion of patients transfused.	Group 1: 17% Group 2: 21.9%	Notes:-
			Number of units transfused	Group 1: 22,991 units Group 2: 30, 194 units	
			Hospital length of stay	Significant improvement reported in Group1	
			Quality of life	Not reported	
			Mortality	Significant improvement reported in Group1	
			Pre-transfusion haemoglobin levels/platelet count/coagulation result	Not reported	

Study	**Goodnough 2014B**				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Goodnough 2014B	Patient group: Adults and Children	To improve transfusion appropriateness at Stanford Hospital and Clinic, Clinical decision	Proportion of inappropriate transfusions	Since the implementation of BPA in July 2010, the percentage of transfusions in patients with pre-	Funding: Not reported

Study	Goodnough 2014B				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Study design: Before and after study Aim of study: To review clinical decision support (CDS) via electronic medical records (EMRs) Comparison: Not applicable Setting: Hospital (Stanford Hospital and Clinics) Duration of follow-up: Not stated	Inclusion criteria: Not stated Exclusion criteria: Not stated	support (CDS) was implemented. An alert triggered when a provider ordered RBCs in a patient with pre-transfusion haemoglobin level above a set threshold (7g/dl for most and 8 g/dl for patients with acute coronary syndrome or post-cardio-thoracic procedure).		transfusion haemoglobin level greater than 8g/dl decreased from 60% to 35% in the 6 months after BPA, with a sustained downtrend to below 30% by 2013 (p<0.001). In absolute terms, CDS reduced annual RBC transfusions by 24%, despite concurrent increases in patient discharge volumes and case mix complexity.	Limitations: -Non-randomised study with no control group
			Proportion of patients transfused. (RBC transfusions)	2008: 29,472 2009: 30,194 2010: 25,304 2011:23,136 2012: 23,008 2013: 22,991	
			Number of units transfused (mean±SD)	Mean number of RBC units received by transfused patients was lower after implementation of BPA (P=0.001)	
			Hospital length of stay days (per 1000 discharges)	2008: 5.79 2009: 5.63	

Study	Goodnough 2014B				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
				2010: 5.55 2011:5.52 2012: 5.59 2013: 5.49 p<0.05	
			Quality of life	Not reported	
			Mortality (30 days) (per 1000 discharges)	2008: 28.3 2009: 28.1 2010: 25.9 2011:25.3 2012: 25.5 2013: 24.4 p<0.05	
			Pre-transfusion haemoglobin levels for all patients , g/dl	There was no difference in admission Hb levels (p=0.11), discharge Hb levels showed a significant (p=0.006) downward trend.	

Study	Hibbs et al.; 2014[71]				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**

Author & Year: Hibbs et al.; 2014[71] Study design: Before and after implementation study Aim of study: To evaluate the effect of a computerised decision support system intervention on blood transfusions. Setting: Nuffield orthopaedic centre, Oxford University Hospitals NHS Trust, UK Duration of follow-up: • Phase 1: 5 month pre-implementation period where blood ordering was implemented without decision support system (DSS) • Phase 2: 5 month period where DSS was implemented without use of ERBI • Phase 3: 5 month period where DSS and ERBI were both implemented.	Patient group: Adults receiving blood transfusions in specialised orthopaedic hospital	Group 1 Intervention - decision support system (DSS) on the computerised physician order entry (CPOE) for blood transfusions. Decision support was based on local evidence-based protocols (Phase 2) Group 2 Intervention - decision support system (DSS) on the computerised physician order entry (CPOE) for blood transfusions followed by electronic remote blood issue (ERBI). (Phase 3) Group 3 Control group where CPOE and DS was not used for ordering blood for transfusions (Phase 1)	Proportion of inappropriate transfusions (transfusions were deemed non-compliant if the pre-transfusion level was ≤80 g/litre)	Group 1: 30 (50.8%) Group 2:21(35%) Group 3:47 (55.3%)	Funding: Not reported Limitations: Non- randomised before and after study Additional outcomes: - Notes:-
			Proportion of patients transfused	No significant difference in proportion of single unit transfusions given across the three time periods	
			Number of units transfused (total)	Group 1: 37 Group 2: 38 Group 3: 55	
			Hospital length of stay	Not reported	
			Quality of life	Not reported	
			Mortality	Not reported	
			Pre-transfusion haemoglobin levels	Group 1: 7.67 g/dl Group 2:8.25 g/dl Group 3:8.22 g/dl	

Study	**Lin et al., 2010 [93]**				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Lin et al., 2010 [93]	Patient group: Adults and children	Computerised transfusion decision support system (CTDSS).	Proportion of inappropriate transfusions	1751/5754 (30.4%)	Funding: Not reported

Study design: Retrospective cohort study. Electronic decision support blood order system and review of clinical hospital information system in same cohort of patients to determine proportion of inappropriate transfusions Aim of study: Investigate physician compliance and appropriateness of platelet use by using a computerised transfusion decision support system (CTDSS). Comparison: Clinical hospital information system review (appropriateness of transfusion according to local guidelines) Setting: Medical University Hospital, Taiwan Duration of follow-up: Review of transfusion episodes between January and December 2008.	Inclusion criteria: All platelet (PLT) transfusion episodes between January 2008 and December 2008 Exclusion criteria: Transfusion episodes without PLT count data within one week before transfusion (for appropriateness of PLT usage). n=5887 transfusion episodes (5754 after exclusion criteria applied) Age in years (mean): Not reported Female: 2407 (40.9%) Drop outs: Not reported	Physician choice from criteria for platelet transfusion before completing order: (1) PLT count of $20x10^9$/litre or less, (2) patients with bleeding and PLT count of $50x10^9$/litre or less, (preparation for surgery and PLT count of $80x10^9$/litre or less, (4) brain, eye or heart surgery and PLT count of $100x10^9$/litre or less, (5) PLT dysfunction, (6) thrombocytopenia, (7) others.	Proportion of patients transfused.	Not reported	Limitations: Non-randomised study with no control group. Additional outcomes: -Physician compliance Reason for PLT use from CTDSS Post-transfusion PLT increment Factors associated with appropriateness (Patient source, episode classification and disease classification)
			Number of units transfused	Not reported	
			Hospital length of stay	Not reported	
			Quality of life	Not reported	
			Mortality	Not reported	
			Pre-transfusion platelet count	No data: 133 (2.3%) $\leq 10x10^9$/litre: 759 (12.9%) $>11x10^9$/litre to $\leq 20x10^9$/litre: 1463 (24.9%) $>21x10^9$/litre to $\leq 50x10^9$/litre: 1877(31.9%) $>51x10^9$/litre to $\leq 80x10^9$/litre: 834 (14.2%) $>81x10^9$/litre to $\leq 100x10^9$/litre: 282 (4.8%) $>100x10^9$/litre: 539 (9.2%)	

Study	Pentti et al., 2003[125]				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Pentti et al., 2003[125] Study design: Prospective cohort study. Before and after implementation of decision support (with third phase – cessation of decision support period) Comparison: Control: no alert generated by online ordering system Setting: Medical-surgical ICU, Helsinki University Hospital, Finland Duration of follow-up: Control period: January-March 2001 (3 month) Intervention period: April-June 2001 (3 month) Control period (cessation of decision support): July-September 2001 (3 month)	Patient group: Adults Inclusion criteria: Consecutive patients admitted to medical-surgical ICU and received at least one transfusion of RBCs, FFP or platelets Exclusion criteria: Group 1 – n=93 Age in years (median IQR, only reported for transfused patients in group 1): 54 (44.5-64.0) Drop outs: Not reported Group 2 - n=105 Age in years (median IQR, only reported for transfused patients in group 2): 55 (42.5-69) Drop outs: Not reported Group 2 - n=92 Age in years (median IQR,	Group 1 Online ordering system for RBCs, FFP and platelets alerts the prescriber if the pre-defined transfusion criteria are not met. Recommended transfusion thresholds for non-bleeding patients used in the study: haemoglobin concentration <80 g/litre for RBCs; thromboplastin time (TT-%) <30 for FFP; platelet count <30x10^9/litre for platelets. Group 2 Control: no alert generated by online ordering system Group 3 Control: cessation of decision support following intervention phase	Proportion of inappropriate transfusions (assessed retrospectively by reviewers)	RBC transfusion episodes: Group 1: 20/259 (8%) Group 2: 90/228 (39%) Group 3: 37/126 (29%) Platelet transfusion episodes: Group 1: 4/23 (17%) Group 2: 24/54 (37%) Group 3: 6/18 (33%) FFP transfusion episodes: Group 1: 3/56 (5%) Group 2: 45/87 (52%) Group 3: 13/38 (34%)	Funding: Not mentioned Limitations: • No mention of blinding • Short follow-up – length of inpatient stay Additional outcomes: • Transfusion decisions according to predefined trigger values. • Pre-transfusion laboratory values Notes: • Baseline demographics not statistically different between non-transfused patients, and transfused patients in all 3 groups • Mortality and age only reported separately for each group for transfused patients, and for all groups in non-transfused patients.
			Proportion of patients transfused (RBC, platelet or FFP transfusion).	Group 1: 53/93 Group 2: 49/105 Group 3: 36/92	
			Number of units transfused	Values given only for total units transfused for RBCs, platelets and FFP across all groups.	
			Hospital length of stay	Not reported	
			Quality of life	Not reported	
			Mortality (only reported for transfused patients for each group separately and for non-transfused patients from all groups)	Transfused patients: Group 1: 19/53 Group 2: 16/49 Group 3: 11/36 Non-transfused patients	

	only reported for transfused patients in group 3): 57.5 (39.5-69.75) Drop outs: Not reported			(all groups): 29/152	
			Pre-transfusion haemoglobin levels preceding RBC transfusions (median IQR)	Group 1: 76 (67-88) Group 2: 80 (75-90) Group3: 78 (73-89)	

Study	**Rana et al., 2006[132]**				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Rana et al., 2006[132] Study design: Retrospective cohort study. Before and after study Aim of study: To compare rates of RBC transfusions and proportions of patients receiving transfusions after implementing a computerised provider order entry (CPOE) decision support system. Comparison: Placebo: no decision support on ordering system Setting: Multidisciplinary ICUs (medical, surgery &	Patient group: Adults Inclusion criteria: Consecutive critically ill patients with anaemia (haemoglobin <10g/dl) admitted to medical, surgical and mixed ICU wards) Exclusion criteria: Patients who denied research authorisation Group 1 - Before implementation of CPOE n=440 Age in years (median IQR): 67 (53-76) Female: 216 (49%) Drop outs: Not reported Group 2 –After	**Group 1** Control – before introduction of decision support **Group 2** Decision support for RBC transfusion. Decision support algorithm justified RBC transfusion if Hb <7 g/Dl or Hb >7 g/dl in the presence of active bleeding, ischaemia or early septic shock. Algorithm for decision support designed by local physicians and endorsed by institutional committees. Communicated to physicians and incorporated into CPOE	Proportion of inappropriate transfusions (classified as transfusion episode when pre-transfusion haemoglobin level was >7 g/dl in the absence of active bleeding, early septic shock or ischaemia. Electronic medical records reviewed for patients with pre-transfusion >7 g/dl)	Group 1: 73 (16.7%) Group 2: 11 (2.7%) (P<0.001 as reported in paper)	Funding: GAN recipient of grant from Bayer Pharmaceuticals and Stryker Limitations: • No mention of blinding • Short follow-up – length of inpatient stay Additional outcomes: • APACHE III score (acute physiology and chronic health evaluation) • Pre-transfusion haematocrit % • Number/rate of transfusion complications • ICU length of stay • ICU mortality • ICU free days
			Proportion of patients transfused	Group 1: 281 (63%) Group 2: 198 (49%) (p<0.001 as reported in paper)	
			Number of units transfused (mean no. of RBC transfusions per ICU admission)	Group 1: 1.08 (2.3) Group 2: 0.86 (2.3) (P < 0.001 as reported in paper)	

mixed), tertiary care hospital, US Duration of follow-up: Control period between January 1, 2004 and April 1, 2004 (3 months). Intervention period between January 1, 2005 and April 1, 2005 (3month). Follow up: inpatient stay	implementation of CPOE n=403 Age in years (median IQR): 66 (53-77) Female: 171 (42%) Drop outs: Not reported	on November 15, 2004.	Hospital length of stay (reported as adjusted for severity adjusted)	Not reported (ICU length of stay was reported)	• Silent cardiac ischaemia (troponin T elevation) • Transfusion related acute lung injury and circulatory overload • Allergic reactions Notes: • Hospital mortality odds ratio adjusted for severity (APACHE III predicted mortality). • Age, haemoglobin and ICU length of stay all reported as median (IQR). • Same study as Fernandez Perez et al., 2007 paper (see above). The 3 month control and intervention periods fall within the 1 year control and intervention periods reported in the other paper. Same ICU wards at Mayo Clinic Rochester Hospitals, Minnesota, US.
			Quality of life	Not reported	
			Mortality (hospital mortality)	Group 1: 52 (11.8%) Group 2: 59 (14.6%) Odds ratio (when adjusted for APACHE III predicted mortality as reported in paper): 1.12 (95% CI 0.69-1.8)	
			Pre-transfusion haemoglobin levels g/dl (median IQR) (Pre-transfusion value for transfused patients but lowest value during ICU stay for non-transfused patients)	Group 1: 8.7 (8.1-9.3) Group 2: 8.5 (7.8-9.2)	

Study	Razavi 2014				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Razavi 2014 Study design: Before and after study Aim of study: To compare transfusion practice in a cardiothoracic surgery division and among individual cardiothoracic surgeons before and after implementation of a novel single-view clinical decision support (CDS) tool within computerised provider order entry (CPOE) coupled with a provider feedback loop. Comparison: Transfusion CDS tool before and after implementation	Patient group: Adults (older than 18 years) Inclusion criteria: All adult patients (18 years or older) who underwent isolated coronary artery bypass grafting (CABG) or isolated surgical aortic valve replacement (SAVR) 1 year before and 1 year after implementation of a transfusion CDS tool. Exclusion criteria: Transfusion of uncross matched units were excluded from the study because orders for emergency release units bypass the normal ordering mechanism. Patients less than 18 years old and patients	The transfusion CDS TOOL was implemented within computerised provider order entry in the electronic health record of a multi-institutional urban hospital system, starting in Sep 2012 as part of an enterprise blood conservation initiative. The CDS tool made use of available but uncommonly used functionality within the electronic health record that enables a required form to be filled out once an order is placed. When a provider signed an order for PRBC, the CDS form showed a display. The provider had to complete the form or cancel the order. The CDS form provided most	Proportion of inappropriate transfusions	Not reported	Funding: Not reported Limitations: -Non-randomised study with no control group
			Proportion of patients transfused.	Not reported	
			Number of units transfused (Intra-operative PRBC units in all patients) (mean±SD)	Pre-intervention: 0.73±1.5 Post-intervention: 0.65±1.4	
			Number of units transfused (Post-operative PRBC units in all patients) (mean±SD)	Pre-intervention: 1.59±2.9 Post-intervention: 1.25±2.5	
			Hospital length of stay (mean±SD) days	Pre-intervention: 8.9±5.5 Post-intervention: 9.4±6.5	
			Quality of life	Not reported	
			Mortality (30 days)	Pre-intervention: 13 (1.8%) Post-intervention: 13 (1.7%)	
			Post-operative surgical site infection	Pre-intervention: 23 (3.1%) Post-intervention: 8 (1.1%)	

Study	Razavi 2014				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Setting: Hospital Duration of follow-up: Pre-intervention (Sep 1 2011 to August 31, 2012) and post-intervention (Sep 1, 2012 to August 31, 2013)	undergoing combination CABG and SAVR procedures were also excluded.	recent haemoglobin level as well as other pertinent vital signs (blood pressure, heart rate, central venous oxygen saturation. The provider had to indicate a major category for the requested blood transfusion reason (acute haemorrhage, anaemia, anticipated blood loss, and other). An other category was present to allow for transfusion in usual circumstances.	Post-operative transfusion events in CABG patients	Pre-intervention: 281 (46.8%) Post-intervention: 228 (37.1%)	
			Post-operative transfusion events in SAVR patients	Pre-intervention: 93 (65%) Post-intervention: 84 (56%)	
			Pre-transfusion haemoglobin levels for all patients , g/dl	Pre-intervention: 8.09±1.5 Post-intervention: 7.65±1.4	

Study	Rothschild et al., 2007 [138]				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Rothschild et al., 2007 [138] Study design:	Patient group: Adult Inclusion criteria:	Group 1 Intervention - decision support (DS) on the computerised physician	Proportion of inappropriate transfusions (retrospective medical	Transfusions prescribed by randomised junior housestaff: Group 1: 804 (59.6%)	Funding: Study funded by a National Heart, Lung and Blood Institute grant

RCT (Junior housestaff randomised to decision support or control, all other physicians in non-randomised group) Aim of study: To evaluate the effect of a computerised decision support system intervention Comparison: No decision support (DS) on CPOE system. All physicians received educational program prior to RCT on the new transfusion guidelines Setting: Academic medical centre, tertiary care hospital, Boston, US Duration of follow-up: • 3 month baseline (phase I) • New set of evidence based guidelines educational program preceded the RCT, new guidelines disseminated to physicians (2 months). • Followed by a 3 month post-educational	• Non-emergency inpatient transfusion • Exclusion criteria: • Orders generated from units in the hospital not using CPOE with DS. • Orders with urgent indications Number of patients not reported for intervention and control group in phase III separately (reported for phase I, II and III separately).	order entry (CPOE) for RBC, platelet and FFP. DS based on local evidence-based guidelines for the transfusion of RBCs, platelets and FFP. Orders matching the dose recommended by the guidelines were processed. Disagree-DS orders were offered a new recommended order that could be accepted or rejected. Rejected DS recommendations then required a reason. Group 2 Control group of junior housestaff and physicians not receiving DS feedback on CPOE system	chart review for orders that do not satisfy the guidelines (disagree with DS) and orders incorrectly evaluated as DS-agree as estimated from random sample chart review of DS-agree orders)	Group 2: 1043 (67.5%) Transfusions prescribed by non-randomised staff: Group 1: 708 (67.4%)	(RFA HL-01-011) Limitations: • Only junior housestaff randomised and blinded • Additional outcomes: • Inappropriate transfusions during baseline phase I and educational phase II (before DS). • Mean dose per transfused patient (mean for each phase, means for control and intervention groups in phase III not reported separately. Notes: • Junior housestaff (453) who ordered most transfusions were stratified by speciality and year of training into blocks and randomly assigned into control and intervention groups using a computerised program to generate the randomised scheme for each block. Junior housestaff not
			Proportion of patients transfused.	Not reported	
			Number of units transfused	Not reported	
			Hospital length of stay	Not reported	
			Quality of life	Not reported	
			Mortality	Not reported	
			Pre-transfusion haemoglobin levels/platelet count/coagulation result	Not reported	

phase (phase II) and 2 months DS reprogramming. • Intervention phase (phase III): 4 month DS intervention or control (reported in this table)					told to which group they were assigned. All other physicians (961) non-randomly. • Individual patients could receive a transfusion from one or more clinicians during an admission (that is, clinician in intervention or control group).

Study	**Scheurer et al., 2010** [142]				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Scheurer et al., 2010 [142] Study design: Retrospective study. Case control study/case series evaluation. Electronic decision support blood order system and chart review compared in same cohort of patients Aim of study: To evaluate the appropriateness of RBC transfusions (by chart review and computerised physician order entry decision support).	Patient group: General medical inpatients Inclusion criteria: General medical inpatients with haemoglobin >9 g/dl who received at least one transfusion of RBCs Exclusion criteria: Not reported n=214 blood transfusion events Age in years (mean):	Computerised physician order entry system (CPOE) with decision support: indicates whether transfusion according to local guidelines is warranted in non-bleeding cases and if yes, how many units are necessary to achieve the desired haematocrit. Clinicians could bypass entering the indication for transfusion by selecting 'active	Proportion of inappropriate transfusions (by chart review of all transfusions)	115/ 214 (54%)	Funding: Not mentioned Limitations: Before and after study with no control group; Additional outcomes: • Decision support bypassed • Reason for override of decision support Appropriateness between chart review and decision support
			Proportion of inappropriate transfusions by decision support system (deemed appropriate by chart review)	45/73 (62%)	
			Proportion of patients transfused.	Not reported	
			Number of units transfused	Not reported	
			Hospital length of stay	Not reported	

Comparison: Medical chart review (appropriateness of transfusion according to local guidelines) Setting: Tertiary care hospital, Boston, US Duration of follow-up: 1 year retrospective review (June 2005 – May 2006)	Drop outs:	bleeding/associated hypovolaemia'. Reason for overriding final decision inputted. Transfusions deemed inappropriate by first reviewer physician were subject to a 2 reviewer consensus by discussion.	Quality of life	Not reported	
			Mortality	Not reported	
			Pre-transfusion haemoglobin levels/platelet count/coagulation result	Not reported	

Study	**Yerrabothala et al.; 2014[189]**				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Yerrabothala et al.; 2014[189] Study design: Before and after implementation study Aim of study: To evaluate the effect of a computerised decision support system intervention on blood transfusions. Setting: Academic medical centre, tertiary care hospital, New Hampshire Duration of follow-up: • Phase 1: 6 month pre-	Patient group: Adults receiving blood transfusions	Group 1 Control group where CPOE and DS was not used for ordering blood for transfusions (pre-implementation period) Group 2 Intervention - decision support (DS) on the computerised physician order entry (CPOE) for blood transfusions. Decision support was based on local evidence-based protocols	Proportion of inappropriate transfusions (retrospective medical chart review for orders that do not satisfy the guidelines (disagree with DS) and orders incorrectly evaluated as DS-agree as estimated from random sample chart review of DS-agree orders)	In first month after implementation, alert fired 342 times and resulted in cancellation of blood order 83 times (24%)	Funding: Not reported Limitations: Non- randomised before and after study Additional outcomes: - Notes:-
			Proportion of patients transfused with 2 RBC units	Group 1:47% Group 2: 15%	
			Number of units transfused	Group 1: Not reported Group 2: Total	

implementation period • Phase 2: 6 month post implementation period -				number of RBC units decreased by 27% (number not reported)	
			Hospital length of stay	Same in Groups 1 and 2	
			Quality of life	Not reported	
			Mortality	Same in Groups 1 and 2	
			Pre-transfusion haemoglobin levels/platelet count/coagulation result	Not reported	

H.10 Electronic patient identification

Study	**Askeland 2008[9]**				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Askeland 2008[9] Study design: Before and after study Comparison: NA Setting: Teaching hospital and	Patient group: The hospital had 50, 00 inpatient admissions, 8,53,000 clinic visits, and 32,000 emergency trauma centre visits. Approximately 34,000 blood components are administered per year.	Group 1: Bar code technology, wireless network and devices: Previously embossed wristbands listing the patient's name, medical record number and date	Computerised Incident reports (CIR)	The number of CIRs regarding problems during the transfusion process dropped from a mean of 41.5 reports per month in the 6 months before the new system was implemented to a mean of 7.2 reports per month after the implementation (83%)	Funding: Not stated Limitations: The absence of a comparison group makes it impossible to know what would have happened without the intervention Notes: No relevant outcomes reported from

comprehensive health care centre Duration of follow-up: 6months		of birth were used to identify patients. The project team selected new wristbands and sample tube labels that were bar coded. A series of in-service educational sessions were conducted to familiarise staff members with the new wrist bands. The bar coded wrist bands were introduced between November 2003 and Feb 2004. The new wrist bands had several advantages including low cost, moisture resistance and comfort. The project team evaluated the reliability, ease of use, functionality and cost of a variety of devices designed to support the bar-code	Sample rejection rate	During 2003 the sample rejection rate was 1.82% again mostly due to ineligible handwriting, transposed medical record numbers, incorrect spelling of the patients name and absence of signatures on the requisition. The sample rejection rate fell to 0.17% after hospital wide implementation of the bar-code based system	the protocol Authors conclusion: The bar-coded computerised tracking system detected and prevented identification and matching errors, thereby reducing the proportion of blood samples rejected and increasing patient safety.
			Prevented Identification error (PIE)- PIE were recorded during any transaction when the mismatches were detected (and warnings generated) between the code labels on the patients wristband, blood sample, requisition, order card, blood product, or anaesthesiology record.	A total of 29 PIEs occurred during sample collection in the first 10 months with a range of 1 to 6 per month. A total of 60 PIEs occurred during the dispense transaction in the first 10 months with a range of 3 to 10 per month. A total of 10 PIEs occurred during the administer transaction in the first 10 months with a range of 0 to 4 per month.	
			Wrong blood or blood product	There were no instances in which a patient received the wrong blood or blood product.	

		based transfusion tracking system including scanners, notebook computers, wireless cards, label printers, and carts. Group 2: NA	Misidentification of an initial blood sample by the bar code system	One incident produced a harmful event. The end result was that a patient who was actually A+ received an O+ unit of RBSS. No transfusion reaction was recorded. This event occurred in the intensive care unit during the night shift shortly after the system was activated. The staff members were using the bar code system was the first time.	
			Samples or requisition received in the blood bank without bar code	These events occurred at a rate of 0.5%. Because the blood bank personnel cannot complete the second transaction properly in such situations, they rejected the samples. In these events the system clearly functioned as intended to prevent potential identification errors.	

Study	**Chan 2004[23]**				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year:	Patient group:	Group 1	Blood transfused to	Group 1: 0	Funding:

Chan 2004[23] Study design: Retrospective study Comparison: Electronic UPI barcode system vs. Conventional second-checker system Setting: Regional hospital, Hongkong Duration of follow-up: 3 years	NA Inclusion criteria: Exclusion criteria: Group 1 – Age in years (mean SD): Female: Drop outs: Group 2 - Age in years (mean SD): Female: Drop outs:	Electronic UPI barcode system. (May 1999 to April 2002) This was designed for use in conjunction with the hospitals standard transfusion protocols. It aimed at verifying and documenting transfusion procedures, by an electronic device, at two critical points known to be associated with high incidence of human error; pre-transfusion blood sampling for the compatibility test and bedside blood administration. The system was not used at the intermediate point-the blood bank-because checking was already part of the existing Laboratory Information System. By the using the electronic UPI barcode system the aim was to transfer correctly a patient's unique number from his or her wristband on to the blood request form,	wrong patients	Group 2: 0 No cases of blood transfusion to wrong patients	Not reported Limitations: Risk of information bias as a result of the retrospective aspect Notes: Limitations of the intervention: Electronic UPI barcode system is unable to prevent error if a wrong patient is approached for blood sampling in the first instance. In that event, the wrong patient's unique identity would be used throughout the transfusion process. Authors conclusion: The electronic barcode system was effective in reducing human error related to bedside transfusion procedures.
			Wrong labelling of blood samples/request forms	Group 1: 13 Group 2: 0 No cases of wrong labelling of blood samples/request forms in the Electronic UPI system. A total of 13 transfusion accidents involving wrong labelling of blood sample tubes or blood request forms were recorded in the convention second checker system	
			Time taken for one procedure (minutes)	Group 1: 6 Group 2: 6 A house officer took 6 minutes to finish the blood sampling procedure using the UPI device. The conventional second checker system required a similar time.	
			Compliance rate of using new device	Group 1: 90% Group 2: 90%	
				The overall compliance rate of using the UPI	

		the blood sample tube, and the blood unit allocated to the patient. Group 2 Conventional second-checker system (May 1995 to April 1999)		device for transfusion process approached 90% as shown by the 2 month hospital wide evaluation survey in 2002. In approximately 10% of cases the conventional second checker system had to be resorted to as a back-up.	

Study	**Davies 2006A[40]**				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Davies 2006A[40] Study design: Before and after study Comparison: NA Setting: Hospital Duration of follow-up:	Patient group: Cardiac surgery patients.	Group 1: The transfusion process in clinical areas for cardiac surgery patients was evaluated at 3 different stages of the transfusion process before and after the implementation of bar code technology and education in cardiac surgery.; blood sample collection; blood collection from the refrigerators in cardiac theatres or the cardiac receiver unit; and blood administration carried out at the cardiac theatres or the cardio-	Verbal identification	4 out of 24 inpatients and 13 out of 26 outpatients were asked to verbally identify themselves by stating their full name and date of birth before the collection of their blood sample for compatibility testing. Following the introduction of the electronic process, all 24 inpatients and 26 outpatients were asked to verbally identify themselves by stating their full name and date of birth	**Funding:** Not stated **Limitations:** The absence of a comparison group makes it impossible to know what would have happened without the intervention **Additional outcomes:** **Notes:** Outcomes not in our protocol. **Authors conclusion:** A bar code patient identification system improved transfusion practice, although areas for improvement were identified.
			Checking details of wrist bands	17 out of 21 inpatients and 2 out of 3 outpatients had details on their	

		thoracic ward. Electronic process of transfusion: The process involved the use of handheld computers that scan information from bar codes. Group 2: N/A		wristband checked before blood sample collection. Following the introduction of electronic process, all patients, even outpatients had the wrist band details checked.	
			Labelling of the blood sample	In the baseline audit sample labelling was carried out correctly in 21 out of 24 inpatients and 23 of 26 outpatients; in other cases date of birth or gender were omitted. Full labelling details were provided in all cases after the implementation of the electronic process.	
			Transfusion documentation	The baseline audit demonstrated that there was very poor documentation of the date and time of the transfusion, and the number of units transfused in all three clinical areas in cardiac surgery. After the introduction of the electronic process, documentation was complete, with a report label printed and included in the patients' medical	

				records.	
			Transfusion process	The patient's wristband was checked against the blood pack in 48 of 50 procedures in the cardiac recovery unit (CRU), 6 out of 10 in theatre and 10 of 10 in the cardio thoracic ward (CTU). After the electronic process was implemented, this improved to 50 of 50 in CRU and 10 of 10 in theatre but did not alter the rate in CTU of 10 of 10. The blood group and the unit number on the blood bag were checked against the compatibility label, and the expiry date was checked, during 4 of 50 procedures in CRU, 1 of 10 in theatre, and 0 of 10 in CTU. After the electronic process was introduced this improved to 50 of 50 in CRU , 10 of 10 in theatre and 10 of 10 in CTU.	
			Incorrect blood component transfused	One documented IBCT was prevented by the electronic process in the	

				CRU. The wrong blood was delivered to the bedside of a patient with a similar name before the electronic blood collection system was in operation. Visual checking failed to identify that the blood was not intended for the patient, but checking with the handheld computer indicated that it was the wrong blood.	

Study	**Miller 2013[106]**				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Miller 2013[106] Study design: Pilot, Before and after study Comparison: 2D barcode technology, patient safety software, hand held PDAs compared to standard care Setting: Tertiary hospital Duration of follow-up: Audits were carried out from 2011 to 2012. In	Patient group: : RBC and platelet transfusion episodes Inclusion criteria: Not reported Exclusion criteria: Not reported Before – n=60 transfusion episodes Age in years (mean SD):	Before: Standard care which includes two staff members performing simultaneous/independent checks immediately prior to transfusion. 30 minutes education/training After: 2D barcode technology, patient safety software, hand held PDAs 30 minutes education/training	Morbidity (renal failure, DIC)	Before: Not reported After: Not reported	Funding: Hospital's 'Whole time medical specialists' fund Limitations: Before and after study design Small number of nurses using the intervention 2D barcode technology limitation: placing the incorrect wristband on the patient
			All-cause mortality at 30 days	Before: Not reported After: Not reported	
			Wrong blood in tube	Before: 57% patients asked to verbally identify themselves (full name, dob) prior to blood administration 36% patients had verbal identification and cross-reference with wristband ID 43% patients had their ID compatibility tag checked and cross-referenced with	

July 2011 the 2D barcode and patient safety-software was introduced 6 weeks after an audit of RBC or platelet transfusion episodes. A repeat audit was performed in September 2012 Pre-implementation Audit 1 Audit 2 Audit 3 Post-implementation Audit 1 Audit 2 2months follow up from implementation of intervention Staff satisfaction survey Follow up of 16 months after use of the new intervention	Not reported Female: Not reported Drop outs: Not reported After - n=80 transfusion episodes (50+30 further) Age in years (mean SD): Female: Not reported Drop outs: Not reported			wristband On 57% occasions blood product details cross-referenced 76% transfusion episodes were checked correctly at the patient's bedside After: 94% patients verbally asked to state name and dob at the beginning of the blood checking process 94% patients had verbal information cross-checked with wristband and with information on PDA (P<0.001) 99% patients had their ID on the compatibility tag checked and cross-referenced with wristband and PDA (P<0.001) On 96% of occasions, blood components were cross-referenced with compatibility tag (P<0.01) 100% transfusion episodes were checked correctly at the patient's bedside	Blood prescribing practice to minimize risk for patients receiving unnecessary blood transfusion Additional outcomes: Notes:
			Blood samples rejected by laboratory (due to incorrect or inadequate	Not reported	

			labelling)		
			Incorrect blood component transfused	Before: After: at 16 months follow up, 1 wristband compatibility label mismatch, 1 blood unit compatibility label mismatch and 1 blood unit already transfused where the nurse tried to begin the transfusion instead of ending the transfusion using the PDA	
			Quality of life	Not reported	
			Admission to ICU post transfusion	Not reported	
			Staff satisfaction survey at 2 months follow up	53% of staff completed the survey, 80% of this group were confident in using the system, and it was easy to use. 70% of this group found the system to be safer compared to standard care.	

Study	**Miyata 2004[107]**				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Miyata 2004[107]	Patient group: N/A	Group 1 Network computer-	Blood-component-recipient identification	In total, 60,032 blood components were transfused over the 3 year	Funding: Not stated

Study design: Before and after study Comparison: NA Setting: National Cardiovascular centre, Japan Duration of follow-up: 3 years	Inclusion criteria: - Exclusion criteria: - Group 1 – Age in years (mean SD): Female: Drop outs: Group 2 - Age in years (mean SD): Female: Drop outs:	assisted transfusion-management system. The host computer at the transfusion service, which stores the transfusion data on recipients and blood components, was linked to computers in operating rooms, surgical ICU and neurological intensive care units, irradiation room and an outpatient clinic for autologous blood collection. In this network a bar code scanner connected to a computer at the bed side identifies each blood component displaying the blood type, product number, expiration date, recipients details concerning compatibility, and state of irradiation. The purpose of the system was to ensure the correct administration of blood components at the bedside by component-recipient identification.		period, and all of them were transfused to the intended recipients perfectly. Component-recipient verification at the bed-side found and prevented one human error, in which blood components were distributed to a wrong operating room by a nurse.	Limitations: The absence of a comparison group makes it impossible to know what would have happened without the intervention Notes: Disadvantages of the network system: 1) It requires a client computer and space at bedside. 2) The failsafe system of the network can be violated by ignoring warning messages, such as the error of non-irradiated blood transfusion. 3)The wrist band has no identification bar code on it, so that a doctor and a nurse in charge select the recipient information by manually entering the recipients identification number in to the system. Authors conclusion: The network computer assisted management system greatly
			Cross-match to transfusion ratio for operations and	Reduced from 2.5% to 1.8%	
			Out-date rate of RBCs	Reduced from 3.9% to 0.32%	

		Group 2 N/A			contributes to safe and efficient transfusion therapy.

Study	**Murphy 2012[112]**				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Murphy 2012[112] 2 audits also contribute to development of this study[40,174] Study design: Before and after study Comparison: Electronic patient identification systems vs. non-electronic systems Setting: Oxford University Hospitals Trust, UK Duration of follow-up: Before implementation: October 2005-September 2006	Patient group: • Retrospective review of transfusion records before implementation of the programme. • This was followed by a review of all transfusion records after implementation of the programme.	Electronic patient identification system: • Electronic blood transfusion management system-bar code patient identification system with hand held computers (system includes identification check at collection of blood for compatibility testing, administration of blood, collection of blood from refrigerators) • System implemented for blood compatibility testing and blood administration in end of 2006 and early 2007. • The electronic patient identification system was linked with the blood bank IT system	Wrong blood in tube (assessed over 1 year before and after implementation) Sample rejected due to mislabelling (assessed over 1 year before and after implementation) Wrong blood transfusions (assessed over 4 years before and after implementation)	Before implementation:1/12,322 After implementation:1/26,690 Before implementation: 1004/31,406 (3.1%) After implementation: 541/44,373(1.2%) Before implementation:6/165,139 (1/27,523) After implementation:2/135,869 (1/67,935)	Funding: NHS Blood and Transplant Haemonetics Corp. (Braintree, MA), Neoteric Technology (Vancouver, Canada) and iSoft (Banbury, UK). Limitations: Before and after study with no matching of control group Notes:

After implementation:		which was linked to the hospital laboratory IT system.			

Study	**Ohsaka 2008[120]**				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**
Author & Year: Ohsaka 2008[120] Study design: Before and after study Comparison: N/A Setting: Hospital Duration of follow-up: 4 years	Patient group: All patients in the inpatient wards expect psychiatric ward, an outpatient clinic of haematology department, and operating room (OR).	Group 1: A transfusion management system was developed that linked hospital information system, a bar code patient blood unit ID system and an automated device for pre-transfusion testing in July 2002. The barcode-blood unit ID system was based on the use of liner bar code (NW7) that imprints a label attached to all allogeneic blood components supplied from a branch of the Japanese Red Cross Blood centre. The patient-blood unit ID system composed 1) a hand held device	Transfusion safety	From July 2002 to December 2006 a total of 49,974 blood components, including 25,691 RBCs, 10,916 platelets and 13,367 FFP were transfused without a single mistransfusion.	Funding: Not stated Limitations: The absence of a comparison group makes it impossible to know what would have happened without the intervention Additional outcomes: Notes: Does not report protocol relevant outcomes. Authors conclusion: A computer assisted transfusion management system and changing transfusion practices appear useful in preventing mistransfusion and in contributing to the appropriate management
			Bed side verification	The mean rate of bed-side verification performed in the inpatient wards, outpatient clinic and OR was 96.3% during 2002 to 2006.	
			Appropriate management of blood components	The mean number of RBC units issued and subsequently returned in the 18 month period immediately before the introduction of the system was 837+130 and 300+64 respectively and in the 18 month period after the introduction of the system	

		incorporating a laser bar code scanner 2) the patients wrist band with bar code and eye-readable ID 3) a wrist band printer 4) an ID badge for the staff with his or her bar code 5) a compatibility report form and compatibility label attached to the blood unit on which bar codes informative of the pre-transfusion testing were imprinted. The transfusion data included the patients details including- surname, first name, patient ID number, and blood group, while blood components details contained blood group, product type and product lot number. Group 2: N/A		were 387+102 and 61+44 respectively. These differences were significant (p<0.0001). Thus the issued to returned ratio significantly decreased (p<0.0001) from 0.30+0.07 to 0.15+0.07 after introduction of the system. The rate of date expired RBC components decreased significantly (p<0.0001) from 0.65+0.55 to 0.30+0.17 % after the introduction of the new system, suggesting that the computer assisted transfusion management system and changed transfusion practices contributed to the appropriate management of RBC components.	of blood components.

Study	**Uriz 2011[176]**				
Study details	**Patients**	**Interventions**	**Outcome measures**	**Effect size**	**Comments**

Author & Year: Uriz 2011[176] Study design: Retrospective study Comparison: Electronic identification System (EIS) vs. manual system Setting: Hospital (520 beds) Duration of follow-up: 2 years (2006 to 2008)	Patient group: Not stated Inclusion criteria: Exclusion criteria: Group 1 – Age in years (mean SD): Female: Drop outs: Group 2 - Age in years (mean SD): Female: Drop outs:	Group 1 Electronic identification system (EIS) The EIS is a computerised autonomous and handy recording system using electronic identification for transfusion safety. It consists of bracelets, barcode labels, portable reader terminals and data management software. This computer assisted device with a bar code reader allows the correct identification of blood products to be transfused, blood samples and patients, as well as tracking each blood component allocated to a particular patient. Group 2 The manual system for controlling safety of transfusion procedure including: a request sheet and the patients' blood sample (both	Traceability of the documentation for transfusions. Traceability in haemovigilance is the ability to trace the history, application or location of each individual unit of blood or blood component, from donor to recipient.	Traceability of the documentation for transfusions using the manual process of controls showed that only 48% of the medical records of transfused patients were free of inaccuracies or in other words showed unbroken traceability of the documentation. After the new electronic system was put in to use in 2005, high values of traceability were obtained, ranging from 99.5±0.3 in 2005 to 99.7±0.3 in 2008. Monthly analyses indicated that traceability was consistently above 99%.	Funding: Not stated Limitations: Limited data obtained from the manual records to perform retrospective analysis. Main one being the cack of comparability of traceability of the documentation observed in 2002 with respect to traceability obtained with the EIS. Additional outcomes: Notes: Authors conclusion: After implementation of the EIS, traceability and compliance reached very high levels, linked to an improvement in transfusion safety.
			Compliance Compliance means the correct completion of controls carried out in the key steps of the transfusion chain, such as patient sample collection and the beginning of the transfusion.	Compliance was 96.1% on average and ranged from 93.1% to 97.9%.	

		identified with an adhesive label) were sent to the Transfusion service, where pre-transfusion tests were performed and manually recorded in the haemotherapy control data base.	Wrong ABO-type transfusion events	The median number of wrong ABO-type transfusion events was 2 per year with manual system. After implementing the EIS, no errors were detected from 2005 to 2008.	

H.11 Patient information

Study	Adams et al. 2011[4]
Aim	To develop a more robust understanding of patients' experience of preparing for and receiving a blood transfusion and to communicate this information to physicians, nurses and other providers in order to enhance their understanding of patients' experiences.
Population	Medically stable adults, aged 18-90 years, had received a blood transfusion over the five week study period, gave voluntary consent for taped interview; patients had to be alert and oriented with stable vital signs. n=21
Setting	Tertiary hospital, Cleveland, Ohio, USA
Study design	Qualitative study- semi-structured interviews
Methods and analysis	Sampling methods: convenience sampling, no attempt to control for sampling bias Data collection was by conducting semi-structured interviews lasting 15-30 minutes. Consent was taken 24 hours after blood transfusion and then interviews were conducted. Open ended questions were asked in a semi-structured interview format. Attempt to deal with researcher bias at the interviewing stage itself (interviewer with prior beliefs about transfusion did not conduct interview so as not to steer patients' responses). Attempt to establish trustworthiness of research data by establishing confirmability (recordings transcribed verbatim), dependability (interviewed participants of various ages, cultural backgrounds), transferability (interviewed until data saturation was reached) and credibility (used actual words of the participants in transcript).

	Different researcher used for each stage of data entry, verification, and theme extraction to establish trustworthiness of the data.
Themes with findings	**Paternalism and decision making- Trust** Patients said that physicians made the decision to transfuse and they rarely questioned the decision. Patients also agreed that they trusted the physicians to make the right decision for them- "I trusted that the doctors were doing what they were supposed to do, what needed to be done. I didn't question the fact of them having to do it or the whole process in general"
	Adequacy of information Information was given to patients before blood transfusion. However, this was not adequate especially regarding the patient's clinical status and transfusion procedures. "They just came in and said, 'You're getting a blood transfusion.'" "They did give me a pamphlet about blood transfusions."
	Concern/comfort level with receiving blood transfusion Concern about blood safety, disease transmission, screening and testing of blood and administration of the transfusion. "I had a lot of worries because they could have the disease and that's what the patients' brochure says about risks, and I was worried about it." "After all the things you hear...I didn't express the worry, but I think about it a little bit."
	Role of the nurse in blood transfusion and delivering information
Limitations	Convenience sampling, unclear how theme saturation was achieved (not reported). Residual researcher bias may still be present. Other sources of bias include interviewer bias (attempt to please the interviewer).
Applicability of evidence	Applicable to the review target population and setting.

Study	**Chan et al. 2005[24]**
Aim	To gain insight into the barriers for effective communication of transfusion information. This was done by assessing patient's understanding of discussion on transfusion, perception of transfusion risk relative to their surgery and anaesthetic and comfort level with accepting blood as a result of the discussion.
Population	Adult patients who had received red cell transfusion within the study period (November 2003-January 2004). n=344 (678 survey distributed, response rate 51%)
Setting	London Health Science Centre, Ontario, Canada
Study design	Patient self-administered survey conducted within 1-3 months of receipt of blood transfusion, anonymous

Methods and Analysis	Survey contained questions measuring recall of the process of consent as well as information from consent discussion on transfusion risks and alternatives. Also included questions measuring patients' assessment of ability to understand discussions, perception of transfusion risk relative to surgery and anaesthetic and comfort level with accepting blood as a result of the discussion. Participation was voluntary, no incentives provided. Data collected were entered into Microsoft Excel and analysed by SPSS software.
Themes with findings	Information received 80% of patients recalled having a discussion and signing a consent form for transfusion.
	Mode of information delivery *Preference for written information* 19% of patients recalled receipt of a pamphlet on transfusion (data on the number of participants who received the pamphlet is not available). There was a positive correlation indicating pamphlet recipients felt better informed and more comfortable with their decision to receive blood (R=0.78, p=0.001)
	Concern/comfort level with receiving blood transfusion 44% of patients did not recall discussing transfusion risks although majority recalled the consent process.
	Satisfaction with information received 62% of patients felt that the discussion was completely understandable; Only 35% of patients indicated that that they felt better informed and more comfortable with the decision to accept blood as a result of the written consent process.
	Risk perception 77% felt that the risk of blood products was less than that of surgery or anaesthetic.
Limitations	No information on validation or piloting of survey. Self-administered survey, no follow up of non-responders. No open ended questions in survey, lack of opportunity to express own views clearly/in detail. Differences may exist in recall depending on how ill the patients were, if survey was given closer to receipt of transfusion (1 month vs. 3 months) Single centre study, may have limited generalizability
Applicability of evidence	Applicable to the review target population and setting.

Study	**Court et al. 2011[33]**

Aim	To evaluate patient perceptions of blood transfusion and what the patient remembers of the consent process.
Population	Adults patients whose blood was cross-matched over a 2 month period, whether they received a transfusion or not. The study excluded inpatients at time of sending out questionnaire. n=164 (337 questionnaires distributed, response rate=48.7%) 132/269 transfused patients (49%) and 32/73 of non-transfused patients (48%) responded.
Setting	The Great Western Hospital, Swindon, UK
Study design	Patient administered survey questionnaire.
Methods and analysis	Survey questionnaire was previously validated in a pilot study. It was sent out by post to the participants.
Themes with findings	Paternalism and decision making- Trust 'As far as I remember, it was just my blood was low and I needed three units of blood. I accepted that the doctor knew best and did not query it at any time. Only had the leaflet afterwards.' 'Please allow patients to be involved in discussions between doctors. Some, like me, are afraid to ask in case we are seen as awkward patients.'
	Information received 59.1% of patients said they were informed they may need a transfusion. 86.7% said that they were explained the reason for the transfusion. 67% said they were informed the benefits of transfusion and 27.8% said they were informed of the risks of transfusion. Quotes from patients- 'Explain the need for a blood transfusion. Give more information about the risks involved.' 'I have regular transfusions, so do not need to be told each time'
	Mode of information delivery 58.8% were explained verbally what the transfusion involves. 26.8% of patents were aware of an information leaflet and 15.5% of patients reported having received a leaflet. 57.7% of patients felt that the best source of information was a doctor, nurse or anaesthetist. 4.1% said that the internet was the best source of information and 2.1% said the information leaflet was the best source of information. *Preference for written information* 'Provide patient leaflet' 'In retrospect I think I should have been more fully informed. An explanatory leaflet would have been helpful'
	Satisfaction with information received 59.8% of patients felt that they had received sufficient information and 61.9% of patents were completely satisfied with the information they received.
	Risk perception

	56.6% patients perceived the risk of transfusion to be less than the risk of surgery while 23.7% of patents felt that the risk was equal to surgery.
	*The study noted that answers to 96% of questions asked by patients were contained in the NHSBT leaflet.
Limitations	Self-administered survey, no follow up of non-responders. Data-analysis methods not reported (role of researcher, interpretation of answers to open-ended questions) Single centre study, may have limited generalizability
Applicability of evidence	Applicable to the review target population and setting.

Study	**Davis et al. 2012[43]**
Aim	To investigate patients' attitudes towards information they were provided with about transfusion and consenting to a transfusion.
Population	Patients who received blood transfusions- includes patients who received one off transfusions (e.g., post-operatively on the ward) and those who were regular transfusion recipients (ambulatory haematology patients). n=110 Health care professionals' views were also sought.
Setting	Imperial College NHS Trust and Oxford University Hospitals NHS Trust, UK
Study design	Cross sectional qualitative survey design
Methods and analysis	Survey was piloted to ensure comprehension. Survey assessed patients' attitudes towards whether a discussion about transfusion took place with the healthcare team, what information they were provided with, satisfaction with information, understanding need for transfusion, recollection of consent for transfusion. Responses to survey items were open ended. Data were collected on hospital wards within 48 hours of the patient being transfused. Research team member went through survey items with patients and helped record their answers. Participant responses to items in the survey were transcribed verbatim and coded into emerging categories by the research team.
Themes with findings	Paternalism and decision making Majority of the remaining patients (67/69) said that they were just told they needed a transfusion. 'I was told I needed a transfusion, but very quickly, and there was no time to ask questions.' One patient reported 'I fully discussed why the transfusion was necessary and the risks and benefits but this was only because I kept asking questions.'
	Information received 61 patients said that consent had been taken before transfusion (55 verbal, 6 written); 27 patients could not remember consenting and 22 patients

	did not have their consent taken. 30/110 patients reported that no discussion at all about the need to have a transfusion took place; 25/30 of these were patients with chronic illness who received regular transfusions.
	Mode of information delivery Only one patient said they were given the NHS leaflet 'receiving a blood transfusion'.
	Satisfaction with information received Majority of the patients (n=82) said they were satisfied with the information that was provided. 22 patients reported that they would have liked to have been given more information. 'I was extremely concerned with the lack of information.' 'I was not asked whether I wanted the transfusion. I was told. No discussion took place and I was not sure if there was an alternative.' Patients receiving one-off transfusion appeared less satisfied with the information provided than those receiving regular transfusions.
Limitations	Researcher helped patients fill out survey- may have introduced bias (researcher bias, interviewer bias). Survey carried out on inpatients- can influence how patients responded (may attempt to please the interviewer) Details of analysis not reported (thematic analysis mentioned but results not grouped by themes). Study conducted in two hospitals and findings may not be generalizable to other hospitals.
Applicability of evidence	Applicable to the review target population and setting.

Study	**Fitzgerald et al. 1999[59]**
Aim	To develop a description of patients' experiences of the blood transfusion process.
Population	People who were able and willing to describe in English their experience of receiving a blood transfusion. n=19
Setting	University of Adelaide, Adelaide, South Australia
Study design	Qualitative study – interviews
Methods and analysis	Interviews ranging from 15-30 minutes with participants being asked to talk about their experience of having a blood transfusion from the time they were told about it. Sampling was considered and it was planned that 20 people would be interviewed (one person was too ill to participate when visited at home). All recordings were transcribed verbatim and transcripts were read while the tapes were played in order for the principal investigator to check for

	accuracy and to ensure that no identifying markers had been left in. Raw data were loaded on to a computer software program, from which the transcriptions were coded line by line. A cross-sectional thematic analysis was undertaken by identifying concepts which were clustered into themes. The interpretation of data was carried out according to the 'interpretative process' (adapted from Thompson et al. 1990)
Themes with findings	Information received- variation Participants reported receiving some information about risks; advice on this was wide ranging from reassurance that it was a safe procedure to advice to donate one's own blood prior to surgery to reduce the risk of infection. '…the doctor explained the reasons , you know, not just the risk of infection, of picking up infections and diseases or whatever from other people's blood, he sort of said that's one of the reasons . But another reason is that your body will just recover better from the operation with your own blood.' Some patients revealed that they did not understand what they had been told; in many cases this lack of understanding did not cause distress. Emergency patients who had no time for preparation could not recollect being given information. People who received transfusions regularly were expecting the transfusion and viewed the information as part of the overall disease and its treatment; they also had the best understanding of the blood transfusion process.
	Mode of information delivery Information was given both verbally and in written form before transfusion. Patients noted that while it was factual, there was little opportunity to discuss issues at length. Formal consent procedure exists but this was not always completed.
	Risk perception Patients mentioned the risk of HIV infection from blood transfusion, but rationalised verbally that the risk was infinitesimal and that the consequence of not being transfused far outweighed the possibility of infection ('...one in a million.') or that it did not matter ('…I'm dying anyway'). The slight risk of infection was accepted as unavoidable.
	Satisfaction with information received Two participants voiced dissatisfaction with the information received and level of discussion. '…the only thing would be, perhaps a bit more information, a bit more time and a bit more discussion.' People were told that the blood transfusion would do them good but on the whole they did not feel better (patients receiving transfusions were all acutely ill, either after surgery, receiving cancer therapy or emergency care, may be a reason for not noticing anything beneficial after transfusion)
Limitations	No information on when the interview was conducted (how long after the transfusion).
Applicability of evidence	Applicable to the review target population and setting.

Study	Friedman et al. 2012[61]
Aim	To evaluate patient's understanding of the principles of blood transfusion as well as proper collection of patients consent; to compare findings with information given by medical residents.
Population	Adult in-patients in the medicine service department who had received with RBC transfusion within the preceding 3 days and had provided consent for transfusion within preceding 7 days of RBC transfusion. n=45
Setting	Tertiary hospital setting, USA
Study design	Bedside survey. Interviews – bedside interviews according to a pre-defined list of questions in survey questionnaire.
Methods and analysis	Interviewer asked questions to the patients at bedside according to a pre-defined list of survey questions. Questions had choice of answers for some questions and the patients could select more than one answer (choice). Data were analysed using GraphPad software.
Themes with findings	Indication for transfusion known 14% of patients were not sure why they were receiving transfusion-the rest of the patients appeared to be aware of the reason for their blood transfusion.
	Information received Patients were aware of the benefits of blood transfusion. 2% of patients said that the benefits had not been discussed with them and 12% were not sure/did not remember the benefits had been discussed with them. Specific benefits were highlighted from the survey list with 51% of patients saying that blood transfusions improve anaemia, 40% saying that they improved strength and 26% citing other benefits not included in the list (not specified). 7% of patients said that the risks of blood transfusion had not been discussed with them and 30% of patients were not sure/did not remember a discussion about the risks of blood transfusion. 33% of patients cited HIV transmission as a risk of blood transmission, 21% cited allergic reactions and 16% cited other risks of blood transfusion which were not included in the list (not specified).
	Mode of information delivery 58% of patients stated that they did not receive the hospital's transfusion health guide which explains information on transfusion benefits, risks and alternatives. 8% of could not recall if they had received the guide; 23% of patents were aware of the guide. Patients also indicated that they would like to receive the *Transfusion Health Guide.* Patients also wanted more information in lay-person terminology.
	Satisfaction with information received 77% of patients indicated that they were satisfied with the consent process. 7% indicated that they would like more time to think before signing

	the consent form. 2% of patents indicated they would like more information about the benefits and 5% wanted more information about the risks of blood transfusion. 88% of patients stated that they had the opportunity to ask questions.
Limitations	Reports that interviewers asked questions in open ended manner, but the interview was not open ended as the choice of answers was fixed and the questions were leading Sampling methods not reported. Possibility of recall bias as consent taken up to 7 days before transfusion. Interobserver variability in the way surveys were conducted could have affected the results. Large number of eligible patients refused participation or could not be surveyed. Not clear if survey was piloted or validated and was fit for purpose.
Applicability of evidence	Applicable to the review target population and setting.

Study	**Murphy et al. 1997[111]**
Aim	To study patients' attitudes to receiving information about blood transfusion or written consent before transfusion.
Population	Patients who had been transfused during current admission and were sufficiently well to answer a questionnaire. Majority of the patients (63%) had been previously transfused for haematological or renal reasons. n=51
Setting	St. Bartholomew's Hospital, UK
Study design	Survey
Methods and analysis	Patients were selected by medical students visiting the medical and surgical wards of a hospital over a period of 3 days. They were given a questionnaire which included an introductory paragraph explaining the purpose of the study. Included questions covered patient information and consent related to transfusion.
Themes with findings	Information received 31% of patients reported receiving any information before transfusion; the rest of the patients did not receive any information or were simply told that they were to receive a transfusion. 92% of patients understood why the transfusion was necessary (anaemia/need to replace blood loss during surgery). No major differences were observed in the responses between the previously transfused and the non-transfused patients (it might be expected that previously transfused patients would be better informed than non-transfused patients).
	Mode of information delivery

	53% of patients indicated that they would have found it helpful to have been provided with written information about blood transfusion. Satisfaction with information received 82% of patients thought that they had received enough information. 20% of patients said that additional information would have been helpful, to have a better understanding of the potential complications of transfusion and to have more details about the exact reason for transfusion in their case.
Limitations	No information on validation or piloting of survey. Self-administered survey. Survey conducted while patient still in hospital; may have influenced responses. Data-analysis methods not reported (role of researcher, interpretation of answers to open-ended questions) Single centre study, may have limited generalizability
Applicability of evidence	Applicable to the review target population and setting.

H.11.1 Checklist for quality assessment

	ADAMS2011	CHAN2005	COURT2011	DAVIS2012	FRIEDMAN2012	FITZGERALD1999	MURPHY1997
Is a qualitative study/ survey an appropriate approach?	✓	✓	✓	✓	✓	✓	✓
Is the study clear in what it seeks to do?	✓	✓	✓	✓	✓	✓	✓
How defensible/rigorous is the research design/methodology?	✓	?	✓	✓	?	✓	?
How well was the data collection carried out?	✓	?	✓	?	?	✓	✓
Is the role of the researcher clearly described?	✓	×	?	✓	✓	?	?
Is the context clearly described?	✓	✓	✓	✓	✓	✓	✓
Were the methods reliable?	✓	?	✓	✓	?	✓	✓
Is the data analysis sufficiently rigorous?	✓	✓	✓	?	?	✓	✓

	ADAMS2011	CHAN2005	COURT2011	DAVIS2012	FRIEDMAN2012	FITZGERALD1999	MURPHY1997
Are the data rich?	?	×	?	✓	×	✓	×
Is the analysis reliable?	✓	✓	✓	✓	✓	✓	✓
Are the findings convincing?	✓	?	✓	✓	?	✓	✓
Are the findings relevant to the aims of the study?	✓	✓	✓	✓	✓	✓	✓
Are the conclusions adequate?	✓	✓	✓	✓	✓	✓	✓

Appendix I: Economic evidence tables

I.1 Erythropoietin and iron

Table 2: Craig 2006[34]

Craig J, Brown H, Eastgate J, Macpherson K, and Wilson S. The use of epoetin alfa before orthopaedic surgery in patients with mild anaemia. Understanding our advice: the use of epoetin alfa before orthopaedic surgery in patients with mild anaemia. United Kingdom. Glasgow: NHS Quality Improvement Scotland (NHS QIS), 2006. Available from: http://www.nhshealthquality.org (Guideline Ref ID CRAIG2006)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Deterministic decision analytic model **Approach to analysis:** Decision tree depicting patients receiving or not receiving allogeneic transfusions. Transfusion recipients had a risk of contracting a transfusion-related illness. **Perspective:** Scottish NHS (UK)	**Population:** Adults with mild anaemia prior to orthopaedic surgery (haemoglobin level between 10-13 g/dl) **Cohort settings:** Start age=67.7 M=38% Weight=70 kg **Intervention 1:** Current practice (no intervention) **Intervention 2:** Erythropoietin alpha 600 units/kg by subcutaneous injection for 3 weeks prior to surgery and on the day of surgery (total 4 doses)	**Total costs (mean per patient):** Intervention 1: £114.90 Intervention 2: £1,349.40 Incremental (2-1): £1,234.50 (CI NR; p=NR) **Currency & cost year:** 2005 UK pounds **Cost components incorporated:** Erythropoietin alpha, administration, allogeneic blood (including associated administration costs) and transfusion-related adverse event and illnesses (hepatitis B and C, HIV, incorrect blood component transfused, transfusion related lung	**QALYs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2-1): 0.00006 (CI NR; p=NR)	**ICER (intervention 2 vs. intervention 1):** £21,193,000 per QALY gained (da) CI: NR Probability intervention 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** One-way sensitivity analyses were conducted. ICER was most sensitive to the number of units transfused, price of erythropoietin alpha and the cost of allogeneic blood. The price of erythropoietin alpha would need to decrease by 95% or the cost of allogeneic blood would need to increase to over £2,750 per unit for erythropoietin alpha to be cost effective at a threshold of £30,000 per QALY gained. Other scenario sensitivity analyses were conducted including if: • Erythropoietin alpha prevented all transfusions the ICER would be £14.1

Time horizon: lifetime **Discounting:** Costs: 3.5%; Outcomes: 3.5%		injury, acute transfusion reaction, transfusion related infection, others).		million per QALY. • Cost of transfusion-related adverse events increased 100 fold the ICER would remain over £21 million. • Loss in quality of life of those with hepatitis B and C and HIV increased to 0.95, the ICER would reduce to £14.2 million per QALY.
Data sources				
Health outcomes: For baseline risks the incidence of procedures (elective and emergency joint replacement operations) and of allogeneic blood transfused in Scotland 2003/4 were incorporated. Effectiveness data for erythropoietin alpha taken from trial by Weber 2005.[184] Risks of transfusion-related adverse events estimated from Serious Hazards of Transfusion reporting, for HIV and hepatitis B and C from 2002-2003 data and for non-viral adverse reactions from 1996-2004 data. National life tables used and life expectancy was assumed to be halved for those contracting HIV. **Quality-of-life weights:** Mean utility values for viral infections from published literature; instrument and tariff unclear, population collected in unclear. No utility values for non-viral reactions identified, a 0.5 utility loss for year of the event assumed. **Cost sources:** Resource use: erythropoietin alpha dosage national recommendations. Unit cost: erythropoietin alpha from British National Formulary, unit of allogeneic blood from UK published source, transfusion-related adverse events and illnesses from United States published sources and administration costs PSSRU and other national sources.				
Comments				
Source of funding: NR. Report is from NHS Quality Improvement Scotland. **Limitations:** Weber 2005[184] was excluded from the clinical review as we were unable to clearly separate results between autologous and allogeneic transfusions. Utility instrument, tariff and population collected in unclear. Side effects of erythropoietin alpha were not included in the model. Risk of adverse events from variant Creutzfeldt-Jakob disease was not included in the model. Costs for transfusion-related adverse reactions from US sources. **Other:** Results for mean costs and QALYs were reported for entire cohort in paper, the cohort size was unclear but appeared to be 10,000 based on methodology, results have been converted here to costs and QALYs per patient. Costs are rounded to nearest thousand pounds as reported in paper.				
Overall applicability[a]: Directly applicable **Overall quality[b]:** Potentially serious limitations				

Abbreviations: CI=95% confidence interval; CUA=cost-utility analysis; da=deterministic analysis; HIV=human immunodeficiency virus; ICER=incremental cost-effectiveness ratio; NR=not reported; QALYs=quality-adjusted life years

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations /Potentially serious limitations / Very serious limitations

Table 3: Davies 2006[41]

Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C. Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: A systematic review and economic model. Health Technology Assessment. 2006; 10(44):1-114. (Guideline Ref ID DAVIES2006)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Decision tree depicting surgical patients receiving either erythropoietin or no erythropoietin. All patients who receive a transfusion have a risk of transfusion or surgical complications and transfusion complications. For allogeneic blood transfusion there is a risk of transfusion transmitted infections. **Perspective:** UK NHS **Time horizon:** 1 month post transfusion **Discounting:** Costs: n/a; Outcomes: n/a	**Population:** Adults undergoing elective non-urgent major surgery (orthopaedic, cardiac and vascular surgery) **Cohort settings:** Start age: NR[a] Male: NR **Intervention 1:** No erythropoietin **Intervention 2:** Erythropoietin (dose between 1,761-3,887 units/ kg, once prior to surgery)	**Total costs (mean per patient):** Intervention 1: £5,006 Intervention 2: £4,958 Incremental (2-1): -£48 (CI NR; p=NR) **Currency & cost year:** 2003-2004 UK pounds **Cost components incorporated:** Cost of erythropoietin (including outpatient visit for administration); transfusion and transfusion-related services; operation and index hospital admission; and adverse events (surgical and transfusion-related).	**QALYs (mean per patient):** Intervention 1: 0.0632 Intervention 2: 0.0632 Incremental (2−1): 0 (CI NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 dominates intervention 1 (pa) Probability Intervention 2 cost-effective (30K threshold): NR **Analysis of uncertainty:** A probabilistic sensitivity analysis was conducted for the base case, but results were only reported versus cell salvage, one of the other comparators in the analysis. Additional analyses were conducted to explore the impact on results of using different structural variables or data sets: • use of transfusion protocol for allogeneic transfusion • surgical procedure (cardiac and orthopaedic) Results indicated that erythropoietin remained dominant. Sensitivity analyses using longer time frames of 1, 10 and 30 years conducted, but results were only reported versus cell salvage.

Data sources
Health outcomes: Baseline probability of transfusion with allogeneic blood and risk of adverse events related to transfusion or surgery, were derived from published systematic reviews and the authors own systematic review. Effectiveness of erythropoietin of proportion transfused from a published systematic review (Laupacis 1998). Number of units transfused for those receiving erythropoietin assumed to be equal to control. Conditional probabilities of adverse events and mortality related to transfusion only (allogeneic blood) were estimated from national surveys of serious hazards of transfusion and other published sources. **Quality-of-life weights:** Utility values for long-standing illness, limiting illness and no long-standing illness from the 1996 Health Survey for England were used in the model for the time between surgery and discharge, discharge to 30 days and one month to one year post surgery, respectively. Authors did not use different utilities for short term transfusion and surgery-related complications (<30 days) as they assumed the impact on quality of life was likely to be minimal compared with the impact of the underlying reason for surgery. The exception was for stroke, for which a utility value was taken from published literature. In addition, for transfusion-related infections at one month to one year after surgery, the utility value for limiting illness was adopted. The tariff of utility values was not specified. **Cost sources:** Resource use: dose of erythropoietin from studies reported in systematic review (Laupacis 1998), pre- and peri-operative use of transfusion related services, adverse events and length of hospital stay were estimated from a number of sources including published systematic reviews, the authors own systematic review, two trial databases held at South Manchester University Hospital Trust and national Hospital Episode Statistics. **Unit costs:** erythropoietin cost from British National Formulary, outpatient visit for administration of erythropoietin from reference costs, transfusion-related services, operation and index hospital admission from South Manchester University Hospital Trust financial records and HS Blood Transfusion Authority; adverse events from published national sources.
Comments
Source of funding: NHS R&D Health Technology Assessment (HTA) Programme. **Limitations:** Model used data for resource use as well as effectiveness from clinical trials that were mostly outside the UK. Effectiveness data from a systematic review from Laupacis 1998, which does not include all of the evidence identified in the clinical review. Side effects of erythropoietin alpha were not included in the model. Short time horizon, no data presented for longer time horizons for these comparators. **Other:** This model included additional comparators other than allogeneic blood including: intra- and post- cell salvage, pre-operative autologous donation, acute normovolaemic haemodilution, antifibrinolytic drugs, fibrin sealants and transfusion triggers. The results of those comparisons have not been reported here. Results of the cell salvage comparator have been reported in the combinations of cell salvage and tranexamic acid review.
Overall applicability[b]: Directly applicable **Overall quality[c]:** Potentially serious limitations

Abbreviations: CI: 95% confidence interval; CUA: cost–utility analysis; ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) Age not specified for the base case. In the analysis of uncertainty when a 10 year time horizon was used, the model was based on a 70 year old member of general population and for the 30 year time horizon it was based on a 50 year old member of general population.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Table 4: Lidder 2007[91,92]

Lidder PG, Sanders G, Whitehead E, Douie WJ, Mellor N, Lewis SJ et al. Pre-operative oral iron supplementation reduces blood transfusion in colorectal surgery - A prospective, randomised, controlled trial. Annals of the Royal College of Surgeons of England. 2007; 89(4):418-421. (Guideline Ref ID LIDDER2007)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcome: units of blood transfused) **Study design:** Within trial analysis (RCT) **Approach to analysis:** Analysis of individual level data, with unit costs applied. **Perspective:** UK NHS **Follow-up:** Two weeks[a] **Discounting:** Costs: n/a; Outcomes: n/a	**Population:** Patients with colorectal cancer fit for resective surgery with haemoglobin level <13.5 g/dl in men and <11.5 g/dl in women. **Patient characteristics:** n=49 Start age=71 M=57% **Intervention 1:** Standard clinical treatment (no intervention) **Intervention 2:** Ferrous sulphate, 200 mg three times a day orally for two weeks prior to surgery	**Total costs (mean per patient):** Intervention 1: £214 Intervention 2: £67 Incremental (2-1): -£147 (CI NR; p=NR) **Currency & cost year:** 2007 UK pounds **Cost components incorporated:** Ferrous sulphate and unit of allogeneic blood.	**Total units of blood transfused (mean per patient):** Intervention 1: 2.1 Intervention 2: 0.7 Incremental (2-1): -1.4 (CI NR; p=NR)	**ICER (intervention 2 vs. intervention 1):** Intervention 2 dominant (da) CI: NR **Analysis of uncertainty:** NR
Data sources				
Health outcomes: Mean units of blood transfused from within RCT. **Quality-of-life weights:** n/a. **Cost sources:** Resource use from within RCT. Unit cost of ferrous sulphate from UK NHS and unit cost of unit of allogeneic blood unclear.				
Comments				
Source of funding: NR. **Limitations:** Health effects not expressed in terms of QALYs, short follow up which does not account for future savings as a result of reduced risk of transfusion-related adverse events / illness, costs of other resource use such as staff costs not included, source of unit costs unclear and no analysis of uncertainty conducted.				

Overall applicability[b]: Partially applicable **Overall quality[c]:** Potentially serious limitations

Abbreviations: CCA=cost-consequence analysis; CI=95% confidence interval; da=deterministic analysis; ICER=incremental cost-effectiveness ratio; n/a=not applicable; NR=not reported; QALYs=quality-adjusted life years

(a) Duration between administration of intravenous iron and surgery.

(b) Directly applicable / Partially applicable / Not applicable;

(c) Minor limitations /Potentially serious limitations / Very serious limitations

Table 5: Luporsi 2012[95]

Luporsi E, Mahi L, Morre C, Wernli J, de PG, Bugat R. Evaluation of cost savings with ferric carboxymaltose in anemia treatment through its impact on erythropoiesis-stimulating agents and blood transfusion: French healthcare payer perspective. Journal of Medical Economics. 2012; 15(2):225-232. (Guideline Ref ID LUPORSI2012)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcome: reduction in blood transfused) **Study design:** Deterministic decision analytic model **Approach to analysis:** Decision tree depicting patients receiving or not receiving allogeneic transfusions post-operatively. **Perspective:** French healthcare payer **Time horizon:** 2-3 weeks[a]	**Population:** Knee and hip surgery patients with peri-operative anaemia. **Cohort settings:** Start age: NR Male: NR **Intervention 1:** Usual practice (no intervention) **Intervention 2:** Ferric carboxymaltose, 1 intravenous injection of 500 mg 2 to 3 weeks prior to surgery.	**Total costs (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2−1): -£166 (CI NR; p=NR) **Currency & cost year:** 2010 Euros (presented here as 2010 UK pounds[b]) **Cost components incorporated:** Ferric carboxymaltose and unit of allogeneic blood.	**Percentage patients receiving blood transfusion:** Intervention 1: 0% Intervention 2: 59% Incremental (2-1): 59% (CI NR; p=NR)	**ICER (intervention 2 versus intervention 1):** Intervention 2 dominant (da) CI: NR **Analysis of uncertainty:** One-way sensitivity analysis revealed that when the difference in the number of patients receiving blood transfusion was reduced to 18% (rather than 59%); the costs of the two arms became equal.

Discounting: Costs: n/a; Outcomes: n/a				
Data sources				
Health outcomes: Source of estimation of number of knee and hip surgery operations in France unclear; expert opinion used to determine proportion of these patients with anaemia; effectiveness of intravenous iron from Cuenca 2005[36,36]. **Quality-of-life weights:** n/a. **Cost sources:** The dosage for ferric carboxymaltose was based on expert opinion and the unit cost on French national health service costs. The unit cost of allogeneic blood was an average of French public and private health unit costs. Volume of blood transfused was unclear.				
Comments				
Source of funding: Funded by Vifor Pharma, manufacturer of Ferinject® (ferric carboxymaltose) **Limitations:** Health effects not expressed as QALYs and short time horizon which does not account for future savings as a result of reduced risk of transfusion-related adverse events / illness, unclear if costs of other resource use such as staff costs are included, dose of ferric carboxymaltose based on expert opinion and minimal analysis of uncertainty (no probabilistic analysis of uncertainty). **Other:** Two additional analyses were reported in this paper but not presented here, evaluating the economic impact of ferric carboxymaltose in chemotherapy-induced anaemia in breast cancer and digestive cancer.				
Overall applicability[c]: Partially applicable **Overall quality[d]:** Potentially serious limitations				

Abbreviations: CCA: cost–consequence analysis; CI: 95% confidence interval; da: deterministic analysis; ICER: incremental cost-effectiveness ratio; n/a=not applicable; NR: not reported; QALYs=quality-adjusted life years.

(a) Duration between administration of intravenous iron and surgery.

(b) Converted using 2010 purchasing power parities[122,122]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations /Potentially serious limitations / Very serious limitations

Table 6: Tomeczkowski2013[171]

Tomeczkowski J, Stern S, Muller A, von HC. Potential cost saving of epoetin alfa in elective hip or knee surgery due to reduction in blood transfusions and their side effects: a discrete-event simulation model. PloS One. 2013; 8(9):e72949. (Guideline Ref ID TOMECZKOWSKI2013)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcome: various health outcomes)	**Population:** Adults hip and knee arthroplasty patients with pre-operative haemoglobin level between 10-13 g/dl	**Pre-operative haemoglobin** 10-10.5 g/dl **Total costs (mean per patient):**	**Pre-operative haemoglobin** 10-10.5 g/dl **Percentage of patients receiving an allogeneic**	**ICER (intervention 2 vs. intervention 1):** Intervention 2 dominant (da) CI: NR **Analysis of uncertainty:** One way sensitivity

Study design: Deterministic decision analytic model **Approach to analysis:** Discreet event simulation model depicting hip and knee arthroplasty patients receiving or not receiving allogeneic transfusions. Analysis conducted for 6 subgroups stratified by pre-operative haemoglobin levels (10 and 13 g/dl). Decision on whether or not a transfusion was required was based on a transfusion trigger of 8.5 g/dl. Transfusion recipients had an increased risk of infection, pneumonia and length of stay. **Perspective:** German healthcare payer **Time horizon:** NR, appears to be duration of hospitalisation **Discounting:** Costs: n/a; Outcomes: n/a	**Cohort settings (range across 6 haemoglobin subgroups):** Start age=71.1–71.9 M=12.1–18.9% **Intervention 1:** Control (no intervention) **Intervention 2:** Erythropoietin alpha, 40,000 IU injections until their haemoglobin level reaches 13.3 g/dl (2 injections on average). Average increase per injection: 0.75 g/dl.	Intervention 1: £5,082 Intervention 2: £4,630 Incremental (2-1): -£452 (CI -£41 to -£773, p=NR) **Pre-operative haemoglobin 12.5-13g/dl:** **Total costs (mean per patient):** Intervention 1: £3,925 Intervention 2: £3,911 Incremental (2-1): -£14 (CI -£8 to -£773, p=NR) **Currency & cost year:** Euros, year NR, assumed to be 2012 (presented here as 2012 UK pounds[a]) **Cost components incorporated:** Erythropoietin alpha (£178 per 40,000 IU), allogeneic blood (including associated administration costs), length of hospital stay and pneumonia.	**blood transfusion:** Intervention 1: 94.4% Intervention 2: 37.3% Incremental (2-1): -57.1% (CI NR; p=NR) **Total units of blood transfused (mean per patient transfused):** Intervention 1: 2.5 Intervention 2: 1.8 Incremental (2-1): -0.7 (CI NR; p=NR) **Pre-operative haemoglobin 10-10.5 g/dl:** **Percentage of patients with receiving an allogeneic blood transfusion:** Intervention 1: 28.4% Intervention 2: 4.9% Incremental (2-1): -23.5% (CI NR; p=NR) **Total units of blood transfused (mean per patient transfused):** Intervention 1: 1.4 Intervention 2: 1.3 Incremental (2-1): -0.1 (CI NR; p=NR)	analyses conducted: • When a restrictive (8 g/dl) transfusion trigger was used, erythropoietin was no longer cost saving, mean additional cost per patient: £26 • When the baseline blood loss was reduced to a lower level, erythropoietin was no longer cost saving, mean additional cost per patient: £223 • When erythropoietin was administered at higher dose(until their haemoglobin level reaches 15 g/dl, average of 4 injections, Weber 2005[184]), erythropoietin was no longer cost saving, mean additional cost per patient: £84 • When the lower 95% CI for transfusion-related length of stay increase parameter is used, erythropoietin was no longer cost saving, mean additional cost per patient: £14 • When the cost of erythropoietin is increased by 25% to reflect the list price, at pre-operative haemoglobin levels of 12-13 g/dl, erythropoietin was no longer cost saving, additional cost per patient is between £26-49

Data sources
Health outcomes: For baseline characteristics such as haemoglobin pre-treatment, length of stay, age, gender taken from German patient data set (including DRG code) of hip and knee arthroplasty patient. Haemoglobin loss during surgery, calculation of volume of blood required to reach and maintain, risk of infection associated with transfusion and risk of pneumonia related to transfusion all from published literature. Effectiveness data in terms of the erythropoietin's ability to raise haemoglobin levels pre-operatively was based on an RCT comparing erythropoietin to autologous donation (Rosencher 2005). Effectiveness of erythropoietin at increasing haemoglobin was reduced for patients with rheumatoid arthritis. **Quality-of-life weights:** n/a **Cost sources:** Resource use: volume of allogeneic blood transfused calculated based on German data set and published literature. Dose of erythropoietin treatment from Rosencher 2005. Unit cost: erythropoietin negotiated costs with hospitals in Germany, allogeneic blood (including staff time, overheads and blood) taken from costing study[148], cost of pneumonia event and hospital stay per day from German national sources.
Comments
Source of funding: Funded by Janssen-Cilag, manufacturer of erythropoietin alpha. **Limitations:** Health effects not expressed as QALYs and time horizon unclear but appears to be short which does not account for future savings as a result of reduced risk of long-term transfusion-related adverse events / illness. Effectiveness data from one study, which has not been included in the clinical review. Cost of administering erythropoietin excluded. Side effects of erythropoietin excluded from model. Cost of erythropoietin is based on negotiated costs which may not reflect current NHS context. **Other:** An additional analysis was reported in this paper but not presented here, evaluating the cost-effectiveness of pre-operative autologous donation.
Overall applicability[b]: Partially applicable **Overall quality[c]:** Potentially serious limitations

Abbreviations: CI=95% confidence interval; CCA=cost-consequence analysis; da=deterministic analysis; ICER=incremental cost-effectiveness ratio; NR=not reported; QALYs=quality-adjusted life years

(a) Converted using 2012 purchasing power parities[122]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations /Potentially serious limitations / Very serious limitations

Table 7: Vitale 2007[179]

Vitale MG, Roye BD, Ruchelsman DE, Roye DP. Preoperative use of recombinant human erythropoietin in pediatric orthopedics: a decision model for long-term outcomes. Spine Journal. United States 2007; 7(3):292-300. (Guideline Ref ID VITALE2007)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis:	**Population:**	**Total costs (mean per**	**QALYs (mean per patient):**	**ICER (intervention 2 vs. intervention 1):**

CUA (health outcome: QALYs) **Study design:** Deterministic decision analytic model **Approach to analysis:** Decision tree depicting patients receiving or not receiving allogeneic transfusions. Patients had a risk of wound infection, transfusion reactions (fatal and non-fatal) and transfusion-related infections. **Perspective:** US healthcare payer[a] **Time horizon:** NR, appears to be lifetime **Discounting:** Costs: NR; Outcomes: NR	Adolescent female patients prior to surgical correction of adolescent idiopathic scoliosis (haemoglobin level NR) **Cohort settings:** Start age=15 M=0% **Intervention 1:** Control (no intervention) **Intervention 2:** Recombinant human erythropoietin (dose and duration NR)	**patient):** Intervention 1: £68 Intervention 2: £374 Incremental (2-1): £306 (CI NR; p=NR) **Currency & cost year:** US dollars, year NR, assumed to be 2005 (presented here as 2005 UK pounds[b]) **Cost components incorporated:** Recombinant human erythropoietin (including administration), allogeneic blood, transfusion-related adverse event and illnesses (hepatitis B and C, HIV, human T-cell lymphotrophic virus, transfusion-related lung injury, bacterial contamination and fatal transfusion reaction) and wound infection.	Intervention 1: 61.6854 Intervention 2: 61.6857 Incremental (2-1): 0.0003 (CI NR; p=NR)	£1,020,000 per QALY gained (da) CI: NR Probability intervention 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** One way sensitivity analysis was conducted. ICER was sensitive to only one of the variables; the average number of transfusions received by a patient in the control arm. The average number of transfusions in the recombinant human erythropoietin arm was calculated from this number. When the average number of transfusion received was greater than 2.3 units, the ICER for recombinant human erythropoietin was below the threshold of $50,000 (£31,809) per QALY. Scenario and threshold analyses conducted. The cost of allogeneic blood would need to increase from £79 per unit to £1,909 per unit for recombinant human erythropoietin to be cost effective.
Data sources				
Health outcomes: For baseline risks, control transfusion rates were taken from retrospective data and risk of transfusion-related infections and non-infections reactions were from published literature and surveillance reports. Effectiveness data for recombinant human erythropoietin referenced as being from a randomised controlled study by Rollo 1995[136], however this study is not a study of recombinant human erythropoietin, therefore unclear which studies the effectiveness data is based upon. **Quality-of-life weights:** Utility values used in the model were from published peer reviewed literature but were not outlined in the study. **Cost sources:** Resource use: volume of allogeneic blood transfused from published literature, no detail provided on dose or duration of recombinant human erythropoietin treatment. Unit cost: recombinant human erythropoietin and treating transfusion related disease and complications from published literature. Allogeneic blood from US hospital charges. Treating wound infection based on author assumption.				

Comments
Source of funding: NR **Limitations:** Utility values used in the model not reported, cost year not reported (assumed to be year of submission of paper, 2005), time horizon not reported (assumed to be lifetime as lifetime costs included in the model), perspective unclear (assumed to be US health care). Effectiveness data from one study, which has not been included in the clinical review. Side effects of recombinant human erythropoietin excluded from model. **Other:** An additional analysis was reported in this paper but not presented here, evaluating the cost-effectiveness of pre-operative autologous donation in adolescent idiopathic scoliosis.
Overall applicability[c]: Partially applicable **Overall quality[d]:** Potentially serious limitations

Abbreviations: CI=95% confidence interval; CUA=cost-utility analysis; da=deterministic analysis; HIV=human immunodeficiency virus; ICER=incremental cost-effectiveness ratio; NR=not reported; QALYs=quality-adjusted life years

(a) Perspective unclear, costs are healthcare costs or adjusted charges in US dollars, therefore a US healthcare payer perspective was assumed.

(b) Converted using 2005 purchasing power parities[122,122]

(c) Directly applicable / Partially applicable / Not applicable

(d) Minor limitations /Potentially serious limitations / Very serious limitations

I.2 Alternatives to blood transfusion in surgical patients- combinations of cell salvage and tranexamic acid

Table 8: Alshryda 2013[6]

Alshryda S, Mason J, Sarda P, Nargol A, Cooke N, Ahmad H et al. Topical (intra-articular) tranexamic acid reduces blood loss and transfusion rates following total hip replacement: a randomized controlled trial (TRANX-H). Journal of Bone and Joint Surgery - Series A. 2013; 95(21):1969-1974. (Guideline Ref ID ALSHRYDA2013A)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcome: percentage requiring allogeneic blood transfusion and volume transfused, blood loss, length of stay, complications including deep vein thrombosis, EQ-5D) **Study design:** Within trial analysis (RCT)	**Population:** Adults undergoing total hip replacement surgery **Patient characteristics:** n=161 Mean age: 64.9 Male: 32% **Intervention 1:** Placebo **Intervention 2:**	**Total costs (mean per patient):** Intervention 1: £1,526 Intervention 2: £1,221 Incremental (2-1): -£305 (CI -610 to 0; p=0.05) **Currency & cost year:** 2010 UK pounds **Cost components incorporated:** Unit cost of allogeneic red blood cells, tranexamic acid	**Percentage receiving allogeneic blood transfusion:** Intervention 1: 32.1% Intervention 2: 12.5% Incremental (2-1): -19.6% (CI NR; p = 0.004) **Total units of allogeneic blood transfused (mean per patient transfused):** Intervention 1: 2.46 Intervention 2: 2	**ICER (intervention 2 versus intervention 1):** Intervention 2 dominates intervention 1 (da) Probability Intervention 2 cost-effective (£20K/30K threshold): n/a **Analysis of uncertainty:** Bootstrapping of costs: Incremental (2-1): -£304 (CI -613 to -15, p = 0.046)

Approach to analysis: Analysis of individual level resource use with unit costs applied. **Perspective:** UK NHS **Follow-up:** 3 months post-surgery **Discounting:** Costs: n/a; Outcomes: n/a	Tranexamic acid (dose not stated, route of administration: topical intra-articular)	and hospital stay.	Incremental (2-1): -0.46 (CI NR; p=NR) **Actual blood loss (ml):** Intervention 1: 1981 Intervention 2: 1617 Incremental (2-1): -364 (CI -742 to 15; p = 0.059) **Length of hospital stay (days):** Intervention 1: 6.2 Intervention 2: 5.2 Incremental (2-1): -1 (CI -2.3 to 0.2; p = 0.109) **EQ-5D at 3 months:** Intervention 1: 0.686 Intervention 2: 0.715 Incremental (2-1): 0.029 (CI NR; p = NR) **All complications (deep vein thrombosis):** Intervention 1: 4 (2) Intervention 2: 7 (2) Incremental (2-1): 3 (0) (CI NR; p=0.413)	
Data sources				
Health outcomes: Percentage requiring allogeneic blood transfusion and volume transfused, blood loss, length of stay, complications including deep vein thrombosis, EQ-5D from within study. **Quality-of-life weights:** Patient elicited EQ-5D values. The tariff of utility values was not specified. **Cost sources:** Resource use from within study. Source of unit cost of allogeneic blood, hospital stay per diem and cost of tranexamic acid not reported but likely to be from institution. Cost of complications and staff time not estimated.				
Comments				
Source of funding: NR. **Limitations:** Health effects not expressed in terms of QALYs, study does not include all interventions in protocol. short follow up which does not				

account for impact of potential risks and costs associated with transfusion related adverse events and illness. Costs do not account for resource use such as staff time and the cost of complications. **Other:**	
Overall applicability[(a)]: Partially applicable	**Overall quality[(b)]:** Potentially serious limitations

Abbreviations: CCA: cost–consequence analysis; CI: 95% confidence interval; da: deterministic analysis; ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; QALYs: quality-adjusted life years

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

Table 9: Davies 2006[41]

Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C. Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: A systematic review and economic model. Health Technology Assessment. 2006; 10(44):1-114. (Guideline Ref ID DAVIES2006)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CUA (health outcome: QALYs) **Study design:** Probabilistic decision analytic model **Approach to analysis:** Decision tree depicting surgical patients receiving either cell salvage or no cell salvage. All patients who receive a transfusion have a risk of transfusion or surgical complications and transfusion complications. For allogeneic blood	**Population:** Adults undergoing elective non-urgent major surgery (orthopaedic, cardiac and vascular surgery) **Cohort settings:** Start age: NR[(a)] Male: NR **Intervention 1:** No cell salvage **Intervention 2:** Cell salvage (intra-operative and post-operative)	**Total costs (mean per patient):** Intervention 1: £5,006 Intervention 2: £4,930 Incremental (2-1): -£76 (CI NR; p = NR) **Currency & cost year:** 2003-2004 UK pounds **Cost components incorporated:** Cost per case of washed cell salvage equipment, maintenance, consumables and staff (the cost of the cell saver machine was discounted at 3.5% over 8 years); transfusion and transfusion-related services;	**QALYs (mean per patient):** Intervention 1: 0.0632 Intervention 2: 0.0680 Incremental (2-1): 0.00477 (CI NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 dominates intervention 1 (pa) Probability Intervention 2 cost-effective (£30K threshold): 91% **Analysis of uncertainty:** A probabilistic sensitivity analysis was conducted for the base case. Additional analyses were conducted to explore the impact on results of using different structural variables or data sets: • timing of cell salvage (intra-operative vs. post-operative) and technique (washed vs. unwashed) • use of transfusion protocol for allogeneic transfusion • surgical procedure (cardiac and orthopaedic) • long term impact of adverse events on

transfusion there is a risk of transfusion transmitted infections. For cell salvage transfusion there is a risk of cell salvage transfusion complications **Perspective:** UK NHS **Time horizon:** 1 month post transfusion **Discounting:** Costs: n/a; Outcomes: n/a		operation and index hospital admission; and adverse events (surgical and transfusion-related).		costs and QALYs (time horizon of analysis: 1, 10 and 30 years) • cost of cell salvage (equipment and activity levels per year) Results indicate that in cardiac surgery, washed intra-operative cell salvage was more likely to be cost effective than unwashed post-operative cell salvage. In orthopaedic surgery, unwashed post-operative cell salvage was more likely to be cost effective than washed intra-operative cell salvage. All other analyses indicated similar results to the base case.
Data sources				
Health outcomes: Probability of transfusion with allogeneic blood and / or cell salvage and risk of adverse events related to transfusion or surgery, were derived from published systematic reviews (Carless 2003)[19] and the authors own systematic review. Conditional probabilities of adverse events and mortality related to transfusion only (autologous or allogeneic blood) were estimated from national surveys of serious hazards of transfusion and other published sources. **Quality-of-life weights:** Utility values for long-standing illness, limiting illness and no long-standing illness from the 1996 Health Survey for England were used in the model for the time between surgery and discharge, discharge to 30 days and one month to one year post surgery, respectively. Authors did not use different utilities for short term transfusion and surgery-related complications (<30 days) as they assumed the impact on quality of life was likely to be minimal compared with the impact of the underlying reason for surgery. The exception was for stroke, for which a utility value was taken from published literature. In addition, for transfusion-related infections at one month to one year after surgery, the utility value for limiting illness was adopted. The tariff of utility values was not specified. **Cost sources:** Resource use: mean number of units of blood transfused (allogeneic and salvaged), pre- and perioperative use of transfusion related services, adverse events and length of hospital stay were estimated from a number of sources including published systematic reviews, the authors own systematic review, two trial databases held at South Manchester University Hospital Trust and national Hospital Episode Statistics. **Unit costs:** cell salvage cost from manufacturer; transfusion, transfusion-related services, operation and index hospital admission from South Manchester University Hospital Trust financial records and NHS Blood Transfusion Authority; adverse events from published national sources.				
Comments				
Source of funding: NHS R&D Health Technology Assessment (HTA) Programme. **Limitations:** Study does not include all interventions in protocol. Model used data for resource use as well as effectiveness from clinical trials that were mostly outside the UK. Effectiveness of transfusion strategies included older technologies (systematic review included studies from 1979) that may be less effective than the newer technologies used to estimate costs (2003-2004). No discounting was reported in the sensitivity analyses where a ten and 30 year time horizon was applied. **Other:** This model included additional comparators other than allogeneic blood including: pre-				

operative autologous donation, acute normovolaemic haemodilution, antifibrinolytic drugs, fibrin sealants, erythropoietin and transfusion triggers. The results of those comparisons have not been reported here. The results for erythropoietin are presented in the erythropoietin and iron section.

Overall applicability[(b)]: Partially applicable **Overall quality[(c)]:** Minor limitations

Abbreviations: CI: 95% confidence interval; CUA: cost–utility analysis; ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) Age not specified for the base case. In the analysis of uncertainty when a 10 year time horizon was used, the model was based on a 70 year old member of general population and for the 30 year time horizon it was based on a 50 year old member of general population.

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Table 10: Klein 2008[84]

Klein AA, Nashef SAM, Sharples L, Bottrill F, Dyer M, Armstrong J et al. A randomized controlled trial of cell salvage in routine cardiac surgery. Anesthesia and Analgesia. 2008; 107(5):1487-1495. (Guideline Ref ID KLEIN2008)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcome: percentage of patients receiving allogeneic blood product transfusion and volume of allogeneic blood products transfused) **Study design:** Within trial analysis (RCT) **Approach to analysis:** Analysis of individual level resource use, with unit costs applied.	**Population:** Adults undergoing nonemergency first time coronary artery bypass grafting and / or cardiac valve surgery. **Cohort settings:** Start age: 68 Male: 76% **Intervention 1:** No cell salvage. Allogeneic blood was transfused during surgery for a haemoglobin level of <7 g/dl and after surgery for a haemoglobin	**Total costs (mean per patient):** Intervention 1: £11,001 Intervention 2: £11,478 Incremental (2-1): £477 (CI NR; p = NR) **Currency & cost year:** 2006-2007 US dollars (presented here as 2007 UK pounds[(a)]) **Cost components incorporated:** Cost of operation room, intensive care unit stay, ward stay, adverse events, red blood cells, other blood	**Percentage receiving allogeneic blood product transfusions (red blood cells, fresh frozen plasma and platelets):** Intervention 1: 32% Intervention 2: 32% Incremental (2-1): 0% (CI NR; p = NR) **Total units of allogeneic red blood cells transfused (mean per patient transfused):** Intervention 1: 3 Intervention 2: 2.58	**ICER (Intervention 2 versus Intervention 1):** Intervention 2 is more costly and more effective at reducing units of allogeneic blood products transfused than intervention 1. Probability Intervention 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** NR

Perspective: UK NHS **Time horizon:** health outcomes: 5 days post-surgery; costs: 30 days post-surgery **Discounting:** Costs: n/a; Outcomes: n/a	level of <8 g/dl. **Intervention 2:** Cell salvage (intra-operative and post-operative). Patients were only transfused allogeneic blood if no salvaged blood was available. The same transfusion protocol for allogeneic blood was used as Intervention 1.	products (fresh frozen plasma and platelets), cell salvage equipment, primary care visits and medication.	Incremental (2-1): -0.42 (CI NR; p = NR) **Total units of allogeneic fresh frozen plasma transfused (mean per patient transfused):** Intervention 1: 4.6 Intervention 2: 3.88 Incremental (2-1): -0.725 (CI NR; p = NR) **Total units of platelets transfused (mean per patient transfused):** Intervention 1: 2.8 Intervention 2: 1.17 Incremental (2-1): -1.63 (CI NR; p = NR)	
Data sources				
Health outcomes: Mean volume of allogeneic blood products transfused and proportion of patients transfused from within RCT. **Quality-of-life weights:** n/a. **Cost sources:** Resource use: duration of surgery, length of hospitalisation in the intensive care unit and post-operative ward, drug use, readmission after initial discharge and visits with the general practitioner and home health nurse all collected prospectively from within RCT. Unit costs: cell salvage from purchase scheme with hospital; blood products from National Blood service; operating room, intensive care unit and ward bed day costs from hospital; and drug costs from the British National Formulary.				
Comments				
Source of funding: NR **Limitations:** Health effects not expressed in terms of QALYs, study does not include all interventions in protocol, follow up for health outcomes and cost is not the same and no analysis of uncertainty conducted. **Other:** Study also presented safety and complications outcomes and found that the two intervention groups were similar in overall number of complications.				
Overall applicability[(b)]: Partially applicable **Overall quality[(c)]:** Potentially serious limitations				

Abbreviations: CCA: cost–consequence analysis; CI: 95% confidence interval; ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) Converted using 2007 purchasing power parities[122]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

Table 11: Rajesparan 2009[131]

Rajesparan K, Biant LC, Ahmad M, Field RE. The effect of an intravenous bolus of tranexamic acid on blood loss in total hip replacement. Journal of Bone and Joint Surgery British Volume. 2009; 91(6):776-783. (Guideline Ref ID RAJESPARAN2009)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcome: percentage requiring allogeneic blood transfusion and volume transfused, blood loss and deep vein thrombosis) **Study design:** Within trial analysis (RCT) **Approach to analysis:** Analysis of individual level resource use with unit costs applied. **Perspective:** UK NHS **Follow-up:** 36 days post-surgery **Discounting:** Costs: n/a; Outcomes: n/a	**Population:** Adults undergoing total hip replacement surgery **Patient characteristics:** N: 73 Mean age (SD): 67.5 (10.3) Male: 64% **Intervention 1:** No tranexamic acid **Intervention 2:** Tranexamic acid (1 g intravenously before surgery)	**Total costs (mean per patient):** Intervention 1: £76.46 Intervention 2: £25.95 Incremental (2-1): -£53.51 (CI NR; p = NR) **Currency & cost year:** UK pounds, year NR, assumed to be 2009 UK pounds based on the date publication submission **Cost components incorporated:** Unit cost of allogeneic red blood cells and tranexamic acid.	**Percentage receiving allogeneic blood transfusion:** Intervention 1: 27% Intervention 2: 8.3% Incremental (2−1): -18.7% (CI NR; p = NR) **Total units of allogeneic blood transfused (mean per patient transfused):** Intervention 1: 2.1 Intervention 2: 2 Incremental (2-1): -0.1 (CI NR; p = NR) **Actual blood loss (ml):** Intervention 1: 1683 Intervention 2: 1372 Incremental (2-1): -311 (CI NR; p = NR) **Deep vein thrombosis:** Intervention 1: 2	**ICER (intervention 2 versus intervention 1):** Intervention 2 dominates intervention 1 (da) Probability Intervention 2 cost-effective (£20K/30K threshold): n/a **Analysis of uncertainty:** NR

			Intervention 2: 1 Incremental (2-1): -1 (CI NR; p = NR)	
Data sources				
Health outcomes: Percentage requiring allogeneic blood transfusion, volume transfused, blood loss and rate of clinical post-operative deep vein thrombosis confirmed by venography from within study. **Quality-of-life weights:** n/a. **Cost sources:** Resource use from within study. Unit cost of allogeneic blood and cost of tranexamic acid from institution.				
Comments				
Source of funding: NR. **Limitations:** Health effects not expressed in terms of QALYs, study does not include all interventions in protocol, short follow up which does not account for impact of potential risks and costs associated with transfusion related adverse events and illness. Costs do not account for resource use such as staff time and no analysis of uncertainty was conducted. **Other:** None of the patients experienced episodes of pulmonary embolism.				
Overall applicability[(a)]: Partially applicable **Overall quality[(b)]:** Potentially serious limitations				

Abbreviations: CCA: cost–consequence analysis; CI: 95% confidence interval; da: deterministic analysis; ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; QALYs: quality-adjusted life years

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

Table 12: Samnaliev 2013[140]

Samnaliev M, Tran CM, Sloan SR, Gasior I, Lightdale JR, Brustowicz RM. Economic evaluation of cell salvage in pediatric surgery. Paediatric Anaesthesia. 2013; 23(11):1027-1034. (Guideline Ref ID SAMNALIEV2013)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcome: percentage of patients receiving allogeneic blood product transfusion and volume of allogeneic blood products transfused)	**Population:** Paediatric patients undergoing orthopaedic (90.2%) or cardiac surgery (9.8%). **Cohort settings:** Start age: 14.1 Male: NR	**Total costs (mean per patient):** Intervention 1: £610 Intervention 2: £997 Incremental (2−1): -£387 (CI: £15 to £1,262; p = NR) **Currency & cost year:** 2010 US dollars (presented	**Percentage receiving allogeneic red blood cell transfusions:** Intervention 1: 100% Intervention 2: 49% Incremental (2-1): -51% (CI NR; p = NR) **Total units of allogeneic red**	**ICER (intervention 2 versus intervention 1):** Intervention 2 dominates intervention 1 (pa) Probability Intervention 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** Probabilistic sensitivity analysis conducted around costs (CI presented in costs column).

Study design: Probabilistic decision analytic model **Approach to analysis:** Decision tree depicting surgical patients receiving either cell salvage or no cell salvage. All patients who receive an allogeneic transfusion have a risk of transfusion-related adverse events. **Perspective:** USA healthcare perspective **Time horizon:** Lifetime **Discounting:** Costs: NR; Outcomes: NR	**Intervention 1:** No cell salvage. **Intervention 2:** Intra-operative cell salvage.	here as 2010 UK pounds[(a)]) **Cost components incorporated:** Cost of cell salvage (including disposables and supplies, cell salvage technician, paediatric anaesthetists), allogeneic transfusion (unit of red blood cells and blood processing including staff time), and costs of transfusion related adverse events.	**blood cells transfused (mean per patient transfused):** Intervention 1: 3.586 Intervention 2: 2.41 Incremental (2-1): -1.096 (CI NR; p = NR)	Subgroup analyses by surgery type (cardiac and orthopaedic). Intervention 2 remains dominant. A series of threshold analysis were conducted to estimate the maximum cost of cell salvage per patient that would still result in cell salvage being cost-saving: • The cost of cell salvage in the base case was £59 per patient and the maximum cost of cell salvage for it to remain cost saving was £446 per patient. • The maximum cost of cell salvage was £113 when it is assumed the incremental (2-1) units transfused is 0.5 and blood processing costs are reduced from £253 per unit to £69 per unit • The maximum cost of cell salvage was £896 when it is assumed the incremental (2-1) units transfused is 1.3 and blood processing costs are increased from £253 per unit to £518 per unit
Data sources				
Health outcomes: Mean volume of allogeneic blood products transfused and proportion of patients transfused based on data for all paediatric surgical patients who were eligible for cell salvage at the Boston Children's Hospital in 2010. Baseline mean volume of allogeneic blood products transfused and proportion of patients transfused based on assumption that number of salvaged units of red blood cells replaces an equivalent amount of units that would have been transfused in absence of cell salvage. Probabilities of transfusion related events from various sources (published literature, national data). **Quality-of-life weights:** n/a. **Cost sources:** Resource use for cell salvage and allogeneic transfusion based on Boston Children's Hospital data, transfusion related adverse events resource use based on hospital and published literature. Unit costs: cell salvage associated costs from Boston Children's Hospital; blood products from US national source; transfusion related adverse events from Boston Children's Hospital and published literature.				
Comments				
Source of funding: Boston Children's Hospital **Limitations:** Health effects not expressed in terms of QALYs, study does not include all interventions in protocol. Effectiveness data from a non-randomised study which were not included in clinical review and therefore does not reflect full body of evidence. Baseline transfusion				

rates based on assumptions. Rate of discounting not reported. **Other:** This model included additional comparators other than allogeneic blood including: pre-operative autologous donation and cell salvage in combination with pre-operative autologous donation. The results of those comparisons have not been reported here.	
Overall applicability[(b)]: Partially applicable	**Overall quality[(c)]:** Potentially serious limitations

Abbreviations: CCA: cost-consequence analysis; CI: 95% confidence interval; CUA: cost–utility analysis; ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) Converted using 2010 purchasing power parities[122]

(b) Directly applicable / Partially applicable / Not applicable

(c) Minor limitations / Potentially serious limitations / Very serious limitations

I.3 Red blood cells

Table 13: Walsh 2013[180]

Walsh TS, Boyd JA, Watson D, Hope D, Lewis S, Krishan A et al. Restrictive versus liberal transfusion strategies for older mechanically ventilated critically ill patients: a randomized pilot trial. Critical Care Medicine. 2013; 41(10):2354-2363. (Guideline Ref ID WALSH2013)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcome: life years) **Study design:** Within-trial (RCT), Walsh 2013[180] **Approach to analysis:** Analysis of individual level resource use, with unit costs applied **Perspective:** UK NHS **Follow-up:** 180 days **Discounting:** Costs:	**Population:** Anaemic older critically ill patients requiring prolonged mechanical ventilation. **Patient characteristics:** n=100 Mean age: Intervention 1: 68 (SD: 8) Intervention 2: 67 (SD: 7) Male: 60% **Intervention 1:** Liberal transfusion (Hb transfusion trigger ≤90	**Total costs (mean per patient):** Intervention 1: £58,796 Intervention 2: £77,061 Incremental (2-1): £18,265 (95% CI -£1,310 to £37,841; p=NR) Cost breakdown: Index ICU episode (mean per patient): Intervention 1: £36,177 Intervention 2: £47,328 Incremental (2-1): £11,151	**Life years (mean per patient):** Intervention 1: NR Intervention 2: NR Incremental (2-1): 0.072 (95% CI -0.01 to 0.155; p=NR) Utility data also reported but not incorporated in cost-effectiveness analysis: SF-6D (median per patient) at 60 days: Intervention 1: 0.57	**ICER (intervention 2 versus intervention 1):** £253,681 per life year gained **Analysis of uncertainty:** Bootstrapping analysis was used to quantify uncertainty in the ICER but was presented graphically.

n/a; Outcomes: n/a	g/litre; target Hb range, 91–110 g/litre) **Intervention 2:** Restrictive transfusion (Hb transfusion trigger ≤70g/litre; target Hb range, 71–90 g/litre)	(95% CI -£3,259 to £25,563; p=NR) All hospital inpatient episodes (mean per patient): Intervention 1: £46,181 Intervention2: £56,878 Incremental (2-1): £10,697 (95% CI -£2,003 to £23,397; p=NR) **Currency & cost year:** 2010 UK pounds **Cost components incorporated:** Length of intensive care unit, high dependency unit and ward stay, self-reported hospital clinic visits, primary care visits and other community based health services.	Intervention 2: 0.56 Incremental mean difference (2-1): -0.04 (95% CI -0.10 to 0.02; p=NR) SF-6D (median per patient) at 180 days: Intervention 1: 0.56 Intervention 2: 0.62 Incremental mean difference (2-1): 0.06 (95% CI -0.01 to 0.14; p=NR)	

Data sources
Health outcomes: Within-trail analysis (RCT), Walsh 2013[180]. **Quality-of-life weights:** Within-trial analysis (RCT): SF-6D derived from SF-12 questionnaire responses. **Cost sources:** Resource use from within RCT; unit costs from Scottish and national sources.
Comments
Source of funding: Academic or government funding (Chief Scientists office, Scotland; the Scottish National Blood transfusion Service; the NHS Lothian Academic Health Science Centre; and the Transfusion Medicine Education and Research Foundation). **Limitations:** Health and resource outcomes based on one RCT of critically ill patients, QALYs not presented despite reporting SF-6D values, short follow-up period, cost of blood transfusion not included in analysis. **Other:** None
Overall applicability[(a)]: Partially applicable **Overall quality[(b)]:** Potentially serious limitations

Abbreviations: CCA: cost–consequence analysis; 95% CI: 95% confidence interval; da: deterministic analysis; Hb: haemoglobin; ICER: incremental cost-effectiveness ratio; n/a: not applicable; NR: not reported; pa: probabilistic analysis; QALYs: quality-adjusted life years

(a) Directly applicable / Partially applicable / Not applicable
(b) Minor limitations / Potentially serious limitations / Very serious limitations

I.4 Platelets

Table 14: Campbell 2014[17]

Campbell HE, Estcourt LJ, Stokes EA, Llewelyn CA, Murphy MF, Wood EM et al. Prophylactic platelet transfusions in patients with blood malignancies: cost analysis of a randomized trial. Transfusion. 2014; 54(10):2394-2403. (Guideline Ref ID CAMPBELL2014)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcome: various health outcomes) **Study design:** Within-trial (RCT), Stanworth 2013[163] **Approach to analysis:** Analysis of individual level resource use, with unit costs applied **Perspective:** UK NHS **Follow-up:** 30 days **Discounting:** Costs: n/a; Outcomes: n/a	**Population:** Patients 16 years or older who were receiving chemotherapy or undergoing stem-cell transplantation and who had or were expected to have thrombocytopenia **Patient characteristics:** n=600 Mean age: 55 Male: 65% **Intervention 1:** Prophylactic transfusion if the platelet count < $10x10^9$ per litre. **Intervention 2:** No prophylaxis if the platelet count <$10x10^9$ per litre	**Total costs (mean per patient):** Intervention 1: £7,623 Intervention 2: £6,821 Incremental (2-1): saves £801 (95% CI -£1,479 to -£113; p<0.05) **Currency & cost year:** 2011/2012 UK pounds **Cost components incorporated:** Platelet and red blood cell allogeneic transfusion, major bleeds (includes costs of additional interventions, investigations and drugs of blood products to diagnose and treat major bleed), haematology ward stay, investigation and	**Platelet units transfused (mean per patient):** Intervention 1: 3.24 Intervention 2: 1.93 Incremental (2-1): saves 1.31 (95% -1.85 to -0.77; p<0.01) **Red blood cell units transfused (mean per patient):** Intervention 1: 2.78 Intervention 2: 3.00 Incremental (2-1): 0.21 (95% CI -0.28 to 0.77; p=NR) **Percentage with major bleeds, WHO grade 3 or 4:** Intervention 1: <1% Intervention 2: 2%	**ICER (intervention 2 versus intervention 1):** na **Analysis of uncertainty:** Bootstrapping analysis was used to quantify uncertainty in the costs. Subgroup analyses of costs conducted looking at autologous hematopoietic stem cell transplantation (HSCT) patients and chemotherapy/allogeneic HSCT patient separately: **Total costs autologous HSCT (mean per patient):** Intervention 1: £6,057 Intervention 2: £6,007 Incremental (2-1): saves £50 (95% CI -£750 to £712; p=NR) **Total costs chemotherapy/allogeneic HSCT (mean per patient):** Intervention 1: £11,318

		medications, serious adverse event-related investigation and medications and serious adverse event-related ICU ward stay.	Incremental (2-1): 2% (95% CI 0% to 3%; p=NR) **Percentage with bleeds, WHO grade 2 or above:** Intervention 1: 43% Intervention 2: 50% Incremental (2-1): 8.4% (95% CI 1.7% to 15.2%; p=0.06) **Haematology ward stay (mean days per patient):** Intervention 1: 14.23 Intervention 2: 13.73 Incremental (2-1): saves 0.50 (95% CI -1.58 to 0.56; p=NR) **Percentage with serious adverse events:** Intervention 1: 7% Intervention 2: 6% Incremental (2-1): saves 1% (95% CI -5% to 3%; p=NR)	Intervention 2: £8,731 Incremental (2-1): saves £2,587 (95% CI -£3,904 to -£1,298; p<0.01) A number of sensitivity analyses were conducted including one where daily treatment costs were assumed to be the same for prophylaxis patients in both subgroups and there was no difference in hospital inpatient stay between trial arms in the chemotherapy/allogeneic HSCT subgroup. This analysis found that the no prophylaxis saves £428 (95% CI -£1,083 to £236) compared to prophylaxis.
Data sources				
Health outcomes: Within-trail analysis (RCT), presented in this paper and in Stanworth 2013.[163] **Quality-of-life weights:** n/a. **Cost sources:** Resource use from use was from a subset of patients from the RCT; unit costs from UK national published sources, hospital finance department and published literature.				
Comments				
Source of funding: Academic or government funding (National Health Service Blood and Transplant Research and Development Committee and the Australian Red				

Cross Blood Service). **Limitations:** Health and resource outcomes based on one of two RCTs comparing prophylaxis to no prophylaxis included in the clinical review, health effects not expressed in terms of QALYs, resource use from a subset of patients included in the trial, short follow up which does not account for impact of potential risks and costs associated with transfusion related adverse events and illness. **Other:** None

Overall applicability[(a)]: Partially applicable **Overall quality[(b)]:** Potentially serious limitations

Abbreviations: CCA: cost–consequence analysis; 95% CI: 95% confidence interval; ICER: incremental cost-effectiveness ratio; ICU: Intensive care unit; n/a: not applicable; NR: not reported; QALYs: quality-adjusted life years; WHO: World Health Organisation.

(a) Directly applicable / Partially applicable / Not applicable

(b) Minor limitations / Potentially serious limitations / Very serious limitations

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