National Clinical Guideline Centre

Draft for consultation

Transfusion

Blood Transfusion

NICE guideline

Methods, evidence and recommendations

18 May 2015

Draft for consultation

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1 # Guideline Development Group members

Name	Role
Professor Michael Murphy	Professor of Blood Transfusion Medicine, University of Oxford and Consultant Haematologist , NHS Blood & Transplant and Oxford University Hospitals
Dr. Shubha Allard	Consultant Haematologist, NHS Blood & Transplant and Barts Health NHS Trust
Mr. David Blackwell	Transfusion Practitioner, Medway NHS Foundation Trust
Mr. Graham Donald	Patient Member
Mr. Kenneth Halligan	Patient Member
Ms. Karen Madgwick	Biomedical Scientist (Transfusion Practitioner), North Middlesex University Hospital NHS Trust
Ms. Mary Marsden	Transfusion Practitioner Nurse Specialist, Central Manchester University Hospitals NHS Foundation Trust
Mr. Robert Morris	Consultant Neurosurgeon, Cambridge University Hospitals NHS Trust
Dr. Helen New	Consultant in Paediatric Haematology and Transfusion Medicine Imperial College Healthcare NHS Trust/NHSBT
Dr. Susan Robinson	Consultant Haematologist, Guy's and St Thomas' NHS Foundation Trust
Dr. Dafydd Thomas	Consultant in Anaesthesia and Critical Care Morriston Hospital
Dr. Timothy Walsh	Professor of Critical Care, Edinburgh University, Queens Medical Research Institute, Edinburgh. Honorary Consultant in Critical Care, Edinburgh Royal infirmary, Lothian University Hospitals Division, Edinburgh.

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3 # NCGC technical team members

Name	Role
Ms. Joanna Ashe	Senior Information Scientist
Miss Tamara Diaz	Project Manager
Mrs. Sophia Kemmis-Betty	Senior Health Economist
Dr. Jennifer Hill	Operations Director
Ms. Kate Lovibond	Health Economics Lead (December 2013 - Apr 2015)
Ms. Grace Marsden	Senior Health Economist (until Nov 2013)
Dr. Smita Padhi	Senior Research Fellow
Dr. Sharangini Rajesh	Research Fellow
Dr. Giulia Zuodar	Document Editor/Process Assistant (from March 2015)
Ms. Lindsay Dytham	Document Editor/Process Assistant (until Mach 2015)

Acknowledgements

The development of this guideline was greatly assisted by the following people:

Name	Role
Ms. Jill Cobb	Information Science Document Delivery, NCGC
Dr. Lee Yee Chong	Senior Research Fellow, NCGC
Mr. David Wonderling	Head of Health Economics, NCGC

1 Guideline summary

1.1 Key priorities for implementation

From the full set of recommendations, the GDG selected [10] key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in the NICE guidelines manual(NICE2014).[209] The reason that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter.

Alternatives to blood transfusion for patients having surgery

Intravenous and oral iron

1. Offer oral iron before and after surgery to people with iron-deficiency anaemia.

Cell salvage and tranexamic acid

2. Offer tranexamic acid to adults undergoing surgery who are expected to have at least moderate blood loss (greater than 500 ml).
3. Consider intra-operative cell salvage with tranexamic acid for patients who are expected to lose a very high volume of blood (for example in complex cardiac and vascular surgery, major obstetric procedures, and pelvic reconstruction and scoliosis surgery).

Red Blood Cells

Thresholds and Targets

4. When using a restrictive red blood cell transfusion threshold, consider a threshold of 70 g/litre and a haemoglobin concentration target of 70–90 g/litre after transfusion.

Doses

5. Consider single-unit red blood cell transfusions for adults (or equivalent volumes, calculated based on body weight, for children or adults who weigh under 50 kg) who do not have active bleeding.

Platelets

Thresholds and Targets

Patients who are not bleeding or having invasive procedures or surgery

6. Offer prophylactic platelet transfusions to patients with a platelet count below $10x10^9$ per litre who are not bleeding or having invasive procedures or surgery, unless they have:
   - chronic bone marrow failure
   - autoimmune thrombocytopenia
   - heparin-induced thrombocytopenia
   - thrombotic thrombocytopenic purpura.

Doses

7. Do not routinely give more than a single dose of platelets in a transfusion.

Fresh Frozen Plasma

8. Do not offer fresh frozen plasma transfusions to correct abnormal coagulation in patients who:
   - are not bleeding and

- are not having invasive procedures or surgery with a risk of clinically significant bleeding.

Prothrombin complex concentrate

9. Offer immediate prothrombin complex concentrate transfusions for the emergency reversal of warfarin anticoagulation in patients with either:
   - severe bleeding or
   - head injury with suspected intra-cerebral haemorrhage.

Patient information

10. Provide verbal and written information to patients who may have or who have had a transfusion, and their family members or carers (as appropriate), explaining:
    - the reason for the transfusion
    - the risks and benefits
    - the transfusion process
    - any transfusion needs specific to them
    - any alternatives that are available, and how they might reduce their need for a transfusion
    - the implications of having a transfusion, such as no longer being able to donate blood
    - that they are encouraged to ask questions.

1.2 Full list of recommendations

1. Do not offer erthropoietin to reduce the need for blood transfusion in patients having surgery.
2. Offer oral iron before and after surgery to patients with iron-deficiency anaemia.
3. Consider intravenous iron before and after surgery for patients with iron-deficiency anaemia who:
   - cannot tolerate or absorb oral iron
   - are diagnosed with functional iron deficiency
   - are diagnosed with iron-deficiency anaemia and the interval to surgery is considered short
   - are unable to adhere to oral iron treatment (see the NICE guideline on medicines adherence).
4. For guidance on managing anaemia in patients with chronic kidney disease, see the NICE guideline on anaemia management in chronic kidney disease.
5. For guidance on managing upper gastrointestinal bleeding, see the NICE guideline on upper gastrointestinal bleeding.
6. Offer tranexamic acid to adults undergoing surgery who are expected to have at least moderate blood loss (greater than 500 ml)
7. Consider tranexamic acid for children undergoing surgery who are expected to have at least moderate blood loss (greater than 10% blood volume).
8. Do not routinely offer cell salvage alone.
9. Consider intra-operative cell salvage with tranexamic acid for patients who are expected to lose a very high volume of blood (for example in complex

cardiac and vascular surgery, major obstetric procedures, and pelvic reconstruction and scoliosis surgery).

10. Monitor the patient's condition and vital signs before, during and after blood transfusions, to detect acute transfusion reactions that may need immediate investigation and treatment.

11. Observe patients who are having or have had a blood transfusion in an environment with adequate staffing and facilities for monitoring and managing acute reactions.

12. Hospitals should consider using electronic patient identification systems to improve the safety and efficiency of the blood transfusion process.

13. Use restrictive red blood cell transfusion thresholds for patients who need red blood cell transfusions and who do not have major haemorrhage or acute coronary syndrome.

14. When using a restrictive red blood cell transfusion threshold, consider a threshold of 70 g/litre and a haemoglobin concentration target of 70–90 g/litre after transfusion.

15. Consider a red blood cell transfusion threshold of 80 g/litre and a haemoglobin concentration target of 80–100 g/litre after transfusion for patients with acute coronary syndrome.

16. Consider setting individual thresholds and haemoglobin concentration targets for each patient who needs regular blood transfusions for chronic anaemia.

17. Consider single-unit red blood cell transfusions for adults (or equivalent volumes, calculated based on body weight, for children or adults who weigh under 50 kg) who do not have active bleeding.

18. After each single-unit red blood cell transfusion (or equivalent volumes, calculated based on body weight, for children or adults who weigh under 50 kg), clinically reassess and check haemoglobin levels, and give further transfusions if needed.

Patients with thrombocytopenia who are bleeding

19. Offer platelet transfusions to patients with thrombocytopenia who have clinically significant bleeding (World Health Organization [WHO] grade 2) and a platelet count below $30x10^9$ per litre.

20. Use higher platelet thresholds (up to a maximum of $100x10^9$ per litre) for patients with thrombocytopenia and either of the following:

- severe bleeding (WHO grades 3 and 4)
- bleeding in critical sites, such as the central nervous system (including eyes).

Patients who are not bleeding or having invasive procedures or surgery

21. Offer prophylactic platelet transfusions to patients with a platelet count below $10x10^9$ per litre who are not bleeding or having invasive procedures or surgery, unless they have:

- chronic bone marrow failure
- autoimmune thrombocytopenia
- heparin-induced thrombocytopenia

- thrombotic thrombocytopenic purpura.

Patients who are having invasive procedures or surgery

22. Consider prophylactic platelet transfusions to raise the platelet count above 50x109 per litre in patients who are having invasive procedures or surgery

23. Consider a higher threshold (for example 50–75x10^9 per litre) in patients with a high risk of bleeding who are having invasive procedures or surgery after taking into account:

- the specific procedure the patient is having
- the cause of the thrombocytopenia
- whether the patient's platelet count is falling
- any coexisting causes of abnormal haemostasis.

24. Consider prophylactic platelet transfusions to raise the platelet count above 100x10^9 per litre in patients having surgery in critical sites, such as the central nervous system (including the posterior segment of the eyes).

25. Do not routinely offer prophylactic platelet transfusions to patients with any of the following:

- chronic bone marrow failure
- autoimmune thrombocytopenia
- heparin-induced thrombocytopenia
- thrombotic thrombocytopenic purpura.

26. Do not offer prophylactic platelet transfusions to patients having procedures with a low risk of bleeding, such as adults having central venous cannulation or any patients having bone marrow aspiration and trephine biopsy.

27. Do not routinely give more than a single dose of platelets in a transfusion.

28. Only consider giving more than a single dose of platelets in a transfusion for patients with severe thrombocytopenia and bleeding in a critical site, such as the central nervous system (including eyes).

29. Clinically reassess the patient's condition and check their platelet count after each platelet transfusion, and give further doses if still needed.

30. Only consider fresh frozen plasma transfusion for patients with clinically significant bleeding but without major haemorrhage if they have abnormal coagulation test results (for example, prothrombin time ratio or activated partial thromboplastin time ratio above 1.5).

31. Do not offer fresh frozen plasma transfusions to correct abnormal coagulation in patients who:

- are not bleeding and
- are not having invasive procedures or surgery with a risk of clinically significant bleeding.

32. Consider prophylactic fresh frozen plasma transfusions for patients with abnormal coagulation who are having invasive procedures or surgery with a risk of clinically significant bleeding.

33. Use a dose of at least 15 ml/kg when giving fresh frozen plasma transfusions.

34. Clinically reassess the patient's condition and repeat the coagulation tests after fresh frozen plasma transfusion, and give further doses if needed.

35. Consider cryoprecipitate transfusions for patients without major haemorrhage who have:

- clinically significant bleeding and
- a fibrinogen level below 1.5 g/litre.

36. Do not offer cryoprecipitate transfusions to correct the fibrinogen level in patients who:

- are not bleeding and
- are not having invasive procedures or surgery with a risk of clinically significant bleeding.

37. Consider prophylactic cryoprecipitate transfusions for patients with a fibrinogen level below 1.0 g/litre who are having invasive procedures or surgery with a risk of clinically significant bleeding.

38. Use an adult dose of 2 pools when giving cryoprecipitate transfusions (for children, use 5–10 ml/kg up to a maximum of 2 pools).

39. Clinically reassess the patient's condition, repeat the fibrinogen level measurement and give further doses if needed.

40. Offer immediate prothrombin complex concentrate transfusions for the emergency reversal of warfarin anticoagulation in patients with either:

- severe bleeding or
- head injury with suspected intra-cerebral haemorrhage.

41. For guidance on reversing anticoagulation treatment in people who have a stroke and a primary intracerebral haemorrhage, see recommendation 1.4.2.8 in the NICE guideline on the initial diagnosis and management of stroke.

42. Consider immediate prothrombin complex concentrate transfusions to reverse warfarin anticoagulation in patients having emergency surgery, depending on the level of anticoagulation and the bleeding risk.

43. Monitor the international normalised ratio (INR) to confirm that warfarin anticoagulation has been adequately reversed, and consider further prothrombin complex concentrate.

44. Provide verbal and written information to patients who may have or who have had a transfusion, and their family members or carers (as appropriate), explaining:

- the reason for the transfusion
- the risks and benefits
- the transfusion process
- any transfusion needs specific to them
- any alternatives that are available, and how they might reduce their need for a transfusion
- the implications of having a transfusion, such as no longer being able to donate blood
- that they are encouraged to ask questions.

45. Document discussions in the patient's notes.
46. Provide the patient and their GP with copies of the discharge summary or other written communication that explains:
    - the details of any transfusions they had
    - the reasons for the transfusion
    - any adverse events.

1.3 Key research recommendations

1. Post-operative cell salvage: For patients having cardiac surgery with a significant risk of post-operative blood loss, is post-operative cell salvage and reinfusion clinically and cost effective in reducing red blood cell use and improving clinical outcomes, compared with existing practice?
    - Why this is important: There was some evidence for benefit from post-operative cell salvage, but the quality was low. Reducing blood loss during cardiac surgery may reduce the risk of complications. However, post-operative cell salvage carries additional cost. Studies are needed to determine whether post-operative cell salvage is more clinically and cost effective than existing practice for patients having cardiac surgery with a significant risk of post-operative blood loss. Important outcomes should include the use of red blood cells and other blood products, clinical outcomes and quality of life.
2. Electronic Decision Support: What is the clinical and cost effectiveness of an electronic decision support system compared with current practice in reducing inappropriate blood transfusions, overall rates of blood transfusion and mortality?
    - Why this is important: The clinical evidence evaluating electronic decision support systems is of low quality. There is also no evidence on their cost effectiveness within the NHS, and this is particularly important because of the potentially high setup and running costs of these systems. An evaluation of the clinical and cost effectiveness of electronic decision support systems for blood transfusion is needed. Important outcomes are rates of inappropriate transfusion, overall rates of transfusion, and patient safety outcomes including mortality and transfusion errors. Secondary outcomes should include length of hospital stay and quality of life; and pre-transfusion haemoglobin levels, platelet count and coagulation results.
3. Red Blood Cell Transfusion: What is the clinical and cost effectiveness of restrictive compared with liberal red blood cell thresholds and targets for patients with chronic cardiovascular disease?
    - Why this is important: The literature suggests that there may be some evidence of harm with the use of restrictive red blood cell thresholds in populations with coronary ischaemia at baseline. In this guideline a

level of 80–100 g/litre was used for patients with acute coronary syndrome, but further studies are needed to determine the optimal transfusion threshold for patients with chronic cardiovascular disease.

1.4 Algorithm

Do you consider the patient needs a blood transfusion?

Yes

Is the patient surgical?

Yes

Consider alternatives for blood transfusion as follows:
- Do not offer erythropoietin to reduce the need for blood transfusion in patients having surgery.
- Offer oral iron before and after surgery to patients with iron-deficiency anaemia.
- Consider intravenous iron before and after surgery for patients with iron deficiency anaemia who:
  - cannot tolerate or absorb oral iron
  - are diagnosed with functional iron deficiency
  - are diagnosed with iron deficient anaemia and the interval to surgery is considered short
  - are unable to adhere to oral iron treatment (see the NICE guideline on medicines adherence).
- For guidance on managing anaemia in patients with chronic kidney disease, see the NICE guideline on anaemia management in chronic kidney disease.
- For guidance on managing upper gastrointestinal bleeding, see the NICE guideline on upper gastrointestinal bleeding.
- Offer tranexamic acid to adults undergoing surgery who are expected to have at least moderate blood loss (greater than 500ml)
- Consider tranexamic acid for children undergoing surgery who are expected to have at least moderate blood loss (greater than 10% blood volume).
- Do not routinely offer cell salvage alone.
- Consider intra-operative cell salvage with tranexamic acid for patients who are expected to lose a very high volume of blood (for example in complex cardiac and vascular surgery, major obstetric procedures, and pelvic reconstruction and scoliosis surgery).

Does the patient ***still*** need a blood transfusion?

Yes

No

Have other alternatives for blood transfusion been considered?
For example, treatment of any underlying cause for anaemia, such as iron deficiency.

Yes

Identify appropriate blood component to be transfused

Give appropriate verbal and written information to the patient and/or carer.
- Provide verbal and written information to patients who may have or who have had a transfusion, and their family members or carers (as appropriate), explaining:
  - the reason for the transfusion
  - the risks and benefits
  - the transfusion process
  - any transfusion needs specific to them
  - any alternatives that are available, and how they might reduce their need for a transfusion
  - the implications of having a transfusion, such as no longer being able to donate blood
  - that they are encouraged to ask questions.
- Document discussions in the patient's notes.
- Provide the patient and their GP with copies of the discharge summary or other written communication that explains:
  - the details of any transfusions they had
  - the reasons for the transfusion
  - any adverse events

Transfuse the patient following the appropriate recommendations for each component (see below)
- Hospitals should consider using electronic patient identification systems to improve the safety and efficiency of the blood transfusion process.

RBC recommendations
- Use restrictive red blood cell transfusion thresholds for patients who need red blood cell transfusions and who do not have major haemorrhage or acute coronary syndrome.
- When using a restrictive red blood cell transfusion threshold, consider a threshold of 70 g/litre and a haemoglobin concentration target of 70-90 g/litre after transfusion.
- When using a restrictive red blood cell transfusion threshold, consider a threshold of 70 g/litre and a haemoglobin concentration target of 70-90 g/litre after transfusion.
- Consider a red blood cell transfusion threshold of 80 g/litre and a haemoglobin concentration target of 80-100 g/litre after transfusion for patients with acute coronary syndrome.
- Consider setting individual thresholds and haemoglobin concentration targets for each patient who needs regular blood transfusions for chronic anaemia.
- Consider single-unit red blood cell transfusions for adults (or equivalent volumes, calculated based on body weight, for children or adults who weigh under 50kg) who do not have active bleeding.
- After each single-unit red blood cell transfusion (or equivalent volumes calculated based on body weight, for children or adults who weigh under 50kg), clinically reassess and check haemoglobin levels, and give further transfusions if needed.

Platelets recommendations
- Offer platelet transfusions to patients with thrombocytopenia who have clinically significant bleeding (World Health Organization [WHO] grade 2) and a platelet count below $30x10^9$ per litre.
- Use higher platelet thresholds (up to a maximum of $100x10^9$ per litre) for patients with thrombocytopenia and either of the following:
  - severe bleeding (WHO grades 3 and 4)
  - bleeding in critical sites, such as the central nervous system (including eyes).
- Offer prophylactic platelet transfusions to patients with a platelet count below $10x10^9$ per litre who are not bleeding or having invasive procedures or surgery, unless they have:
  - chronic bone marrow failure
  - autoimmune thrombocytopenia
  - heparin-induced thrombocytopenia
  - thrombotic thrombocytopenic purpura
- Consider prophylactic platelet transfusions to raise the platelet count above $50x10^9$ per litre in patients undergoing invasive procedures.or surgery
- Consider a higher threshold (for example 50-$75x10^9$ per litre in patients with a high risk of bleeding who are having invasive procedures or surgery after taking into account:
  - the specific procedure the patient is having
  - the cause of the thrombocytopenia
  - whether the patient's platelet count is falling
  - any coexisting causes of abnormal haemostasis).
- Consider prophylactic platelet transfusions to raise the platelet count above $100x10^9$ per litre in patients having surgery in critical sites, such as the central nervous system (including the posterior segment of the eyes).
- Do not routinely offer prophylactic platelet transfusions to patients with any of the following:
  - chronic bone marrow failure
  - autoimmune thrombocytopenia
  - heparin-induced thrombocytopenia
  - thrombotic thrombocytopenic purpura.
- Do not offer prophylactic platelet transfusions to patients having procedures with a low risk of bleeding, such as adults having central venous cannulation or any patients having bone marrow aspiration and trephine biopsy.
- Do not routinely give more than a single dose of platelets in a transfusion.
- Only consider giving more than a single dose of platelets in a transfusion for patients with severe thrombocytopenia and bleeding in a critical site, such as the central nervous system (including eyes).
- Clinically reassess the patient's condition and check their platelet count after each platelet transfusion, and give further doses if still needed.

FFP recommendations
- Only consider fresh frozen plasma transfusion for patients with clinically significant bleeding but without major haemorrhage if they have abnormal coagulation test results (for example, prothrombin time ratio or activated partial thromboplastin time ratio above 1.5).
- Do not offer fresh frozen plasma transfusions to correct abnormal coagulation in patients who:
  - are not bleeding **and**
  - are not having invasive procedures or surgery with a risk of clinically significant bleeding.
- Consider prophylactic fresh frozen plasma transfusions for patients with abnormal coagulation who are having invasive procedures or surgery with a risk of clinically significant bleeding.
- Use a dose of at least 15 ml/kg when giving fresh frozen plasma transfusions.
- Clinically reassess the patient's condition and repeat the coagulation tests after fresh frozen plasma transfusion, and give further doses if needed.

Cryoprecipitate recommendations
- Consider cryoprecipitate transfusions for patients without major haemorrhage who have:
  - clinically significant bleeding and
  - a fibrinogen level below 1.5 g/litre.
- Do not offer cryoprecipitate transfusions to correct the fibrinogen level in patients who:
  - are not bleeding and
  - are not having invasive procedures or surgery with a risk of clinically significant bleeding.
- Consider prophylactic cryoprecipitate transfusions for patients with a fibrinogen level below 1.0 g/litre who are having invasive procedures or surgery with a risk of clinically significant bleeding.
- Use an adult dose of 2 pools when giving cryoprecipitate transfusions (for children, use 5 – 10 ml/kg up to a maximum of 2 pools).
- Clinically reassess the patient's condition, repeat the fibrinogen level measurement and give further doses if needed.

Prothrombin complex concentrate recommendations
- Offer immediate prothrombin complex concentrate transfusions for the emergency reversal of warfarin anticoagulation in patients with either:
  - severe bleeding or
  - head injury with suspected intra-cerebral haemorrhage.
- Consider immediate prothrombin complex concentrate transfusions to reverse warfarin anticoagulation in patients having emergency surgery, depending on the level of anticoagulation and the bleeding risk.
- Monitor the international normalised ratio (INR) to confirm that warfarin anticoagulation has been adequately reversed, and consider further prothrombin complex concentrate.

- Monitor the patient's condition and vital signs before, during and after blood transfusions, to detect acute transfusion reactions that may need immediate investigation and treatment.
- Observe patients who are having or have had a blood transfusion in an environment with adequate staffing and facilities for monitoring and managing acute reactions.

2 Introduction

Blood transfusions are common in clinical practice. In 2013, NHS Blood and Transplant issued 1.71 million units of red blood cells, 271,000 units of platelets, 230,000 units of fresh frozen plasma and 158,000 units of cryoprecipitate to hospitals in England and North Wales. An estimated 430,000 patients received a red blood cell transfusion in 2002[a], a further study has not been conducted but the number of patients transfused is likely to be 10 – 20% less given the reduction in blood use since 2002.

Despite considerable efforts to ensure the safety of blood transfusions, they are associated with significant risks. The Serious Hazards of Transfusion (SHOT) scheme estimated that in 2013 the risk of transfusion-related death was 8 per million blood components issued, and the risk of transfusion-related major morbidity was 51.8 per million blood components issued.[b] The most common cause of death was transfusion-associated circulatory overload associated with transfusion, for example, transfusion associated circulatory overload (TACO).

There is evidence from national audits of transfusion practice that[c]:

- some patients are receiving the wrong blood components
- the choice of blood component is not always based on clinical findings and laboratory parameters
- patients are not always monitored for the adverse effects of transfusion, and these effects are not always managed correctly.

Accurate patient identification is a crucial step. Giving the wrong patient a blood transfusion is an avoidable serious hazard of transfusion, and can result from errors made anywhere in the transfusion process.

There has been an approximate 25% decline in the transfusion of red blood cells in England in the last 15 years. The red blood cell transfusion rate declined from 45.5 to 36 units per 100,000 people between 1999 and 2009,[291] and since then has dropped further to around 31.5 units per 100,000 people. This rate is a little higher than in Northern Ireland, the Netherlands and Canada, but is considerably lower than in the United States. In contrast, the use of platelets and fresh frozen plasma has been increasing. The proportion of red blood cells used between 1999 and 2009 in surgical patients has declined from 41% to 29% of all red cells transfused, and in medical patients has increased from 52 to 64% of all red cells transfused. Use in obstetrics and gynaecology has remained stable at 6%[d].

There is evidence from several national audits that inappropriate over-use of all blood components is at around 20%[e]. This is wasteful of a scarce and costly resource and puts patients at unnecessary risk.

This guideline provides guidance on:

- the appropriate use of blood components
- alternatives to transfusion for surgical patients
- ensuring patient safety, including monitoring for transfusion reactions

[a] Wells AW, Llewelyn CA, Casbard A, Johnson AJ, Amin M, Ballard S et al. (2009) The EASTR Study: indications for transfusion and estimates of transfusion recipient numbers in hospitals supplied by the National Blood Service. Transfusion Medicine 19(6): 315–28

[b] Bolton-Maggs PHB, Poles D, Watt A and Thomas D (2014) The 2013 SHOT annual report,

[c] NHS Blood and Transplant (2013) National comparative audit of blood transfusion,

[d] Tinegate H, Chattree S, Iqbal A, Plews D, Whitehead J, Wallis JP (2013) Ten-year pattern of red blood cell use in the North of England. Transfusion 53(3): 483–9

[e] Bolton-Maggs PHB, Poles D, Watt A and Thomas D (2014) The 2013 SHOT annual report,

- providing patients with information about transfusion.

This guideline focuses on the general principles of transfusion. To do this, it was necessary to limit the scope by excluding:

- patient groups with special transfusion needs, such as foetuses, neonates and children under 1 year old, pregnant women, and patients with haemoglobinopathies
- specialist areas already covered by NICE guidelines, for example, anaemia in chronic kidney disease, upper gastrointestinal bleeding and trauma and massive haemorrhage
- the use and administration of blood products, such as intravenous immunoglobulin, anti-D and recombinant activated factor VII
- diagnosis of anaemia
- near-patient testing for haemoglobin concentration and haemostasis
- laboratory procedures relating to the safety and quality of blood, including pre-transfusion compatibility testing.

3 Development of the guideline

3.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of healthcare. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC).
- The NCGC establishes a Guideline Development Group.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the ‘full guideline’ contains all the recommendations, plus details of the methods used and the underpinning evidence
- the ‘NICE guideline’ lists the recommendations
- ‘information for the public’ is written using suitable language for people without specialist medical knowledge
- NICE Pathways brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

3.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is:

'to develop a cross cutting clinical guideline on the assessment for and management of transfusion'.

3.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising health professionals and researchers as well as lay members developed this guideline (see the list of Guideline Development Group members and the acknowledgements).

The National Institute for Health and Care Excellence (NICE) funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Professor Mike Murphy in accordance with guidance from NICE.

The group met approximately every 5 – 6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

3.3.1 What this guideline covers

This guideline will cover adults (aged 16 years and above) and children (over 1 year and under 16 years of age) For further details please refer to the scope in Appendix A and the review questions in Section 4.1.

3.3.2 What this guideline does not cover

This guideline will not cover neonates and infants up to 1 year of age; and foetuses. For further details please refer to the scope in Appendix A and the review questions in Section 4.1.

3.3.3 Relationships between the guideline and other NICE guidance

3.3.3.1 General

- Patient experience in adult NHS services (2012) NICE guideline CG138
- Medicines adherence (2009) NICE guideline CG76

3.3.3.2 Published: Condition-specific

- Intrapartum care (2014) NICE guideline CG190
- Erythropoiesis-stimulating agents (epoetin and darbepoetin) for the treatment of cancer-treatment induced anaemia (including review of TA142) (2014) NICE technology appraisal guidance 323
- Intravenous fluid therapy in adults (2013) NICE guideline CG 174
- Ulcerative colitis (2013) NICE guideline CG166
- Acute upper gastrointestinal bleeding (2012) NICE guideline CG141
- Caesarean section (2011) NICE guideline CG132

- Anaemia management in people with chronic kidney disease (2011) NICE guideline CG114
- Neonatal jaundice (2010) NICE guideline CG98
- Intraoperative blood cell salvage during radical prostatectomy or radical cystectomy (2008) NICE interventional procedure guidance 258
- Intraoperative blood cell salvage in obstetrics (2005) NICE interventional procedure guidance 144
- Preoperative tests (2003) NICE guideline CG3
- Stroke: diagnosis and initial management of acute stroke and transient ischaemic attack (TIA) (2008), NICE guideline CG 68

3.3.3.3 NICE is developing the following guidance:

- Anaemia management in chronic kidney disease (update). NICE guideline. Publication May 2015.
- Major trauma. NICE guideline. Publication expected February 2016.
- Major trauma services. NICE guideline. Publication expected February 2016.
- Intravenous fluids therapy in children. NICE guideline. Publication expected October 2015.
- Intrapartum care for high risk women. NICE guideline. Publication date to be confirmed.

4 Methods

This chapter sets out in detail the methods used to review the evidence and to generate the recommendations that are presented in subsequent chapters. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual 2012.[209]

4.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews and in a framework of setting, population, interventions, context and evaluation for qualitative reviews.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence, and facilitated the development of recommendations by the GDG. The review questions were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (Appendix A).

A total of 21 review questions were identified as part of this guideline.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Table 1: Review questions

Chapter	Type of review	Review questions	Outcomes
5. Iron and erythropoietin	Intervention	What is the clinical- and cost-effectiveness of oral iron, IV iron and erythropoietin in reducing blood transfusion requirements in surgical patients?	• Number of patients needing allogeneic transfusions-CRITICAL • Number of units or volume transfused CRITICAL • All-cause mortality at 30 days-CRITICAL • Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Infections-IMPORTANT • Serious adverse events as reported in study-IMPORTANT • Thrombotic complications-IMPORTANT • Bleeding-IMPORTANT
6. Combinations of cell salvage and tranexamic acid	Intervention *Network meta-analysis undertaken*	What is the clinical and cost-effectiveness of using alternatives to blood transfusion (cell salvage or tranexamic acid alone or in combination with one another) to reduce blood transfusion requirements?	• Number of patients needing allogeneic transfusions-CRITICAL • Number of units or volume transfused CRITICAL • All-cause mortality at 30 days-CRITICAL • Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Infections-IMPORTANT • Serious adverse events as reported in study-IMPORTANT • Thrombotic complications-IMPORTANT
10 Red blood cells	Intervention	What is the clinical- and cost-effectiveness of red blood cell transfusion at	• Number of patients needing allogeneic transfusions-CRITICAL • Number of units or volume transfused-

Chapter	Type of review	Review questions	Outcomes
		different haemoglobin concentrations?	CRITICAL • All-cause mortality at 30 days-CRITICAL • Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Infections-IMPORTANT • Acute and delayed serious adverse events as reported in study-IMPORTANT • New cardiac events (Myocardial infarction, Cardiac failure)-IMPORTANT
10 Red blood cells	Intervention	What is the clinical- and cost-effectiveness of different target levels of post-transfusion haemoglobin concentrations for red blood cell transfusion?	• Number of patients needing allogeneic transfusions-CRITICAL • Number of units or volume transfused-CRITICAL • All-cause mortality at 30 days-CRITICAL • Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Infections-IMPORTANT • Acute and delayed serious adverse events as reported in study-IMPORTANT • New cardiac events (Myocardial infarction, Cardiac failure)-IMPORTANT
11 Red blood cells	Intervention	What is the clinical- and cost-effectiveness of different doses of red blood cell transfusion?	• Number of patients needing allogeneic transfusions-CRITICAL • Number of units or volume transfused-CRITICAL • All-cause mortality at 30 days-CRITICAL • Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Infections-IMPORTANT • Acute and delayed serious adverse events as reported in study-IMPORTANT • New cardiac events (Myocardial infarction, Cardiac failure)-IMPORTANT
12 Platelets	Intervention	What is the clinical- and cost-effectiveness of platelet transfusion at different platelet count thresholds?	• Bleeding (reported as WHO grade 2 and above or equivalent)-CRITICAL ○ Occurrence of bleeding (in non-bleeding patients) ○ Cessation of bleeding (in bleeding patients) • Number of patients needing allogeneic transfusions-IMPORTANT • Number of units or volume transfused-IMPORTANT • All-cause mortality at 30 days-CRITICAL • Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Infections-CRITICAL • Serious adverse events as reported in

Chapter	Type of review	Review questions	Outcomes
			study-CRITICAL
12 Platelets	Intervention	What is the clinical- and cost-effectiveness of different target levels of post-transfusion platelet counts?	• Bleeding (reported as WHO grade 2 and above or equivalent)-CRITICAL ○ Occurrence of bleeding (in non-bleeding patients) ○ Cessation of bleeding (in bleeding patients) • Number of patients needing allogeneic transfusions-IMPORTANT • Number of units or volume transfused-IMPORTANT • All-cause mortality at 30 days-CRITICAL • Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Infections-CRITICAL • Serious adverse events as reported in study-CRITICAL
13 Platelets	Intervention	What is the clinical- and cost-effectiveness of different doses of platelet transfusion?	• Bleeding (reported as WHO grade 2 and above or equivalent)-CRITICAL ○ Occurrence of bleeding (in non-bleeding patients) ○ Cessation of bleeding (in bleeding patients) • Number of patients needing allogeneic transfusions-IMPORTANT • Number of units or volume transfused-IMPORTANT • All-cause mortality at 30 days-CRITICAL • Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Infections-CRITICAL • Serious adverse events as reported in study-CRITICAL
14 Fresh frozen plasma	Intervention	What is the clinical- and cost-effectiveness of transfusions of fresh frozen plasma (FFP) to treat and prevent bleeding?	• Bleeding (reported as WHO grade 2 and above or equivalent)-CRITICAL ○ Occurrence of bleeding (in non-bleeding patients) ○ Cessation of bleeding (in bleeding patients) • Number of patients needing allogeneic red cell transfusions-IMPORTANT • Number of units or volume of red cells transfused-IMPORTANT • All-cause mortality at 30 days-CRITICAL • Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Serious adverse events as reported in study-CRITICAL • Infections-CRITICAL

Chapter	Type of review	Review questions	Outcomes
			• Correction of abnormal coagulation tests-IMPORTANT
14 Fresh frozen plasma	Intervention	What is the clinical- and cost-effectiveness of different target levels of post-transfusion haemostasis tests with the use of fresh frozen plasma FFP for prophylactic transfusions?	• Bleeding (reported as WHO grade 2 and above or equivalent)-CRITICAL ○ Occurrence of bleeding (in non-bleeding patients) ○ Cessation of bleeding (in bleeding patients) • Number of patients needing allogeneic red cell transfusions-IMPORTANT • Number of units or volume of red cells transfused-IMPORTANT • All-cause mortality at 30 days-CRITICAL • Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Serious adverse events as reported in study-CRITICAL • Infections-CRITICAL • Correction of abnormal coagulation tests-IMPORTANT
14 Fresh frozen plasma	Intervention	What is the clinical- and cost-effectiveness of different doses of fresh frozen plasma (FFP) for transfusion?	• Bleeding (reported as WHO grade 2 and above or equivalent)-CRITICAL ○ Occurrence of bleeding (in non-bleeding patients) ○ Cessation of bleeding (in bleeding patients) • Number of patients needing allogeneic red cell transfusions-IMPORTANT • Number of units or volume of red cells transfused-IMPORTANT • All-cause mortality at 30 days-CRITICAL • Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Serious adverse events as reported in study-CRITICAL • Infections-CRITICAL • Correction of abnormal coagulation tests-IMPORTANT
15 Cryoprecipitate	Intervention	What is the clinical- and cost-effectiveness of transfusions of cryoprecipitate to treat and prevent bleeding?	• Bleeding (reported as WHO grade 2 and above or equivalent)-CRITICAL ○ Occurrence of bleeding (in non-bleeding patients) ○ Cessation of bleeding (in bleeding patients) • Number of patients needing allogeneic red cell transfusions-IMPORTANT • Number of units or volume of red cells transfused-IMPORTANT • All-cause mortality at 30 days-CRITICAL

Chapter	Type of review	Review questions	Outcomes
			• Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Serious adverse events as reported in study-CRITICAL • Infections-CRITICAL • Correction of abnormal coagulation tests-IMPORTANT
15 Cryoprecipitate	Intervention	What is the clinical- and cost-effectiveness of different target levels of post-transfusion haemostasis tests with the use of cryoprecipitate for prophylactic transfusions?	• Bleeding (reported as WHO grade 2 and above or equivalent)-CRITICAL ○ Occurrence of bleeding (in non-bleeding patients) ○ Cessation of bleeding (in bleeding patients) • Number of patients needing allogeneic red cell transfusions-IMPORTANT • Number of units or volume of red cells transfused-IMPORTANT • All-cause mortality at 30 days-CRITICAL • Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Serious adverse events as reported in study-CRITICAL • Infections-CRITICAL • Correction of abnormal coagulation tests-IMPORTANT
16 Cryoprecipitate	Intervention	What is the clinical- and cost-effectiveness of different doses of cryoprecipitate for transfusion?	• Bleeding (reported as WHO grade 2 and above or equivalent)-CRITICAL ○ Occurrence of bleeding (in non-bleeding patients) ○ Cessation of bleeding (in bleeding patients) • Number of patients needing allogeneic red cell transfusions-IMPORTANT • Number of units or volume of red cells transfused-IMPORTANT • All-cause mortality at 30 days-CRITICAL • Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Serious adverse events as reported in study-CRITICAL • Infections-CRITICAL • Correction of abnormal coagulation tests-IMPORTANT
17 Prothrombin complex concentrates	Intervention	What is the clinical- and cost-effectiveness of transfusions of prothrombin complex concentrates (PCC) to treat and prevent bleeding?	• Bleeding (reported as WHO grade 2 and above or equivalent)-CRITICAL ○ Occurrence of bleeding (in non-bleeding patients) ○ Cessation of bleeding (in bleeding patients)

Chapter	Type of review	Review questions	Outcomes
			• Number of patients needing allogeneic red cell transfusions-IMPORTANT • Number of units or volume of red cells transfused-IMPORTANT • All-cause mortality at 30 days-CRITICAL • Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Serious adverse events as reported in study-CRITICAL • Infections-CRITICAL • Correction of abnormal coagulation tests-IMPORTANT
17 Prothrombin complex concentrates	Intervention	What is the clinical- and cost-effectiveness of different target levels of post-transfusion haemostasis tests with the use of prothrombin complex concentrates (PCC) for prophylactic transfusions?	• Bleeding (reported as WHO grade 2 and above or equivalent)-CRITICAL ○ Occurrence of bleeding (in non-bleeding patients) ○ Cessation of bleeding (in bleeding patients) • Number of patients needing allogeneic red cell transfusions-IMPORTANT • Number of units or volume of red cells transfused-IMPORTANT • All-cause mortality at 30 days-CRITICAL • Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Serious adverse events as reported in study-CRITICAL • Infections-CRITICAL • Correction of abnormal coagulation tests-IMPORTANT
18 Prothrombin complex concentrates	Intervention	What is the clinical- and cost-effectiveness of different doses of prothrombin complex concentrates (PCC) for transfusion?	• Bleeding (reported as WHO grade 2 and above or equivalent)-CRITICAL ○ Occurrence of bleeding (in non-bleeding patients) ○ Cessation of bleeding (in bleeding patients) • Number of patients needing allogeneic red cell transfusions-IMPORTANT • Number of units or volume of red cells transfused-IMPORTANT • All-cause mortality at 30 days-CRITICAL • Quality of life-IMPORTANT • Length of hospital stay-IMPORTANT • Serious adverse events as reported in study-CRITICAL • Infections-CRITICAL • Correction of abnormal coagulation tests-IMPORTANT
7	Intervention	What is the clinical- and	• Quality of life-IMPORTANT

Chapter	Type of review	Review questions	Outcomes
Monitoring for acute transfusion reactions		cost-effectiveness of monitoring for acute reactions at different times in relation to the transfusion?	• Length of hospital stay-IMPORTANT • Mortality (all causes) at 30 days-CRITICAL • Transfusion related mortality at 30 days-CRITICAL • Acute transfusion reaction/serious adverse events of transfusion-CRITICAL • Morbidity (ICU admission, renal failure, DIC) (dichotomous)-IMPORTANT • Admission to hospital or ICU post transfusion (day or in-patient)-IMPORTANT
9. Electronic patient identification	Intervention	What are the clinical- and cost-effectiveness of electronic patient identification systems such as patient identification band, bar code or radiofrequency identification (RFID) to ensure patient safety during blood transfusions?	• Quality of life-IMPORTANT • Mortality (all causes) at 30 days-CRITICAL • Transfusion related mortality at 30 days-CRITICAL • Incorrect blood component transfused-CRITICAL • Incorrect labelling (Incorrect blood in tube and Rejected blood samples)-CRITICAL • Morbidity (ICU admission, renal failure, DIC)-IMPORTANT
8 Electronic decision support	Intervention	What is the clinical- and cost-effectiveness of electronic decision-support blood order systems to reduce inappropriate blood transfusions?	• Proportion of inappropriate transfusions - CRITICAL • Proportion of patients transfused- CRITICAL • Number of units transfused -CRITICAL • Hospital length of stay-IMPORTANT • Quality of life -IMPORTANT • Mortality-CRITICAL • Pre-transfusion haemoglobin levels/platelet count/coagulation result-IMPORTANT
19. Patient information	Qualitative	What is the information and support patients under consideration for a blood transfusion and their family members or carers would value and how would they prefer to receive it?	Themes emerging from patients' views regarding information and support, their preferences and satisfaction levels.

4.2 Searching for evidence

4.2.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within The guidelines manual 2012.[209] Databases were searched using relevant medical subject headings, free-text terms and study-type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English. All searches were conducted in MEDLINE, Embase, and The Cochrane Library. Additional subject

specific databases were used for some questions: CINAHL for monitoring and patient information; HMIC for decision support and patient identification; PsycINFO for patient information. All searches were updated on 29 January 2015. No papers published after this date were considered.

Search strategies were quality assured by cross-checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews, and asking GDG members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix G.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on the websites listed below from organisations relevant to the topic. Searching for unpublished literature was not undertaken. All references sent by stakeholders were considered.

- Guidelines International Network database (www.g-i-n.net)
- National Guideline Clearing House (www.guideline.gov/)
- National Institute for Health and Care Excellence (NICE) (www.nice.org.uk)
- National Institutes of Health Consensus Development Program (consensus.nih.gov/)
- NHS Evidence Search (www.evidence.nhs.uk/).

4.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to transfusion in the NHS Economic Evaluation Database (NHS EED), the Health Technology Assessment database (HTA) and the Health Economic Evaluations Database (HEED) with no date restrictions. Additionally, the search was run on MEDLINE and Embase using a specific economic filter, from 2012, to ensure recent publications that had not yet been indexed by the economic databases were identified. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English.

The health economic search strategies are included in Appendix G. All searches were updated on 29 January 2015. No papers published after this date were considered.

4.3 Evidence of effectiveness

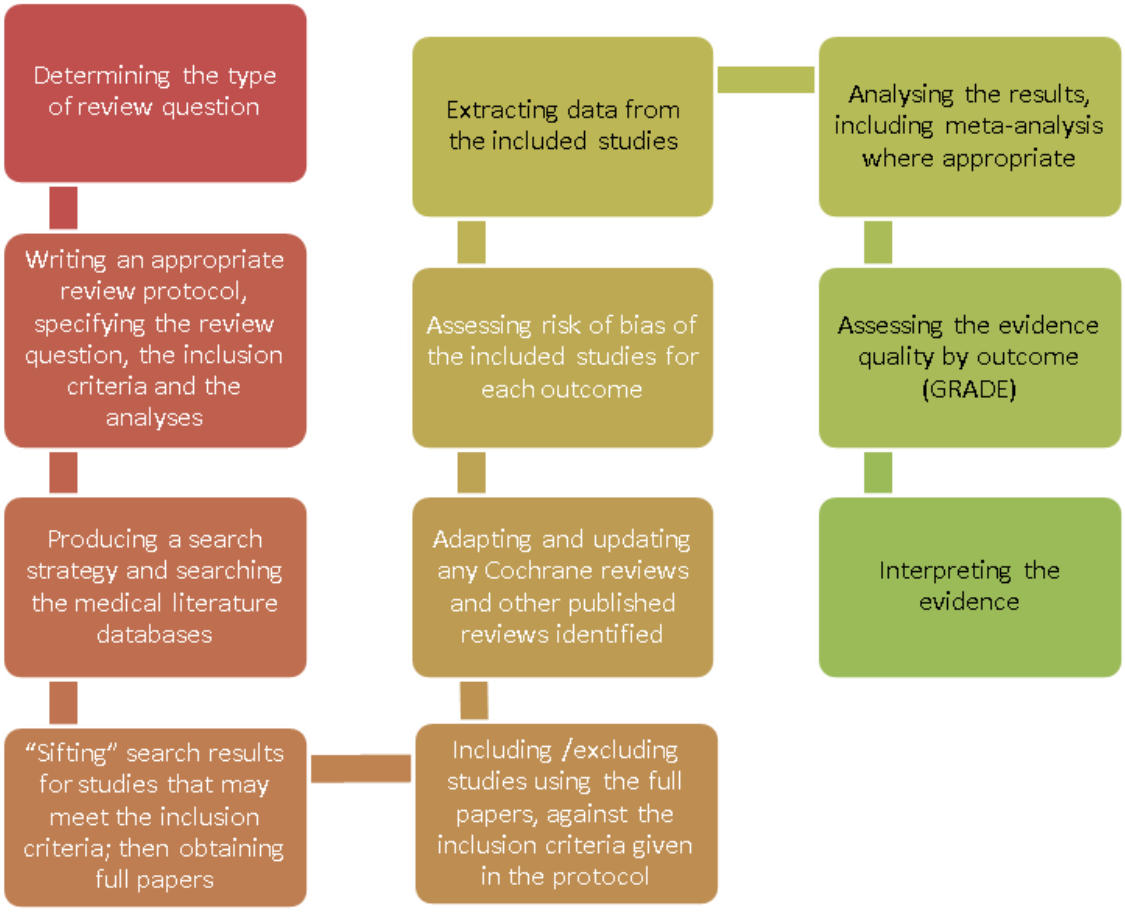
The evidence was reviewed following the steps shown schematically in Figure 1:

- Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population (review protocols are included in Appendix C).
- Relevant studies were critically appraised using the appropriate checklist as specified in The guidelines manual.[209]
- Key information was extracted on the study's methods, PICO factors and results. These were presented in summary tables (in each review chapter) and evidence tables (in Appendix H).
- Summaries of evidence were generated by outcome (included in the relevant review chapters) and were presented in GDG meetings:

- Randomised studies: data were meta-analysed where appropriate and reported in GRADE profiles (for intervention reviews).
- Observational studies: data were presented as a range of values in GRADE profiles.
- Qualitative studies: each study was summarised in a table where possible, otherwise presented in a narrative.

A 20% sample of each of the above stages of the reviewing process was quality assured by a second reviewer to eliminate any potential of reviewer bias or error.

Figure 1: Step-by-step process of review of evidence in the guideline



4.3.1 Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix C. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix P. The GDG was consulted about any uncertainty regarding inclusion or exclusion.

The GDG also discussed the relative importance of different outcomes when drafting the protocol for each review question and the outcomes were classified as critical or important. The importance of the outcomes was directly related to the focus of the guideline which is to optimise the use of blood and blood products without compromising on patient safety and clinical effectiveness. To this effect, the outcomes on number of patients receiving allogeneic transfusions, number of units of blood transfused, mortality and adverse events were classified as critical outcomes. The importance varied slightly across reviews based on the focus of the review, for example, in the review on electronic patient identification, the main focus was on patient safety and therefore, incorrect blood component transfused and incorrect labelling of samples (incorrect blood in tube and rejected blood samples) were classified as critical outcomes.

The guideline population was defined to be people who are receiving a blood transfusion or are at risk of receiving a blood transfusion. For some review questions (alternatives to blood transfusion), the review population was limited to surgical patients who are receiving blood transfusions.

Randomised trials, non-randomised trials, and observational studies were included in the evidence reviews as appropriate.

Conference abstracts were not automatically excluded from the review but were initially assessed against the inclusion criteria and then further processed only if no other full publication was available for that review question.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

The review protocols are presented in Appendix C.

4.3.2 Methods of combining clinical studies

4.3.2.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes, such as number of patients receiving allogeneic blood transfusions, mortality, incidence of infections and serious adverse events.

For continuous outcomes, measures of central tendency (mean) and variation (standard deviation) were required for meta-analysis. Data for continuous outcomes, such as number of units of allogeneic blood transfused and length of stay in hospital, were analysed using an inverse variance method for pooling weighted mean differences and, where the studies had different scales, standardised mean differences were used. A generic inverse variance option in RevMan5 was used if any studies reported solely the summary statistics and 95% confidence interval (95% CI) or standard error; this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics (p values or 95% CIs); meta-analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects. Consequently, aspects of quality assessment such as imprecision of effect could not be assessed for evidence of this type.

Stratified analyses were predefined for some review questions at the protocol stage when the GDG identified that these strata are different in terms of biological and clinical characteristics and the interventions were expected to have a different effect on subpopulations. For example, the population in reviews evaluating the threshold and target levels for platelet transfusion were stratified on the basis of haematology and non-haematology patients and the presence or absence of bleeding.

Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at $p<0.1$ or an I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity). Where considerable heterogeneity was present, we carried out predefined subgroup analyses as was defined in the individual review protocols. Sensitivity analysis based on the quality of studies was also carried out, eliminating studies

at overall high risk of bias (randomisation, allocation concealment and blinding, missing outcome data).

Assessments of potential differences in effect between subgroups were based on the chi-squared tests for heterogeneity statistics between subgroups. If no sensitivity analysis was found to completely resolve statistical heterogeneity then a random-effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect.

The means and standard deviations of continuous outcomes were required for meta-analysis. However, in cases where standard deviations were not reported, the standard error was calculated if the p values or 95% CIs were reported and meta-analysis was undertaken with the mean and standard error using the generic inverse variance method in RevMan5. Where p values were reported as 'less than', a conservative approach was undertaken. For example, if p value was reported as 'p≤0.001', the calculations for standard deviations will be based on a p value of 0.001. If these statistical measures were not available then the methods described in Section 16.1.3 of the Cochrane Handbook (March 2011) 'Missing standard deviations' were applied as the last resort.

For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software, for the median event rate across the control arms of the individual studies in the meta-analysis. Absolute risk differences were presented in the GRADE profiles and in clinical summary of findings tables, for discussion with the GDG.

For binary outcomes, absolute event rates were also calculated using the GRADEpro software using event rate in the control arm of the pooled results.

4.3.2.2 Network meta-analysis

A network meta-analysis (NMA) was conducted for two review questions which evaluated interventions which are alternatives to blood transfusion in surgical patients. The treatments evaluated were different types of cell salvage and tranexamic acid, alone or in combination with one another. This type of analysis simultaneously compares multiple treatments in a single meta-analysis, preserving the randomisation of RCTs included in the reviews of direct comparisons trials. The aim of the NMA was to include all relevant evidence in order both to answer questions on the clinical effectiveness of interventions when no direct comparison was available and to give a ranking of treatments in terms of efficacy. The output was expressed as the probability of each treatment being the best for an outcome and as effect estimates for how much each treatment is better than the other treatments included in the network.

A hierarchical Bayesian NMA was performed using the software WinBUGS version 1.4. We used statistical models for fixed and random effects that allowed inclusion of multi-arm trials and accounts for the correlation between arms in the trials with any number of trial arms. The model was based on original work from the University of Bristol.[299] The checklist 'Evidence Synthesis of Treatment Efficacy in Decision Making: A Reviewer's Checklist' [4] was completed.

As is the case for ordinary pairwise meta-analysis, NMA may be conducted using either fixed-effects or random-effects models. For pairwise meta-analysis, a fixed effects model was used in the first instance. For the networks set up in our NMA, both fixed- and random-effect models were performed. These models were then compared based on residual deviance and deviance information criteria (DIC). The model with the smallest DIC is estimated to be the model that would best predict a replicate dataset which has the same structure as that currently observed. A small difference in DIC between the fixed and random effects models (3–5 points) implies that the better fit obtained by adding random effects does not justify the additional complexity. However, if the difference in DIC between a fixed and random effect model was smaller than 5 points and the models made very similar inferences, then we reported the fixed-effects model results as that makes fewer assumptions than the random-effect model, contains fewer parameters and is easier to interpret clinically.

Heterogeneity was assessed in the results of the random-effects model by using the method described by Dias et al.[85,319] which compares the size of the treatment effect to the extent of between-trials variation. This method tries to answer the question of what is the reasonable confidence interval of the log odds ratio of an outcome for the prediction of the confidence interval of the log odds ratio of the same outcome of a future trial of infinite size.

Inconsistency in the networks was tested by comparing any available direct and indirect treatment comparison and testing the null hypothesis that the indirect evidence was not different from the direct evidence on the odds ratio scale using the normal distribution. Inconsistency was identified if the mean estimates (mean odds ratios) of the direct comparisons were outside the confidence intervals of the odds ratios as generated from the NMA output.

There were 3 main outputs from the NMA:

- estimated log odds ratios (ORs) (with their 95% credible intervals) were calculated for comparisons of the direct and indirect evidence
- the probability that each treatment was best, based on the proportion of Markov chain iterations in which each treatment had the highest probability of achieving the outcomes selected in the network(s)
- a ranking of treatments compared to baseline groups (presented as the median rank and its 95% credible intervals).

Further details of the network structure, rationale and stratification of risk groups can be found in chapter 6 and Appendix L.

4.3.2.3 Data synthesis for qualitative study reviews

Where possible, a meta-synthesis was conducted to combine qualitative study results. The aim of the synthesis of qualitative data was to describe the main factors that may influence the experience of care of the person receiving blood transfusion and to enable the GDG to develop recommendations to improve this experience. Whenever studies identified a qualitative theme, this was extracted and the main characteristics were summarised. When all themes were extracted from studies, common concepts were categorised and tabulated. This included information on how many studies had identified this theme. A frequently identified theme may indicate an important issue for the review, but frequency of theme is not the only indicator of importance. Study type and population in qualitative research can differ widely, meaning that themes that may only be identified by one or a few studies can provide important new information. Therefore, for the purpose of the qualitative review in this guideline, the categorisation of themes was exhaustive, that is, all themes were accounted for in the synthesis. The GDG could then draw conclusions on the relative merits of each of the themes and how they may help in forming recommendations.

4.3.3 Type of studies

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust type of study design that could produce an unbiased estimate of the intervention effects. If the GDG believed RCT data were not appropriate or there was limited evidence from RCTs, well-conducted non-randomised studies were included. Please refer to Appendix C for full details on the study design of studies selected for each review question. For example, due to a lack of randomised controlled trials for the review on electronic decision support, a number of before and after implementation studies were included in this review.

Where data from observational studies were included, the GDG decided that the results for each outcome should be presented separately for each study and meta-analysis was not conducted.

4.3.4 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCTs and, where appropriate, observational studies, were evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. Results were presented in GRADE profiles ('GRADE tables'), which consist of 2 sections: the 'Clinical evidence profile' table includes details of the quality assessment, while the 'Clinical evidence summary of findings' table includes pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the 'Clinical evidence profile' table if it was apparent.

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 2. Each element was graded using the quality levels listed in Table 3. The main criteria considered in the rating of these elements are discussed below (see Section 4.3.5 Grading of evidence). Footnotes were used to describe reasons for grading a quality element as having serious or very serious problems. The ratings for each component were summed to obtain an overall assessment for each outcome (Table 4).

Table 2: Description of the elements in GRADE used to assess the quality of intervention studies

Quality element	Description
Risk of bias ('Study limitations')	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies

Table 3: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence
Serious	The issues are serious enough to downgrade the outcome evidence by 1 level
Very serious	The issues are serious enough to downgrade the outcome evidence by 2 levels

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Level	Description
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
Very low	Any estimate of effect is very uncertain

4.3.5 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

11. A quality rating was assigned, based on the study design. RCTs start as High, observational studies as Low, and uncontrolled case series as Low or Very low.
12. The rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose–response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down by 1 or 2 points respectively.
13. The downgraded or upgraded marks were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted respectively.
14. The reasons or criteria used for downgrading were specified in the footnotes.

The details of the criteria used for each of the main quality elements are discussed further in sections 4.3.6 to 4.3.9.

4.3.6 Risk of bias

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error; for example, if a study was to be carried out several times and there was a consistently wrong answer, the results would be inaccurate.

The risk of bias for a given study and outcome is associated with the risk of over- or underestimation of the true effect.

The risks of bias are listed in Table 5.

A study with a poor methodological design does not automatically imply a high risk of bias; the bias is considered individually for each outcome and it is assessed whether poor design will impact on the estimation of the intervention effect.

Table 5: Risk of bias in randomised controlled trials

Risk of bias	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (this is a major problem in 'pseudo' or 'quasi' randomised trials with, for example, allocation by day of week, birth date, chart number)
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated
Incomplete accounting of patients and outcome events	Missing data not accounted for and failure of the trialists to adhere to the intention-to-treat principle when indicated

Risk of bias	Explanation
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results
Other risks of bias	For example: • Stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • Use of unvalidated patient-reported outcomes • Recruitment bias in cluster-randomised trials

4.3.6.1 Qualitative studies

For qualitative studies, quality was assessed using the NICE checklist for qualitative studies (Appendix I in The guidelines manual).[209]. The risk of bias was assessed across 6 domains:

- theoretical approach
- study design
- data collection
- validity
- analysis
- ethics.

The critical appraisal of the studies included was done using the NICE checklist for qualitative studies. A thematic analysis based on the observations from different studies was conducted. The quality of evidence was assessed for each theme based on a modified GRADE approach of assessing the limitations of the evidence (as a proxy for risk of bias assessment), applicability of the study (as a proxy for indirectness) and the coherence of findings (as a proxy for inconsistency) across the studies contributing to that theme. No assessment of imprecision was undertaken as these are qualitative data and therefore a summative quantitative assessment was not considered applicable here.

4.3.7 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (that is, there is heterogeneity or variability in results), this suggests true differences in underlying treatment effect.

Heterogeneity in meta-analyses was examined and sensitivity and subgroup analyses performed as pre-specified in the protocols (Appendix C).

When heterogeneity exists (chi-squared $p<0.1$, I-squared inconsistency statistic of >50%, or evidence from examining forest plots), but no plausible explanation can be found (for example, duration of intervention or different follow-up periods), the quality of evidence was downgraded by 1 or 2 levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I-squared and chi-squared values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

4.3.8 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

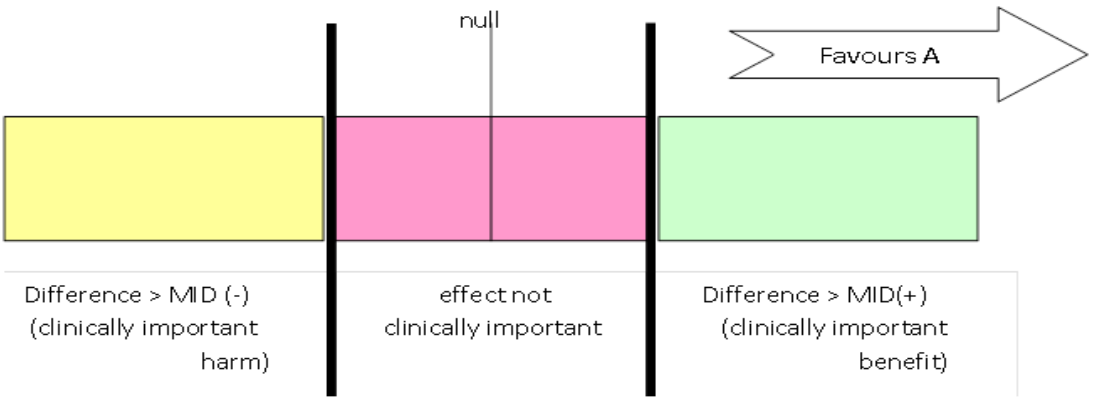
4.3.9 Imprecision

Imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that it is not clear whether there is a clinically important difference between interventions or not. Therefore, imprecision differs from the other aspects of evidence quality, in that it is not really concerned with whether the point estimate is accurate or correct (has internal or external validity); instead, it is concerned with the uncertainty about what the point estimate is. This uncertainty is reflected in the width of the confidence interval.

The 95% confidence interval (95% CI) is defined as the range of values that contain the population value with 95% probability. The larger the trial, the smaller the 95% CI and the more certain the effect estimate.

Imprecision in the evidence reviews was assessed by considering whether the width of the 95% CI of the effect estimate is relevant to decision-making, considering each outcome in isolation. Figure 2 considers a positive outcome for the comparison of treatment A versus B. Three decision-making zones can be identified, bounded by the thresholds for clinical importance (minimal important difference – MID) for benefit and for harm. The MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B by an amount that is clinically important to patients (favours B).

Figure 2: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot



When the confidence interval of the effect estimate is wholly contained in one of the 3 zones (for example, clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit, or the effect is not clinically important, or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of 2 zones, it is uncertain in which zone the true value of effect estimate lies, and therefore there is uncertainty over which decision to make (based on this outcome alone). The confidence interval is consistent with 2 decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by 1 level ('serious imprecision').

If the confidence interval of the effect estimate crosses into 3 zones, this is considered to be very imprecise evidence because the confidence interval is consistent with 3 clinical decisions and there is a considerable lack of confidence in the results. The evidence is therefore downgraded by 2 levels in the GRADE analysis ('very serious imprecision').

Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the GDG to estimate an MID or to say whether they would make different decisions for the 2 confidence limits.

The literature was searched for established MIDs for the selected outcomes in the evidence reviews. In addition, the GDG was asked whether they were aware of any acceptable MIDs in the clinical community. No MIDs were identified in the literature and the GDG considered it clinically acceptable to use the GRADE default MID to assess imprecision: a 25% relative risk reduction or relative risk increase was used, which corresponds to clinically important thresholds for a risk ratio of 0.75 and 1.25 respectively. This default MID was used for all the outcomes in the interventions evidence reviews.

4.3.10 Assessing clinical importance

The GDG assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies. . The GDG were asked to assess if the absolute risk difference for each outcome was indicative of a clinically important benefit or harm and this was noted accordingly. Generally, the GDG considered for most of the outcomes in the intervention reviews that if at least 100 participants per 1000 (10%) achieved (if positive) the outcome of interest in the intervention group compared to the comparison group, then this intervention would be considered beneficial. However for some outcomes this differed and was assessed on a case by case basis. For example, if evaluating mortality with a relative risk of 1.25 (1.15, 3.30) and an absolute risk reduction of 75 more per 1000 participants, the GDG were asked if 75 more deaths per 1000 was a clinically important harm and this was noted accordingly. The same point estimate but in the opposite direction would apply if the outcome was negative.

This assessment was carried out by the GDG for each critical outcome, and an evidence summary table was produced to compile the GDG's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

4.3.11 Evidence statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical effectiveness evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by outcome and encompass the following key features of the evidence:

- the number of studies and the number of participants for a particular outcome
- a brief description of the participants
- an indication of the direction of effect (if one treatment is beneficial or harmful compared to the other, or whether there is no difference between the 2 tested treatments)
- a description of the overall quality of evidence (GRADE overall quality).

4.4 Evidence of cost-effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical- and cost-effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost-effectiveness') rather than the total implementation cost.[209] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost-effectiveness related to the key clinical issues being addressed in the guideline was sought. The health economist:

- Undertook a systematic review of the published economic literature.
- Undertook new cost-effectiveness analysis in priority areas.

4.4.1 Literature review

The health economist:

- Identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained.
- Reviewed full papers against pre-specified inclusion and exclusion criteria to identify relevant studies (see below for details).
- Critically appraised relevant studies using the economic evaluations checklist as specified in The guidelines manual.[209]
- Extracted key information about the studies' methods and results into evidence tables (included in Appendix H).
- Generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question) – see below for details.

4.4.1.1 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost–benefit and cost–consequences analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies that only reported cost per hospital (not per patient), or only reported average cost-effectiveness without disaggregated costs and effects, were excluded. Literature reviews, abstracts, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (Appendix F of The guidelines manual[209] and the health economics review protocol in Appendix D).

When no relevant economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implications of the recommendations.

4.4.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows an assessment of applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The guidelines manual.[209] It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and incremental cost-effectiveness ratio for the base case analysis in the evaluation, as well as information about the assessment of uncertainty in the analysis. See Table 6 for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[225]

Table 6: Content of NICE economic evidence profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making[(a)]: • Directly applicable – the study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost-effectiveness. • Partially applicable – the study fails to meet one or more applicability criteria, and this could change the conclusions about cost-effectiveness. • Not applicable – the study fails to meet one or more of the applicability criteria, and this is likely to change the conclusions about cost-effectiveness. Such studies would usually be excluded from the review.
Limitations	An assessment of methodological quality of the study[(a)]: • Minor limitations – the study meets all quality criteria, or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost-effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusions about cost-effectiveness. • Very serious limitations – the study fails to meet one or more quality criteria, and this is highly likely to change the conclusions about cost-effectiveness. Such studies would usually be excluded from the review.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
Cost-effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

(a) Applicability and limitations were assessed using the economic evaluation checklist in Appendix G of The guidelines manual (2012)[209]

4.4.2 Undertaking new health economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in selected areas. Priority areas for

new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

The GDG identified the use of cell salvage, tranexamic acid (TXA) or both in combination in people undergoing surgery as the highest priority area for original economic modelling. Economic evaluations identified in the systematic literature search indicate that cell salvage and TXA are likely to be cost-effective individually compared with standard treatment (no intervention or placebo). However, uncertainty remained regarding whether one may be more cost-effective than the other (head-to-head comparison) or whether they are more cost-effective when given in combination.

The following general principles were adhered to in developing the cost-effectiveness analysis:

- Methods were consistent with the NICE reference case.[206]
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results.
- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data were not available, GDG expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NCGC.

Full methods for the cost-effectiveness analysis for TXA and cell salvage are described in Appendix M.

4.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[208] In general, an intervention was considered to be cost-effective if either of the following criteria applied (given that the estimate was considered plausible):

- the intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
- the intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter, with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance'.[208]

When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

4.4.4 In the absence of economic evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost-effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs, alongside the results of the clinical review of effectiveness evidence.

The UK NHS costs reported in the guideline are those that were presented to the GDG and were correct at the time recommendations were drafted. They may have changed subsequently before the time of publication. However, we have no reason to believe they have changed substantially.

4.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in Appendices H and I.
- Summaries of clinical and economic evidence and quality (as presented in Chapters 1–11).
- Forest plots (Appendix K).
- Results of network meta-analysis (Appendix L).
- A description of the methods and results of the cost-effectiveness analyses undertaken for the guideline (Appendix M).

Recommendations were drafted on the basis of the GDG's interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the GDG took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the GDG's values and preferences), and the confidence the GDG had in the evidence (evidence quality). Secondly, whether the net benefit justified any differences in costs was assessed.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs compared to the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (see Section 4.5.1 below).

The GDG considered the 'strength' of recommendations. This takes into account the quality of the evidence but is conceptually different. Some recommendations are 'strong' in that the GDG believes that the vast majority of healthcare and other professionals and patients would choose a particular intervention if they considered the evidence in the same way that the GDG has. This is generally the case if the benefits clearly outweigh the harms for most people and the intervention is likely to be cost-effective. However, there is often a closer balance between benefits and harms, and some patients would not choose an intervention whereas others would. This may happen, for example, if some patients are particularly averse to some side effect and others are not. In these circumstances the recommendation is generally weaker, although it may be possible to make stronger recommendations about specific groups of patients.

The GDG focused on the following factors in agreeing the wording of the recommendations:

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.

- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions (see Section 9.3 in The guidelines manual).[209]

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

4.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the GDG considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

4.5.2 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website.

4.5.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

4.5.4 Disclaimer

Healthcare providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of this guideline and the literature used in support of this guideline.

4.5.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

5 Oral iron, IV iron and erythropoietin

Iron is a vital component of the oxygen-binding haemoglobin component of red blood cells. Iron deficiency is a common cause of anaemia, affecting over 2 billion people worldwide.

Oral iron is effective in the long-term treatment of iron-deficiency anaemia, but bioavailability is limited by gastric absorption. Compliance with oral iron courses may be poor due to side effects including nausea and gastric irritation. Intravenous iron may be used when oral preparations are not effective or tolerated, or in acute clinical situations.

Administration of iron is an effective treatment for pre- and post-operative anaemia and can normalise pre-operative haemoglobin levels. Its use can reduce peri-operative morbidity and mortality, and reduce the requirements for blood transfusion following surgery.

5.1 Review question: What is the clinical- and cost-effectiveness of oral iron, IV iron and erythropoietin in reducing blood transfusion requirements in surgical patients?

For full details see review protocol in Appendix C.

Table 7: PICO characteristics of review question

Population	• Adults • Children Surgical patients with anaemia or at risk of anaemia. WHO definition of anaemia- Hb level <12 g/dl for females, Hb<13 g/dl for males, Hb<11.0 g/dl for children (0.5–5.0 years). Hb <11.5 g/dl for Hb children (5–12 years), Hb<12.0 g/dl for teens (12–15 years).
Intervention	Oral iron IV iron Erythropoietin (EPO); Erythropoietin (alfa) Erythropoietin (EPO); Erythropoietin (beta) Erythropoietin(EPO); Erythropoietin (zeta) Erythropoietin(EPO); Erythropoietin (theta) Oral iron + IV iron Oral iron + Erythropoietin IV iron +Erythropoietin Oral iron + IV iron + Erythropoietin Placebo
Comparison	All interventions will be compared with each other
Outcomes	• Quality of life • Number of units transfused • Length of hospital stay • Mortality (all causes) at 30 days • Mortality (transfusion related) at 30 days • Infections (includes pneumonia, surgical site infection, UTI and septicaemia/bacteremia) at Within 30 days of surgery • Number of patients needing transfusions • Bleeding

	• Serious adverse events (as described in studies) • Mortality (all causes) • Thrombosis
Study designs	• RCTs • Systematic reviews

5.2 Clinical evidence

We searched for randomised trials comparing the effectiveness of oral iron, intravenous iron and erythropoietin (EPO) in reducing blood transfusion requirements in surgical patients or patients at risk of anaemia.

- From 39 studies, 41 papers reporting data were included in the review.[17,23,31,36,56,68,72,79,83,89,93,100,103,111,127,152,154,161,164,167,171,173,179,186,205,223,234,241,242,264,267,280,285,296,313,323,326] Evidence from these is summarised in the clinical evidence summary (Table 9-Table 16). See also the study selection flow chart in Appendix E, forest plots in Appendix K, GRADE tables in in Appendix J, clinical evidence tables in Appendix H and clinical studies exclusion list in Appendix P.
- Eight studies reported no outcomes of interest and were not included in the analysis.[17,31,68,164,234,285,296,313]
- No relevant clinical studies comparing erythropoietin plus IV iron with erythropoietin plus oral iron were identified.
- One Cochrane review comparing EPO with placebo/no treatment was included.[83]
- The studies evaluated patients undergoing surgery for different reasons (for example, cardiac, orthopaedic or colorectal cancer).
- The studies also differed with respect to:
  - the baseline haemoglobin levels
  - transfusion administered according to a pre-specified protocol/ physician's discretion.
- For more details on the study characteristics, see the summary of included studies (Table 8) and clinical evidence tables (Appendix H).

5.2.1 Summary of included studies

Table 8: Summary of studies included in the review

Study	Population (baseline Hb levels)	Intervention/ comparison	Outcomes
Anon 1993 & Laupacis 1996[36,173]	Elective hip replacement (mean Hb: 13.7 g/dl)	EPO vs. placebo (concomitant oral iron)	• Number of patients transfused • Deep vein thrombosis
Aufricht 1994[17]	Cardiopulmonary bypass	Oral iron vs. no treatment	• No outcomes of interest
Bisbe 2014[23]	TKA (total knee arthroplasty) patients with post-operative anaemia.	Oral iron vs. IV iron	• Length of hospital stay • Number of patients transfused • Quality of life (Total EQ-5D scores) • Deep vein thrombosis
Brolin 1998[31]	Roux-en-Y gastric bypass	Oral iron vs.	• No outcomes of interest

Study	Population (baseline Hb levels)	Intervention/ comparison	Outcomes
		placebo	
Crosby 1994[68]	Coronary artery bypass surgery	Oral iron vs. placebo	• No outcomes of interest
Dambria 1997[72]	Coronary bypass patients (mean Hb: 14.1 g/dl)	EPO vs. placebo (concomitant oral iron)	• No. of patients transfused • No. of units transfused per patient • Mortality • Serious adverse events
Deandre 1996[79]	Major elective orthopaedic surgery (mean Hb: 13.56 g/dl)	EPO vs. placebo (concomitant oral iron)	• No. of units transfused per patient • Mortality • Serious adverse events
Devon 2009[83] (Cochrane review)- includes 4 papers: Christodoulakis 2005,[56] Heiss 1996,[127] Qvist 1999,[242] Kettlehack 1998[161])	Colorectal cancer (Hb: <13.5 g/dl)	EPO vs. placebo (concomitant oral or IV iron except Christodoulakis)	• Proportion of patients receiving at least 1 unit of blood • No. of units transfused per patient • Post-operative mortality • Thromboembolic complications
Dousias 2003[89]	Hysterectomy (Hb:≥9 or <12 g/dl)	Oral iron + EPO vs. oral iron	• No. of patients transfused • No. of units transfused per patient • Length of hospital stay
Edwards 2009[93]	Colorectal cancer surgery (Hb: at least 13.5 g/dl in men and 12.5 g/dl in women)	IV iron vs. placebo	• No. of patients transfused • No. of units transfused per patient • Length of hospital stay
Faris 1996[100]	Major orthopaedic surgery (mean Hb: 13.1 g/dl)	EPO vs. placebo (concomitant oral iron)	• No. of patients transfused • No. of units transfused per patient • Serious adverse events
Feagan 2000[103]	Total hip replacement (mean Hb: around 12.5 g/dl)	EPO vs. placebo (concomitant oral iron)	• No. of patients transfused • No. of units transfused per patient • Deep vein thrombosis or pulmonary embolism
Garrido-Martin 2012[111]	Cardiac surgery (mean Hb: around 14 g/dl	IV iron vs. placebo	• No. of patients transfused
Karkouti 2006[152]	Cardiac or orthopaedic surgery (mean Hb: around 14 g/dl	IV iron + EPO vs. IV iron vs. Placebo	• No. of patients transfused • Serious adverse events
Kateros 2010[154]	Patients with intertrochanteric fractures. All fractures managed with sliding crew and plating. Pre-treatment Hb level of 10.2 g/dl (range 9.6-2.7 g/dl)	EPO + IV iron vs. IV iron	• Serious adverse events • Length of hospital stay • Number of units transfused

Study	Population (baseline Hb levels)	Intervention/ comparison	Outcomes
Kim 2009[164]	Pre-operative anaemia in patients with menorrhagia	Oral iron vs. IV iron	• No outcomes of interest
Kosmadakis 2003[167]	Gastrointestinal tract cancer surgery	EPO vs. placebo (concomitant oral iron)	• No. of patients transfused • Length of stay • Deep vein thrombosis
Larson 2001[171]	Hysterectomy (mean Hb: around 10 g/dl)	Oral iron + EPO vs. oral iron	• No. of patients transfused • No. of units transfused per patient • Length of hospital stay • Infections
Lidder 2007[179]	Colorectal cancer surgery (mean Hb: 12.4 or 13.4 g/dl)	Oral iron vs. no treatment	• No. of patients transfused • No. of units transfused per patient
Madi 2004[186]	Cardiac surgery (mean Hb: around 14 g/dl)	IV iron + EPO vs. IV iron vs. Placebo	• No. of patients transfused • Mortality
Na 2011[205]	Total knee replacement (mean Hb: 12.1 g/dl)	IV iron + EPO vs. no treatment	• No. of patients transfused
Olijhoek 2001[223]	Elective orthopaedic surgery. Each patient had pre-treatment Hb level ≥10 to ≤13 g/dl	EPO + IV iron or oral iron vs. IV iron or oral iron	• Serious adverse events • Thrombotic events • Mortality
Parker 2010[234]	Hip fracture surgery	Oral iron vs. no treatment	• No outcomes of interest
Podesta 2000[241]	Elective coronary and valve surgery (mean Hb: 14 g/dl)	Oral iron + EPO vs. oral iron	• No. of patients transfused • No. of units transfused per patient • Mortality (intra-operatively)
Scott 2002[264]	Head and neck cancer (mean Hb: 12.2 g/dl)	EPO vs. placebo (concomitant oral iron)	• No. of patients transfused • No. of units transfused per patient • Serious adverse events
Serrano-Trenas 2011[267]	Hip fracture patients (mean Hb: around 12 g/dl	IV iron vs. no treatment	• No. of patients transfused • Mortality (intra-operatively) • Length of stay • Infections
Sowade 1997[280]	Open heart surgery (mean Hb: around 14 g/dl)	EPO vs. placebo (concomitant oral iron)	• No. of patients transfused • Mortality • Serious adverse events
Stowell 2009[284]	Elective spinal surgery (mean baseline Haemoglobin 12.2 (0.80) g/dl)	EPO + oral iron vs. oral iron	• Mortality • DVT • Other thrombovascular events (cerebrovascular accident, transient ischaemic attack, myocardial ischaemia, myocardial infarction,

Study	Population (baseline Hb levels)	Intervention/ comparison	Outcomes
			pulmonary embolism)
Sutton 2004[285]	Total hip and knee arthroplasty	Oral iron vs. placebo	• No outcomes of interest
Tsuji 1995[296]	Gastrectomy	EPO + IV iron vs. IV iron	• No outcomes of interest
Weatherall 2004[313]	Orthopaedic surgery	Oral iron vs. no treatment	• No outcomes of interest
Weltert 2010[317]	Off-pump coronary artery bypass. Baseline Hb: Recombinant human erythropoietin (HRE): 13.18±1.21 g/dl and control group: 13.44±1.20 g/dl	EPO vs. placebo	• Mortality (45 days) • Deep vein thrombosis • Number of patients transfused • Infection (pneumonia)
Wurnig 2001[323]	Elective surgery (mainly cardiac and orthopaedic) (mean Hb: around 13 g/dl)	EPO vs. placebo (concomitant oral iron)	• No. of patients transfused • Mortality • Deep vein thrombosis
Yoo 2011[326]	Valvular heart surgery (Hb <12 g/dl in women and <13 g/dl in men)	IV iron + EPO vs. placebo	• No. of patients transfused • No. of units transfused per patient • Mortality • Length of hospital stay

EPO – erythropoietin

5.2.2 Clinical evidence summary (Summary GRADE profiles)

Table 9: Erythropoietin compared with placebo for surgical patients

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/no erythropoietin	Risk difference with Erythropoietin (95% CI)
All-cause mortality at 30 days	1209 (7 studies)	LOW[a,b] due to risk of bias, imprecision	RR 1.55 (0.79 to 3.07)	23 per 1000	12 more per 1000 (from 5 fewer to 47 more)
Number of patients transfused	1663 (12 studies)	VERY LOW[a,c] due to risk of bias, inconsistency	RR 0.59 (0.53 to 0.67)	503 per 1000	206 fewer per 1000 (from 166 fewer to 236 fewer)
Number of units transfused per patient	809 (7 studies)	VERY LOW[a,d,e] due to risk of bias, inconsistency, imprecision			The mean number of units transfused per patient in the intervention groups was 0.69 lower (0.89 to 0.49 lower)
Serious adverse events	844 (6 studies)	VERY LOW[a,f,g] due to risk of bias, inconsistency, imprecision	RR 0.92 (0.57 to 1.5)	83 per 1000	7 fewer per 1000 (from 35 fewer to 41 more)
Thrombosis	976 (5 studies)	VERY LOW[a,g] due to risk of bias, imprecision	RR 1.37 (0.73 to 2.56)	32 per 1000	12 more per 1000 (from 9 fewer to 49 more)
Infection	320 (1 study)	-	Not estimable	-0 in both groups.	-
Length of hospital stay	63 (1 study)	MODERATE[a,h] due to risk of bias			The mean length of hospital stay in the intervention groups was 3.00 lower (3.36 to 2.64 lower)

(a) Most information is from studies at high risk of bias
(b) Confidence interval crosses one default MID (1.25) and line of no effect
(c) Significant heterogeneity. I^2=62%.
(d) Significant heterogeneity. I^2=60%.
(e) Confidence interval crosses one default MID and line of no effect
(f) Heterogeneity. I^2=30%.
(g) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect
(h) Unclear randomisation and allocation concealment

Table 10: IV iron compared with placebo/no IV iron for surgical patients

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/no IV iron	Risk difference with IV iron (95% CI)
All-cause mortality at 30 days	280 (2 studies)	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.1 (0.49 to 2.47)	71 per 1000	7 more per 1000 (from 36 fewer to 105 more)
Number of patients transfused	467 (5 studies)	LOW[a,c] due to risk of bias, imprecision	RR 0.77 (0.59 to 0.99)	373 per 1000	86 fewer per 1000 (from 4 fewer to 153 fewer)

Length of hospital stay	200 (1 study)	LOW[c,d] due to risk of bias, imprecision			The mean length of hospital stay in the intervention groups was 0.6 higher (1.34 lower to 2.54 higher)
Serious adverse events	21 (1 study)	LOW[e] due to risk of bias	Not estimable	0 in both groups	
Infections	200 (1 study)	VERY LOW[b,d] due to risk of bias, imprecision	RR 1.23 (0.63 to 2.42)	130 per 1000	30 more per 1000 (from 48 fewer to 185 more)

(a) Most information is from studies at high risk of bias
(b) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect
(c) Confidence interval crosses one default MID and line of no effect
(d) No blinding
(e) 7/38 (18%) patients missing data. Low frequency of events means this could impact on results. Study reports the trial was underpowered for the outcomes under assessment and that it stopped early because of recruitment problems.

Table 11: Oral iron compared with placebo/no oral iron for surgical patients

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo/no oral iron	Risk difference with Oral iron (95% CI)
Number of patients transfused	154 (2 studies)	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 0.84 (0.6 to 1.19)	506 per 1000	81 fewer per 1000 (from 203 fewer to 96 more)

(a) Most information is from studies at high risk of bias
(b) Significant heterogeneity. I^2=66%.
(c) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect

Table 12: Erythropoietin plus IV iron compared with placebo for surgical patients

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Placebo	Risk difference with Erythropoietin + IV iron (95% CI)
All-cause mortality at 30 days	154 (2 studies)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.33 (0.01 to 7.93)	13 per 1000	9 fewer per 1000 (from 13 fewer to 90 more)
Number of patients transfused	283 (4 studies)	VERY LOW[a,c] due to risk of bias, inconsistency	RR 0.51 (0.39 to 0.67)	592 per 1000	290 fewer per 1000 (from 195 fewer to 361 fewer)
Number of units transfused per patient	182 (2 studies)	LOW[d] due to inconsistency			The mean number of units transfused per patient in the intervention groups was 0.76 lower (1 to 0.52 lower)
Length of hospital stay	74 (1 study)	LOW[e] due to imprecision			The mean length of hospital stay in the intervention groups was 2.2 lower (5.1 lower to 0.7 higher)
Serious adverse events	20 (1 study)	LOW[f] due to risk of bias	Not estimable		0 in both groups

(a) Most information is from studies at high risk of bias

(b) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect
(c) Significant heterogeneity. I^2=69%.
(d) Significant heterogeneity. I^2=93%.
(e) Confidence interval crosses one default MID and line of no effect
(f) 7/38 (18%) patients missing data. Low frequency of events means this could impact on results. Study reports the trial was underpowered for the outcomes under assessment and that it stopped early because of recruitment problems.

Table 13: Oral iron compared with IV iron for surgical patients

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with IV iron	Risk difference with oral iron (95% CI)
Number of patients transfused	228 (2 studies)	LOW[a,b] due to risk of bias, imprecision	RR 1.28 (0.83 to 1.95)	204 per 1000	57 more per 1000 (from 35 fewer to 193 more)
Length of hospital stay	121 (1 study)	HIGH			The mean length of hospital stay in the intervention groups was 0.30 lower (0.79 lower to 0.19 higher)
Deep vein thrombosis	121 (1 study)	LOW[c] due to imprecision	RR 0.32 (0.01 to 7.64)	17 per 1000	12 fewer per 1000 (from 17 fewer to 113 more)
Quality of life	121 (1 study)	HIGH			The mean quality of life in the intervention groups was 0.00 higher (0.23 lower to 0.23 higher)

(a) Unclear randomisation, allocation concealment and unclear missing data (Garrido-Martin 2012)
(b) Confidence interval crosses one default MID (1.25) and line of no effect
(c) Confidence interval crosses one default MID and line of no effect

Table 14: Erythropoietin plus IV iron compared with IV iron for surgical patients

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with IV iron	Risk difference with Erythropoietin + IV iron (95% CI)
All-cause mortality at 30 days	80 (1 study)	MODERATE[a] due to risk of bias	Not estimable		0 in both groups
Number of patients transfused	101 (2 studies)	VERY LOW[b,c] due to risk of bias, imprecision	RR 0.76 (0.35 to 1.65)	235 per 1000	56 fewer per 1000 (from 153 fewer to 153 more)
Serious adverse events	99 (2 studies)	MODERATE[b] due to risk of bias	Not estimable		0 in both groups

(a) Unclear allocation concealment and blinding
(b) Most information is from studies at high risk of bias
(c) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect

Table 15: Erythropoietin plus oral iron compared with oral iron for surgical patients

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Oral iron	Risk difference with Erythropoietin+ Oral iron (95% CI)
All-cause mortality at	880	VERY LOW[a,b] due to risk of bias,	RR 0.88 (0.39 to	27 per	3 fewer per 1000

30 days	(2 studies)	imprecision	1.96)	1000	(from 17 fewer to 26 more)
Number of patients transfused	141 (3 studies)	MODERATE[a] due to risk of bias	RR 0.06 (0.02 to 0.25)	438 per 1000	412 fewer per 1000 (from 329 fewer to 430 fewer)
Length of hospital stay	81 (2 studies)	MODERATE[a] due to risk of bias			The mean length of hospital stay in the intervention groups was 0.22 lower (0.61 lower to 0.18 higher)
Infections	32 (1 study)	VERY LOW[b,c] due to risk of bias, imprecision	RR 0.5 (0.05 to 4.98)	125 per 1000	62 fewer per 1000 (from 119 fewer to 498 more)
Deep vein thrombosis	680 (1 study)	LOW[d,e] due to risk of bias, imprecision	RR 2.29 (0.95 to 5.49)	21 per 1000	27 more per 1000 (from 1 fewer to 92 more)
Other thrombovascular events	680 (1 study)	VERY LOW[b,d] due to risk of bias, imprecision	RR 1.71 (0.68 to 4.3)	21 per 1000	15 more per 1000 (from 7 fewer to 68 more)

(a) Most information is from studies at high risk of bias
(b) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect
(c) Unclear randomisation, blinding and allocation concealment.
(d) Open label. No blinding.
(e) Confidence interval crosses one default MID and line of no effect

Table 16: Erythropoietin plus IV iron or oral iron compared with placebo plus IV iron or oral iron for surgical patients

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo + IV iron or oral iron	Risk difference with EPO+ IV iron or oral iron (95% CI)
Mortality	110 (1 study)	MODERATE[a] due to risk of bias	Not estimable		
Serious adverse events	110 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.3 (0.01 to 7.19)	19 per 1000	13 fewer per 1000 (from 19 fewer to 119 more)
Thrombosis	110 (1 study)	MODERATE[a] due to risk of bias	Not estimable		

(a) Allocation concealment not reported
(b) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect

5.3 Economic evidence

Published literature

One study comparing oral iron with no iron and one comparing intravenous iron with no intravenous iron were identified.[179,184] Four studies comparing erythropoietin with placebo or no erythropoietin were identified.[66,77,293,308] These are summarised in the economic evidence profiles below (Table 17, Table 18 and Table 19).

See also the study selection flow chart in Appendix E and study evidence tables in Appendix H.

Table 17: Economic evidence profile: oral iron versus standard clinical treatment

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (units of blood transfused)	Cost-effectiveness (£/units of blood transfused saved)	Uncertainty
Lidder 2007[179] (UK)	Partially applicable(a)	Potential serious limitations[(b)]	Within trial analysis (RCT) of pre-operative iron supplementation in patients with colorectal cancer fit for respective surgery (with haemoglobin level below 13.5 g/dl in men and 11.5 g/dl in women). Analysis of individual level data, with unit costs applied.	Saves £147[(c)]	Saves 1.4 units[(d)]	Oral iron is dominant	No analysis reported

(a) Health effects not expressed as QALYs.
(b) Short time horizon 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.
(c) 2007 UK pounds. Costs incorporated are: ferrous sulphate and unit cost of allogeneic blood.
(d) Mean units of blood transfused from within trial.

Table 18: Economic evidence profile: intravenous iron versus usual practice

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (proportion receiving blood transfusion)	Cost-effectiveness (£/reduction in blood transfusion)	Uncertainty
Luporsi 2012[184] (France)	Partially applicable[(e)]	Potential serious limitations[(f)]	Decision analytic economic model comparing two treatment strategies for pre-operative anaemia in knee and hip surgery patients.	Saves £166[(g)]	59% reduction[(h)]	Intravenous iron is dominant	One-way sensitivity analysis revealed that when the difference in the number of patients receiving blood transfusion was reduced to 18% (rather than 59%), costs of the 2 arms became equal.

(e) French health care payer perspective, health effects not expressed as QALYs.
(f) 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 (intravenous iron) based on expert opinion, volume of blood transfused unclear, and minimal analysis of uncertainty (no probabilistic analysis of uncertainty). Funded by manufacturer of intravenous iron Ferinject®.
(g) 2010 Euros converted into UK pounds using the purchasing power parities.[226] Costs incorporated are: ferric carboxymaltose and unit cost of allogeneic blood.
(h) Percentage reduction in blood transfused following intravenous ferric carboxymaltose from Cuenca 2007.[70]

Table 19: Economic evidence profile: erythropoietin versus no intervention or standard current practice

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Craig 2006[66] (Scotland)	Directly applicable	Potentially serious limitations[(a)]	Decision tree depicting orthopaedic surgery patients (pre-operative haemoglobin level tween 10 and 13g/dl) receiving or not receiving allogeneic blood transfusions. Transfusion recipients had a risk of contracting a transfusion-related illness. Interventions: erythropoietin alpha vs. no intervention	£1,235[(b)]	0.00006 QALYs[(c)]	£21,193,000 per QALY gained	One way sensitivity analysis: ICER most sensitive to cost of erythropoietin alpha and allogeneic blood and number of units transfused. Price of erythropoietin would need to decrease by 95% or allogeneic blood would need to be greater than £2,750 per unit for erythropoietin alpha to be cost-effective (below £30,000 per QALY).

(a) Weber 2005[314] 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.
(b) 2005 UK pounds. Costs incorporated are: erythropoietin alpha, administration, allogeneic blood (including associated administration costs), transfusion-related adverse events and illnesses.
(c) Effectiveness data for erythropoietin alpha taken from trial by Weber 2005.[314] The incidence of procedures (elective and emergency joint replacement operations) and of baseline allogeneic blood transfused in Scotland 2003/4 were incorporated. 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 19996-2004 data. National life tables used (adjusted for HIV). Mean utility values for viral infections from published sources. Utility values for non-viral infections based on assumptions.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Davies 2006[77] (UK)	Directly applicable	Potentially serious limitations**Error!**	Decision tree depicting surgical patients receiving or not receiving allogeneic blood transfusions. All patients who	Saves £48**Error! Reference source not**	No difference**Error! Reference source not**	Erythropoietin dominant	A probabilistic sensitivity analysis was conducted for the base case, but results were only reported versus cell salvage, one of the

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
		Reference source not found.	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. Interventions: erythropoietin vs. no intervention	**found.**	**found.**		other comparators in the analysis (not presented here). 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.

(d) 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.

(e) 2003-2004 UK pounds. Costs incorporated are: erythropoietin (including outpatient visit for administration); transfusion and transfusion-related services; operation and index hospital admission; and adverse events (surgical and transfusion-related).

(f) 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.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Vitale 2007[308] (USA)	Partly applicable**Error! Reference source not**	Potentially serious limitations**Error! Reference**	Decision tree depicting adolescent female idiopathic scoliosis surgical patients receiving or not receiving allogeneic transfusions. Patients	£306**Error! Reference source not found.**	0.0003 QALYs**Error! Reference source not found.**	£1,020,000 per QALY gained	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

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
	found.	**source not found.**	had a risk of wound infection, transfusion reactions (fatal and non-fatal) and transfusion-related infections. Interventions: erythropoietin alpha vs. no intervention				control arm. 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.

(g) US healthcare payer perspective, no discounting and no reporting of utilities used in the model.

(h) 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). Side effects of erythropoietin excluded from model.

(i) 2005 US dollars converted into UK pounds using the purchasing power parities.[226] Costs incorporated are: recombinant human erythropoietin (including administration), allogeneic blood, transfusion-related adverse event and illnesses, and wound infection.

(j) Effectiveness data for recombinant human erythropoietin referenced as being from a randomised controlled study by Rollo 1995[252]; however, this study is not a study of recombinant human erythropoietin, therefore unclear which studies the effectiveness data is based upon. Control transfusion rates from retrospective data and risk of transfusion-related infections and non-infections reactions from published literature and surveillance reports. Utility values used in the model were from published peer reviewed literature but were not outlined in the study

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Tomeczkowski 2013[293] (Germany)	Partially applicable**Error! Reference source not found.**	Potentially serious limitations**Error! Reference source not found.**	Discreet event simulation model depicting hip and knee arthroplasty surgery patients (pre-operative haemoglobin (Hb) level tween 10 and 13 g/dl, stratified as 6 subgroups) receiving or not receiving allogeneic transfusions. 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. Interventions: erythropoietin alpha vs. no intervention	Pre-operative Hb 10-10.5 g/dl: saves £452 Pre-operative Hb 12.5-13 g/dl: saves £14**Error! Reference source not found.**	Number transfused: Pre-operative Hb 10-10.5 g/dl: 57.1% fewer Pre-operative Hb 12.5-13 g/dl: 23.5% fewer Units transfused: Pre-operative	Erythropoietin dominant	One-way sensitivity 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

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
					Hb 10-10.5 g/dl: 0.7 units fewer Pre-operative Hb 12.5-13 g/dl: 0.1 units fewer**Error! Reference source not found.**		injections, Weber 2005[314]), 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

(k) German healthcare payer perspective. Health effects not expressed as QALYs.

(l) 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. Cost year not reported (assumed to be year prior to submission of paper 2012).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.

(m) 2012 Euros converted to UK pounds using the purchasing power parities.[226] Costs incorporated are: Erythropoietin alpha (£178 per 40,000IU), allogeneic blood (including associated administration costs), length of hospital stay and pneumonia.

(n) 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).

Economic considerations

Craig 2006[66] reported that the price of erythropoietin alpha would need to decrease by 95% for erythropoietin alpha to be cost effective (below £30,000 per QALY). The cost of erythropoietin alpha (Eprex, Janssen) has decreased from £76.61 for 10,000 units in 2005 (as reported in Craig 2006[66]) to £55.31 for 10,000 units in 2014 (BNF 67[147]). This 28% decrease in price is not sufficient for erythropoietin alpha to be cost effective (below £30,000 per QALY).

The GDG wanted to know in terms of blood units how much transfusion would need to be reduced for erythropoietin to be cost neutral. The following approach was taken to calculate the minimum number of units avoided for erythropoietin to be cost neural:

$$\boldsymbol{Minimum\ units\ avoided\ for\ Erythropoeitin\ to\ be\ cost\ neutral} = \boldsymbol{CostErythropoeitin/CostSubsequentUnits}$$

The cost of erythropoietin and of a subsequent unit of red blood cell transfused are summarised in Table 20 and Table 21, respectively.

Table 20: Cost of erythropoietin (including administration)

Item	Cost	Source
Erythropoietin alpha	£815	Based on the dosage used in Craig 2006,[66] 4 doses of 40,000IU of erythropoietin (three prior to surgery and one on day of surgery) and unit cost of Binocrit from BNF 67.[147]
Administration per dose	£24	Cost of administration at a GP surgery, taken from Craig 2006,[66] based on 2005 costs.
Total	£887	Assumes administration costs would occur for three doses prior to surgery only.

Table 21: Cost of transfusion per unit

Item	Cost	Source
Unit of red blood cells	£167	Based on cost of transfusing a subsequent unit, estimated as part of the cost-effectiveness analysis conducted for this guideline (for detail see S APPENDIX M).

Based on these costs, the mean minimum number of units avoided per person for erythropoietin to be cost neural is 5.3 units. The clinical evidence indicates that the mean units avoided was approximately 0.55.

Unit costs

Relevant unit costs are provided in Appendix N to aid consideration of cost-effectiveness.

5.4 Evidence statements

Clinical

Erythropoietin versus placebo:

Twelve RCTs compared EPO versus placebo. The evidence showed clinically important benefit with EPO for the outcomes number of patients transfused, number of units transfused and length of stay.

The evidence suggested that that there was higher mortality and thrombosis in patients receiving EPO, but there was considerable uncertainty. The evidence suggested no difference of effect between patients receiving EPO and placebo with respect to serious adverse events and infection, but there was some uncertainty. The quality of evidence ranged from low to very low..

No evidence was identified for quality of life.

IV iron versus placebo:

Five RCTs compared IV iron with placebo. The evidence suggested thatfewer numbers of patients were transfused when they received IV iron but there was some uncertainty. The evidence suggested that there was higher length of hospital stay and more infections in patients receiving IV iron, but there was considerable uncertainty. The evidence showed that there was no important difference between the groups for the outcomes mortality and serious adverse events, but there was some uncertainty. The quality of evidence ranged from low to very low. .

No evidence was identified for quality of life.

Oral iron versus placebo:

Two RCTs compared oral iron with placebo. The evidence suggested that fewer numbers of patients were transfused in patients receiving oral iron, but there was considerable uncertainty. The evidence was of very low quality.

No evidence was identified for critical outcomes such as number of units transfused, thrombosis and mortality at 30 days; and important outcomes such as length of stay in hospital, serious adverse events, infections and quality of life.

Erythropoietin plus IV iron versus placebo:

Four RCTs compared EPO plus IV iron with placebo. The evidence showed clinically important benefit for EPO plus IV iron for the outcomes numbers of patients transfused and numbers of units transfused. The evidence suggested lower mortality and length of hospital stay with EPO plus IV iron, but there was considerable uncertainty. There was no difference between the groups for the outcome on serious adverse events. The evidence was of low and very low quality.

No evidence was identified for thrombosis (critical outcome) and quality of life (important outcome).

Oral iron versus IV iron:

Two RCTs compared oral iron with IV iron.. The evidence suggested that there were fewer numbers of patients transfused with IV ironbut there was considerable uncertainty. The evidence suggested that length of hospital stay may be lower and fewer patients may have deep vein thrombosis in patients receiving oral iron, but there was considerable uncertainty..There was no difference between the groups for the outcome on quality of life. The quality of evidence ranged from high to low.

No evidence was identified for critical outcomes such as number of units transfused, and mortality at 30 days and important outcomes such as serious adverse events and infections.

Erythropoietin plus IV iron versus IV iron alone:

Two RCTs compared EPO plus IV iron with IV iron. The evidence suggested that fewer numbers of patients were transfused when receiving EPO plus IV iron but there was considerable uncertainty. There was no difference between the groups for the outcomes of mortality (all cause at 30 days) and serious adverse events.

The evidence was of moderate to very low quality.

No evidence was identified for critical outcomes such as number of units transfused and thrombosis, and important outcomes such as length of stay in hospital, infections and quality of life.

Erythropoietin plus oral iron versus oral iron:

Four RCTs compared EPO plus oral iron with oral iron. The evidence showed clinically important benefit for EPO plus oral iron for the outcome numbers of patients transfused. The evidence suggested that there was lower mortality (all cause at 30 days), infections, and length of hospital stay in patients receiving EPO plus oral iron, however there was considerable uncertainty. The evidence suggested deep vein thrombosis and other thrombovascular events were higher in patients receiving EPO plus oral iron but there was considerable uncertainty. The evidence quality ranged from moderate to very low quality.

No evidence was identified for the important outcomes such as serious adverse events and quality of life.

Erythropoietin plus IV iron or oral iron versus oral iron or IV iron:

One RCT compared EPO plus IV iron or oral iron with oral iron or IV iron. The evidence suggested that there were fewer serious adverse events with EPO plus oral iron or IV iron, but there was considerable uncertainty. There was no important difference between the groups for the outcomes mortality (all cause at 30 days) and thrombosis. The evidence ranged from moderate to very low quality.

No evidence was identified for the critical outcomes, such as number of patients transfused and number of units transfused, and important outcomes such as length of stay in hospital, infections and quality of life.

Economic

One cost–consequence analysis found that oral iron (ferrous sulphate) was less costly and more effective than no intervention in reducing blood transfusion requirements in anaemic surgical patients (£147 less per patient, 1.4 fewer units of blood transfused per patient). This analysis was assessed as partially applicable with potential serious limitations.

One cost–consequence analysis found that IV iron (ferrous carboxymaltose) was less costly and more effective than no intervention in reducing blood transfusion requirements in anaemic surgical patients (£166 less per patient, 59% reduction in proportion receiving blood transfusion). This analysis was assessed as partially applicable with potential serious limitations.

One cost-utility analysis found that erythropoietin alpha was not cost-effective compared to no intervention in reducing blood transfusion requirements in anaemic surgical patients (ICER: £21,193,000 per QALY gained). This analysis was assessed as directly applicable with potentially serious limitations.

One cost-utility analysis found that erythropoietin was dominant (less costly, no difference in effectiveness) compared to no intervention in reducing blood transfusion requirements in surgical patients. This analysis was assessed as directly applicable with potentially serious limitations.

One cost-utility analysis found that erythropoietin was not cost-effective compared to no intervention in reducing blood transfusion requirements in adolescent female idiopathic surgical patients (ICER: £1,020,000 per QALY gained). This analysis was assessed as partially applicable with potentially serious limitations.

One cost consequence analysis found that erythropoietin was dominant (less costly, more effective) compared to no intervention in reducing blood transfusion requirements in knee and hip arthroplasty surgical patients. This analysis was assessed as partially applicable with potentially serious limitations.

5.5 Recommendations and link to evidence

	1. Do not offer erthropoietin to reduce the need for blood transfusion in patients having surgery.
Relative values of different outcomes	The GDG agreed that the number of patients transfused, number of units transfused, and mortality at 30 days were critical outcomes for decision making. Length of stay in hospital, serious adverse events, thrombosis, infections and quality of life were considered to be important outcomes.
Trade off between clinical benefits and harms	Evidence from 14RCTs comparing EPO with placebo/no EPO showed that there was evidence of clinically important benefit with the use of EPO for the outcomes number of patients transfused, number of units transfused and length of hospital stay. However, there was also evidence of an increase in mortality and the number of patients with thrombotic complications in the EPO group compared to the placebo group, but there was considerable uncertainty in the effect estimates. The evidence suggested no difference of effect between patients receiving EPO and placebo with respect to serious adverse events and infection, but there was some uncertainty in the effect estimates. No evidence was identified for the outcome quality of life. The GDG considered that the benefit from a reduction in the numbers of patients transfused, units transfused and length of hospital stay was offset by a potential increase in mortality and thrombotic complications. There was no evidence available for the outcomes new cardiac events and quality of life.
Economic considerations	Four economic analyses were identified. Two cost-utility analyses found that EPO was not cost-effective compared with no intervention in reducing blood transfusion requirements in surgical patients. Both of these analyses reported very high ICERs (£1,020,000 per QALY and £21,193,000 per QALY). A sensitivity analysis in one of these papers suggested that the cost of EPO would need to reduce by 95% in order for its use to be considered cost-effective. The GDG considered UK relevant unit costs and noted that the required 95% reduction in cost is not reflected in current prices. Of note, in both these analyses, a small QALY gain was observed for those receiving erythropoietin. However, the GDG noted that these analyses were based on single studies that were not included in the clinical review. Furthermore, neither analysis captured adverse events associated with erythropoietin. Two further studies (one cost-utility and one cost-consequence analysis) found that EPO was dominant compared with no intervention in reducing blood transfusion requirements in surgical patients. In both studies, the GDG agreed that the cost of EPO was lower than current prices. Furthermore, sensitivity analyses in one of these papers indicated that EPO was no longer cost-saving when a restrictive transfusion trigger of 8g/dl was used; the baseline blood loss was reduced; the dose of EPO was increased; the cost of EPO was increased (to closer reflect list prices).

	Based on the unit cost of EPO (£887) and the unit cost of transfusing one unit of red blood cells (£167), a threshold analysis was conducted indicating that the mean units of blood that would need to be avoided to offset the cost of EPO was approximately 5.3. The clinical evidence identified in this review indicated that the mean units avoided with EPO was approximately 0.55. Given the high additional expense of EPO, and mixed clinical evidence of both benefit and harm, the GDG agreed that the use of EPO is not cost-effective for reducing blood transfusion requirements in surgical patients.
Quality of evidence	The quality of evidence for all the critical outcomes was of very low quality, except for mortality where the evidence was of low quality. Key issues with this review were in relation to the variability between the studies. There were differences with respect to baseline haemoglobin levels across the studies and it was not always possible to determine if patients were anaemic at baseline as most of the studies did not report baseline haemoglobin values by gender. Also in studies where patients were reported to be anaemic at baseline, it was not clear from the studies if the haemoglobin level was corrected before surgery. There was a lack of evidence for the paediatric population. The GDG felt it reasonable that the same recommendations should apply for children as for adults. Studies also differed with respect to the use of transfusion protocols and differences within the protocols themselves. Two of the economic evaluations were assessed as directly applicable with potentially serious limitations and two were assessed as partially applicable with potentially serious limitations.
Other considerations	The GDG discussed the applicability of the recommendation with respect to patients in whom transfusion is not an option based upon: • Refusal of blood transfusion -Refusal of blood components may or may not be based upon religious beliefs, for example Jehovah's Witnesses • Lack of availability of blood of the appropriate blood type(s) due to red cell antibodies- The GDG noted that EPO may be considered as an option in anaemic patients who refuse blood transfusion or if there is a lack of availability of blood of the appropriate blood type(s) The GDG noted that EPO is recommended for use in some non-surgical patients where it had been prescribed for other causes, for example, chronic renal disease. Please refer NICE guidance on Chronic Kidney Disease[207] and Anaemia Management in Chronic Kidney Disease. Although the GDG decided that EPO should not be recommended, other interventions are available to reduce transfusion in surgical patients (please see the recommendations related to Cell Salvage, Tranexamic Acid, and Oral and IV Iron).

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Recommendations	**2. Offer oral iron before and after surgery to patients with iron-deficiency anaemia.**
Relative values of different outcomes	The GDG considered the mortality (all-causes at 30 days), transfusion related mortality and, number of patients transfused as the critical outcomes for decision making. Other outcomes including, number of units transfused, thrombotic complications, length of stay, serious

	adverse events, infections and quality of life were considered to be important outcomes.
Trade-off between clinical benefits and harms	Evidence from 2 RCTs comparing oral iron with placebo/no oral iron showed that fewer patients were transfused in the oral iron group compared to placebo; but there was considerable uncertainty in the effect estimates. The GDG noted the potential for side effects of oral iron, for example, nausea and gastric discomfort, and the risk of accidental overdose in children. There was no evidence available for the following outcomes: mortality, number of units transfused, thrombotic complications, quality of life, infections, serious adverse events, infections and length of hospital stay. Evidence from 2 RCTs comparing oral iron with IV iron suggested that fewer numbers of patients were found to be transfused in the IV iron group compared to oral iron, but there was considerable uncertainty in the effect estimates. The evidence showed clinically important benefit for oral iron for the outcome length of hospital. The evidence suggested that there were fewer patients with deep vein thrombosis in the oral iron group, but there was considerable uncertainty in the effect estimates. . There was no important difference between oral iron and IV iron for the outcome of quality of life. There was no evidence available for the following outcomes: number of units transfused, quality of life, thrombotic complications and serious adverse events. There was no specific evidence available for use of oral iron in paediatrics; the GDG agreed that the same recommendations should apply for children as for adults, as children may be iron deficient and would be likely to benefit from iron replacement prior to surgery in the same way as adults.
Economic considerations	A cost–consequence analysis was identified which found that oral iron was both less costly and more effective than no intervention in reducing blood transfusion requirements in anaemic surgical patients. The GDG considered the unit costs of oral iron and discussed the related administrative costs. They concluded that use of oral iron was likely to be cost effective. No relevant economic evaluation was identified comparing oral iron and iv iron. The unit costs of both oral and IV iron were calculated and presented to the GDG. The unit cost of oral iron therapy was £2.90 per month and IV iron therapy (including drug cost, staff time, clinic space, administrator time and transport) was £230.09 per high dose low frequency regimen. The clinical evidence found that there may be a lower rate of transfusion with IV iron which could potentially offset this cost, however this evidence was low quality and as such the GDG had low confidence in this effect. Given the higher cost of IV iron and as the clinical evidence indicated that there was no clinically important difference in quality of life between those receiving oral versus intravenous iron the GDG concluded it was unlikely that IV iron would be a cost effective alternative when both were appropriate options. Therefore, the GDG recommended oral iron unless patients cannot tolerate or absorb oral iron; are diagnosed with anaemia less than 14 days before surgery, or may not be able to adhere to oral iron treatment, in which case IV iron should be considered.
Quality of evidence	The quality of evidence for all the critical outcomes in this review was of very low quality, except for number of patients transfused when comparing oral iron and IV iron. In this case, the evidence was of low

	quality. Key issues with this review were in relation to the variability between the studies. There were differences with respect to baseline haemoglobin levels across the studies and it was not always possible to determine if patients were anaemic at baseline as most of the studies did not report baseline haemoglobin values by gender. Also in studies where patients were reported to be anaemic at baseline, it was not clear from the studies if the haemoglobin level was corrected before surgery. Studies also differed with respect to the use of transfusion protocols and differences within the protocols themselves. There was a lack of evidence for the paediatric population. The GDG felt it reasonable that the same recommendations should apply for children as for adults. The economic evaluation was assessed as partially applicable with potentially serious limitations.
Other considerations	• The GDG considered the issue of patient preference, noting that patients may prefer to be prescribed oral iron instead of having IV iron administered. However, the GDG agreed that the success of oral iron therapy is also largely dependent on compliance of the patient (see Medicines Adherence guideline). • The GDG noted the importance of iron therapy with particular reference to patients with iron deficiency in whom blood transfusion is not an option, as this may be the only source of treating anaemia. • The GDG also discussed the relevance of the duration of iron therapy prior to surgery. The GDG agreed that oral iron would be useful in raising haemoglobin levels if prescribed for a period of approximately 2 weeks. This was considered to be particularly important in light of the current pressures on waiting times for surgery and cancer treatment. It was also noted that this introduces logistic challenges of identifying patients with iron deficiency at sufficient time pre-surgery for the intervention to be given. • The GDG also discussed the importance of diagnosis of the type of anaemia before considering the use of oral iron. Although the review did not differentiate between patients based on the time of administration of oral iron therapy, the GDG noted on the basis of their clinical experience that post-surgical patients may be more likely to be truly responsive to iron therapy as the mechanism of developing anaemia is usually blood loss. • The GDG also considered practical issues such as dosing regimens of oral iron and thresholds below which oral iron therapy should be administered. Although these were not explicitly evaluated in the context of this review, the GDG felt that these were practical issues for consideration in clinical practice and related guidance on these topics should be followed by the prescribing clinician. For related guidance please refer the NICE guideline on Anaemia management in chronic kidney disease.

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Recommendations	**3. Consider intravenous iron before and after surgery for patients with iron-deficiency anaemia who:** • **cannot tolerate or absorb oral iron**

	• **are diagnosed with functional iron deficiency** • **are diagnosed with iron-deficiency anaemia and the interval to surgery is considered short** • **are unable to adhere to oral iron treatment (see the NICE guideline on medicines adherence).** **4. For guidance on managing anaemia in patients with chronic kidney disease, see the NICE guideline on anaemia management in chronic kidney disease.** **5. For guidance on managing upper gastrointestinal bleeding, see the NICE guideline on upper gastrointestinal bleeding.**
Relative values of different outcomes	The GDG considered the mortality (all causes at 30 days), transfusion related mortality and number of patients transfused as the critical outcomes for decision making. Other outcomes including and number of units transfused thrombotic complications, length of stay, serious adverse events, infections and quality of life were considered to be important outcomes.
Trade-off between clinical benefits and harms	Evidence from 5 RCTs comparing IV iron with placebo showed that IV iron was more effective than placebo at reducing the number of patients transfused, but there was some uncertainty. Length of hospital stay and infections appeared to be higher in the IV iron group compared to placebo group; but there was too much uncertainty within the effect estimates to allow confident interpretation of clinical benefit or harm for these two outcomes. There was no important difference of effect between patients receiving IV iron and placebo with respect to mortality at 30 days and serious adverse events, but there was some uncertainty in the effect estimates. Evidence from two RCTs comparing oral iron with IV iron suggested that fewer numbers of patients were found to be transfused in the IV iron group compared to oral iron, but there was considerable uncertainty in the effect estimates. The evidence showed clinically important benefit for oral iron for the outcome length of hospital. The evidence suggested that there were fewer patients with deep vein thrombosis in the oral iron group, but there was considerable uncertainty in the effect estimates. . There was no important difference between oral iron and IV iron for the outcome of quality of life. There was no evidence available for the following outcomes: number of units transfused, quality of life, thrombotic complications and serious adverse events. The GDG considered the side effects of intravenous iron, as all preparations carry a small risk of adverse reactions which can be life threatening if not treated promptly. However, the benefits outweigh the risks for the treatment of iron deficiency when administration of oral iron is ineffective or poorly tolerated. Patients should be closely monitored for signs of hypersensitivity during or for at least 30 minutes after each administration. Intravenous iron is contraindicated in patients with known hypersensitivity to any parenteral iron product, and should not be used to treat pregnant women in the first trimester [98] .

	Both oral iron and IV were considered to be clinically effective for treating anaemia in surgical patients but due to patient preferences oral iron was considered to be the first option for treatment. IV iron was reserved for patients where oral iron may not be suitable [98]. Based on their knowledge and experience, the GDG noted that oral iron may not be appropriate in people who cannot tolerate or absorb oral iron, are diagnosed with functional iron deficiency, are diagnosed with anaemia, and the interval to surgery is considered short and/or are unable to adhere to oral iron treatment (see the NICE guideline on medicines adherence). Although there was no specific evidence available for the use of IV iron in paediatrics, the GDG agreed that the same recommendations should apply for children as for adults as the accepted clinical indications for IV iron are the same for both groups. .
Economic considerations	A cost–consequence analysis was identified which found that IV iron was both less costly and more effective than no intervention in reducing blood transfusion requirements in anaemic surgical patients. The GDG considered the variance in unit costs of IV iron and discussed related administrative costs. No relevant economic evaluation was identified comparing oral iron and iv iron. The unit costs of both oral and IV iron were calculated and presented to the GDG. The unit cost of oral iron therapy was £2.90 per month and IV iron therapy (including drug cost, staff time, clinic space, administrator time and transport) was £230.09 per high dose low frequency regimen. The clinical evidence found that there may be a lower rate of transfusion with IV iron which could potentially offset this cost difference, however this evidence was low quality and as such the GDG had low confidence in this effect. Given the higher cost of IV iron and as the clinical evidence indicated that there was no clinically important difference in quality of life between those receiving oral versus intravenous iron the GDG concluded it was unlikely that IV iron would be a cost effective alternative when both were appropriate options. Therefore, the GDG recommended oral iron unless patients cannot tolerate or absorb oral iron; are diagnosed with anaemia less than 14 days before surgery or may not be able to adhere to oral iron treatment, in which case IV iron should be considered.
Quality of evidence	The quality of evidence for all the critical outcomes in this review was of very low quality, except for number of patients transfused when comparing oral iron and IV iron. In this case, the evidence was of low quality. The identification of specific groups where oral iron may not be suitable and therefore IV iron was appropriate for use was based on the consensus expert opinion of the GDG members. Key issues with this review were in relation to the variability between the studies. There were differences with respect to baseline haemoglobin levels across the studies and it was not always possible to determine if patients were anaemic at baseline as most of the studies did not report baseline haemoglobin values by gender. Also in studies where patients were reported to be anaemic at baseline, it was not clear from the studies if the haemoglobin level was corrected before surgery. Studies also differed with respect to the use of transfusion protocols and differences within the protocols themselves. There was a lack of evidence for the paediatric population. The GDG felt it

	reasonable that the same recommendations should apply for children as for adults. The economic evaluation was assessed as partially applicable with potentially serious limitations.
Other considerations	• The GDG considered the issue of patient preference, noting that patients may prefer to be prescribed oral iron instead of having IV iron administered. However, the GDG agreed that the success of oral iron therapy is also largely dependent on compliance of the patient (see Medicines Adherence guideline). • The GDG discussed the importance of iron therapy with particular reference to patients in whom blood transfusion is not an option, as this may be the only source of building up haemoglobin stores. • The group also considered patients who may have malabsorption syndrome (for example, people with severe Crohns disease), in which case IV Iron would be preferred. • The GDG agreed that oral iron would be useful in raising haemoglobin levels if prescribed for a period of approximately 2 weeks. The GDG noted, based on their experience, that in cases of emergency surgery, IV iron could be prescribed and would be more effective in improving haemoglobin levels in the limited time available. The GDG also discussed the importance of diagnosing the type of anaemia before considering the use of IV iron. Although the review did not differentiate between patients based on the time of administration of oral iron therapy, the GDG noted on the basis of their clinical experience that post-surgical patients may be more likely to be truly responsive to iron therapy as the mechanism of developing anaemia is usually blood loss.

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6 Alternatives to transfusion: Cell salvage and tranexamic acid

As part of the Department of Health initiative on patient blood management in addition to safety of blood transfusion, there is a clear focus to improve clinical outcomes in patients by preventing exposure to donor blood. This has resulted in the need for appropriate use of blood and use of alternatives to blood transfusion.

Cell salvage and tranexamic acid have both been used in surgical patients as alternatives to blood transfusion.

Cell salvage

Cell salvage is a procedure whereby blood loss during or after surgery is collected and then re-transfused to the patient.

Salvage of blood both intra-operatively and post-operatively and its re-transfusion has been used for many years with the aim of reducing the frequency and the volume of allogeneic blood transfusion for a number of surgical procedures. Intra-operative cell salvage involves collection of shed blood during surgery followed by re-transfusion. This is carried out by using a cell salvage device. Post-operative cell salvage involves collection of blood from post-operative drains and re-transfusion.

Cell salvage has been used in many hospitals in combination with other measures for minimising blood use in surgical patients. This has contributed to a marked decreased use of red cell transfusion in surgical patients in England over the last 15 years.

A Cochrane review found evidence for the effectiveness of this strategy but many of the studies included were small and of poor quality.[38] The studies analysed often did not provide adequate data on outcome, survival or quality of life and so valid analysis could not be made to evaluate the cost-effectiveness of such interventions.

Tranexamic acid

Tranexamic acid is an antifibrinolytic. It is a synthetic derivative of the amino acid lysine that inhibits fibrinolysis (clot break down) by blocking the lysine binding sites on plasminogen.

The recent CRASH-2 randomised placebo-controlled trial which assessed the effects of tranexamic acid on death, vascular occlusive events and blood transfusion in trauma patients with significant haemorrhage reported tranexamic acid safely reduced all-cause mortality and risk of death due to bleeding. The haemostatic response to vascular injury in trauma is similar to the response to major surgery. A Cochrane review reported that antifibrinolytics reduce blood loss during surgery and the receipt of allogeneic red cell without increasing the risk of post-operative complications.[128] In contrast, the CRASH-2 trial in trauma patients did not find a substantial reduction in the receipt of a blood transfusion or the amount of blood transfused in the tranexamic acid group.

The data have been reviewed to determine the clinical and cost-effectiveness of tranexamic acid in reducing blood transfusion requirements in surgical patients in light of widespread use and safety data post -CRASH-2.

The use of tranexamic acid and cell salvage alone or in combination with each other is examined in this review.

6.1 Review question: What is the clinical and cost-effectiveness of using alternatives to blood transfusion (cell salvage or tranexamic acid alone or in combination with one another) to reduce blood transfusion requirements?

The objective of this review question was to evaluate if the combination of cell salvage and tranexamic acid was more clinically and cost-effective than either of them alone.

Table 22: PICO characteristics of review question

<table>
<tr><td>Population</td><td>Surgical patients
• Adults
• Children (over the age of 1)</td></tr>
<tr><td>Intervention(s)</td><td>High and moderate risk groups (see review strategy for definitions):
• Intra-operative cell salvage (ICS)
• Post-operative cell salvage (PCS)
• Intra-operative plus post-operative cell salvage (ICS+PCS)
• Tranexamic acid (TXA)
• Intra-operative cell salvage plus TXA (ICS+TXA)
• Post-operative cell salvage plus TXA (PCS+TXA)
• Intra-operative cell salvage plus post-operative cell salvage plus TXA (ICS+PCS+TXA)
• Standard treatment
Low risk group (see review strategy for definitions):
• Tranexamic acid
• Standard treatment</td></tr>
<tr><td>Comparison(s)</td><td>All of the above, alone or in combination, compared with one another within each risk group.</td></tr>
<tr><td></td><td>Matrix of treatment comparisons
<table>
<tr><th>Comparisons</th><th>ICS</th><th>P CS</th><th>ICS+PCS</th><th>TXA</th><th>ICS+TXA</th><th>PCS+TXA</th><th>ICS+PCS+ TXA</th><th>Standard treatment</th></tr>
<tr><td>ICS</td><td></td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr>
<tr><td>P CS</td><td></td><td></td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr>
<tr><td>ICS+PCS</td><td></td><td></td><td></td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr>
<tr><td>TXA</td><td></td><td></td><td></td><td></td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr>
<tr><td>ICS+TXA</td><td></td><td></td><td></td><td></td><td></td><td>✓</td><td>✓</td><td>✓</td></tr>
<tr><td>PCS+TXA</td><td></td><td></td><td></td><td></td><td></td><td></td><td>✓</td><td>✓</td></tr>
<tr><td>ICS+PCS+TXA</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>✓</td></tr>
<tr><td>Standard treatment</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
</table></td></tr>
<tr><td>Outcomes</td><td>• Number of patients needing allogeneic transfusions - critical
• Number of units of allogeneic blood transfused / volume of allogeneic blood transfused (in ml) - critical
• All-cause mortality at 30 days - critical
• Quality of life - critical
• Length of stay (hospitalisation) - important
• Infections - important</td></tr>
</table>

	• Thrombotic complications - important • Serious adverse events (as defined by study) – important
Study design	Randomised controlled trials

For full details see review protocol in Appendix C.

6.2 Methodology of clinical evidence review

6.2.1 Background

The GDG was keen to identify the best combination of alternatives to blood transfusion in surgical patients.

Two preliminary clinical evidence reviews showed that cell salvage and tranexamic acid were both clinically and cost-effective when compared independently with standard treatment. Standard treatment was defined as either the administration of placebo or usual care. However, the GDG was keen to understand whether:

- one intervention was more effective than the other
- the combination of cell salvage and tranexamic acid was better than either intervention
- there were specific population groups in which one intervention or combination may be more effective.

To this effect, the evidence was reviewed again, based on the stratification of the surgical populations into three groups (see section 6.2.2 below), as proposed by the GDG. Further details of the methodology of the review are explained in subsequent sections.

6.2.2 Stratification of risk groups and pre-defined subgroup analysis

The GDG stratified the population on the basis of baseline risk of requiring a blood transfusion which was noted to be collectively dependent on a number of factors including:

- the type of surgery
- the use of different transfusion protocols and blood transfusion at different thresholds
- the baseline and pre-operative haemoglobin level of the patient
- any pre-operative management received by the patient to correct anaemia
- autologous donation of blood prior to surgery.

Accurate stratification of the population by baseline risk requires classification of individual patients within trials into different risk groups taking into account all of the above factors. It was acknowledged that the data for such an exercise were not available from randomised controlled trials. No individual participant data meta-analysis was available in this topic area.

The GDG agreed that stratification of patients into risk groups based on the expected volume of blood loss determined solely by the type of surgery was an acceptable approximation of the above classification. Although it was not possible to stratify the population accurately taking into account all factors influencing the risk of receiving a blood transfusion, it was agreed that these factors would be explored by way of subgroup analysis in case of heterogeneity.

The surgeries were grouped into three strata:

- **High risk surgeries** were defined as surgeries where blood loss is expected to be greater than 1 litre.

- **Moderate risk surgeries** were defined as surgeries where blood loss is expected to be between 500 ml and 1 litre.
- **Low risk surgeries** were defined as surgeries where blood loss is expected to be less than 500 ml.

It was noted that cell salvage is appropriate only for surgeries in the high and moderate risk groups where blood loss is expected to be greater than 1 unit (approximately 500 ml).

As blood loss is expected to be less than 500 ml, cell salvage is not a feasible option in the low risk surgery group and, therefore, effectiveness of only tranexamic acid compared with standard treatment was evaluated in this group.

It was noted that the volumes outlined in the above classification may not be applicable to surgeries in children. In children, the classification was therefore done by taking into consideration both the type of surgery and the blood volume.

- In children the GDG agreed that moderate blood loss would be defined as blood loss greater than 10% of blood volume.
- In adults, high degree of blood loss was defined as blood loss greater than 1 litre; the GDG agreed that a corresponding equivalent blood loss with respect to body weight in children would qualify as a high degree of blood loss.

This is further reflected in the outcomes analysed in the review for children where the volume of blood transfused was used an outcome rather than the units of allogeneic blood transfused.

6.2.3 Exclusion of studies published before 2003

Change in surgical practice over the last decade has resulted in less blood loss due to more attention being given to achieving haemostasis to avoid unnecessary bleeding. A change in surgical practice by some practitioners to not use post-operative drains has largely eliminated post-operative cell salvage as a blood conservation technique and the accepted indications for intra-operative cell salvage have extended.

The GDG agreed that substantial changes in transfusion practice over time with respect to the use of cell salvage meant that studies published prior to 2003 were not relevant to current clinical practice and would not inform the decision making process or the economic model. These changes were in relation to:

- selection of patients for cell salvage (intra-operative cell salvage and post-operative cell salvage)
- surgical technique.

The GDG noted that the above rationale does not impact on the effectiveness of tranexamic acid, and all RCTs evaluating the effectiveness of tranexamic acid were included in the clinical review (no date restriction was applied). The effectiveness of tranexamic acid is related to inhibition of fibrinolysis and not to changes in surgical technique and therefore it is relevant to include all studies regardless of when they were published.

A preliminary subgroup analysis of all trials for both interventions showed that there were differences between studies on cell salvage conducted before and after 2003. This finding was not observed in trials conducted to evaluate the efficacy of tranexamic acid. This reinforced the GDG's decision to exclude trials on cell salvage conducted prior to 2003, but include the data for tranexamic acid with no date restrictions.

6.2.4 Grouping of doses and routes of administration of tranexamic acid

The GDG agreed that all doses and routes of administration of tranexamic acid will be evaluated together. This was based on GDG consensus and supported by a preliminary subgroup analysis which showed no differences between different routes of administration of tranexamic acid.

6.3 Clinical evidence

We searched for randomised controlled trials comparing the effectiveness of different interventions in the protocol (see matrix of treatment comparisons).

Five Cochrane reviews were identified in this topic area which met the inclusion criteria[38,128,158,159,237]; These reviews independently evaluated the effect of either cell salvage or tranexamic acid in reducing blood transfusion requirements. However, these reviews did not evaluate the effectiveness of combinations of cell salvage or tranexamic acid. As the studies included in these reviews do provide data on the effectiveness of combination of these interventions, these reviews have been included as part of this clinical evidence review and data from individual studies have been extracted again with respect to combinations of cell salvage and tranexamic acid as interventions (if present), and the analysis has been adapted accordingly.

The process of re-extracting the data included checking all studies identified in the previously published reviews and in the update searches (since the cut off dates of the Cochrane reviews) which compared cell salvage or tranexamic acid with standard treatment. All studies were checked to confirm the concomitant treatments in both arms (these may have included either cell salvage or tranexamic acid). The studyinterventions were reclassified based on this and the studies were grouped into a specific risk category as defined above (see section 1.3.2). The GDG discussed the patient population in each study and stratified them in one of the risk groups based on the expected blood loss.

Data relevant to the comparisons in the current review protocol on combinations of cell salvage and tranexamic acid were extracted from these reviews and reanalysed.

Pairwise meta-analysis was conducted for each risk group (high, moderate and low) based on the stratification agreed by with the GDG and for adults and children separately. Results are presented for each risk group.

For the outcome on number of units of allogeneic transfusions received by participants, the mean number of units was analysed in participants who received transfusions. In some studies where it was unclear if the mean number of units was calculated over the number of participants who received transfusions or over the total number of participants randomised to that intervention, we assumed the former and have downgraded the evidence for outcome reporting bias.

Evidence was found for the following comparisons in each risk group and the results have been presented accordingly.

A summary of the studies, classified by risk groups and included in this review is presented in the tables 22-25 below.

Table 23: Summary of studies- Adults- High risk group

Study	Intervention	Comparator	Risk group
Adults- High risk			
Aghdaii 2012[5]	Standard Treatment	ICS	High
Ahn2012[7]	Standard Treatment	TXA	High
Andreasen2004[13]	Standard Treatment	TXA	High

Study	Intervention	Comparator	Risk group
Armellin2001[14]	Standard Treatment	TXA	High
Baric2007[18]	Standard Treatment	TXA	High
Blauhut1994[25]	Standard Treatment	TXA	High
Casati2001[43]	Standard Treatment	TXA	High
Casati2004[44]	ICS	ICS+TXA	High
Coffey1995[59]	Standard Treatment	TXA	High
Corbeau1995[63]	Standard Treatment	TXA	High
Dalmau2000[74]	Standard Treatment	TXA	High
Damgard2006[75]	Standard Treatment	ICS	High
Debonis2000[80]	Standard Treatment	TXA	High
Dellamore2012[82]	Standard Treatment	TXA	High
Diprose2005[87]	ICS	ICS+TXA	High
Esfandiari2013[96]	Standard Treatment	TXA	High
Fawzy2009[102]	Standard Treatment	TXA	High
Ghaffari2012[113]	Standard Treatment	TXA	High
Ghavidel 2014[8]	Standard Treatment	TXA	High
Hardy1998[122]	Standard Treatment	TXA	High
Horrow1991[134]	Standard Treatment	TXA	High
Jares2003[143]	Standard Treatment	TXA	High
Jiminez2007[144]	ICS	ICS+TXA	High
Karski2005[153]	Standard Treatment	TXA	High
Katoh1997[155]	Standard Treatment	TXA	High
Katsaros1996[156]	Standard Treatment	TXA	High
Klein2008[165]	TXA	ICS+PCS+TXA	High
Krohn2003[168]	Standard Treatment	TXA	High
Kuitunen2005[169]	ICS	ICS+TXA	High
Later2009[172]	ICS	ICS+TXA	High
Lundin2014[183]	Standard Treatment	TXA	High
Mansour2004[187]	Standard Treatment	TXA	High
Mehraein2007[191]	Standard Treatment	TXA	High
Menichetti1996[192]	Standard Treatment	TXA	High
Mercer2004[193]	Standard Treatment	ICS	High
Murphy2004[199]	Standard Treatment	ICS+PCS	High
Murphy2005[200]	Standard Treatment	ICS	High
Murphy2006[201]	ICS+PCS	ICS+PCS+TXA	High
Naumenko2003[210]	Standard Treatment	PCS	High
Nouraei2013[219]	Standard Treatment	TXA	High
Pleym2003[240]	Standard Treatment	TXA	High
Pleym2005[239]	Standard Treatment	PCS	High
Reyes2011[250]	TXA	ICS+TXA	High
Santos2006[260]	Standard Treatment	TXA	High
Shi2013[271]	Standard Treatment	TXA	High
Shi2013a[272]	Standard Treatment	TXA	High

Study	Intervention	Comparator	Risk group
Sirvinkas2007 [273]	Standard Treatment	PCS	High
Speekenbrink1995[281]	Standard Treatment	TXA	High
Taghaddomi2009[286]	Standard Treatment	TXA	High
Vanek2005[302]	Standard Treatment	TXA	High
Vermeijden2015[304]	Standard Treatment	ICS	High
Wang2012[312]	Standard Treatment	TXA	High
Wei2006[316]	Standard Treatment	TXA	High
Wiefferink2007[318]	Standard Treatment	ICS+PCS	High
Wu2006[322]	Standard Treatment	TXA	High
Zhao2003[330]	Standard Treatment	PCS	High

Table 24: Summary of studies-Adults- Moderate risk group

Study	Intervention	Comparator 1	Comparator 2	Risk group
Adults – Moderate risk				
Abuzakuk2007[1]	Standard Treatment	PCS	-	Moderate
Aguilera2013[6]	Standard Treatment	TXA	-	Moderate
Alshryda2013[10]	Standard Treatment	TXA	-	Moderate
Alvarez2008[11]	PCS	PCS+TXA	-	Moderate
Amin2008[12]	Standard Treatment	PCS	-	Moderate
Atay2010i[16]	Standard Treatment	PCS	-	Moderate
Atay2010ii[16]	Standard Treatment	PCS	-	Moderate
Benoni1996[19]	Standard Treatment	TXA	-	Moderate
Benoni2000[21]	Standard Treatment	TXA	-	Moderate
Benoni2001[20]	Standard Treatment	TXA	-	Moderate
Bidolegui2014[22]	Standard Treatment	TXA	-	Moderate
Bradshaw2012[29]	Standard Treatment	TXA	-	Moderate
Caglar2008[33]	Standard Treatment	TXA	-	Moderate
Charoeanch2011[50]	Standard Treatment	TXA	-	Moderate
Charoeanch2012[49]	Standard Treatment	TXA	-	Moderate
Cheng2005[53]	Standard Treatment	PCS	-	Moderate

Study	Intervention	Comparator 1	Comparator 2	Risk group
Cip2013[57]	Standard Treatment	ICS	-	Moderate
Claeys2007[58]	Standard Treatment	TXA	-	Moderate
Crescenti2011[67]	Standard Treatment	TXA	-	Moderate
Dakir2014[73]	Standard Treatment	TXA	-	Moderate
Dramis2006[92]	Standard Treatment	PCS	-	Moderate
Ellis2001[94]	Standard Treatment	TXA	-	Moderate
Engel2001[95]	Standard Treatment	TXA	-	Moderate
Farrokhi2011[101]	Standard Treatment	TXA	-	Moderate
Garneti2004[110]	Standard Treatment	TXA	-	Moderate
Georgiadis2013[112]	Standard Treatment	TXA	-	Moderate
Gill2009[114]	Standard Treatment	TXA	-	Moderate
Good2003[116]	Standard Treatment	TXA	-	Moderate
Gungorduk2011[120]	Standard Treatment	TXA	-	Moderate
Hiipala1995[130]	Standard Treatment	TXA	-	Moderate
Hiipala1997[131]	Standard Treatment	TXA	-	Moderate
Horstmann2013[135]	Standard Treatment	ICS	-	Moderate
Horstmann2014[136]	Standard Treatment	PCS	-	Moderate
Horstmann2014a[137]	Standard Treatment	ICS+PCS	-	Moderate
Husted2003[138]	Standard Treatment	TXA	-	Moderate
Ishida2011[140]	Standard Treatment	TXA	-	Moderate
Jansen1999[142]	Standard Treatment	TXA	-	Moderate
Johansson2005[145]	Standard Treatment	TXA	-	Moderate
Karimi2012[151]	Standard Treatment	TXA	-	Moderate
Kazemi2010[157]	Standard Treatment	TXA	-	Moderate

Study	Intervention	Comparator 1	Comparator 2	Risk group
Kim 2014ii[163]	Standard Treatment	TXA	-	Moderate
Kim2014i[163]	Standard Treatment	TXA	-	Moderate
Lee2013[177]	Standard Treatment	TXA	-	Moderate
Lemay2004[178]	Standard Treatment	TXA	-	Moderate
Macgillvray2010[185]	Standard Treatment	TXA	-	Moderate
Moonen2007[196]	Standard Treatment	PCS	-	Moderate
Niskanen2005[217]	Standard Treatment	TXA	-	Moderate
Oremus2014[224]	PCS	PCS+TXA	-	Moderate
Orpen2006[227]	Standard Treatment	TXA	-	Moderate
Rajesparan2009[243]	Standard Treatment	TXA	-	Moderate
Raviraj2012[247]	Standard Treatment	TXA	-	Moderate
Roy2012[254]	Standard Treatment	TXA	-	Moderate
Sadeghi2007[257]	Standard Treatment	TXA	-	Moderate
Sa-ngasoongsong2011[255]	Standard Treatment	TXA	-	Moderate
Sa-ngasoongsong2013[256]	Standard Treatment	TXA	-	Moderate
Seo2013[266]	Standard Treatment	TXA	-	Moderate
Shahid2013[269]	Standard Treatment	TXA	-	Moderate
Smith2007[275]	Standard Treatment	PCS	-	Moderate
Soosman2006[277]	Standard Treatment	PCS	-	Moderate
Soosman2014[278]	Standard Treatment	PCS	ICS+PCS	Moderate
Sorin1999[279]	Standard Treatment	TXA	-	Moderate
Tanaka2001[287]	Standard Treatment	TXA	-	Moderate
Thomassen2012[290]	TXA	ICS+PCS+TXA	-	Moderate
Thomassen2014[289]	Standard Treatment	PCS	-	Moderate
Tripkovic2008[295]	Standard Treatment	PCS	-	Moderate

Study	Intervention	Comparator 1	Comparator 2	Risk group
Vijay2013[306]	Standard Treatment	TXA	-	Moderate
Wong2008[321]	ICS	ICS+TXA	-	Moderate
Wong2010[320]	Standard Treatment	TXA	-	Moderate
Yang2014[324]	Standard Treatment	TXA	-	Moderate
Yue2015[327]	Standard Treatment	TXA	-	Moderate
Zacharopoulos2007[328]	Standard Treatment	PCS	-	Moderate
Zhang2008[329]	Standard Treatment	ICS	-	Moderate
Zohar2004[332]	Standard Treatment	TXA	-	Moderate

Table 25: Summary of studies-Adults- Low risk group

Study	Intervention	Comparator	Risk group
Adults- Low risk group			
Albirmawy 2013[10]	TXA	Standard Treatment	Low
Jabalameli 2006[141]	TXA	Standard Treatment	Low
Kaewpradub 2011[148]	TXA	Standard Treatment	Low
Rannikko 2004[245]	TXA	Standard Treatment	Low
Sankar 2012[259]	TXA	Standard Treatment	Low
Tsutsumimoto 2011[297]	TXA	Standard Treatment	Low

Table 26: Summary of studies- Children- High risk group

Study	Intervention	Comparator	Risk group
Chauhan 2003[51]	TXA	Standard Treatment	High
Sethna 2005[268]	ICS+TXA	ICS	High
Verma 2014[303]	TXA	Standard Treatment	High
Zonis 1996[333]	TXA	Standard Treatment	High

6.3.1 Results from pair wise meta-analysis

For summary GRADE profiles from pairwise meta-analysis, refer to sections 6.3.1.1– 6.3.1.4.

The results of the pairwise meta-analysis are presented for each comparison and outcome in each risk group. Results are presented separately for adults and children. For forest plots of pairwise comparisons, refer to Appendix K.

6.3.1.1 Evidence from pair wise comparisons: adults - high risk group

Table 27: Intra-operative cell salvage versus standard treatment

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard treatment	Risk difference with intra-operative cell salvage (95% CI)
No. exposed to allogeneic blood	251 (4 studies)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.74 (0.58 to 0.93)	Study population	
				532 per 1000	138 fewer per 1000 (from 37 fewer to 223 fewer)
Units of allogeneic blood transfused	223 (4 studies)	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision			The mean units of allogeneic blood transfused in the intervention groups was 0.78 lower (1.37 to 0.19 lower)
Mortality at up to 30 days	424 (7 studies)	VERY LOW[a,d] due to risk of bias, imprecision	RR 0.97 (0.64 to 1.47)	Study population	
				89 per 1000	3 fewer per 1000 (from 32 fewer to 42 more)
Any infection	250 (4 studies)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.4 (0.18 to 0.87)	Study population	
				151 per 1000	90 fewer per 1000 (from 20 fewer to 124 fewer)
Hospital length of stay	80 (1 study)	VERY LOW[a,d] due to risk of bias, imprecision			The mean hospital length of stay in the intervention groups was 0.2 lower (1.26 lower to 0.86 higher)

(a) The majority of the evidence was at very high risk of bias.
(b) The confidence interval crosses one MID.
(c) Downgraded by one increment due to heterogeneity, I^2=65%.
(d) The confidence interval crosses both MIDs.

Table 28: Post-operative cell salvage versus standard treatment

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard treatment	Risk difference with post-operative cell salvage (95% CI)
No. exposed to allogeneic blood	262 (4 studies)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.6 (0.45 to 0.81)	Study population	
				390 per 1000	156 fewer per 1000 (from 74 fewer to 214 fewer)
Units of allogeneic blood transfused	60 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision			The mean units of allogeneic blood transfused in the intervention groups was 1.02 lower (1.19 to 0.85 lower)
Mortality at up to 30 days	50 (1 study)	VERY LOW[a,c] due to risk of bias, imprecision	RR 3 (0.13 to 70.3)	Study population	
				0 per 1000	-
Any infection	90 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.15 (0.02 to 1.15)	Study population	
				163 per 1000	139 fewer per 1000

					(from 160 fewer to 24 more)
Hospital length of stay	90 (1 study)	LOW[a] due to risk of bias			The mean hospital length of stay in the intervention groups was 7.13 lower (9.12 to 5.14 lower)

(a) The majority of the evidence was at very high risk of bias.
(b) The confidence interval crosses one MID.
(c) The confidence interval crosses both MIDs.

Table 29: Intra-operative cell salvage plus post-operative cell salvage versus standard treatment

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard treatment	Risk difference with intra-operative cell salvage + post-operative cell salvage (95% CI)
No. exposed to allogeneic blood	230 (2 studies)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.69 (0.54 to 0.89)	Study population	
				632 per 1000	196 fewer per 1000 (from 70 fewer to 291 fewer)
Mortality at up to 30 days	196 (1 study)	VERY LOW[a,c] due to risk of bias, imprecision	RR 0.33 (0.03 to 3.09)	Study population	
				31 per 1000	21 fewer per 1000 (from 30 fewer to 65 more)
Any infection	196 (1 study)	VERY LOW[a,c] due to risk of bias, imprecision	RR 0.98 (0.14 to 6.82)	Study population	
				21 per 1000	0 fewer per 1000 (from 18 fewer to 120 more)
Length of hospital stay	196 (1 study)	VERY LOW[a,c] due to risk of bias, imprecision			The mean length of hospital stay in the intervention groups was 2.8 higher (2.11 lower to 7.71 higher)

(a) The majority of the evidence is at very high risk of bias.
(b) The confidence interval crosses one MID.
(c) The confidence interval crosses both MIDs.

Table 30: Intra-operative cell salvage plus tranexamic acid versus intra-operative cell salvage

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with intra-operative cell salvage	Risk difference with intra-operative cell salvage +TXA (95% CI)
No. exposed to allogeneic blood	514 (5 studies)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.71 (0.6 to 0.85)	Study population	
				556 per 1000	161 fewer per 1000 (from 83 fewer to 222 fewer)
Units of blood transfused	170 (2 studies)	VERY LOW[a,c] due to risk of bias, inconsistency			The mean units of blood transfused in the intervention groups was 1.56 lower (1.84 to 1.29 lower)
Mortality at 30 days	352 (4 studies)	VERY LOW[a,d] due to risk of bias, imprecision	RR 1.04 (0.07 to 16.41)	Study population	
				10 per 1000	0 more per 1000 (from 9 fewer to 147 more)

Length of stay in hospital	252 (2 studies)	VERY LOW[a,d] due to risk of bias, imprecision			The mean length of stay in hospital in the intervention groups was 0.68 higher (0.81 lower to 2.17 higher)

(a) *The majority of the evidence is at very high risk of bias.*
(b) *The confidence interval crosses one MID.*
(c) *Downgraded by one increment due to heterogeneity; I^2=61%.*
(d) *The confidence interval crosses both MIDs.*

Table 31: Intra-operative cell salvage and tranexamic acid versus tranexamic acid

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TXA	Risk difference with intra-operative cell salvage +TXA (95% CI)
No. exposed to allogeneic blood	63 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.79 (0.43 to 1.45)	Study population	
				448 per 1000	94 fewer per 1000 (from 256 fewer to 202 more)
Mortality at 30 days	63 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 7.71 (0.43 to 137.53)	Study population	
				0 per 1000	-
Infections	63 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.07 (0.32 to 3.6)	Study population	
				138 per 1000	10 more per 1000 (from 94 fewer to 359 more)
Length of stay in hospital	63 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision			The mean length of stay in hospital in the intervention groups was 2.1 higher (3.36 lower to 7.56 higher)

(a) *The majority of the evidence is at very high risk of bias.*
(b) *The confidence interval crosses both MIDs.*

Table 32: Post-operative cell salvage plus tranexamic acid versus tranexamic acid

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TXA	Risk difference with post-operative cell salvage +TXA (95% CI)
No. of patients with allogeneic blood transfusion	34 (1 study)	LOW[a] due to risk of bias	Not estimable		

(a) *The majority of the evidence is at very high risk of bias.*

Table 33: Intra-operative cell salvage plus post-operative cell salvage plus tranexamic acid versus intra-operative cell salvage plus post-operative cell salvage

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with intra-operative cell salvage + post-operative cell salvage	Risk difference with intra-operative cell salvage + post-operative cell salvage + TXA (95% CI)
No. exposed to	100	VERY LOW[a,b]	RR 0.93	Study population	

allogeneic blood	(1 study)	due to risk of bias, imprecision	(0.49 to 1.77)	280 per 1000	20 fewer per 1000 (from 143 fewer to 216 more)
Units of blood transfused	27 (1 study)	VERY LOW[a,c] due to risk of bias, imprecision			The mean units of blood transfused in the intervention groups was 0.25 higher (0.32 lower to 0.82 higher)
Mortality at 30 days	100 (1 study)	LOW[a] due to risk of bias	Not estimable		

(a) The majority of the evidence was at very high risk of bias.
(b) The confidence interval crosses both MIDs.
(c) The confidence interval crosses one MID.

Table 34: Intra-operative cell salvage plus post-operative cell salvage plus tranexamic acid versus tranexamic acid

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TXA	Risk difference with intra-operative cell salvage + post-operative cell salvage + TXA (95% CI)
No. exposed to allogeneic blood	213 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.02 (0.68 to 1.54)	Study population	
				297 per 1000	6 more per 1000 (from 95 fewer to 161 more)
Any infection	213 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.31 (0.41 to 4.15)	Study population	
				45 per 1000	14 more per 1000 (from 27 fewer to 142 more)

(a) The majority of the evidence is at very high risk of bias.
(b) The confidence interval crosses both MIDs.

Table 35: Tranexamic acid versus standard treatment

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard treatment/placebo - high risk – adults	Risk difference with TXA (95% CI)
No. of patients needing blood transfusions	4105 (38 studies)	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 0.71 (0.63 to 0.81)	Study population	
				475 per 1000	138 fewer per 1000 (from 90 fewer to 176 fewer)
No. of units of blood transfused - all patients	1918 (16 studies)	LOW[a,b] due to risk of bias, inconsistency			The mean no. of units of blood transfused - all patients in the intervention groups was 0.83 lower (1.17 to 0.5 lower)
Mortality	3771 (31 studies)	VERY LOW[a,c,d] due to risk of bias, inconsistency, imprecision	RR 0.52 (0.31 to 0.87)	Study population	
				19 per 1000	9 fewer per 1000 (from 2 fewer to 13 fewer)
Length of hospital stay	182 (3 studies)	MODERATE[a] due to risk of bias			The mean length of hospital stay in the intervention groups was 0.08 lower (0.35

					lower to 0.18 higher)
Infections	100 (1 study)	LOW[a,c] due to risk of bias, imprecision	RR 0.62 (0.31 to 1.24)	Study population	
				320 per 1000	122 fewer per 1000 (from 221 fewer to 77 more)
Thrombotic complications	986 (10 studies)	LOW[a,c] due to risk of bias, imprecision	RR 0.48 (0.18 to 1.23)	Study population	
				25 per 1000	13 fewer per 1000 (from 20 fewer to 6 more)

(a) Majority of the evidence was at high risk of bias.
(b) Downgraded by one increment due to heterogeneity, I^2=72%.
(c) Confidence interval crosses one MID.
(d) Downgraded by one increment as the point estimate varies widely across studies, unexplained by subgroup analysis.

6.3.1.2 Evidence from pairwise comparisons: adults - moderate risk group

Table 36: Intra-operative cell salvage versus standard treatment

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard treatment	Risk difference with intra-operative cell salvage (95% CI)
No. exposed to allogeneic blood	384 (3 studies)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.74 (0.5 to 1.12)	Study population	
				250 per 1000	65 fewer per 1000 (from 125 fewer to 30 more)

(a) Majority of the evidence was at very high risk of bias.
(b) Confidence interval crosses one MID.

Table 37: Post-operative cell salvage versus standard treatment

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard treatment	Risk difference with post-operative cell salvage (95% CI)
No. exposed to allogeneic blood	2641 (14 studies)	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 0.58 (0.41 to 0.83)	Study population	
				163 per 1000	68 fewer per 1000 (from 28 fewer to 96 fewer)
Units of allogeneic blood transfused	1335 (8 studies)	VERY LOW[a,c,d] due to risk of bias, inconsistency, imprecision			The mean units of allogeneic blood transfused in the intervention groups was 0.82 lower (1.31 to 0.33 lower)
Infection	1025 (4 studies)	VERY LOW[a,e] due to risk of bias, imprecision	RR 1.79 (0.53 to 6.07)	Study population	
				7 per 1000	6 more per 1000 (from 3 fewer to 37 more)
Hospital length of stay	205 (3 studies)	VERY LOW[a,e] due to risk of bias, imprecision			The mean hospital length of stay in the intervention groups was 0.37 lower (1.73 lower to 0.99 higher)

(a) *Majority of the evidence was at very high risk of bias.*
(b) *Downgraded by one increment due to heterogeneity, I^2= 67%.*
(c) *Confidence interval crosses one MID.*
(d) *Downgraded by one increment due to heterogeneity, I^2=88%.*
(e) *Confidence interval crosses both MIDs.*

Table 38: Intra-operative cell salvage plus post-operative cell salvage versus standard treatment

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard treatment	Risk difference with intra-operative cell salvage + post-operative cell salvage (95% CI)
No. exposed to allogeneic blood	1097 (2 studies)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.84 (0.54 to 1.33)	Study population	
				81 per 1000	13 fewer per 1000 (from 37 fewer to 27 more)
Units of allogeneic blood transfused	77 (1 study)	LOW[a] due to risk of bias			The mean units of allogeneic blood transfused in the intervention groups was 0.81 higher (0.49 higher to 1.13 higher)
Infection	118 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 3.32 (0.14 to 79.77)	Study population	
				0 per 1000	-
Length of stay	118 (1 study)	VERY LOW[a,c] due to risk of bias, imprecision			The mean length of stay in the intervention groups was 0.2 higher (0.2 lower to 0.6 higher)
Mortality	118 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 3.32 (0.14 to 79.77)	Study population	
				0 per 1000	-

(a) *Majority of the evidence is at very high risk of bias.*
(b) *Confidence interval crosses both MIDs.*
(c) *Confidence interval crosses one MID.*

Table 39: Intra-operative cell salvage plus tranexamic acid versus intra-operative cell salvage

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with intra-operative cell salvage	Risk difference with intra-operative cell salvage + TXA (95% CI)
No. exposed to allogeneic blood	147 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.78 (0.5 to 1.2)	Study population	
				405 per 1000	89 fewer per 1000 (from 203 fewer to 81 more)
Units of blood transfused	147 (1 study)	VERY LOW[a,c] due to risk of bias, imprecision			The mean units of blood transfused in the intervention groups was 0.46 lower (1.1 lower to 0.18 higher)
Length of stay in hospital	147 (1 study)	VERY LOW[a,c] due to risk of bias, imprecision			The mean length of stay in hospital in the intervention groups was 0.72 higher (0.85 lower to 2.29 higher)

(a) *Majority of the evidence was at very high risk of bias.*
(b) *Confidence interval crosses one MID.*
(c) *Confidence interval crosses both MIDs.*

Table 40: Post-operative cell salvage plus tranexamic acid versus post-operative cell salvage

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with post-operative cell salvage	Risk difference with post-operative cell salvage + TXA (95% CI)
No. exposed to allogeneic blood	193 (2 studies)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.37 (0.12 to 1.14)	Study population	
				112 per 1000	71 fewer per 1000 (from 99 fewer to 16 more)
Thrombotic complications	98 (1 study)		RR 0.2 (0.01 to 4.06)	Study population	
				41 per 1000	33 fewer per 1000 (from 40 fewer to 125 more)

(a) Majority of the evidence is at very high risk of bias.
(b) Confidence interval crosses one MID.

Table 41: Intra-operative cell salvage plus post-operative cell salvage plus tranexamic acid versus tranexamic acid

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with TXA	Risk difference with intra-operative cell salvage + post-operative cell salvage +TXA (95% CI)
No. exposed to allogeneic blood	197 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.73 (0.33 to 1.63)	Study population	
				129 per 1000	35 fewer per 1000 (from 86 fewer to 81 more)
Units of blood transfused	197 (1 study)	LOW[a] due to risk of bias	Not estimable		

(a) Majority of the evidence was at very high risk of bias.
(b) Confidence interval crosses both MIDs.

Table 42: Tranexamic acid versus standard treatment

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard treatment: adults - moderate risk	Risk difference with TXA (95% CI)
No. exposed to allogeneic transfusions	4577 (52 studies)	LOW[a,b] due to risk of bias, inconsistency	RR 0.45 (0.38 to 0.52)	Study population	
				351 per 1000	193 fewer per 1000 (from 165 fewer to 218 fewer)
No. of units of blood transfused - All Patients	644 (9 studies)	LOW[a,c] due to risk of bias, inconsistency			The mean no. of units of blood transfused - all patients in the intervention groups was 0.88 lower (1.22 to 0.54 lower)
Mortality	1071 (9 studies)	VERY LOW[a,d,e] due to risk of bias, inconsistency, imprecision	RR 0.73 (0.15 to 3.66)	Study population	
				4 per 1000	1 fewer per 1000 (from 3 fewer to 10 more)

Length of hospital stay	1332 (9 studies)	VERY LOW[a,f,g] due to risk of bias, inconsistency, imprecision			The mean length of hospital stay in the intervention groups was 0.25 lower (0.59 lower to 0.09 higher)
Infections	586 (6 studies)	VERY LOW[a,d,e] due to risk of bias, inconsistency, imprecision	RR 0.93 (0.22 to 3.93)	Study population	
				10 per 1000	1 fewer per 1000 (from 8 fewer to 30 more)
Thrombotic complications	5179 (48 studies)	LOW[a,g] due to risk of bias, imprecision	RR 0.69 (0.44 to 1.07)	Study population	
				19 per 1000	6 fewer per 1000 (from 11 fewer to 1 more)

(a) Majority of the evidence was at high risk of bias.
(b) Downgraded by one increment due to heterogeneity, I^2=55%.
(c) Downgraded by one increment due to heterogeneity, I^2=89%.
(d) Downgraded by one increment due to heterogeneity; the point estimate varies widely across studies, unexplained by subgroup analysis.
(e) Confidence interval crosses both MIDs.
(f) Downgraded by one increment due to heterogeneity, I^2=61%.
(g) Confidence interval crosses one MID.

Table 43: Intra-operative cell salvage +Post-operative cell salvage versus Post-operative cell salvage

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Post op CS	Risk difference with Intraop CS+Post op CS (95% CI)
Number of patients transfused	642 (1 study)	LOW[a,b] due to risk of bias, imprecision	RR 0.70 (0.42 to 1.16)	103 per 1000	31 fewer per 1000 (from 60 fewer to 16 more)
Units of allogeneic blood transfused	56 (1 study)	MODERATE[a] due to risk of bias			The mean units of allogeneic blood transfused in the intervention groups was 2.23 higher (1.92 to 2.54 higher)

(a) Majority of the evidence was at high risk of bias.
(b) Confidence interval crosses one MID.

6.3.1.3 Evidence from pairwise comparisons: adults - low risk group

Table 44: Tranexamic acid versus standard treatment

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo - low	Risk difference with TXA (95% CI)

				risk - adults	
No. of patients receiving allogeneic transfusions (route)	626 (4 studies)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.83 (0.3 to 2.29)	Study population	
				23 per 1000	4 fewer per 1000 (from 16 fewer to 29 more)
No. of patients receiving allogeneic transfusions (route) - Topical TXA	400 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.2 (0.01 to 4.14)	Study population	
				10 per 1000	8 fewer per 1000 (from 10 fewer to 31 more)
No. of patients receiving allogeneic transfusions (route) - Oral TXA	136 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.13 (0.36 to 3.53)	Study population	
				76 per 1000	10 more per 1000 (from 48 fewer to 192 more)
Blood loss (type of surgery-topical TXA)) - Orthognathic surgery	0 (1 study)	MODERATE[a] due to risk of bias			The mean blood loss (type of surgery-topical TXA) - orthognathic surgery in the intervention groups was 0.93 higher (0.73 to 1.2 higher)
Blood loss (type of surgery-topical TXA) - otolaryngeal surgery	0 (2 studies)				The mean blood loss (type of surgery-topical TXA) - otolaryngeal surgery in the intervention groups was 0.74 higher (0.73 to 0.76 higher)

(a) Majority of the evidence was at high risk of bias.
(b) Confidence interval crosses both MIDs.

6.3.1.4 Evidence from pair wise comparisons: Children - high risk group

Table 45: Intra-operative cell salvage plus tranexamic acid versus intra-operative cell salvage

Outcomes	**No. of Participants (studies) Follow up**	**Quality of the evidence (GRADE)**	**Relative effect (95% CI)**	**Anticipated absolute effects**	
				Risk with intra-operative cell salvage - type of surgery	**Risk difference with intra-operative cell salvage + TXA (95% CI)**
Number of patients transfused - Post 2003	44 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.85 (0.56 to 1.3)	Study population	
				714 per 1000	107 fewer per 1000 (from 314 fewer to 214 more)
Total blood transfused - Post 2003	44 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision			The mean total blood transfused - post 2003 in the intervention groups was 325 lower (685.06 lower to 35.06 higher)
Total blood loss - Post 2003	44 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision			The mean total blood loss - post 2003 in the intervention groups was 855 lower (1408.15 to 301.85 lower)

(a) Majority of the evidence was at very high risk of bias.
(b) Confidence interval crosses both MIDs.

Table 46: Tranexamic acid versus standard treatment

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Standard treatment	Risk difference with TXA (95% CI)
Post-operative blood loss - post 2003	120 (1 study)	MODERATE[a] due to risk of bias			The mean post-operative blood loss - post 2003 in the intervention groups was 16 lower (21.13 to 10.87 lower)
Length of stay	83 (1 study)	LOW[b] due to risk of bias, imprecision			The mean length of stay in the intervention groups was 0.1 higher (0.37 lower to 0.57 higher)

(a) Majority of the evidence was at high risk of bias.
(b) Confidence interval crosses one MID.

6.3.2 Network meta-analysis

A network meta-analysis (NMA) was performed for the treatments outlined in the matrix to help inform the recommendations.

Separate networks were formed for outcomes in each of the risk groups as follows.

In the high risk group, networks were developed for:

- Number of patients exposed to allogeneic transfusions
- Number of units transfused
- Length of stay in hospital

In the moderate risk group, networks were developed for:

- Number of patients exposed to allogeneic transfusions
- Number of units transfused

The baseline risk was defined as the risk of achieving the outcome of interest in the standard treatment group.

For details on the network meta-analysis, refer Appendix L.

For results from network meta-analysis, refer to sections 6.3.2–6.3.7.

For rank-o-grams of the network meta-analysis, refer to section 6.3.7.

6.3.3 Adults: high risk group

Table 47 to Table 50 summarise the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison per outcome in the high risk group.

Table 47: Network 1: Number exposed to allogeneic transfusions

Comparison		Risk ratio	
		Direct (mean)	NMA (median)
Versus standard	TXA vs. standard treatment	0.72 (0.64, 0.81)	0.6189 (0.4474, 0.9006)
	PCS vs. standard treatment	0.60 (0.45, 0.81)	0.3596 (0.1268, 0.8032)

Comparison		Risk ratio	
		Direct (mean)	NMA (median)
treatment	ICS vs. standard treatment	0.81 (0.70, 0.93)	0.7885 (0.517, 0.9855)
	ICS+PCS vs. standard treatment	0.69 (0.54, 0.89)	0.6482 (0.3422, 0.9548)
	ICS+TXA vs. standard treatment	-	0.4924(0.2471, 0.8621)
	ICS+PCS+TXA vs. standard treatment	-	0.638 (0.3177, 0.96)
Versus TXA	PCS vs. TXA	-	0.5837 (0.2341, 1.046)
	ICS vs. TXA	-	1.204 (0.9287, 1.766)
	ICS+PCS vs. TXA	-	1.007 (0.6355, 1.552)
	ICS+TXA vs. TXA	0.79 (0.43, 1.45)	0.7957 (0.4656, 1.15)
	ICS+PCS+TXA vs. TXA	1.02 (0.68, 1.54)	0.9945 (0.5964, 1.546)
Versus PCS	ICS vs. PCS	-	2.105 (1.08, 5.768)
	ICS+PCS vs. PCS	-	1.717 (0.8541, 4.706)
	ICS+TXA vs. PCS	-	1.338 (0.6426, 3.478)
	ICS+PCS+TXA vs. PCS	-	1.685 (0.8127, 4.704)
Versus ICS	ICS+PCS vs. ICS	-	0.8406 (0.4553, 1.311)
	ICS+TXA vs. ICS	0.71 (0.60, 0.85)	0.64 (0.3993, 0.9151)
	ICS+PCS+TXA vs. ICS	-	0.8284 (0.4272, 1.318)
Versus ICS+PCS	ICS+TXA vs. ICS+PCS	-	0.7951 (0.3925, 1.388)
	ICS+PCS+TXA vs. ICS+PCS	0.93 (0.49, 1.77)	0.9863 (0.5695, 1.649)
Versus ICS+TXA	ICS+PCS+TXA vs. ICS+TXA	-	1.235 (0.6869, 2.557)

Table 48: Network 2: Units of allogeneic blood transfused

Comparison		Mean difference	
		Direct (mean)	NMA (median)
Versus standard treatment	ICS vs. standard treatment	-0.78 (-1.37, -0.19)	-0.818 (-1.671, -0.1148)
	TXA vs. standard treatment	-0.83 (-1.17, -0.5)	-0.8536 (-1.343, -0.4843)
	PCS vs. standard treatment	-1.02 (-1.19, -0.86)	-1.021 (-2.29, 0.2511)
	ICS+TXA vs. standard treatment	-	-2.16 (-3.444, -0.9444)
Versus ICS	TXA vs. ICS	-	-0.03479 (-0.8862, 0.8435)
	PCS vs. ICS	-	-0.2067 (-1.609, 1.375)
	ICS+TXA vs. ICS	-1.56 (-1.84, -1.29)	-1.346 (-2.291, -0.3032)
Versus TXA	PCS vs. TXA	-	-0.1725 (-1.438, 1.243)
	ICS+TXA vs. TXA	-	-1.309 (-2.589, 0.03418)
Versus PCS	ICS+TXA vs. PCS	-	-1.141 (-2.965, 0.6136)

Table 49: Network 3: Length of stay in hospital

Comparison		Mean difference	
		Direct (mean)	NMA (median)
Versus	TXA vs. standard treatment	-0.08 (0.35, 0.18)	-0.1266 (-0.9664, 0.4938)

Comparison		Mean difference	
		Direct (mean)	NMA (median)
standard treatment	ICS vs. standard treatment	-0.22 (-1.16, 0.72)	-0.1668 (-1.346 , 1.041)
	PCS vs. standard treatment	-7.13 (-9.12, -5.14)	-7.123 (-9.394, -4.869)
	ICS+PCS vs. standard treatment	2.80 (-2.11, 7.71)	2.83 (-2.182, 7.842)
	ICS+TXA vs. standard treatment	-	0.6375 (-1.306, 2.607)
Versus TXA	ICS vs. TXA	-	-0.03038 (-1.315, 1.428)
	PCS vs. TXA	-	-6.987 (-9.315, -4.577)
	ICS+PCS vs. TXA	-	2.977 (-2.077, 8.056)
	ICS+TXA vs. TXA	2.10 (-3.36, 7.56)	0.7759 (-1.204, 2.864)
Versus ICS	PCS vs. ICS	-	-6.962 (-9.537, -4.427)
	ICS+PCS vs. ICS	-	2.994 (-2.137, 8.15)
	ICS+TXA vs. ICS	0.68 (-0.81, 2.17)	0.8029 (-0.8243, 2.432)
Versus PCS	ICS+PCS vs. PCS	-	9.961 (4.498, 15.46)
	ICS+TXA vs. PCS	-	7.748 (4.834, 10.78)
Versus ICS+PCS	ICS+TXA vs. ICS+PCS	-	-2.196 (-7.537, 3.248)

Table 50: Results of pairwise meta-analysis

Comparison	No. of studies	Effect size (Relative risk/Mean difference)
Outcome: Infections		
ICS vs. standard treatment	3	0.40 [0.18, 0.87]
PCS vs. standard treatment	1	0.15 [0.02, 1.15]
ICS + PCS vs. standard treatment	1	0.98[0.14, 6.82]
TXA vs. standard treatment	2	0.61 (0.32, 1.18)
ICS +TXA vs. TXA	1	1.07 (0.32, 3.60)
ICS+PCS+TXA vs. TXA	1	1.31 (0.41, 4.15)
Outcome: Thrombotic complications		
TXA vs. standard treatment	4	0.48 (0.18, 1.23)
Outcome: Mortality		
ICS vs. standard treatment	5	0.65 (0.27, 1.59)
PCS vs. standard treatment	1	3 (0.13, 70.30)
ICS + PCS vs. standard treatment	1	0.33 (0.03, 3.09)
TXA vs. standard treatment	17	0.52 (0.31, 0.87)
ICS + TXA vs. ICS	1	1.04 (0.07, 16.41)
ICS + TXA vs. TXA	1	7.71 (0.43, 137.53)

6.3.4 Adults: Moderate risk group

Table 51 to Table 51 summarise the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions, together with the results of the NMA in terms of risk ratios for every possible treatment comparison per outcome in adults in the moderate risk group.

Table 51: Network 4: Number exposed to allogeneic transfusions

Comparison		Risk ratio	
		Direct (mean)	NMA (median)
Versus standard treatment	TXA vs. standard treatment	0.45 (0.38, 0.52)	0.2637 (0.1555, 0.7161)
	PCS vs. standard treatment	0.58 (0.41, 0.83)	0.5546 (0.3012, 0.9111)
	ICS vs. standard treatment	0.74 (0.50, 1.12)	0.7996 (0.2924, 1.466)
	ICS+PCS vs. standard treatment	0.84 (0.54, 1.33)	0.6637 (0.1941, 1.345)
	ICS+PCS+TXA vs. standard treatment	-	0.2118 (0.02899, 0.9152)
	PCS+TXA vs. standard treatment	-	0.208 (0.02931, 0.8688)
	ICS+TXA vs. standard treatment	-	0.6146 (0.08566, 1.899)
Versus TXA	PCS vs. TXA	-	1.906 (1.133, 3.492)
	ICS vs. TXA	-	2.552 (1.102, 7.319)
	ICS+PCS vs. TXA	-	2.091 (0.7929, 6.512)
	ICS+PCS+TXA vs. TXA	0.73 (0.33, 1.63)	0.7393 (0.1268 , 3.145)
	PCS+TXA vs. TXA	-	0.7304 (0.1222, 2.971)
	ICS+TXA vs. TXA	-	1.866 (0.3508, 9.221)
Versus PCS	ICS vs. PCS	-	1.315 (0.5614, 3.565)
	ICS+PCS vs. PCS	0.70 (0.42, 1.16)	1.114 (0.3976, 2.982)
	ICS+PCS+TXA vs. PCS	-	0.3891 (0.05739, 1.652)
	PCS+TXA vs. PCS	0.37 (0.12, 1.14)	0.383 (0.06477, 1.323)
	ICS+TXA vs. PCS	-	1.036 (0.1687, 4.425)
Versus ICS	ICS+PCS vs. ICS	-	0.8597 (0.2174, 2.754)
	ICS+PCS+TXA vs. ICS	-	0.2875 (0.03492, 1.381)
	PCS+TXA vs. ICS	-	0.2833 (0.03496, 1.263)
	ICS+TXA vs. ICS	0.78 (0.50, 1.20)	0.7911 (0.1602, 2.309)
Versus ICS+PCS	ICS+PCS+TXA vs. ICS+PCS	-	0.3499 (0.04127, 1.872)
	PCS+TXA vs. ICS+PCS	-	0.3449 (0.0427, 1.657)
	ICS+TXA vs. ICS+PCS	-	0.937 (0.1237, 5.031)
Versus ICS+PCS+TXA	PCS+TXA vs. ICS+PCS+TXA	-	0.9854 (0.09827, 9.512)
	ICS+TXA vs. ICS+PCS +TXA	-	2.528 (0.2924, 28.61)
Versus PCS+TXA	ICS+TXA vs. PCS +TXA	-	2.583 (0.3143, 28.64)

Table 52: Network 5: Units of allogeneic blood transfused

Comparison		Mean difference	
		Direct (mean)	NMA (median)
Versus standard treatment	TXA vs. standard treatment	-0.88 (-1.22, -0.54)	-0.9028 (-1.397, -0.4369)
	PCS vs. standard treatment	-0.82 (-1.31, -0.33)	-0.8217 (-1.364, -0.2834)
	ICS+PCS vs. standard treatment	0.81 (0.49, 1.13)	1.11(-0.1026, 2.313)
Versus TXA	PCS vs. TXA	-	0.0816(-0.6285, 0.8177)
	ICS+PCS vs. TXA	-	2.013(0.7254, 3.317)

Comparison		Mean difference	
Versus PCS	ICS+PCS vs. PCS	2.23 (1.92, 2.54)	1.932(0.7209, 3.136)

Table 53: Results of pairwise meta-analysis

Comparison	No. of studies	Effect size (Relative risk/Mean difference)
Outcome: Units of allogeneic blood		
ICS +TXA vs. ICS	1	-0.46 (-1.10, 0.18)
Outcome: Infections		
PCS vs. standard treatment	2	1.79 (0.53, 6.07)
ICS+PCS vs. standard treatment	1	3.32 (0.14, 79.77)
TXA vs. standard treatment	3	0.93 (0.22, 3.93)
Outcome: Length of stay		
PCS vs. standard treatment	3	-0.37(-1.73, 0.99)
ICS+PCS vs. standard treatment	1	0.20 (-0.20, 0.60)
ICS +TXA vs. ICS	1	0.72 (-0.85, 2.29)
TXA vs. standard treatment	10	-0.25 (-0.59, 0.09)
Outcome: Mortality		
TXA vs. standard treatment	3	0.73 (0.15, 3.66)
ICS+PCS vs. standard treatment	1	3.32 (0.14, 79.77)
Outcome: Thrombotic complications		
PCS+TXA vs. PCS	1	0.2 (0.01, 4.06)
TXA vs. standard treatment	22	0.69(0.44, 1.07)

6.3.5 Adults: Low risk group

Table 54 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions for tranexamic acid versus standard treatment per outcome in adults in the low risk group.

Table 54: Results of pair wise meta-analysis

Comparison	Outcome	No. of studies	Effect size (Relative risks/ Mean difference)
TXA vs. standard treatment	No. exposed to allogeneic blood	2	0.83 (0.30, 2.29)
	Blood loss (log odds ratio)	3	0.74 (0.73, 0.76)

6.3.6 Children: High risk group

Table 55 summarises the results of the conventional meta-analyses in terms of risk ratios generated from studies directly comparing different interventions for tranexamic acid versus standard treatment per outcome in children in the high risk group.

Table 55: Results of pair wise meta-analysis

Comparison	Outcome	No. of studies	Effect size (Relative risks/ Mean difference)
ICS +TXA vs. ICS	No. exposed to allogeneic blood	1	0.85 (0.56, 1.30
	Total blood transfused	1	-325.00(-685.06, 35.06)
	Total blood loss	1	-855.00 (-1408.15, -301.85)
	Length of stay	1	0.10 (-0.37, 0.57)
TXA vs. standard treatment	Post-operative blood loss	2	-12.62 (-16.79, -8.45)
	Length of stay	1	0.1 (-0.37, 0.57)

6.3.7 Rank-o-grams from network meta-analysis

6.3.7.1 Adults: High risk

Figure 3: Number of patients receiving allogeneic transfusions

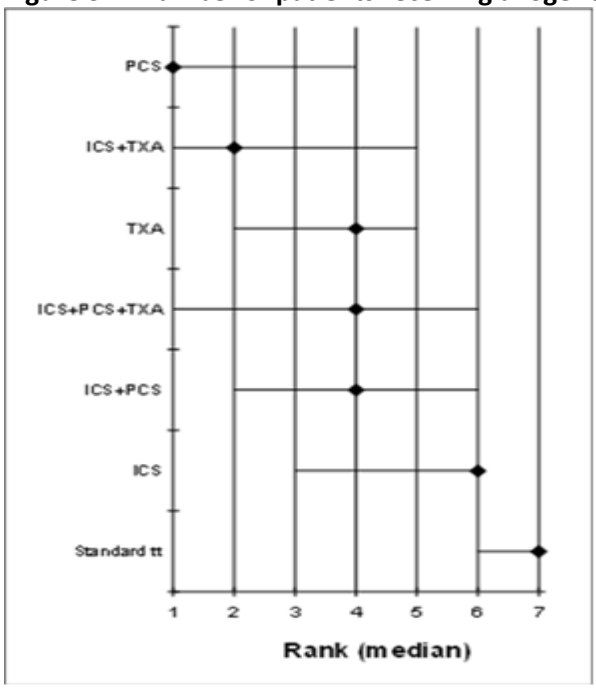
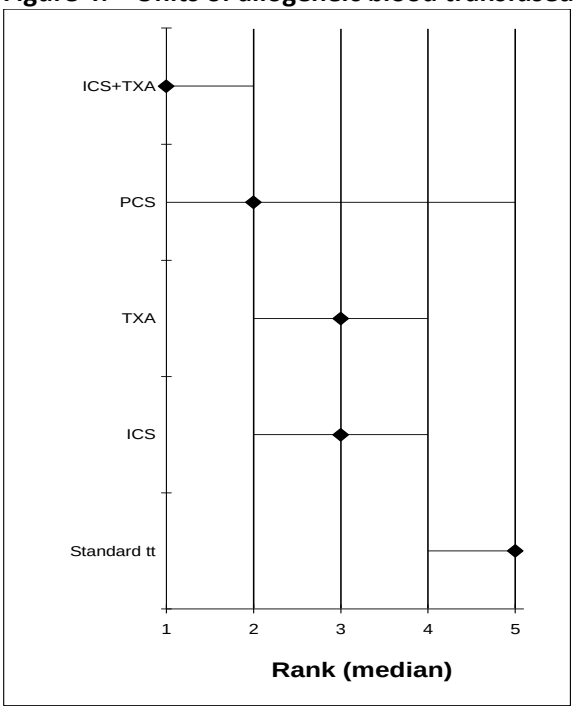
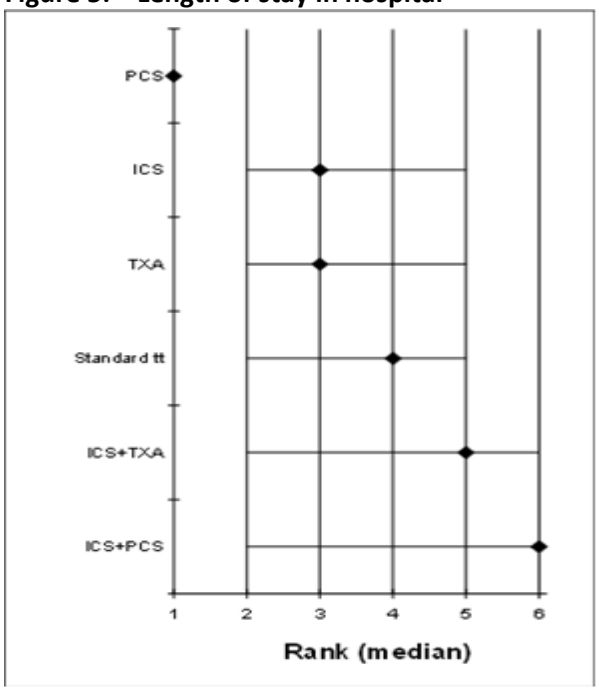


Figure 4: Units of allogeneic blood transfused



1

Figure 5: Length of stay in hospital



2

6.3.7.2 Adults: Moderate risk

Figure 6: Number of patients receiving allogeneic transfusions

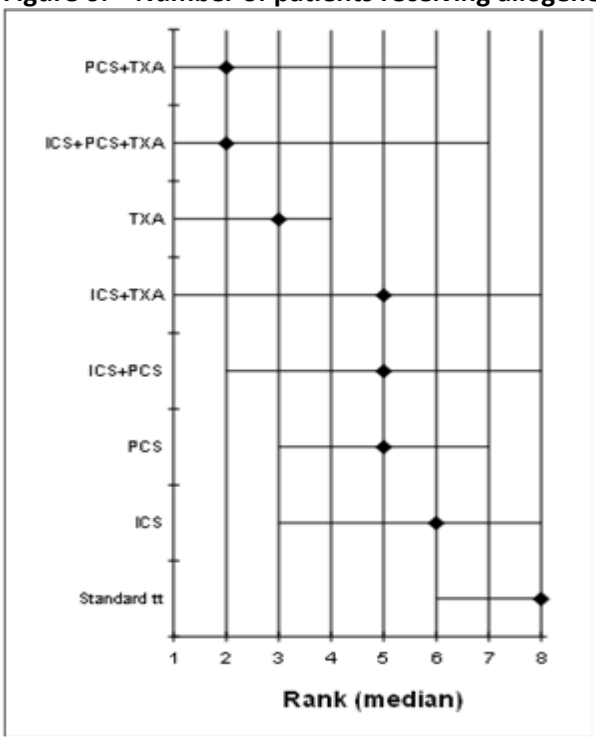
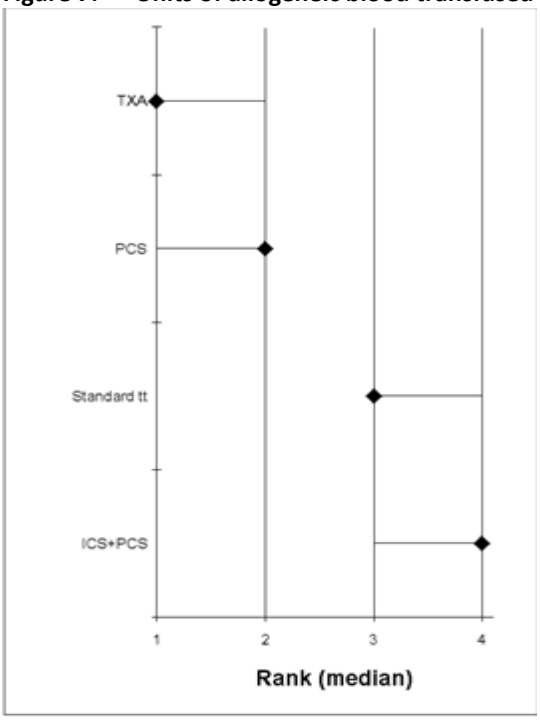


Figure 7: Units of allogeneic blood transfused



6.4 Economic evidence

Published literature

Three economic evaluations were identified comparing cell salvage with no cell salvage and have been included in this review.[77,165,258] Two economic evaluations were identified comparing TXA with placebo or no TXA and have been included in this review.[9,243] These are summarised in the economic evidence profile below (Table 56 and Table 57) and the economic evidence tables in Appendix I.

Eight economic evaluations relating to cell salvage were identified but were excluded due to a combination of methodological limitations and the availability of more applicable evidence.[26,37,69,88,197,198,200,246,262] Six economic evaluations relating to TXA were identified but were excluded due to the availability of more applicable evidence.[114,115,139,182,232,305] These are summarised in Appendix Q, with reasons for exclusion given.

No economic evaluations were identified comparing cell salvage with TXA or relating to the combination of both.

See also the economic article selection flow diagram in Appendix F.

Economic evidence profile

Table 56: Economic evidence profile: cell salvage versus no cell salvage

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (mean per patient)	Cost-effectiveness	Uncertainty
Davies 2006[77] (UK)	Partially applicable[(a)]	Minor limitations[(b)]	Decision tree depicting adult elective non-urgent major surgery patients (orthopaedic, cardiac and vascular) receiving either cell salvage (intra-operative or post-operative) or no cell salvage. 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. For cell salvage transfusion there is a risk of cell salvage transfusion complications.	Saves £76[(c)]	0.00477 QALYs[(d)]	Cell salvage is dominant	A probabilistic sensitivity analysis was conducted for the base case. Probability cell salvage cost-effective (30K threshold): 91% Additional analyses were conducted to explore the impact on results of using different structural variables or data sets. 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.

(a) Study does not include all interventions in protocol.

(b) 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.

(c) 2003-2004 UK pounds. Costs incorporated are cost per case of washed cell salvage equipment, maintenance, consumables and staff (base case); transfusion and transfusion-related services; operation and index hospital admission; and adverse events (surgical and transfusion-related).

(d) Probability of transfusion, risks of adverse events related to transfusion or surgery from published systematic reviews and the authors own systematic review. Utility values for health states with long-standing illness, limiting illness and no long-standing illness from the 1996 Health Survey for England as well as a utility value for stroke was taken from published literature. Tariffs not specified.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (mean per patient)	Cost-effectiveness	Uncertainty
Klein 2008[165] (UK)	Partially applicable[(e)]	Potentially serious limitations[(f)]	Within trial analysis (RCT) of adults undergoing non-emergency first time coronary artery bypass grafting and / or cardiac valve surgery receiving either cell salvage (intra-operative and post-operative) or no cell salvage. Analysis of individual level resource use, with unit costs applied.	£477[(g)]	Saves 0.42, 0.725 and 1.63 units of allogeneic red blood cells, fresh frozen plasma and platelets transfused, respectively. No difference in percentage receiving allogeneic blood product transfusions**Error! Reference source not found.**	Cell salvage is more costly and more effective at reducing units of allogeneic blood products transfused	No analysis reported

(e) Health effects not expressed as QALYs. Study does not include all interventions in protocol.

(f) Follow up for health outcomes and cost is not the same and no analysis of uncertainty conducted. Follow up for health outcomes and cost is not the same and no analysis of uncertainty conducted

(g) 2006-2007 US dollars converted into UK pounds using the purchasing power parities [226]. Costs incorporated are: cost of operation room, intensive care unit stay, ward stay, adverse events, red blood cells, other blood products (fresh frozen plasma and platelets), cell salvage equipment, primary care visits and medication.

(h) Mean volume of allogeneic blood products transfused and proportion of patients transfused from within trial.

(i) Health effects not expressed as QALYs. US healthcare payer perspective. Study does not include all interventions in protocol.

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (mean per patient)	Cost-effectiveness	Uncertainty
Samnaliev 2013[258] (USA)	Partially applicable**Error! Reference source not found.**	Potentially serious limitations**Error! Reference source not found.**	Decision tree depicting paediatric orthopaedic and cardiac surgical patients receiving either intra-operative cell salvage or no cell salvage. All patients who receive an allogeneic transfusion have a risk of transfusion-related adverse events.	Saves £387**Error! Reference source not found.**	51% fewer patients transfused. Saves 1.096 units of allogeneic red blood cells (per patient transfused)	Intra-operative cell salvage is dominant	Probabilistic sensitivity analysis conducted around costs (CI: £15 to £1,262). 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

(j) Effectiveness data from a non-randomised study which was 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.

(k) 2010 US dollars converted into UK pounds using the purchasing power parities.[226] Costs incorporated are: 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.

(l) 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).

Table 57: Economic evidence profile: Tranexamic acid versus no tranexamic acid or placebo

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (mean per patient)	Cost-effectiveness	Uncertainty
Rajesparan 2009[243] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	Within trial analysis (RCT) of adults undergoing total hip replacement. Analysis of individual level resource use with unit costs applied. TXA administered intravenously.	Saves £54[(c)]	Saves 0.1 units of allogeneic blood transfused (per patient transfused)[(d)]	Tranexamic acid is dominant	No analysis reported
Alshryda 2013A[9] (UK)	Partially applicable[(e)]	Potentially serious limitations[(f)]	Within trial analysis (RCT) of adults undergoing total hip replacement. Analysis of individual level resource use with unit costs applied. TXA administered topically (intra-articular)	Saves £305[(g)]	Saves 0.46 units of allogeneic blood transfused (per patient transfused)[(h)]	Tranexamic acid is dominant	Bootstrapping of costs. Tranexamic acid saves £304 (CI -613 to -15, p=0.046)

(a) Health effects not expressed in terms of QALYs. Study does not include all interventions in protocol.

(b) 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 or for treatment of thrombotic complications and no analysis of uncertainty conducted.

(c) UK pounds, year NR, assumed to be 2009 UK pounds based on the date publication submission. Resource use from within study. Unit cost of allogeneic blood and cost of tranexamic acid from institution.

(d) Other health outcomes presented and available in full evidence table. Percentage requiring allogeneic blood transfusion, volume transfused, blood loss and rate of clinical post-operative deep vein thrombosis confirmed by venography from within study.

(e) Health effects not expressed in terms of QALYs. Study does not include all interventions in protocol.

(f) 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.

(g) 2010 UK pounds. Resource use from within study. 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.

(h) Other health outcomes presented and available in full evidence table. Percentage requiring allogeneic blood transfusion and volume transfused, blood loss, length of stay, complications including deep vein thrombosis, EQ-5D from within study.

6.4.1 New cost-effectiveness analysis

A key clinical issue identified by the GDG was which intervention to offer at the time of surgery to reduce the need for allogeneic blood transfusions: cell salvage, tranexamic acid (TXA) or both in combination. The GDG wanted to understand if one intervention was more effective than the other, if the combination of cell salvage and TXA was better than either intervention and if there were specific population groups in which one intervention or combination may be more effective.

Cell salvage is a procedure whereby blood loss during or after surgery is collected and then re-transfused to the patient with the aim of reducing the need of allogeneic blood transfusion. TXA is an antifibrinolytic pharmacological agent administered at the time of surgery with the aim of reducing bleeding and thus reducing the need for allogeneic blood transfusion. Reducing the use of allogeneic blood is of economic importance as it is a scarce and costly resource. In addition, transfusion of allogeneic blood is potentially associated with transfusion-related complications.

The clinical evidence suggested that cell salvage and TXA were both clinically effective compared to placebo. In addition, it suggested that in some patient groups cell salvage in combination with TXA is more effective at reducing the number of people transfused and volume transfused compared to TXA alone. As described above, economic evaluations identified in the systematic literature search indicated that cell salvage and TXA are likely to be cost-effective individually compared to standard treatment (no intervention or placebo). However, uncertainty remained regarding whether one may be more cost-effective than the other (head-to-head comparison) or whether they are more cost-effective when given in combination. As a result, this topic was identified by the GDG as the highest economic priority for original economic modelling.

Below is a summary of the analysis that was undertaken. For full details please see Appendix M Cost-effectiveness analysis: tranexamic acid and cell salvage.

6.4.1.1 Methods

A cost-utility analysis was undertaken to evaluate whether cell salvage (intra-operative and post-operative), TXA, a combination of both or standard treatment (no cell salvage or TXA) is the most cost-effective option for reducing allogeneic blood transfusion in adults undergoing surgery at moderate or high risk of bleeding. A decision tree-based model was used to estimate lifetime quality-adjusted life years (QALYs) and costs from a current UK NHS and personal social services perspective. The analysis was conducted in accordance with the NICE reference case unless otherwise stated including discounting at 3.5% for costs and QALYs.

Two population subgroups were analysed in the model: adults undergoing surgery at moderate risk of bleeding (0.5-1 litres) and high risk of bleeding (>1 litre). These subgroups were selected in line with the analysis of the clinical data (see Section 6.2 for further details). Studies that were categorised as high risk were predominantly RCTs on cardiovascular surgery and for the moderate risk they were orthopaedic surgery. Adults undergoing surgery at low risk of bleeding (<0.5 litres) were not included in the analysis as they would not be eligible for cell salvage because there would not be sufficient blood loss. Children undergoing surgery were not included in this analysis as insufficient clinical evidence was identified for this population to allow for modelling.

The comparators for each population subgroup were selected based on the availability of evidence from the clinical review in discussion with the GDG. It was agreed that only interventions with data on both proportion transfused and volume transfused would be included in the model as the GDG felt that it was not possible to make assumptions for these critical outcomes.

Comparators for the high risk of bleeding subgroup were: standard treatment, TXA, intra-operative cell salvage (ICS), post-operative cell salvage (PCS), ICS+TXA. Comparators for the moderate risk of bleeding subgroup were: standard treatment, TXA, PCS, ICS+PCS.

Key inputs in the model were the proportion of people receiving an allogeneic transfusion and the volume of allogeneic blood transfused (in those that received a transfusion). Differences in proportions of patients transfused and volumes of blood transfused will translate to differences in costs between interventions. The clinical evidence also suggested a clinically and statistically significant decrease in 30-day mortality with TXA in the high risk group and therefore it was felt it was important to incorporate mortality into the model. The GDG also wished to incorporate differences between interventions in terms of adverse events as this may impact costs and QALYs. Adverse events could be intervention-related or transfusion-related. This impact was incorporated into the model in terms of differences in length of hospitalisation – this was then associated with a reduced quality of life and additional costs. Although the model did not explicitly model acute transfusion and treatment-related adverse events, the GDG judged length of stay to be a reasonable proxy for these acute events. This is because the ultimate impact of acute adverse event will be to prolong the patient's hospital stay while they are managed. For more information regarding the rationale behind this approach to modelling, please refer to the technical report in Appendix M.

A number of assumptions were made when developing the model. The key assumptions are outlined below but are also discussed in more detail in subsequent sections of this report and in Appendix M:

- People entering the model are eligible for each intervention listed for that subgroup.
- All allogeneic transfusions given in the model were red blood cell transfusions.
- The mortality rate after 30 days was the same for all people entering the model, irrespective of the intervention received or transfusion.
- TXA was administered intravenously.
- Cell salvage technicians were already trained and therefore the cost of training was not incorporated.
- Cell salvage equipment was available on lease via consumable charges.
- Post-operative cell salvage was unwashed.
- ICS and / or PCS were conducted for all people assigned to that intervention.

Model inputs were based on clinical evidence identified in the systematic review and network-meta analyses (NMA) undertaken for the guideline, supplemented by additional data sources as required. These are described in full in the technical report in Appendix M. All model inputs and assumptions were validated by the GDG.

The cost of each intervention took into account staff time (where additional to no intervention), drug costs, equipment and consumables. The cost of each intervention is summarised in Table 58 and is described in full in Appendix M.

Table 58: Intervention costs

Intervention	Cost	Source
ICS	£295	PSSRU 2013,[71] NHS Supply Chain Catalogue April 2014,[215] BNF 67,[147] NICE Clinical Guideline CG174,[206] Crotty 2006[69]
PCS	£88	PSSRU 2013,[71] NHS Supply Chain Catalogue April 2014[215]
ICS+PCS	£350	PSSRU 2013,[71] NHS Supply Chain Catalogue April 2014,[215] BNF 67,[147] NICE Clinical Guideline CG174,[206] Crotty 2006[69]
TXA (high risk subgroup)	£19	Total dose 6000 mg, slow IV injection followed by continuous IV infusion. BNF 67,[147] eMIT July 201,[461] NHS Supply Chain Catalogue April 2014,[215] NICE Clinical Guideline CG174[206]

Intervention	Cost	Source
TXA (moderate risk subgroup)	£9	Total dose 3000 mg slow IV injection. BNF 67,[147] eMIT July 2014[61]
ICS +TXA	£314	Sum of ICS and TXA (high risk subgroup)

Abbreviations: BNF = British National Formulary; eMIT = Electronic Market Information Tool; ICS = intra-operative cell salvage; IV = intravenous; PSSRU = Personal Social Services Research Unit; PCS = post-operative cell salvage; TXA = tranexamic acid

The cost of allogeneic transfusion used in the analysis was £192.17 for the first unit transfused, and £167.31 per subsequent unit transfused. A cost of £22.02 per person was applied to those who were not transfused in the model; this cost covers the cost blood grouping and antibody screening which is required for all surgical patients. Note that for those that are transfused this cost is incorporated into the cost of the first unit of blood. The breakdown of resource use, costs and assumptions are described in full in Appendix M.

6.4.1.2 Results

In the base case analysis for the high risk subgroup (treatment options: standard treatment, ICS, PCS, TXA and ICS+TXA), TXA was found to be the most cost-effective option. Results are summarised below in Table 59 in terms of costs, QALYs and cost-effectiveness (incremental net monetary benefit, probability costs effective and ranking). TXA was found to have the greatest benefits for patients (highest QALYs) largely due to a reduction in mortality at 30 days that was not seen with other treatment options. TXA had the second lowest cost after PCS; this was driven by a combination of the lowest intervention cost, moderate blood savings and a small saving due to a reduced length of stay. Of note, TXA was not the most blood saving intervention; it was the combination of ICS and TXA that resulted in the greatest blood savings.

Table 59: Base case analysis results (probabilistic analysis), cost-effectiveness, high risk

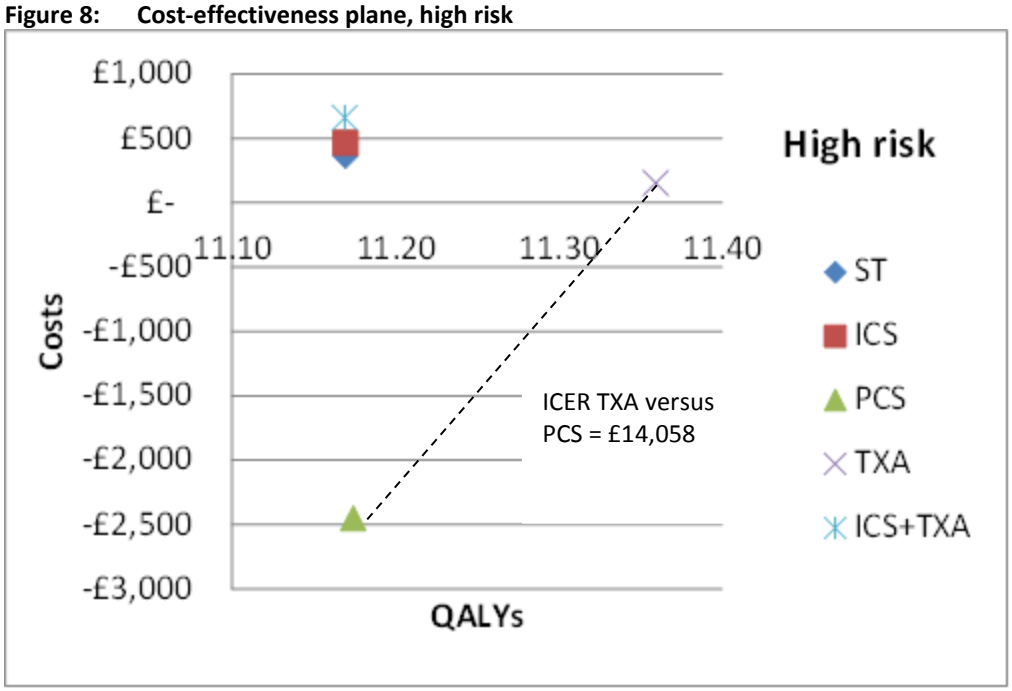
Analysis	Incremental QALYs vs ST	Incremental costs vs ST	INMB at £20K(a)	Probability most CE option	Rank (95% CI)
ST			£0	0%	3 (3, 5)
ICS	0.000	£104	-£102	0%	4 (3, 5)
PCS	0.005	-£2,815	£2,908	28%	2 (1, 2)
TXA	0.190	-£212	£4,009	72%	1 (1, 2)
ICS+TXA	0.000	£295	-£303	0%	5 (3, 5)

Abbreviations: CE = cost-effective; CI = confidence intervals; ICS = intra-operative cell salvage; INMB = incremental net monetary benefit; PCS = post-operative cell salvage; QALYs = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid.

(a) INMB = NMB intervention A – NMB ST; Highest INMB = most cost-effective option at a £20,000 per QALY threshold; a negative INMB means that ST is more cost-effective than this option.

The mean costs and QALYs from the probabilistic analysis have also been presented graphically on the cost-effectiveness plane in Figure 8. All interventions with the exception of PCS are dominated by TXA which has both lower costs and greater health benefits. PCS has lower costs than TXA but also lower QALYs. The incremental cost-effectiveness ratio of TXA versus PCS is £14,058 per QALY.

Figure 8: Cost-effectiveness plane, high risk



(b) Abbreviations: ICER = incremental cost-effectiveness ratio; ICS = intra-operative cell salvage; INMB = incremental net monetary benefit; PCS = post-operative cell salvage; QALY = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid

In the base case analysis for the moderate risk subgroup (treatment options: standard treatment, ICS+PCS, PCS and TXA), TXA was found to be the most cost-effective option. Results are summarised below in Table 60 in terms of costs, QALYs and cost-effectiveness (incremental net monetary benefit, probability costs effective and ranking). There was no difference in the incremental QALYs versus standard treatment between interventions to the 3rd decimal place. TXA had the lowest costs compared to all other interventions due to a combination of the lowest intervention cost, greatest savings associated with blood costs and length of stay.

Table 60: Base case analysis results (probabilistic analysis), cost-effectiveness, moderate risk

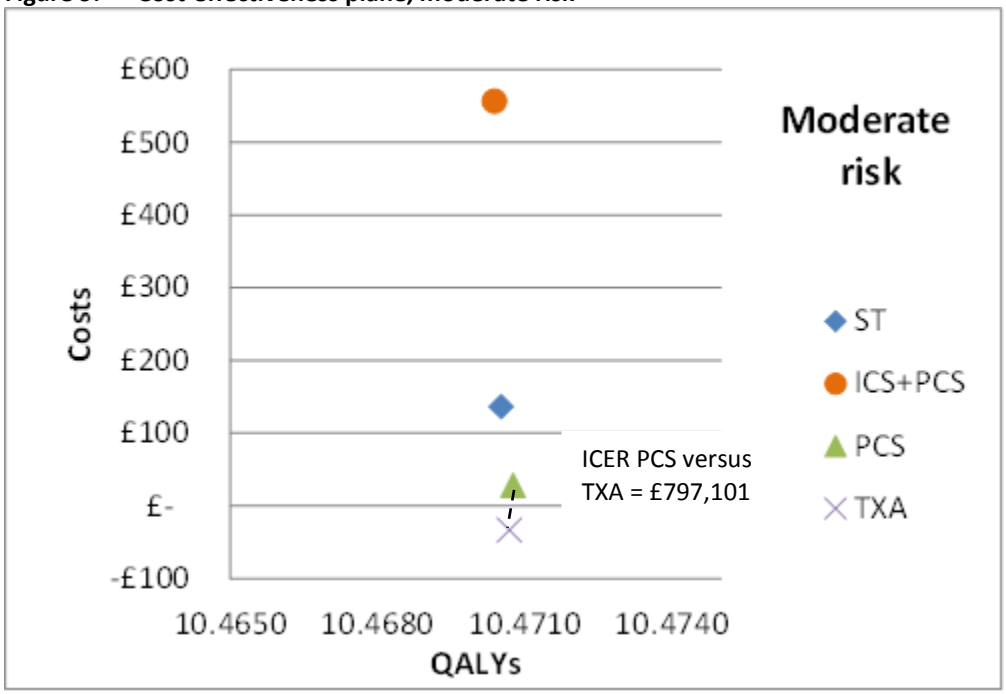
Analysis	Incremental QALYs vs ST	Incremental costs vs ST	INMB at £20K(a)	Probability most CE option	Rank (95% CI)
ST			£0	0%	3 (2, 3)
ICS+PCS	0.000	£420	-£423	0%	4 (4, 4)
PCS	0.000	-£108	£113	40%	2 (1, 3)
TXA	0.000	-£169	£173	60%	1 (1, 2)

Abbreviations: CI = confidence intervals; ICS = intra-operative cell salvage; INMB = incremental net monetary benefit; PCS = post-operative cell salvage; QALYs = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid

(a) INMB = NMB intervention A – NMB ST; Highest INMB = most cost-effective option at a £20,000 per QALY threshold; a negative INMB means that ST is more cost-effective than this option.

The mean costs and QALYs from the probabilistic analysis have also been presented graphically on the cost-effectiveness plane in Figure 9. All interventions with the exception of PCS are dominated by TXA which has both lower costs and greater health benefits. PCS has higher costs than TXA but lower QALYs. The incremental cost-effectiveness ratio of PCS versus TXA is £797,101 per QALY.

Figure 9: Cost-effectiveness plane, moderate risk



(a) Abbreviations: ICER = incremental cost-effectiveness ratio; ICS = intra-operative cell salvage; INMB = incremental net monetary benefit; PCS = post-operative cell salvage; QALY = quality adjusted life years; ST = standard treatment; TXA = tranexamic acid

A wide range of sensitivity analyses were undertaken, these included exploring uncertainty in the clinical effectiveness in terms of mortality, number transfused, volume transfused and length of stay; baseline transfusion and mortality rates; cost of interventions and blood transfusion and use of hospital length of stay as a proxy. For full details of the sensitivity analyses undertaken please see the technical report in Appendix M.

This conclusion was robust to all sensitivity analyses with the exception of three in the high risk group. The first was where the baseline mortality rate at 30 days was reduced to 0%. In this analysis, PCS became most cost-effective strategy. However, while this mortality rate was the lower end of the range observed in the RCTs included in the review, the GDG considered this scenario implausible for a high risk subgroup and likely due chance as a result of low event rates and so it did not impact decision making. A further two sensitivity analyses in the high risk group resulted in PCS becoming the most cost-effective option. These were analyses where the mortality after 30 days and the quality of life were adjusted to reflect MI and stroke populations. The results indicated that the QALY difference between TXA and PCS was reduced compared to difference observed in the base case. This impact on QALYs occurs because patients are less well (higher mortality rate and worse quality of life) and therefore they have less to gain from TXA's mortality benefit. When combined with the very low total costs of PCS (which are driven by the length of stay savings), PCS is the most cost-effective option. The GDG highlighted concerns with the length of stay data for PCS in the high risk group, that is that the length of stay estimate was informed by one study only and that this study had an unusually high baseline length of stay which likely accounted for the large difference in length of stay reported. To explore this further, these two sensitivity analyses were combined with a sensitivity analysis to account for the unusually large difference in length of stay for PCS. When these analyses were combined, TXA returned to being the most cost-effective option, thus indicating that the length of stay data for PCS is a key driver. The GDG considered that these sensitivity analyses highlighted some uncertainty in the base case, however the further exploration mitigated the need for this to impact their decision making.

The GDG felt that, while TXA alone was found to be the most cost-effective option overall, for certain patients with particularly high blood loss, the addition of cell salvage to TXA may still be a cost-effective option on the basis that:

1. The mechanisms of action are different for TXA and cell salvage and so it was considered that the relative benefit of cell salvage over TXA is likely to be greater with increased blood loss:
    a. TXA is an anti-fibrinolytic drug that is administered in advance and reduces the risk of blood loss, therefore reducing the need for allogeneic transfusions
    b. With cell salvage, lost blood is collected and re-transfused to the patient, thus also reducing the need for allogeneic transfusions
    c. The GDG considered that while TXA would help reduce allogeneic transfusion up to a point (due to reducing blood loss), the potential to collect blood lost and re-transfuse it with cell salvage is unlimited – the greater the volume of blood lost the greater the volume that can be salvaged
    d. Due to this, it was felt that at very high levels of blood loss the relative benefit of TXA in combination with cell salvage over TXA alone was likely to be greater.
2. The mortality benefit seen with TXA alone was likely to also be achieved with ICS+TXA.

It was not possible to explore this within the context of RCT level clinical data. On this basis a series of exploratory threshold analyses were undertaken to quantitatively explore this scenario, for details of the methodology see the technical report in Appendix M. These analyses indicated that the combination of ICS and TXA could potentially become the cost-effective strategy in particular patients or patient groups where the probability of being transfused and the volume transfused is expected to be very high, if it was assumed that ICS+TXA had the same mortality benefit as TXA and that relative treatment benefits for ICS were maintained or increased. These analyses assumed that cell salvage is set up and used for all patients (as in the primary analyses).

6.4.1.3 Interpretation & limitations

This analysis suggests that TXA is the most cost-effective strategy for reducing allogeneic blood transfusion in adults undergoing surgery. Uncertainties in the analysis were explored through probabilistic sensitivity analyses of the base case for each subgroup and extensive sensitivity analyses which did not change conclusions with the exception of three sensitivity analyses in the high risk group. In the first sensitivity analysis, the baseline 30-day mortality was reduced to 0%. The GDG discussed this input and agreed that a 0% mortality rate in this risk group was not plausible and likely due to chance as a result of low event rates observed in the trials. The group therefore felt the results of this sensitivity analysis were not significant and did not change the overall conclusion. A further two sensitivity analyses, where the mortality after 30 days and the quality of life were adjusted to reflect MI and stroke populations, resulted in PCS becoming the most cost-effective option. This outcome was due to the smaller difference in QALYs between PCS and TXA and the very low total costs of PCS (as a result of length of stay savings). To explore this further, these two sensitivity analyses were combined with a sensitivity analysis to account for the unusually large difference in length of stay for PCS. This resulted in TXA returning to being the most cost effective option. The GDG considered that these sensitivity analyses highlighted some uncertainty in the base case, however the further exploration mitigated the need to change the overall conclusion.

PCS was the most cost saving intervention in the high risk group; this was due primarily to the large reduction in hospital length of stay. As described above, when the mortality effect of TXA was removed, PCS had the highest QALYs which were attributable to the reduced length of stay. Furthermore, when the QALY difference between PCS and TXA was reduced, as seen with the MI and stroke sensitivity analyses, the length of stay savings were a key driver in establishing the most cost-effective option. The length of stay data for this comparator was based on one RCT with a high baseline length of stay. The GDG had concerns about the applicability of this evidence and therefore sensitivity analyses adjusting for this length of stay and excluding length of stay were undertaken. These resulted in TXA remaining the most cost-effective option.

The GDG highlighted that PCS may have use when blood is lost in chest drains in cardiac surgical patients, which is in a minority of cases. However, they acknowledged that in current practice it may not be considered an appropriate intervention for all high risk surgeries on its own, particularly in patients who have extensive bleeding post-operatively and therefore may require reoperation to stem the bleeding (rather than PCS). The GDG noted that this was unlike ICS, which could be used across all high risk surgeries.

Intra-operative cell salvage is used widely across the NHS in current practice, particularly in surgeries with high risk of bleeding. The GDG accepted that TXA alone was the most cost-effective option overall based on the available evidence, but considered that for certain patients with particularly high blood loss the addition of ICS to TXA may be a cost-effective option. This was on the basis that the mechanisms of action are different for TXA and cell salvage and so it was considered that the relative benefit of cell salvage over TXA in terms of avoiding allogeneic transfusions is likely to increase with greater blood loss. The evidence identified in the clinical review was not able to support or refute this because no data was available in such a population and it was not possible to explore this very high risk population within the context of RCT level clinical data. In addition, they felt that in reality the mortality benefit seen with TXA alone was likely to also be achieved with TXA+ICS and the reason that this has not been observed in the evidence could be attributed to a lack of data. A series of exploratory threshold analyses were therefore undertaken within the cost-effectiveness analysis to help the GDG explore whether conclusions might change under these assumptions. These exploratory threshold analyses indicated that under certain circumstances, like those described above, it is plausible that the combination of ICS and TXA may become a cost-effective option. However, it is highlighted that these scenarios are theoretical and not based on evidence.

As in the base case analysis, these exploratory threshold analyses assumed that patients bleeding risk is assessed in advance and if they are considered to be very high risk then ICS is set up and used for all patients, that is the cost is incurred for all patients. This implies that the patients or patient group this analysis applies to is identifiable in advance. However, the GDG acknowledged the difficulty of predicting a patient's bleeding risk. They noted that for some cases, it may be possible to predict risk prior to surgery based on type of surgery and patients' characteristics, thus allowing ICS to be set-up in advance. In other cases, troublesome bleeding may occur during surgery, for example when there is trauma to a vessel, and the equipment would need to be set up during surgery. The costs may be cheaper than those reported in this analysis if ICS is only set up for those who need it during surgery; however, some of the benefit of ICS may be lost due to delays in setting up equipment. Furthermore, in hospitals where the number of surgical patients eligible for ICS is expected to be low, hiring cell salvage equipment may not be feasible due to the requirement from manufacturers of having a minimum disposable order. For these hospitals, purchasing the equipment may be the only solution and this may make the intervention no longer a cost-effective option.

The objective of this analysis was to identify the intervention that provided the greatest health benefit (quantified in terms of QALYs) at an acceptable cost to the NHS (that is with an acceptable incremental cost-effectiveness ratio as per NICE methodological guidance). The GDG highlighted that another objective for these interventions is to conserve allogeneic blood, as it is a scarce resource. Although this was not the objective set out in our analysis, if this objective were to be considered, the combination of ICS and TXA would be the favoured intervention for the high risk group in terms of effectiveness, but cost-effectiveness would be unclear as there is no threshold for this. The group did highlight that there is currently no shortage of allogeneic blood in the UK and so were satisfied that using the cost per QALYs analysis was appropriate for decision making for the guideline. As well as conserving allogeneic blood, another objective may be to limit exposure to allogeneic blood to account for unquantifiable unknown risks.

Another benefit of avoiding allogeneic transfusion, which was not incorporated into the model, is that it eases cross-matching if these individuals need transfusions in the future, as they will not have antibodies.

This new economic analysis was assessed as directly applicable with minor limitations.

Mortality differences

The results of the high risk subgroup analysis are dependent on the mortality benefit obtained with TXA and not with other treatments. The GDG discussed why the mortality benefits might be seen with TXA and no other treatment options, especially those with similar or greater blood savings. While they felt it was not possible to establish this, they noted the different mechanisms of actions of TXA versus cell salvage options and they were satisfied that the clinical evidence for TXA was robust. They did also consider it plausible that this benefit would be seen with combination treatments of cell salvage with TXA and that it may be a lack of data that accounts for the lack of effect seen in the evidence review. This was explored in a series of sensitivity analyses and even when ICS+TXA was attributed the same mortality benefit as TXA alone, TXA remained the most cost-effective option due to the high cost of ICS relative to the additional blood savings.

The data from the clinical review for the other comparators demonstrated a great deal of uncertainty around the estimates. As a result, the GDG decided not to use the clinical review data in the base case for these comparators, and instead assumed there was no mortality difference compared to standard treatment. A sensitivity analysis was conducted where the clinical review data was used and it found that TXA remained the most cost-effective option.

Cost of cell salvage

The GDG noted that the cost of ICS disposables in the analysis was likely to be higher than prices available to hospitals through negotiations with suppliers. These lower costs could not be included as they are not publicly available. The cost of the disposables was explored in a sensitivity analysis, this demonstrated that the conclusion was not sensitive to changes in this input. The GDG considered the results of this sensitivity analysis to be important as it indicates that even if the cost of the ICS disposables was lower, TXA would remain the dominant strategy. The GDG noted that this sensitivity analysis along with the exploratory threshold analyses imply that ICS (alone or in combination with TXA) should not be used for all high risk surgeries but rather it should be reserved for those cases with high baseline risk of transfusion and high expected volume of blood loss.

Length of stay data as a proxy for the impact of acute adverse events

A limitation of this analysis is the use of length of stay as a proxy for the impact of acute transfusion- and treatment-related adverse events. Alternatives were considered during development such as explicitly modelling these events; however it was felt that this would be overly complicated and there was a lack of data to inform this approach. The GDG concluded that in principle length of stay was a reasonable proxy for the impact of these acute events. The GDG noted the general issue of length of stay data being impacted by setting (e.g. country) and in particular that there was an unusually large difference in length of stay for PCS in the high risk group that might be accounted for due to the unusually high baseline length of stay in that study. The GDG considered omitting length of stay from the base case analysis but felt that attempting to capture the impact on patients outweighed this concern. Furthermore they felt it was preferable to maintain the link with the clinical data review in the base case analysis. It was agreed that this issue required exploration in sensitivity analyses and taking into consideration when interpreting results.

A further limitation of this approach was that it used utility values from a different patient population which was not surgical patients receiving or not receiving transfusions. However, more relevant data was not identified.

To address these limitations, as part of the sensitivity analyses, length of stay was excluded, and therefore differences in quality of life and related costs. Removing length of stay did not change the conclusions.

ICS in moderate risk group

The GDG noted that ICS is still being used for orthopaedic surgeries (first time knee or hip replacements) which are considered to be at moderate risk of bleeding. There was limited evidence for the use of ICS in these types of surgery, half of which was from prior to 2003 and therefore was not incorporated in the analysis. As highlighted in Section 6.2.3, the GDG agreed that substantial changes in transfusion practice over time with respect to the use of cell salvage meant that studies published prior to 2003 were not relevant to current clinical practice. Studies published before 2003 therefore should not inform the decision making process or the economic model. Although the use of ICS in moderate risk surgery was not assessed in our economic analysis, the GDG highlighted that as blood loss has decreased now in these surgery types, ICS may not be a cost-effective strategy.

Adverse events

A further limitation is the exclusion of long term transfusion-related adverse events. Between 2010 and 2013, SHOT reported two transfusion-transmitted infections with hepatitis B, two of hepatitis E and one of Parvovirus B19 in the UK.[27] The GDG acknowledged the importance of these infections in considerations of transfusion safety, but observed that they were extremely rare and were unlikely to impact on the results of the economic model. Had these infections been incorporated into the analysis, they would have favoured the interventions that reduced the exposure to allogeneic blood. For the moderate risk group, this would have further supported the use of TXA, which was the most blood saving intervention. In the high risk group, this would have increased the benefit of ICS+TXA. However, it is considered unlikely to change the conclusions.

The main adverse event for TXA was considered to be thrombotic complications. The clinical evidence review suggested there was a non-significant reduction of risk of thrombotic complications for TXA compared to placebo; therefore the GDG decided that it was unnecessary to include this outcome in the model. If it had been modelled explicitly, the results would have been even more favourable towards TXA as the thrombotic events were lower in those receiving TXA compared to placebo.

6.5 Evidence statements

Clinical

Adults - High risk group

- A network meta-analysis of 56 studies comparing seven treatments suggested that PCS is ranked as the best treatment, ICS+TXA is ranked second, TXA, ICS+PCS+TXA and ICS+PCS are jointly ranked fourth and standard treatment ranked least effective at reducing the number of adult patients receiving allogeneic transfusions in the high risk group; there was, however, considerable uncertainty. Based on the pair-wise meta-analysis, efficacy as assessed by number of patients receiving allogeneic transfusions favours tranexamic acid, post-operative cell salvage, intra-operative cell salvage and the combination of intra-operative and post-operative cell salvage over standard treatment and the combination of intra-operative cell salvage and tranexamic acid over intra-operative cell salvage.

- A network meta-analysis of 23 studies comparing five treatments suggested that ICS+TXA is ranked as the best treatment, PCS is ranked second, TXA and ICS are jointly ranked third, and standard treatment ranked least effective at reducing the number of units of allogeneic blood transfusions in adult patients in the high risk group, but there was considerable uncertainty. Based on the pair-wise meta-analysis, efficacy as assessed by reduced number of units of allogeneic transfusions received favours intra-operative cell salvage, post-operative cell salvage, tranexamic acid over standard treatment, and the combination of intra-operative cell salvage and tranexamic acid over intra-operative cell salvage.
- A network meta-analysis of 10 studies comparing six treatments suggested that PCS is ranked as the best treatment, ICs and TXA are jointly ranked third, standard treatment is ranked fourth, ICS+TXA is ranked fifth and ICS+PCS is ranked least effective at reducing length of stay in hospital in adult patients in the high risk group; there was, however, considerable uncertainty. Based on the pair-wise meta-analysis, efficacy as assessed by reduced length of stay in hospital favours post-operative cell salvage over standard treatment.
- Based on the pairwise meta-analysis, efficacy as assessed by the reduction in mortality favours tranexamic acid over standard treatment. The evidence also suggests that tranexamic acid may be better with respect to infections and thrombotic complications than standard treatment, but there is some uncertainty.

Adults - Moderate risk group

- A network meta-analysis of 73 studies comparing eight treatments suggested that PCS+TXA is ranked as the best treatment, ICS +TXA is ranked second, TXA is ranked fourth, ICS+TXA, ICS+PCS and PCS are jointly ranked fifth, ICS is ranked sixth and standard treatment is ranked least effective at reducing the number of adult patients receiving allogeneic transfusions in the moderate risk group; there was, however, considerable uncertainty. Based on the pair-wise meta-analysis, efficacy as assessed by number of patients receiving allogeneic transfusions favours the use of post-operative cell salvage or tranexamic acid over standard treatment. PCS+TXA was also found to be better than PCS alone, but there was some uncertainty.
- A network meta-analysis of 16 studies comparing four treatments suggested TXA and PCS are jointly ranked as the best treatment, standard treatment is ranked third and ICS+PCS is ranked least effective at reducing the number of units of allogeneic blood transfusions in adult patients in the moderate risk group, but there was some uncertainty. Based on the pair-wise meta-analysis, efficacy as assessed by reduced number of units of allogeneic transfusions received suggests that the ICS+TXA may be better than use of ICS alone, but there is some uncertainty.
- Based on the pairwise meta-analysis, efficacy as assessed by the reduction in mortality, infections and thrombotic complications favours tranexamic acid over standard treatment but there was considerable uncertainty.

Adults- Low risk group

- Based on the pairwise meta-analysis, efficacy as assessed by the number of patients receiving allogeneic transfusions favours tranexamic acid, but there is some uncertainty.

Children-High risk group

- Based on the pairwise meta-analysis, efficacy as assessed by the number of children receiving allogeneic transfusions and the total blood transfused favours ICS+TXA over TXA alone, but there is some uncertainty. The evidence favours tranexamic acid over standard treatment for efficacy as assessed by post-operative blood loss. Efficacy as assessed by length of stay in hospital favours standard treatment over tranexamic acid, but there is some uncertainty.

Economic

- One cost–utility analysis found that intra-operative and peri-operative cell salvage were dominant (less costly and more effective) compared with no cell salvage (allogeneic blood transfusion only) in reducing blood transfusion requirements for adults undergoing elective non-urgent major surgery. This analysis was assessed as partially applicable with minor limitations.
- One cost–consequence analysis found that cell salvage (intra-operative and post-operative) was more costly and more effective than no cell salvage (allogeneic blood transfusion only) (£477 more per patient, 0.42, 0.725 and 1.63 fewer units of allogeneic red blood cells, fresh frozen plasma and platelets transfused per patient, respectively) in reducing blood transfusion requirements for adults undergoing non-emergency cardiac surgery. This analysis was assessed as partially applicable with potentially serious limitations.
- One cost–consequence analysis found that cell salvage (intra-operative) was dominant (less costly and more effective) compared with no cell salvage in reducing blood transfusion requirements for paediatric orthopaedic or cardiac surgery patients. This analysis was assessed as partially applicable with potentially serious limitations.
- Two cost–consequence analyses found that tranexamic acid was dominant (less costly and more effective) compared with placebo or no tranexamic acid for reducing blood transfusion requirements in adult surgical patients undergoing total hip replacement. These analyses were assessed as partially applicable and with potential serious limitations.
- No relevant economic evaluations were identified that included tranexamic acid or post-operative cell salvage as a comparator in reducing blood transfusion requirements for paediatric surgical patients.
- An original cost-utility analysis found that in surgical patients at high risk of bleeding, tranexamic acid was the most cost-effective option when compared with standard treatment, intra-operative cell salvage, post-operative cell salvage and the combination of tranexamic acid and intra-operative cell salvage. It was dominant (less costly and more effective) compared to all options except post-operative cell salvage. It was cost-effective compared to post-operative cell salvage (ICER: £14,058 per QALY gained). This analysis was assessed as directly applicable with minor limitations.
- An original cost-utility analysis found that in surgical patients at moderate risk of bleeding, tranexamic acid was the most cost-effective option when compared to standard treatment, post-operative cell salvage and the combination of intra-operative cell salvage and post-operative cell salvage. It was dominant (less costly and more effective) compared to all options except post-operative cell salvage. It was cost-effective compared to post-operative cell salvage (ICER: £797,101 per QALY gained). This analysis was assessed as directly applicable with minor limitations.

6.6 Recommendations and link to evidence

Recommendations	6. **Offer tranexamic acid to adults undergoing surgery who are expected to have at least moderate blood loss (greater than 500 ml)** 7. **Consider tranexamic acid for children undergoing surgery who are expected to have at least moderate blood loss (greater than 10% blood volume).**
Relative values of	The GDG agreed that the number of patients transfused, number of units

different outcomes	transfused and mortality were critical outcomes for decision making. Other outcomes which were considered to be important in the decision making process were length of stay in hospital, quality of life and adverse events (infection, thrombotic complications).
Trade off between clinical benefits and harms	The evidence from studies in adults showed that in surgeries which were expected to lead to moderate or high blood loss (500 ml-1 litre and >1 litre respectively), tranexamic acid (TXA) was the most clinically and cost-effective option. This was based on clinical evidence from the network meta-analysis, results from the pair wise meta-analysis and the results of the health economic model. The inclusion criteria of studies in these analyses are explained in the methodology section of this chapter (see 6.2.3 for more information). Note that cost effectiveness is discussed in the section following this one. In adults undergoing surgery, where blood loss was expected to be high, the evidence showed that TXA demonstrated clinical benefit with respect to all critical outcomes (number of patients transfused, number of units transfused and mortality). However, the network meta-analysis showed that a combination of intra-operative cell salvage (ICS) and TXA was the most clinically effective option with respect to reducing the number of patients transfused and number of units of allogeneic blood transfused. Therefore, the GDG noted that the addition of ICS to TXA reduces overall allogeneic blood requirements where blood loss is expected to be high. Furthermore, results from the pair wise meta-analysis comparing TXA with standard treatment showed a significant decrease in mortality and no significant differences were observed for any other intervention with respect to 30 day mortality. The GDG noted that it was unclear why the mortality benefit seen with TXA alone was not seen with the combination of TXA and cell salvage but it seemed possibly that it was to be due to the lack of data rather than a difference in effect. All interventions with the exception of the combination of ICS+TXA and ICS + post-operative cell salvage (PCS) showed a decrease in length of stay compared with standard treatment. The incidence of infections and thrombotic complications were less with TXA when compared to standard treatment. The pair wise meta-analysis also suggested that there was no difference between the combination of ICS and TXA and TXA alone with respect to incidence of infections. TXA had the best evidence of mortality benefit, not seen elsewhere, and good evidence of effectiveness in terms of number transfused and volume transfused over placebo, although it was not the most blood saving compared to all other interventions. The economic model which translates different outcomes into a single health metric, QALYs, found that TXA has the greatest QALYs largely due to the mortality benefit. For adults undergoing surgery, where blood loss was expected to be moderate (500 ml-1 litre), the evidence showed that TXA was the most clinically effective option. The network meta-analysis demonstrated the benefit of using TXA in comparison with all other interventions with respect to number of patients transfused. Results from the pair-wise meta-analysis suggested that TXA was more effective than standard treatment in reducing the number of units of allogeneic blood transfused, length of stay in hospital and thrombotic complications. There was no difference in the incidence of infections between TXA and standard treatment. There was also evidence of benefit for mortality for TXA versus standard treatment; however there was high imprecision and therefore the GDG were uncertain of the effect on mortality in this risk group. Overall QALYs were very similar between interventions in this risk group as mortality was not incorporated in the economic model due to uncertainty. In children, the evidence suggested that the combination of ICS with TXA may result in fewer patients transfused and a lesser volume of total blood transfused in

	comparison with the use of ICS alone. This evidence, however, was of very low quality from a single study in scoliosis surgery. For the comparison of TXA with standard treatment, the evidence suggested that TXA may result in reduction of post-operative blood loss. This evidence was of moderate quality. All evidence was from studies in children who were expected to have high blood loss. No evidence was identified for children who were expected to have moderate blood loss. For this group, the GDG extrapolated the evidence from adults to inform the recommendation for children. Based on the above clinical considerations and economic considerations described below, the GDG recommended the use of TXA for both adults and children undergoing surgery where blood loss is expected to be moderate or high. However, it was acknowledged that the evidence was more limited for children, including uncertainty as to the correct dose of TXA for children, and the paediatric recommendation has been extrapolated from evidence in adults. As such, the recommendation is "consider" rather than "offer" in children to enable a more individualised approach depending on the clinical situation and patient subgroup.
Economic considerations	No economic evaluations were identified comparing all relevant interventions, that is TXA or cell salvage, alone or in combination. Two economic evaluations were identified comparing TXA with placebo or no TXA in total hip replacement adult surgery patients and found that TXA was dominant, that is it reduced costs and improved health outcomes.[9,243] These studies were assessed as partially applicable with potentially serious limitations. No economic evaluations were identified for TXA in paediatric surgical patients. Health economic considerations for cell salvage and combinations of cell salvage with TXA are discussed in subsequent LETRs. The question of whether TXA, cell salvage or a combination of both should be used in surgical patients was prioritised for original economic modelling by the GDG. Two population subgroups were analysed in the model, adults undergoing surgery at moderate risk of bleeding (0.5-1 litres) and high risk of bleeding (>1 litre) in line with how the clinical effectiveness evidence was analysed. The comparators for each population subgroup were selected based on the availability of evidence from the clinical review in discussion with the GDG. Model inputs were based on clinical evidence identified in the systematic review and network-meta analyses undertaken for the guideline, supplemented by additional data sources as required. Total costs took into account intervention costs (staff time [where additional to no intervention], drug costs, equipment and consumables) and downstream costs including blood costs and short-term treatment- and transfusion-related adverse events (through the use of hospital length of stay as a proxy). The new economic model found that in both the moderate and high risk subgroups, TXA was the most cost-effective option for reducing allogeneic blood transfusion in adults undergoing surgery. In the high risk group, TXA was found to have the greatest benefits for patients (highest QALYs) largely due to a reduction in mortality at 30 days that was not seen with other treatment options. TXA had the second lowest cost after PCS; this was driven by a combination of the lowest intervention cost, moderate blood savings and a small saving due to a reduced length of stay. Of note, TXA was not the most blood saving intervention; it was the combination of ICS and TXA that resulted in the greatest blood savings. In the moderate risk group, there was no difference in the incremental QALYs versus standard treatment between interventions to the 3rd decimal place. TXA had the lowest costs compared to all other interventions due to a combination of the lowest intervention cost, greatest savings associated with blood costs and length of stay.

	The conclusion that TXA alone was the most cost-effective option was robust to a wide range of sensitivity analyses including exploring uncertainty in the clinical effectiveness in terms of mortality, number transfused, volume transfused and length of stay; baseline transfusion and mortality rates; cost of interventions and blood transfusion and use of length of stay in the model. In the high risk group, two sensitivity analyses were undertaken where the mortality after 30 days and the quality of life were adjusted to reflect MI and stroke populations, resulted in PCS becoming the most cost-effective option. This outcome was driven primarily by the very low total costs of PCS (as a result of length of stay savings). To explore this further, these two sensitivity analyses were combined with a sensitivity analysis to account for the unusually large difference in length of stay for PCS. This resulted in TXA returning to being the most cost effective option. Based on these additional analyses, the GDG did not feel the need to change the overall conclusion. This new economic analysis was assessed as directly applicable with minor limitations. Paediatric surgical patients were not included in this analysis as insufficient clinical evidence was identified for this population to allow for modelling. Based on this limited clinical evidence in children, the low intervention cost of TXA and the cost-effectiveness evidence in adults, the GDG judged it highly likely that TXA would be a cost-effective option in paediatric surgical patients.
Quality of evidence	The evidence from pairwise meta-analysis on TXA ranged from moderate to low quality for the critical and important outcomes. The recommendation is based on the evidence of clinical and cost-effectiveness.
Other considerations	The GDG acknowledged the breadth of the evidence base and the conclusive nature of the evidence in relation to the use of TXA in reducing allogeneic blood transfusion requirements in adult surgical patients. The GDG had confidence in making the recommendation based on the vast evidence base for adult surgeries and felt that it was unlikely that similar future research trials would change the direction of effect seen. The GDG was aware of reports of seizures related to high doses of TXA, but no evidence of excess reports from RCTs was found to support this. The GDG noted variation in thromboprophylaxis in the trials and made the recommendation on the assumption that hospitals will be following the recommendations on adult VTE prophylaxis in NICE guidance CG 92. The GDG noted the risk of thrombosis is lower in most paediatric groups and that there are no equivalent paediatric VTE prophylaxis guidelines so local policy should be followed. The GDG members, including the lay representatives, felt it should be standard practice to offer TXA for adults and that information about TXA should be included in patient information leaflets on blood transfusion and alternatives to blood transfusion. There was variation in the doses of TXA administered in the trials. The loading dose of TXA used in the trials involving adult patients undergoing cardiac surgery ranged from 2.5 mg/kg to 100 mg/kg. The maintenance dose of TXA for the cardiac surgery trials, ranged from 0.25 mg/kg/hour to 4.0 mg/kg/hour delivered over 1 to 12 hours. When oral TXA was used, again, there was variation in the dose and prescription regimens. Intravenous TXA was administered peri-operatively, with the first dose being administered pre-operatively in the majority of the trials evaluating its effectiveness. The prescriber should follow dosing as recommended in the summary of product characteristics. The GDG noted that the timing of first administration of TXA was important for the TXA to be effective in reducing blood

	transfusion requirements in surgical patients. Of note, in the economic model, for costing purposes, the following dose listed in the BNF was used for the high risk subgroup: slow IV injection (general fibrinolysis) 1 g every 6-8 hours followed by continuous IV infusion 25-50 mg/kg over 24 hours. For the moderate risk group the following dose listed in the BNF was used: slow IV injection (general fibrinolysis) 1 g every 6-8 hours. It was noted that there is wide variation in clinical practice in the dosage of TXA used in children. This was reflected in the variation in the dose of TXA used in the limited number of trials in children and, therefore, there is uncertainty regarding the optimal dose of TXA in children. Prior to analysis of studies, the GDG considered risk and amount of bleeding and defined low, moderate and high expected blood loss in adults as <500ml, 500ml-1 litre and >1 litre, respectively. This enabled recommendations to be based upon expected blood loss. This risk stratification was applicable to adults only. The GDG noted that these expected volumes of blood loss do not apply to the risk stratification for children; the GDG judged the equivalent of moderate blood loss in children to be 10% of blood volume. The GDG specifically did not list individual types of surgery for the recommendation and instead used expected blood loss as this enables type of surgery, individual bleeding risk and local practise to be taken into consideration when implementing recommendations. Evidence with respect to TXA, in surgical patients at low risk of bleeding (< 500 ml), was inconclusive and of very low quality. The GDG therefore did not make a recommendation for this risk group.

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Recommendations	**8. Do not routinely offer cell salvage alone.**
Relative values of different outcomes	The GDG agreed that the number of patients transfused, number of units transfused and mortality were critical outcomes for decision making. Other outcomes which were considered to be important in the decision making process were length of stay in hospital, quality of life and adverse events (infection, thrombotic complications).
Trade off between clinical benefits and harms	There was evidence of effectiveness for some of the critical outcomes for the use of ICS alone in the high and moderate risk groups in adult surgical patients. Although there was some evidence of clinical effectiveness of ICS and PCS alone and in combination with one another in comparison with standard treatment from the pairwise meta-analysis with respect to number of patients transfused and number of units of allogeneic blood transfused, TXA was more effective than cell salvage in the moderate risk group and the combination of ICS and TXA was more effective than cell salvage in the high risk group when reviewed in the network meta-analysis. Although the results of the network meta-analyses showed that PCS was ranked as the best treatment for number of patients transfused and length of stay, and ranked above TXA for number of units transfused in the high risk group, the GDG highlighted that PCS may have limited use, for example, when blood is lost in chest drains in cardiac surgical patients, which is in a minority of cases. They acknowledged that in current practice it may not be considered an appropriate intervention for all high risk surgeries on its own, particularly in patients who have extensive bleeding post-operatively and therefore may require reoperation to stem the bleeding (rather than PCS). The GDG noted that this was unlike ICS, which could be used across all high risk surgeries. The GDG noted that further research was therefore required in this specific group to establish the effectiveness of PCS in high risk surgeries and made a recommendation for further research in this area

	(see section 6.6.1). No evidence was identified for the comparison of ICS or PCS alone with standard treatment in children. There was very low quality evidence which suggested that the combination of ICS with TXA may result in fewer patients transfused and a lesser volume of total blood transfused in comparison with the use of ICS alone. All evidence was from studies in children who were at high risk of blood loss. No evidence was identified for children who were at moderate or low risk of blood loss. Based on this, and the new economic model, the GDG decided to not recommend the routine use of cell salvage alone in both adults and children. The combination of cell salvage with TXA was more likely to be cost-effective than cell salvage alone and was recommended by the GDG (see recommendation 9. below). However, it is acknowledged there are paediatric patient groups, such as some paediatric cardiac surgery patients, in whom cell salvage may be used and TXA may be considered inappropriate (please see 'Other considerations').
Economic considerations	No economic evaluations were identified comparing all relevant interventions, that is TXA or cell salvage, alone or in combination. Two economic evaluations comparing ICS+PCS with no cell savage in cardiac and or orthopaedic surgical adult patients were identified. The first was a cost-utility analysis by Davies 2006[77] which found that cell salvage (ICS or PCS) was dominant compared to no cell salvage. This analysis was assessed as partially applicable with minor limitations. The second by Klein 2008[165] was a cost-consequence analysis based on a single RCT which found that ICS+PCS was more costly and more effective at reducing the number of units transfused than no cell salvage. This analysis was assessed as partially applicable with potentially serious limitations. Finally a cost-utility analysis by Samnaliev 2013[258] comparing ICS with no cell salvage in orthopaedic and cardiac surgical paediatric patient found that ICS was dominant compared to no cell salvage. This analysis was assessed as partially applicable with potentially serious limitations. Note, the effectiveness data used in the analysis was from a non-randomised trial and therefore not reported in the clinical evidence. No economic evaluations were identified for the use of PCS alone in paediatric surgical patients. The evidence from the new economic model conducted indicated that PCS alone in the high and moderate risk of bleeding subgroups was not a cost-effective option in adult surgical patients. PCS was the most cost saving intervention in the high risk group; this was due primarily to the large reduction in hospital length of stay. When the mortality effect of TXA was removed, PCS had the highest QALYs which were attributable to the reduced length of stay. Furthermore, when the QALY difference between PCS and TXA was reduced, as seen insensitivity analyses where mortality and quality of life were adjusted to reflect MI and stroke populations, the length of stay savings were a key driver in establishing the most cost-effective option. The length of stay data for this comparator was based on one RCT with a high baseline length of stay. The GDG had concerns about the applicability of this evidence and therefore sensitivity analyses adjusting for this length of stay and excluding length of stay were undertaken. These resulted in TXA remaining the most cost-effective option. In the high risk group, ICS alone was also not a cost-effective intervention for reducing allogeneic transfusions in adult surgical patients. In the moderate risk group, there were no data identified in the clinical review for ICS in relation to the volume of allogeneic blood transfused. As a result, we were unable to include ICS alone in the analysis without making assumptions for this outcome. We were

	unable to establish from our analysis whether or not using ICS alone in this group would be a cost-effective intervention. The GDG felt that the new economic analysis conducted for this guideline superseded the published studies which were based on older clinical evidence[77] and in the case of two analyses[165, 258] on single trials and do not include all relevant treatment options. Furthermore for the two studies that found that cell salvage was dominant to usual care, the cost of cell salvage used in their analyses was less than the cost used in our analysis[77,258] and were not considered by the GDG to be reflective of the current NHS context. The GDG extrapolated the findings of the new economic model in adults to children. However, as noted above in the trade-off between clinical benefits and harms, special consideration should be given for some paediatric patient groups (please see other considerations).
Quality of evidence	This recommendation was based on low to very low quality evidence from the pair wise meta-analysis and the network meta-analysis and the results of our economic model.
Other considerations	The GDG discussed the advantages of using cell salvage. One particular advantage highlighted was that, with the use of cell salvage, allogeneic blood transfusion can be avoided, minimising all complications of transfusion including red cell alloimmunisation, that is, developing red cell antibodies causing difficulties in identifying compatible blood for future transfusions if needed. Although the GDG recommended against routinely offering cell salvage alone in adults and children, it was noted that special consideration should be given for its use in paediatric cardiac surgery patients. The GDG acknowledged that cell salvage is widely used during paediatric cardiac surgery to reduce exposure to allogeneic blood whereas TXA may not always be used in the same clinical situations due to uncertainty about the optimal dose and possible side effects.

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Recommendations	**9. Consider intra-operative cell salvage with tranexamic acid for patients who are expected to lose a very high volume of blood (for example in complex cardiac and vascular surgery, major obstetric procedures, and pelvic reconstruction and scoliosis surgery).**
Relative values of different outcomes	The GDG agreed that the number of patients transfused, number of units transfused and mortality were critical outcomes for decision making. Other outcomes which were considered to be important in the decision making process were length of stay in hospital, quality of life and adverse events (infection, thrombotic complications).
Trade off between clinical benefits and harms	In the high risk group, the evidence from the network meta-analysis in adults showed that the combination of ICS and TXA was the most clinically effective in reducing the number of patients transfused as well as the number of units of allogeneic blood transfused. No evidence of mortality benefit observed for the combinations of ICS and TXA in the high risk group. The GDG noted that it is unclear why the mortality benefit seen with TXA alone was not seen with the combination of ICS and TXA but it seemed possibly that it was to be due to a lack of data rather than a difference in effect. Although the evidence showed that the combination of ICS and TXA was not cost-effective in patients who were expected to have blood loss greater than 1 litre and so was not recommended, the GDG noted that there may be a sub-group of

	patients within this group who were at very high risk of blood loss and may require more blood transfusions (for example in complex cardiac and vascular surgery, major obstetric procedures, and pelvic reconstruction and scoliosis surgery). The GDG anticipated that due to the higher volume of blood loss in these patients, the decision to use the combination of ICS with TXA may be cost-effective, as the total costs (cost of blood saved and cost of interventions) would be less than that of TXA. The GDG discussed that when the rate of blood loss is very high, TXA may be effective only up to a point in reducing blood loss. The GDG felt that in such cases, as cell salvage utilises shed blood as opposed to TXA which is an anti-fibrinolytic, it may be more effective in reducing the need of allogeneic blood transfusion. Although there was a lack of evidence to support this, the GDG felt this was a highly plausible scenario. In addition, the GDG felt that the mortality benefit of TXA may be maintained when it is administered in combination with ICS. The combination of these two assumptions would result in similar QALYs for both interventions. In children, there was very limited and low quality evidence which suggested that the combination of ICS with TXA may result in fewer patients transfused and a lesser volume of total blood transfused in comparison with the use of ICS alone. The GDG therefore felt that the combination of ICS and TXA should be an option for situations where people are at risk of very high blood loss.
Economic considerations	No economic evaluations were identified including the combination of ICS+TXA. As discussed above, the GDG felt that, while TXA alone was found to be the most cost-effective option overall in the original economic evaluation, for certain patients with particularly high blood loss the addition ICS to TXA may still be a cost-effective option. This was discussed on the basis that the mechanisms of action are different for TXA and cell salvage and so it was considered that the relative benefit of ICS over TXA is likely to increase with increased blood loss and that the mortality benefit seen with TXA alone was likely to also be achieved with TXA+ICS. Of note, changing this latter assumption alone did not change the conclusions on the analysis. Although the results of the base case analysis do not provide support for this recommendation, exploratory threshold analyses indicated that the combination of ICS and TXA could potentially become the cost-effective strategy in particular patients or patient groups where the probability of being transfused and the volume transfused is expected to be very high, if it was assumed that ICS+TXA had the same mortality benefit as TXA and that relative treatment benefits for ICS were maintained or increased. These analyses assumed that patients bleeding risk is assessed in advance and if they are considered to be very high risk then ICS is set up and used for all patients, that is the cost is incurred for all patients. Based on the limited clinical evidence in children and the economic analysis conducted in adults, the GDG agreed to extrapolate their conclusions about cost-effectiveness in adults to children as well.
Quality of evidence	The quality of evidence for the combinations of ICS+TXAin the high risk group from the network meta-analysis was of very low quality for all outcomes in both adults and children. It was not possible to explore the effectiveness of ICS+TXA in the very high risk subgroup within the context of RCT level clinical data (for details see other considerations). This recommendation was based on results from the network meta-analysis, economic modelling and further threshold analysis as well as the consensus expert opinion of the GDG members.
Other considerations	The GDG discussed the challenges in identifying the specific sub-group of patients in whom the combination of ICS and TXA would be clinically and cost-effective and

	noted that some of these patients could be identified based on the complex nature of some surgeries (for example, scoliosis surgery or reconstructive hip and knee surgeries). The GDG noted that there was a lack of clinical evidence on these specific types of surgeries with respect to the combination of ICS and TXA. The GDG also noted that it was difficult to identify this particular group of patients from RCT data as many of the patients who were classified as high risk could well require greater amounts of blood transfusion based on their individual patient characteristics, such as baseline haemoglobin levels, pre-operative anaemia management and thresholds for blood transfusion according to local protocols. We explored these factors by sub-group analyses. The analysis was limited by the non-availability of patient level data. Consequently, it was acknowledged that these factors, alone or in combination with one another, may give rise to a group of patients whose blood transfusion needs may be significantly greater than other patients in the high risk group. The GDG anticipated that the combination of ICS and TXA may prove to be clinically as well as cost-effective in this group. The GDG discussed the advantages of using cell salvage. One particular advantage highlighted was that, with the use of cell salvage, allogeneic blood transfusion can be avoided, minimising all complications of transfusion including red cell alloimmunisation, that is, developing red cell antibodies causing difficulties in identifying compatible blood for future transfusions if needed. The GDG noted that it was important that healthcare personnel using the technique should be adequately trained in order to minimise the chance of errors occurring.

6.6.1 Research Recommendations

1. **Post-operative cell salvage: For patients having cardiac surgery with a significant risk of post-operative blood loss, is post-operative cell salvage and reinfusion clinically and cost effective in reducing red blood cell use and improving clinical outcomes, compared with existing practice?**
   - **Why this is important: There was some evidence for benefit from post-operative cell salvage, but the quality was low. Reducing blood loss during cardiac surgery may reduce the risk of complications. However, post-operative cell salvage carries additional cost. Studies are needed to determine whether post-operative cell salvage is more clinically and cost effective than existing practice for patients having cardiac surgery with a significant risk of post-operative blood loss. Important outcomes should include the use of red blood cells and other blood products, clinical outcomes and quality of life.**

7 Monitoring for acute reactions

Safe and effective transfusion of blood and blood components involves many steps. A small, but important, part of the overall process is the taking and recording of observations on the patient before and during the transfusion.

It is essential that any reaction to the component begin transfused is noted and reported. Historically, non-invasive monitoring of the patient's pulse, blood pressure, temperature and respiratory rate has been used to ensure any reaction is noticed and acted on by staff. Recommendations and practice vary on the timings of these observations and there is little evidence to support when or what monitoring should be performed.

National audits have revealed considerable improvements in the standardisation and documentation of monitoring in line with recommendations set out by the British Committee for Standards in Haematology (BCSH). Even without evidence it would seem sensible to perform and record observations on patients undergoing treatment with blood products, particularly in cases where patients are unable to inform staff that they do not feel well while having a transfusion.

7.1 Review question: What is the clinical- and cost-effectiveness of monitoring for acute reactions at different times in relation to the transfusion?

For full details see review protocol in Appendix C.

Table 61: PICO characteristics of review questions

Population	• Adults and young people (aged 16 years and above) • Children (under 16 years of age)
Interventions	• Standard practice for monitoring for acute transfusion reactions (ATR) • No standard practice/alternatives for monitoring for acute transfusion reactions (ATR)
Comparisons	• Standard practice for monitoring for acute transfusion reactions (ATR) versus No standard practice/alternatives for monitoring for acute transfusion reactions (ATR)
Outcomes	• Quality of life • Length of hospital stay • Mortality (all causes) • Acute transfusion reaction/serious adverse events of transfusion • Morbidity (ICU admission, renal failure, DIC) • Admission to ICU post transfusion (day or in-patient) • Admission to hospital post transfusion (day patient) • Monitoring • Transfusion-related mortality at 30 days
Study designs	• RCTs • Systematic reviews • Before and after studies • Cohort studies

7.2 Clinical evidence

We looked for RCTs, systematic reviews, before and after studies and cohort studies which compared standard monitoring practices for transfusion with alternative monitoring practices for transfusion. The alternative monitoring practices differed from the standard monitoring with respect to frequency of monitoring as well components of monitoring (clinical signs to be monitored).

No studies were found which met the criteria set in the review protocol.

One abstract of an unpublished study was identified which met the criteria in the review protocol.[84] The study was a literature review comparing the effectiveness of different frequencies of monitoring vital signs in patients receiving transfusion.

Four audit reports were also identified which did not meet the review protocol criteria. However, the GDG agreed that the findings from these audits were helpful in informing the consensus opinion of the group. Most of these audits were based on the guidelines for transfusion recommended by the British Committee for Standards in Haematology (BCSH).[30] The table below provides a summary of these audit reports. See also the study selection flow chart in Appendix E, study evidence tables in Appendix H and excluded studies list in Appendix P.

Table 62: Summary of audit reports on monitoring for blood transfusion

Study id.	Aim of audit	Methods	Findings
Cottrell et al. 2013[64]	To measure clinical bedside practice in UK hospitals delivering transfusion services against the British Committee for Standards in Haematology (BCSH, 2009)[30] guidelines. The audit was conducted by the National Comparative Audit for Blood Transfusion (NCABT).	With respect to monitoring of the transfused patient, 3 standards were evaluated: • Pulse, blood pressure, temperature and respiratory rate are measured before transfusion (within 60 minutes before start of transfusion). • Pulse, blood pressure and temperature are measured 15 minutes after transfusion starts. • Pulse, blood pressure and temperature are measured at the end of each transfused unit (within 60 minutes of completion). A total of 247 sites participated in the audit: 211 NHS sites and 36 independent sits provided data on 9250 transfusions.	Pre-transfusion observations: • 84.9% of patients had all four observations measured pre-transfusion • Inpatient compliance with all 4 observations was 86.7%; outpatient compliance with all four observations was 78.3%. • Compliance was 84.6% for adults and 88.2% for children. Observations at 15 minutes of transfusion: • 46.8% of patients were observed at 15 minutes exactly. • Overall, the observations were made within 30 minutes in 86.1% of patients. • 9.4% of patients had delayed observations (>30 minutes). • 3.9% of patients had no observations recorded. Post-transfusion observations: • 84.1% of patients had post-transfusion observations recorded. • 15.3% of patients did not have any post-transfusion observations recorded; of these, 14.8% were in outpatients.

Study id.	Aim of audit	Methods	Findings
Parris et al. 2007[235]	To audit blood transfusion practice against the British Committee for Standards in Haematology (BCSH) (1999) guidelines.	With respect to monitoring of patents receiving blood transfusion, practice was evaluated against the BCSH standards: 'The patients' vital signs should be monitored before administering a unit of blood, 15 minutes after start of transfusion and on completion of transfusion' (BCSH et al 1999).[30]	• One third of all patients had no vital signs recorded within the first 30 minutes of transfusion commencing. • 13% of all patients had no record of observations during the entire transfusion.
Novis et al. 2003[220]	To measure quality indicators of frequency of vital sign monitoring according to the benchmarks set by the College of American Pathologists Q-Probes program. Two audits were undertaken at different time points (in 1994 and 2000)	Quality indicators for monitoring during blood transfusion included: • Vital signs checked prior to initiating transfusion. • Vital signs checked during the first 15 minutes of transfusion. • Vital signs checked after the first 15 minutes of transfusion.	**1994:** • 96.9 % of all patients had their vital signs checked prior to initiating transfusion. • 90.7% of all patients had their vital signs checked during the first 15 minutes of transfusion. • 89.7% of all patients had their vital signs checked after the first 15 minutes of transfusion. • 81.6% of all patients had all of the above listed vital signs monitoring intervals completed. **2000:** • 98.1% of all patients had their vital signs checked prior to initiating transfusion. • 92.7% of all patients had their vital signs checked during the first 15 minutes of transfusion. • 95.1% of all patients had their vital signs checked after the first 15 minutes of transfusion. • 88.3% of all patients had all of the above listed vital signs monitoring intervals completed.
Taylor et al. 2008[288]	Study reports results of the 2005 National Comparative Audit of Blood Transfusion and compares results of earlier audits conducted in 1995, 1998 and 2003.	Data on bedside practice from 211 NHS sites were evaluated as part of the audit. Frequency of vital sign monitoring was audited and compared.	**1995** • In pre-treatment observations, 78% had temperature recorded, 77% had pulse recorded, and 75% had blood pressure recorded. • 49% had temperature recorded within 30 minutes of transfusion. • 51% had pulse recorded within 30 minutes of transfusion. • 14% had no observations during treatment at all. **1998** • In pre-treatment observations, 89% had

Study id.	Aim of audit	Methods	Findings
			temperature recorded, 87% had pulse recorded, and 81% had blood pressure recorded. • 57% had pulse recorded within 30 minutes of transfusion. • 9% had no observations during treatment at all. **2003** • In pre-treatment observations, 74% had temperature recorded, 76% had pulse recorded, and 75% had blood pressure recorded. • 58% had temperature recorded within 30 minutes of transfusion. • 59% had pulse recorded within 30 minutes of transfusion. • 12% had no observations during treatment at all. **2005** • In pre-treatment observations, 90% had temperature recorded, 91% had pulse recorded, and 91% had blood pressure recorded. • 64% had temperature recorded within 30 minutes of transfusion. • 65% had pulse recorded within 30 minutes of transfusion. • 13% had no observations during treatment at all.

7.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow diagram in Appendix F.

Unit costs

Relevant unit costs are provided in Appendix N to aid consideration of cost-effectiveness.

7.4 Evidence statements

Clinical

No clinical evidence was identified for this review.

Economic

No relevant economic evaluations were identified.

7.5 Recommendations and link to evidence

Recommendations	10. Monitor the patient's condition and vital signs before, during and after blood transfusions, to detect acute transfusion reactions that may need immediate investigation and treatment.
Relative values of different outcomes	The GDG considered mortality and morbidity as critical outcomes. Other outcomes considered for decision making included length of stay in hospital, admission to ICU post transfusion, admission to hospital post transfusion (for day patients), and quality of life.
Trade-off between clinical benefits and harms	Whilst no evidence evaluating the clinical effectiveness (or harms) of monitoring for acute transfusion reactions was identified, the GDG agreed that the tests are non-invasive and fairly acceptable to patients and the time spent monitoring patients would allow the early detection and treatment of acute transfusion reactions. To enable rapid identification of acute transfusion reactions, the GDG recommended that people should be monitored before, during and after blood transfusions.
Economic considerations	No economic evidence was identified. The cost of nurse time for monitoring has been estimated to be £42.50 to £85.00 per transfusion (30 to 60 minutes of nurse time based on BCSH guidelines).[30] However, this cost does not reflect future savings resulting from early detection and treatment of acute transfusion reactions, or potential improvements in health outcomes for patients. Monitoring is primarily a patient-safety issue, and having considered the economic implications, the GDG felt that the possible benefits (in terms of health outcomes for patients and reduced future costs) are likely to outweigh the upfront cost of nurse time. The frequency and timing of monitoring recommended by the GDG is already considered common practice and therefore should not be an additional cost.
Quality of evidence	No clinical evidence was identified in this topic area. The recommendation is based on the consensus expert opinion of the GDG members. There was no specific evidence available for the paediatric population for this recommendation. The GDG felt it reasonable that the same recommendations should apply for children as for adults.
Other considerations	The British Committee for Standards in Haematology (BCSH) has published guidelines, which provide more detail about monitoring patients during transfusions. The GDG considered data from audit reports (see section 7.2, clinical evidence review for details) which measured current practice in monitoring of patients receiving blood transfusions against standards laid down by the BCSH guidelines. It was observed that there have been improvements in monitoring practices over time. The GDG considered these standards and monitoring strategies and made a consensus recommendation based on their knowledge and experience of the monitoring of patients receiving blood transfusions. The GDG was also aware of haemovigilance data from the Serious Hazards of Transfusion (SHOT) reports which indicate that the majority of acute transfusion reactions occur during the first minutes of transfusion.(ref) It was felt that monitoring during this time period would help in early identification of any adverse reactions. The GDG noted that the frequency of monitoring depended on the type of patient receiving a transfusion, for example, children and unconscious patients may require more frequent monitoring during blood transfusions.

Recommendations	11. Observe patients who are having or have had a blood transfusion in an environment with adequate staffing and facilities for monitoring and managing acute reactions.

Relative values of different outcomes	The GDG considered mortality and morbidity as critical outcomes. Other outcomes considered for decision making included length of stay in hospital, admission to ICU post transfusion, admission to hospital post transfusion (for day patients), and quality of life.
Trade-off between clinical benefits and harms	Whilst no evidence evaluating the clinical effectiveness (or harms) of monitoring for acute transfusion reactions was identified, the GDG agreed that the tests are non-invasive and fairly acceptable to patients and the time spent monitoring patients would allow the early detection and treatment of acute transfusion reactions. In order to safely care for people having a transfusion and to undertake monitoring as recommended, hospitals need to ensure that the facilities are suitable to allow observations, monitoring and management of acute reactions.
Economic considerations	No economic evidence was identified. The cost of nurse time for monitoring has been estimated to be £42.50 to £85.00 per transfusion (30 to 60 minutes of nurse time based on BCSH guidelines).[30] However, this cost does not reflect future savings resulting from early detection and treatment of acute transfusion reactions, or potential improvements in health outcomes for patients. Monitoring is primarily a patient-safety issue, and having considered the economic implications, the GDG felt that the possible benefits (in terms of health outcomes for patients and reduced future costs) are likely to outweigh the upfront cost of nurse time.
Quality of evidence	No clinical evidence was identified in this topic area. The recommendation is based on the consensus expert opinion of the GDG members. There was no specific evidence available for the paediatric population for this recommendation. The GDG felt it reasonable that the same recommendations should apply for children as for adults.
Other considerations	The British Committee for Standards in Haematology (BCSH) has published guidelines, which provide more detail about monitoring patients during transfusions. The GDG considered data from audit reports (see section xx7.2, clinical evidence review for details) which measured current practice in monitoring of patients receiving blood transfusions against standards laid down by the BCSH guidelines. It was observed that there have been improvements in monitoring practices over time. The GDG considered these standards and monitoring strategies and made a consensus recommendation based on their knowledge and experience of the monitoring of patients receiving blood transfusions.

8 Electronic decision support

Electronic decision devices are a useful tool to support the clinical users in their decision to transfuse, the aim being to reduce inappropriate blood transfusions. It allows the indications for transfusion to be readily available during the requesting process following the patient clinical review. Some applications are in a checklist format that can be used to further inform staff. The use of these devices, depending on the software and application, can assist in preventing over-ordering and duplication of orders, allow users to see what has been prescribed and reduce pressure on transfusion staff by minimising phone enquiries.

These systems can be used to support local policies and guidelines related to transfusion practice and allow benchmarking and review of practice.

8.1 Review question: What is the clinical- and cost-effectiveness of electronic decision-support blood order systems to reduce inappropriate blood transfusions?

For full details see review protocol in Appendix C.

Table 63: PICO characteristics of review question

Population	• Adults and young people (aged 16 years and above) • Children (under 16 years of age)
Intervention	• Electronic decision-support blood order systems (blood ordering is done in an online system and alerts are sent to doctors; for example, an alert may point out that, based on Hb level or platelet count, the transfusion is outside guidelines and indicate that the order should be cancelled unless additional justification is provided) • Standard care (no decision-support blood order systems) • Non-electronic decision support systems (for example, staff review of requests and discussions between laboratory and clinicians; not electronic, may include checklists)
Comparison	• Electronic decision-support blood order systems vs. standard care • Electronic decision-support blood order systems vs. non-electronic decision support systems
Outcomes	• Proportion of inappropriate transfusions • Proportion of patients transfused • Number of units transfused • Hospital length of stay • Quality of life • Mortality • Pre-transfusion haemoglobin levels/platelet count/coagulation result
Study designs	• RCTs • Systematic reviews • Before and after studies • Cohort studies

8.2 Clinical evidence

We searched for randomised trials, systematic reviews, before and after studies and cohort studies evaluating the effectiveness of electronic decision support systems in reducing inappropriate transfusions.

Fifteen studies were included in the review.[2,47,48,104,118,129,180,236,244,253,263,325,248,52,117] Evidence from these is summarised in the adapted clinical GRADE evidence profile below. See also the study selection flow chart in Appendix E, study evidence tables in Appendix H and exclusion list in Appendix P.

- The majority of the studies were before and after implementation studies which evaluated the number of inappropriate transfusions prior to and after implementation of an electronic decision support system.
- There was variation in the types of electronic systems used (some studies used computerised algorithms to aid decision making, some studies had alerts at different thresholds and some studies had an electronic checklist that had to be answered to give a blood transfusion).
- None of the studies met the protocol criteria entirely - that is, details of any non-electronic checking that may have taken place prior to implementation of the electronic systems were not provided, which resulted in studies not having control groups.
- There was variation as to how the outcomes were reported across the studies and not all outcomes in the review protocol were reported. Quality of life was not reported in any of the studies.
- Since the studies are in different population groups and also have different study designs, the results have not been pooled into a meta-analysis. Individual effect sizes across studies have been presented. A customised GRADE clinical evidence profile is presented which evaluates the quality of the evidence for the different outcomes.

8.2.1 Summary of included studies

Table 64: Summary of studies included in the review

Study	Population, study design, n	Intervention	Outcomes reported
Adams 2011[2]	Children Before and after cohort study (retrospective) n=6786	Computerised physician order entry system (CPOE) alert generated before prescription order if patients was normotensive for >6hr and Hb level >7 g/dl	• Proportion of patents transfused • Hospital length of stay • Mortality • Pre-transfusion haemoglobin levels
Chang 2011[47]	Hospital inpatients Retrospective cohort study (retrospective review of transfusion episodes in the study period). n=9931 transfusion episodes No comparison group	Computerised transfusion decision support system used for ordering transfusion of fresh frozen plasma.	• Proportion of inappropriate transfusions
Chang 2012[48]	Hospital inpatients Retrospective cohort study (retrospective	Computerised transfusion decision support system used for ordering transfusion of RBC.	• Proportion of inappropriate transfusions

Study	Population, study design, n	Intervention	Outcomes reported
	review of transfusion episodes in the study period). No comparison group		
Chen 2015[52]	Inpatient healthcare providers Retrospective review	Provider –best practice alert (BPA) interaction data were collected from January 2011 to August 2012 from the hospital electronic medical record.	• No protocol outcomes reported • overriding the BPA and continuing with transfusion (indirect outcome)
Fernandez 2007[104]	Critically ill patients (adults) Before and after cohort study in 2 separate group of patients n=2200 (1100 before and 1100 after)	Computerised physician order entry system with decision support incorporated into an existing electronic transfusion ordering system; decision support algorithm justified RBC transfusion if Hb>7g/ dl in the presence of active bleeding, ischaemia or early septic shock.	• Proportion of patients transfused • Number of units transfused • Hospital length of stay (in median, IQR) • Mortality • Pre-transfusion haemoglobin levels (in median, IQR)
Goodnough 2014[118]	Adults; stable, medical and surgical(post-operative) patients receiving blood transfusions	Clinical decision support system with computerised physician order entry system for blood ordering; decision support algorithm justified RBC transfusion if Hb <7 g/dl or if Hb<8 g/dl in acute coronary syndrome.	• Proportion of patients transfused • Number of units transfused • Hospital length of stay (in median, IQR) • Mortality
Goodnough 2014 B[117]	Adults and children receiving blood transfusions Before and after study	Clinical decision support (CDS)	• Proportion of inappropriate transfusions • Proportion of patients transfused. (RBC transfusions) • Number of units transfused • Hospital length of stay days (per 1000 discharges) • Quality of life • Mortality (30 days) (per 1000 discharges) • Pre-transfusion haemoglobin levels for all patients , g/dl
Hibbs2014[129]	Adult inpatients in a specialised	Electronic decision support system followed by addition of electronic	• Proportion of inappropriate

Study	Population, study design, n	Intervention	Outcomes reported
	orthopaedic hospital	remote blood issue (ERBI)	transfusions • Proportion of patients transfused • Number of units transfused • Pre-transfusion haemoglobin levels
Lin 2010[180]	Adults and children Retrospective cohort study (retrospective review of transfusion episodes in the study period). n=5754 transfusion episodes No comparison group	Computerised transfusion decision support system used for ordering transfusion of platelets	• Proportion of inappropriate transfusions
Pentti 2003[236]	Adults (patients admitted to medical and surgical ICU and received at least one transfusion) Before and after cohort study. n=290	Online ordering system alerted the prescriber if pre-defined transfusion criteria not met.	• Proportion of inappropriate transfusions • Proportion of patients transfused • Mortality • Pre-transfusion haemoglobin levels
Rana 2006[244]	Critically ill patients with anaemia admitted to medical, surgical and mixed ICU wards Before and after retrospective cohort study n=843 (440 before implementation, 403 after implementation)	Computerised physician order entry system with incorporated decision support algorithm justifying RBC transfusion if Hb <7 g/dl or Hb >7 g/dl in the presence of active bleeding, ischaemia or early septic shock.	• Proportion of inappropriate transfusions • Proportion of patients transfused • Number of units transfused • Mortality • Pre-transfusion haemoglobin levels (in median, IQR)
Razavi 2014[248]	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. Before and after study	The transfusion clinical decision support (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.	• Number of units transfused (Intra-operative PRBC units in all patients) • Number of units transfused (Post-operative PRBC units in all patients) • Hospital length of stay • Quality of life • Mortality (30 days) • Post-operative

Study	Population, study design, n	Intervention	Outcomes reported
			surgical site infection • Post-operative transfusion events in CABG patients • Post-operative transfusion events in SAVR patients • Pre-transfusion haemoglobin levels for all patients , g/dl
Rothschild 2007[253]	Adult patients. Study randomised junior house staff to decision support and control groups US study	Decision support on computerised physician order entry for RBC, platelets and FFP. Decision support based on thresholds provided by local evidence based guidelines	• Proportion of inappropriate transfusions
Scheurer 2010[263]	General medical inpatients Case series evaluation (retrospective) n=214 blood transfusion episodes	Computerised physician order entry system with decision support	• Proportion of inappropriate transfusions
Yerrabothala 2014[325]	Adult inpatients receiving blood transfusions.	Computerised physician order entry system with decision support	• Proportion of inappropriate transfusions • Proportion of patients transfused with 2 RBC units • Number of units transfused • Length of stay in hospital • Mortality

1

2

Table 65: Modified GRADE evidence profile: Electronic decision support

Quality assessment						Effect size	Quality	Importance
Study	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**			
Proportion of inappropriate transfusions								
Scheurer 2010	Cohort study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	115/214 (54%)	Very low	
Chang 2011	Cohort study					6779/9931(68.5%)	Very low	
Rana 2006	Cohort study					RR: 0.16 [0.09, 0.31]	Very low	
Lin 2010	Cohort study					1751/5754 (30.4%)	Very low	
Hibbs 2014	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	55.3% (before implementation) and 35% (after implementation)	Very low	
Yerrabothala 2014	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	24% of blood orders were cancelled in first month after implementation of decision support system	Very low	
Goodnough 2014B	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	The percentage of transfusions in patients with pre-transfusion haemoglobin level greater than 8g/dl decreased from 60% to 35% in the 6 months after implementation of BPA in July 2010, with a sustained downtrend to below 30% by 2013 ($p<0.001$). In absolute terms, CDS reduced annual RBC transfusions by 24%,	Very low	

Quality assessment						Effect size	Quality	Importance
Study	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**			
Proportion of patients transfused								
Adams 2011	Cohort study	Very serious limitations(a)	No serious inconsistency	No serious indirectness	Not applicable	RR: 0.66 [0.57, 0.78]-Acute care ward RR: 0.81 [0.74, 0.89]-Paediatric ICU	Very low	
Fernandez 2007	Cohort study					RR:0.91 [0.83, 0.98]	Very low	
Rana 2006	Cohort study					RR: 0.77 [0.68, 0.87]	Very low	
Goodnough 2014	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	21.9% (before implementation) and 17% (after implementation)	Very low	
Hibbs 2014	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	No significant difference in proportion of transfusions before and after implementation	Very low	
Yerrabothala 2014	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	Proportion of patient transfused with 2 RBC units decreased from 47% to 15%	Very low	
Goodnough 2014B	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	(BPA introduced in 2010) 2008: 29,472 2009: 30,194 2010: 25,304 2011:23,136 2012: 23,008 2013: 22,991	Very low	
Chen 2015	Retrospective review	Very serious limitations[(a)]	No serious inconsistency	serious indirectness	Not applicable	The ordering provider proceeded to override the	Very low	

Quality assessment						Effect size	Quality	Importance
Study	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**			
				[b]		BPA and continued with transfusion in 98% of cases (10,442/10, 642)		
Razavi 2014	Before and after study	Very serious limitations[a]	No serious inconsistency	No serious indirectness	Not applicable	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%)	Very low	
Number of units transfused								
Fernandez 2007	Cohort study	Very serious limitations[a]	No serious inconsistency	No serious indirectness	Not applicable	MD -0.20 [-0.35, -0.05]	Very low	
Rana 2006	Cohort study					MD -0.22 [-0.53, 0.09]	Very low	
Goodnough 2014	Before and after study	Very serious limitations[a]	No serious inconsistency	No serious indirectness	Not applicable	30, 194 units before implementation and 22,991 units after implementation	Very low	
Hibbs 2014	Before and after study	Very serious limitations[a]	No serious inconsistency	No serious indirectness	Not applicable	Before implementation: 55 units transfused, After implementation: 37 units (with decision support) and 38 units (with decision support and	Very low	

Quality assessment						Effect size	Quality	Importance
Study	Design	Risk of bias	Inconsistency	Indirectness	Imprecision			
						ERBI)		
Goodnough 2014B	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	Mean number of RBC units received by transfused patients was lower after implementation of BPA (P=0.001)	Very low	
Razavi 2014	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	(Intra-operative PRBC units in all patients) (mean±SD): Pre-intervention: 0.73±1.5 Post-intervention: 0.65±1.4 (Post-operative PRBC units in all patients) (mean±SD): Pre-intervention: 1.59±2.9 Post-intervention: 1.25±2.5	Very low	
Hospital length of stay (days)								
Adams 2011	Cohort study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	MD -1.66 [-2.80, -0.52]	Very low	
Goodnough 2014	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	Significant improvement after implementation	Very low	
Yerrabothala 2014	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	Same in both groups	Very low	
Goodnough 2014B	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	(BPA introduced in 2010) 2008: 5.79	Very low	

Quality assessment						Effect size	Quality	Importance
Study	Design	Risk of bias	Inconsistency	Indirectness	Imprecision			
						2009: 5.63 2010: 5.55 2011:5.52 2012: 5.59 2013: 5.49 p<0.05		
Razavi 2014	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	Pre-intervention: 8.9±5.5 Post-intervention: 9.4±6.5	Very low	
Mortality								
Fernandez 2007	Cohort study	Very serious limitations(a)	No serious inconsistency	No serious indirectness	Not applicable	RR: 1.29[1.02, 1.63]	Very low	
Rana 2006	Cohort study					RR: 1.24 [0.88, 1.75]	Very low	
Goodnough 2014	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	Significant improvement after implementation	Very low	
Yerrabothala 2014	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	Same in both groups	Very low	
Goodnough 2014B	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	Mortality at 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 (BPA introduced in 2010)	Very low	
Razavi 2014	Before and after	Very serious	No serious	No serious	Not applicable	Pre-intervention: 13	Very low	

Quality assessment						Effect size	Quality	Importance
Study	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**			
	study	limitations[(a)]	inconsistency	indirectness		(1.8%) Post-intervention: 13 (1.7%)		
Pre-transfusion haemoglobin levels								
Adams 2011	Cohort study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	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)	Very low	
Rana 2006	Cohort study					Group 1: 8.7 (8.1-9.3) Group 2: 8.5 (7.8-9.2)	Very low	
Hibbs 2014	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	8.22 g/dl in pre-implementation group; 7.67 g/dl (with decision support) and 8.25 (with decision support and ERBI).	Very low	
Goodnough 2014B	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	There was no difference in admission Hb levels (p=0.11), discharge Hb	Very low	

Quality assessment								
Study	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Effect size**	**Quality**	**Importance**
						levels showed a significant (p=0.006) downward trend.		
Razavi 2014	Before and after study	Very serious limitations[(a)]	No serious inconsistency	No serious indirectness	Not applicable	Pre-intervention: 8.09±1.5 Post-intervention: 7.65±1.4	Very low	

(a) Majority of the studies in this review were retrospective cohort studies (some with no control groups) or before and after studies.
(b) Indirect outcome as the study reports number of transfusions due to overriding of BPA (best practice alert)

8.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow diagram in Appendix F.

8.4 Evidence statements

Clinical

Fifteen studies assessed the efficacy of electronic decision support. The evidence showed that the proportion of inappropriate transfusions, proportion of patients transfused, number of units transfused, hospital length of stay and pre-transfusion haemoglobin levels appeared to be lower in patients with the use of electronic decision support

Evidence from five studies for mortality was unclear; two studies showed that mortality appeared to be higher with use of electronic decision support; two studies showed that mortality appeared to be lower with the use electronic decision support, and evidence from one study showed that there was no difference in mortality before and after the use of electronic decision support. The evidence was of very low quality.
No evidence was identified for outcomes such as quality of life, platelet count and coagulation results.

Economic

No relevant economic evaluations were identified.

8.5 Recommendations and link to evidence

Recommendation	No recommendation for clinical practice was made. Please see the research recommendations section.
Relative values of different outcomes	The GDG considered the proportion of inappropriate transfusions, mortality, the number of patients transfused and the number of units transfused as the critical outcomes for decision making. Other important outcomes included quality of life and pre-transfusion haemoglobin levels, platelet count, coagulation results and length of stay in hospital.
Trade-off between clinical benefits and harms	The clinical evidence suggested that using electronic decision support systems for blood ordering may reduce the number of patients transfused, the number of units transfused, the proportion of inappropriate transfusions and the length of stay in hospital. Some studies found an increase and some a decrease in mortality with the use of these systems but the evidence was of very low quality. No evidence was identified for the outcomes of quality of life and pre-transfusion haemoglobin levels, platelet count or coagulation results. The GDG discussed and noted that the evidence was inconclusive, as well as being of very low quality, and did not feel that it was therefore possible to make a recommendation for clinical practice at this time. The GDG made a recommendation for further research.

Economic considerations	No relevant economic evaluations or unit costs were identified for electronic decision support blood order systems. The GDG agreed that the cost of such a system will vary depending on whether or not other electronic systems are already in place. For example, the GDG did not anticipate the cost would be high if the system was an add-on to an electronic patient record interfaced with laboratory information systems. The GDG suggested that any increase in the time taken in blood ordering would be offset by a reduction in time in the laboratory. The GDG noted that the potential benefits seen in the clinical evidence such as reduced units transfused could result in cost savings; however the evidence was low quality. In addition, the GDG highlighted that this system could be used for auditing purposes, thus allowing for the identification and management of poor transfusion practice. This, in turn, could also reduce unnecessary transfusion and save money. As no economic evidence was available and the clinical evidence was inconclusive, the GDG concluded that it is not possible to make a judgement as to whether or not such systems are likely to be cost-effective.
Quality of evidence	The quality of evidence for all outcomes was very low. The majority of the evidence was from non-randomised before-and-after studies.
Other considerations	The GDG agreed that electronic decision support systems for blood ordering were likely to improve audit trails and documentation of the transfusion process leading to improvement in traceability and transparency. The GDG noted that electronic decision support systems may be most effective in areas where transfusion is badly managed or does not follow guidelines. The GDG noted that these systems are not currently widely used in the NHS. The GDG also discussed practical aspects of implementation of these systems. It was noted that these systems should ideally be a part of the wider IT infrastructure of hospitals. The GDG also discussed mechanical issues that may arise with the use of these systems (for example, IT network failure), which could lead to delays in ordering blood. Back-up systems are therefore necessary. The GDG was not certain of the clinical benefits or disadvantages of these systems and the clinical evidence was inconclusive, so the GDG was unable to make a recommendation in this topic area. As a result, the GDG agreed that further research on this topic area would help to guide decision making on implementation of these systems in the NHS. The GDG drafted a research recommendation on this topic. (See the Research recommendation in section **Error! Reference source not found.**)

8.5.1 Research Recommendations

2. Electronic Decision Support: What is the clinical and cost effectiveness of an electronic decision support system compared with current practice in reducing inappropriate blood transfusions, overall rates of blood transfusion and mortality?

- **Why this is important: The clinical evidence evaluating electronic decision support systems is of low quality. There is also no evidence on their cost effectiveness within the NHS, and this is particularly important because of the potentially high setup and running costs of these systems. An evaluation of the clinical and cost effectiveness of electronic decision support systems for blood transfusion is needed. Important outcomes are rates of inappropriate**

transfusion, overall rates of transfusion, and patient safety outcomes including mortality and transfusion errors. Secondary outcomes should include length of hospital stay and quality of life; and pre-transfusion haemoglobin levels, platelet count and coagulation results.

9 Electronic patient identification

Despite several years of formal training and competency assessment in blood transfusion, the biggest risk of an adverse event still relates to human error occurring in the process. A majority of these errors are made by staff who have been deemed competent in the process. The most serious of these errors are those that result in the transfusion of the wrong blood because of patient misidentification at the point of pre-transfusion sampling or when administering a transfusion. In order to address this, electronic patient identification systems have been developed. These systems involve prompting staff to carry out key steps in the process and electronically identifying the patient via the scanning of the patient's wristbands and blood components to ensure the transfusion is given to the intended recipient.

The use of these systems also ensures that the correct steps are followed in the correct order and reduces the possibility of human error occurring.

9.1 Review question: What are the clinical- and cost-effectiveness of electronic patient identification systems such as patient identification band, bar code or radiofrequency identification (RFID) to ensure patient safety during blood transfusions?

For full details see review protocol in Appendix C.

Table 66: PICO characteristics of review question

Population	• Adults and young people (Aged 16 years and above) • Children (under 16 years of age)
Intervention	• Electronic patient identification systems (including bar codes and Radio frequency Identification tags) • Non-electronic patient identification systems (standard practice of checking wrist bands) • Non-electronic patient identification systems (standard practice of checking wrist bands +use of checklists by one nurse) • Non-electronic patient identification systems (standard practice of checking wrist bands +use of checklists by 2 nurses) • Non-electronic patient identification systems (use of checklists by 2 nurses) • Non-electronic patient identification systems use of checklists by one nurse) • No patient identification system
Comparison	• All interventions will be compared to one another
Outcomes	• Quality of life • Mortality (all causes) at 30 days • Transfusion-related mortality at 30 days • Incorrect blood component transfused • Incorrect labelling (Incorrect blood in tube and Rejected blood samples) • Morbidity (ICU admission, renal failure, DIC)
Study designs	• RCTs • Systematic reviews • Non randomised study • Quasi-RCT • Before and after study

9.2 Clinical evidence

We searched for randomised trials, systematic reviews, before and after studies and cohort studies evaluating the effectiveness of electronic patient identification systems in reducing errors in transfusion.

Ten studies were included in the review.[15,45,194,195,203,221,222,230,300] Evidence from these is summarised in the adapted clinical GRADE evidence profile below. See also the study selection flow chart in Appendix E, study evidence tables in Appendix H and exclusion list in Appendix P.

- The majority of the studies were before and after studies or retrospective reviews of implementation of electronic patient identification programmes in hospitals.
- There was variation as to how the outcomes were reported across the studies and not all outcomes in the review protocol were reported. Some studies did not report any of the outcomes as outlined in the protocol but reported other outcomes (surrogate outcomes). Quality of life was not reported in any of the studies.
- Since the studies are in different population groups and also have different study designs, the results have not been pooled into a meta-analysis. Individual effect sizes across studies have been presented. A customised GRADE clinical evidence profile is presented which evaluates the quality of the evidence for the different outcomes.

9.2.1 Summary of included studies

Table 67: Summary of studies included in the review

Study	Population, setting, study design	Intervention/comparison	Outcomes
Ohsaka 2008[222]	Inpatients, Haematology outpatients, surgical patients Hospital, Japan Before and after study	Bar code patient blood unit ID system and an automated device for pre-transfusion testing	• No outcomes directly meeting protocol criteria were reported • Surrogate outcomes reported (see evidence table)
Askeland 2008[15]	All transfusion at a teaching hospital, Iowa, USA, Before and after study	Bar coded wristbands supported by transfusion tracking system composed of scanners, notebook computers, wireless cards, label printers, and carts.	• Sample rejection rate • Wrong blood product (surrogate for wrong blood in tube) • Prevented identification error • Computerised incident reports
Chan 2004[45]	Retrospective review of a program implementation Regional hospital, Hong Kong	Electronic UPI (unique patient identification) barcode system implemented for 3 years	• Wrong labelling of blood products/ forms (surrogate for samples rejected by laboratory for mislabelling) • Wrong blood transfused • Compliance • Time taken for procedure
Miyata 2004[195]	All transfusion within study period. Division of Transfusion Medicine, National	Network computer-assisted transfusion-management system which allows accurate	• Blood-component-recipient identification • Cross-match to transfusion ratio for operations

Study	Population, setting, study design	Intervention/comparison	Outcomes
	Cardiovascular Centre, Japan	blood component recipient identification at the bedside.	• Out-date rate of RBCs
Uriz 2011[300]	All transfusion performed in hospital within study period Tertiary hospital, Barcelona, Spain	Electronic identification System (EIS- Gricode) comprising of bracelets, barcode labels, portable reader terminals and data management software. This was compared with manual checking of patient identification details	• Wrong ABO-type transfusion events (surrogate for incorrect blood component transfused) • Compliance • Traceability
Pagliaro 2009[230]	Review of a program implementing the electronic patient identification system in a tertiary hospital (36 wards) over 5 years. Italy	I-TRAC Plus system which consists of an identification bracelet (barcoded wrist band) and a handheld portable computer to identify patients and blood bags by a portable scanner.	• Cases of patient misidentification avoided
Murphy2012[203] 2 audits contribute to development of this study[76,298]	Retrospective review of transfusion records before implementation of the programme followed by a review of all transfusion records after implementation of the programme. Before and after study Oxford University Hospitals Trust, UK	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)	• Wrong blood in tube • Blood sample rejection • Wrong blood transfusions • Mismatches • Blood wastage
Nuttall 2013[221]	Retrospective study of transfusion errors before and after implementation of an electronic patient identification system. Mayo Clinic, Rochester, USA	Barcode based blood identification system.	• Cases of patient misidentification before and after implementation of the program • Near miss transfusion episodes
Miller 2013[194]	60 transfusion episodes were audited. Haematology/Oncology day clinic of a tertiary hospital, Australia Audit	2D barcode technology with hand held PDAs (personal digital assistants) compared with standard care	• Checking of practice against audit standards

Table 68: Modified GRADE profile: Electronic patient identification systems versus non-electronic systems/no patient identification

Quality assessment						Effect size	Quality	Importance
Study	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**			
Wrong blood in tube								
Askeland 2008	Before and after study	Very serious limitations[(a)]	No serious inconsistency	serious indirectness [(b)]	Not applicable	After implementation: 0 Before implementation: NR	Very low	
Pagliaro 2009	Retrospective review of program					12 cases of patient misidentification avoided with the electronic system over 5 years	Very low	
Murphy 2012	Before and after study					Before implementation:1/12,322 After implementation: 1/26,690	Very low	
Blood samples rejected by the laboratory (due to incorrect or inadequate labelling)								
Askeland 2008	Cohort study	Very serious limitations[(a)]	No serious inconsistency	serious indirectness [(b)]	Not applicable	Before: 1.82% After (implementation): 0.17%	Very low	
Chan 2004	Cohort study					Before: 13 After: 0	Very low	
Murphy 2012	Before and after study					Before implementation:1004/31, 406 After implementation: 541/44,373	Very low	
Incorrect blood component transfused								
Chan 2004	Cohort study	Very serious limitations(a)	No serious inconsistency	serious indirectness	Not applicable	Before: 0 After:0	Very low	

Quality assessment						Effect size	Quality	Importance
Study	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**			
Uriz 2011	Cohort study			[b]		Manual system: 2 per year After implementing the EIS= 0 (from 2005 to 2008)	Very low	
Nuttall 2013	Cohort study (before and after)					Before implementation: 1 in 64, 806 units or 1.5 per 100, 000 transfusions After implementation: 1 in 304, 136 U or 0.3 per 100, 000 transfusions		
Murphy 2012	Before and after study					Before implementation:1/27,523 After implementation: 1/67,935		
All-cause mortality at 30 days- not reported								
Admission to ICU post transfusion- not reported								
Morbidity (renal failure, DIC)- not reported								
Quality of life- not reported								

(a) Most of the studies were before and after studies with no control groups
(b) Outcomes were surrogate for those outlined in the protocol

9.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow diagram in Appendix F.

Unit costs

A study by Murphy et al 2012[203] reports on transfusion practice prior to and following implementation of an electronic blood transfusion management system (including electronic patient identification) in a hospital trust in England. This study was excluded from the review as it only reports the costs of the electronic system, and does not provide any form of incremental analysis, that is the cost of the cost of transfusion management prior to the implementations of the electronic system. In the absence of economic evidence, the costs reported in Murphy et al 2012 are highlighted here to aid consideration of cost-effectiveness.

The annual cost of the system were estimated to be £390,308 a year (reported as 2011 US dollars, converted using 2011 purchasing power parities[226]) based on a managed service contract with a commercial supplier. This cost includes:

- leasing of the hardware (beside handheld computers and printers)
- electronically controlled blood refrigerators
- software licenses
- training costs.

The study reported that the cost was equivalent to £11 per blood component based on a usage of 34,500 blood components a year.

The study reported estimates of efficiency gains as a result of the implementation of this electronic blood transfusion management system including:

- savings in nursing time (1 vs. 2 nurses and 50% reduction in time spent on pre-transfusion bedside checking)(saving £566,614 a year)
- reduced laboratory staff time due to fewer rejected samples (saving £22,400 a year)
- reduced cost due to reduced RBC unit wastage (saving £22,400 a year)
- reduced blood costs as a result of reduced usage of RBC units (only partially attributable to the electronic system) (saving £444,612 a year).

Of note, the source of unit costs used for these calculations is not reported in the study.

9.4 Evidence statements

Clinical

Ten studies assessed the efficacy of electronic patient identification systems. The evidence suggested that electronic patient identification systems may be beneficial with respect to improving the following outcomes: wrong blood in tube, blood samples rejected by the laboratory (due to incorrect or inadequate labelling), and number of incorrect blood component transfusions**.** The evidence was of very low quality.

No evidence was identified for outcomes such as all-cause mortality, morbidity, admission to ICU post-transfusion and quality of life.

Economic

No relevant economic evaluations were identified.

9.5 Recommendations and link to evidence

Recommendations	12. Hospitals should consider using electronic patient identification systems to improve the safety and efficiency of the blood transfusion process.
Relative values of different outcomes	The GDG considered all-cause mortality, transfusion-related mortality, incorrect blood component transfused, incorrect blood in tube or incorrect labelling leading to rejected blood samples as critical outcomes for decision making. Other important outcomes included morbidity, and overall quality of life. The GDG also took into consideration outcomes such as the prevention of patient identification errors and near-miss events when making recommendations. It was agreed that, in the absence of some studies reporting the outcomes outlined in the protocol, these outcomes were close surrogates and provided valuable information.
Trade-off between clinical benefits and harms	The evidence suggested that using electronic patient identification systems may reduce the number of incidents of wrong blood in tube, blood samples rejected and incorrect blood component transfused. Reducing these outcomes would improve patient safety as it should translate into a reduction in the number of acute transfusion reactions, morbidity and mortality. A reduction in the number of rejected samples should also reduce delays in the provision of blood components and patients needing to have further blood samples taken. No clinical evidence was identified with respect to all-cause mortality, morbidity, admission to ICU post-transfusion or quality of life. There should be minimal discomfort or harms to patients from these systems.
Economic considerations	No economic evaluations were identified for electronic patient identification systems that met the inclusion criteria. In the absence of economic evidence, the GDG considered the costs reported in a UK study by Murphy et al 2012[203]. This study estimated that the annual cost of an electronic blood transfusion management system was £390,308 based on a managed service contract with a commercial supplier. This cost included the leasing of hardware (bedside handheld computers and printers), electronically controlled blood refrigerators, software licenses and training costs. While not a full incremental analysis, the study reported estimates of efficiency gains as a result of the implementation of this system, including savings in nursing and laboratory staff time, reduced RBC unit wastage and reduced blood costs as a result of reduced usage of RBC units. The GDG considered the areas where savings could be made and felt the findings in this study were reasonable on the basis of the group's experience and the clinical evidence. The GDG referred to a Quality Innovation Prevention and Productivity (QIPP) document which outlines a 'Proven Quality and Productivity' case study by the same research group which reported net savings.[228] However, the case study did not provide details of the calculations behind these savings and so was not included in the literature review for this guideline. The GDG agreed that the costs would vary depending on the existing IT infrastructure and chosen system within trusts and the individual hospital's transfusion rates and processes. The GDG suggested that an added economic benefit from such systems is that

	traceability obligations would be demonstrated to regulators as well as met more effectively than under current, manual systems. Finally, the GDG acknowledged that utilising a similar electronic process in other hospital areas, for example, prescription services, could achieve further cost savings. The GDG concluded that it was likely that the cost of the electronic patient system would be largely offset by savings in staff time and blood wastage, particularly if utilised by other hospital areas other than transfusion. Given this and the benefits in improving patient safety, it was judged likely to be cost-effective.
Quality of evidence	The quality of evidence for all outcomes was very low. The majority of the evidence was from non-randomised before and after studies. The GDG discussed the practical issues associated with conducting studies with better study designs on the implementation of electronic patient identification systems and agreed that such studies are difficult to conduct. The recommendation is based on very low quality evidence and the consensus expert opinion of the GDG members.
Other considerations	The GDG considered that although there was very weak evidence of benefit, practice shows that use of electronic patient identification systems improves patient safety. This was paramount in the transfusion process and the GDG was unanimous in their decision to recommend the use of these systems. The GDG agreed that electronic patient identification systems improved the documentation of the transfusion process leading to improvement in traceability of blood and transparency of each step in the transfusion process. Clear audit trails also help to identify the number of staff requiring training and the specific development needs of staff involved in the transfusion process at different levels. Moreover, mandatory competency training could be linked to the transfusion process. All staff should be aware of the steps of the patient identification process and the rationale for it, and know how to revert to a manual system of cross checking and verification if the need arises. The GDG also noted that there is always a chance of human error, even in staff who have been trained and assessed as being competent in the transfusion process. The electronic systems help in minimising the chance of human error. The GDG discussed practical aspects of implementation of electronic patient identification systems for transfusion. Ideally, these should be part of and compatible with the wider information technology systems in the hospital. One study conducted in the UK, Murphy et al., provides details of how these may be implemented (refer to QIPP document for further relevant details (http://arms.evidence.nhs.uk/resources/qipp/29453/attachment).[228] These systems could be used for other hospital services, such as prescription services, which could translate into benefits beyond the scope of transfusion. Another advantage of electronic patient identification systems was the ability to provide sequential prompts, which also promotes best practice. It was agreed that these advantages of electronic patient identification systems resulted in more consistent practice than with standard manual procedures and improved the patient's confidence in the robustness of the process for receiving the correct blood. The GDG discussed current practice in the NHS and the prevalence of electronic patient identification systems. A national audit published in 2011 reported that electronic patient identification systems used at the bedside were available in 12% of transfusions.[214]

10 Red blood cell transfusion: thresholds and targets

Red Blood Cells (RBCs) carry oxygen to cells. Anaemia reduces the oxygen carrying capacity of blood, but compensatory physiological responses (increased cardiac output; increased oxygen extraction by organs) mean healthy humans can tolerate anaemia to remarkably low haemoglobin concentrations when the circulating blood volume is maintained, for example with crystalloid fluid infusion. RBC transfusions are used to replace blood lost during haemorrhage or to increase a low haemoglobin concentration occurring for other reasons (for example, bone marrow failure or haemolysis).

Transfusion of stored RBCs carries risks and the timing of RBC transfusion, especially in relation to the 'trigger' haemoglobin concentration and target haemoglobin range, is an important clinical decision. The aim is to transfuse RBCs when the clinical benefits outweigh the risks. In addition, conserving RBC supplies for those patients in whom they are most clinically and cost-effective is vital, as RBCs are an increasingly scarce and costly treatment.

This chapter reviews the available evidence for the clinical and cost-effectiveness of RBC transfusions in different clinical situations. In addition, the evidence for particular sub-groups of patients in whom the tolerance of anaemia, and therefore the risk to benefit balance for RBC transfusion, may differ, is reviewed. These include patients in whom the disease being treated could mean physiological compensation for anaemia may be compromised, for example, by heart disease or critical illness.

10.1 Review question: What is the clinical- and cost-effectiveness of red blood cell transfusion at different haemoglobin concentrations?

For full details see review protocol in Appendix C.

Table 69: PICO characteristics of review question

Population	• Adults • Children • Young people • Exclusions: Patients receiving exchange transfusions
Intervention	• Low (restrictive) haemoglobin thresholds for transfusion (as defined by the trial) • High (liberal) haemoglobin thresholds for transfusion (as defined by the trial)
Comparison	• Low (restrictive) haemoglobin thresholds versus high (liberal) haemoglobin thresholds
Outcomes	• All-cause mortality at 30 days • Quality of life • New cardiac event (myocardial infarction, cardiac failure) • Length of stay in hospital • Infections (for example, pneumonia) • Number of patients needing transfusions • Number of units transfused/Volume in ml (in children) • Acute and delayed serious adverse events as reported in study (TACO and TRALI, iron overload).
Study designs	• RCTs • Systematic reviews

10.2 Review question: What is the clinical- and cost-effectiveness of different target levels of post-transfusion haemoglobin concentrations for red blood cell transfusion?

For full details see review protocol in Appendix C.

Table 70: PICO characteristics of review question

Population	• Adults • Children • Young people • Exclusions: Patients receiving exchange transfusions
Intervention	• High haemoglobin target levels for transfusion (as defined by the trial) • Low haemoglobin target levels for transfusion (as defined by the trial)
Comparison	• High haemoglobin target levels versus low haemoglobin target levels
Outcomes	• All-cause mortality at 30 days • Quality of life • New cardiac event (Myocardial infarction, Cardiac failure) • Length of stay in hospital • Infections (for example, pneumonia) • Number of patients needing transfusions • Number of units transfused/Volume in ml (in children) • Acute and delayed serious adverse events as reported in study (TACO and TRALI, iron overload).
Study designs	• RCTs • Systematic reviews

Table 71: PICO characteristics of review questions

10.3 Methodology of clinical evidence review (threshold haemoglobin concentrations and target haemoglobin levels for blood transfusion)

The GDG was interested in establishing the most clinical and cost-effective haemoglobin thresholds at which blood transfusion should be administered and the target haemoglobin levels to which blood transfusion should be given. To this effect, two separate review questions were drafted as follows:

- What is the clinical and cost-effectiveness of red blood cell transfusion at different haemoglobin concentrations?
- What is the clinical and cost-effectiveness of different target levels of post-transfusion haemoglobin concentration for red blood cell transfusion?

The comparisons in each review included restrictive and liberal haemoglobin concentrations compared with one another. For full details see review protocols in Appendix C (C.1 and C.2).

On reviewing the evidence, it was acknowledged that the two reviews were very closely interlinked.

- The studies evaluated restrictive and liberal strategies such that patients transfused at restrictive haemoglobin thresholds received blood until restrictive haemoglobin target levels were attained and vice versa. As a result, the data for the individual reviews are confounded and it is not possible to comment on threshold or target haemoglobin levels independently.
- The majority of the studies aimed to establish the effectiveness of different haemoglobin thresholds. In addition, some studies reported the target haemoglobin concentrations to which patients were transfused in each group. No evidence was identified independently on the effectiveness of different target haemoglobin levels irrespective of the thresholds of blood transfusion.

In light of the above, we have presented one combined evidence review with separate results for the sections on thresholds and target levels of haemoglobin concentrations. The evidence on the effectiveness of different target haemoglobin levels will be viewed in the context of the corresponding haemoglobin threshold levels at which the patients received blood transfusion.

10.4 Clinical evidence

RBC thresholds

We searched for systematic reviews and randomised controlled trials for addressing effectiveness of red blood transfusion at different haemoglobin concentrations.

Thirty-three studies were included in the review;[24,28,32,39,42,60,99,105,107,108,119,121,123,124,133,146,170,181,188,238,276,315,335] these are summarised in Table 72 below. Evidence from these studies is summarised in the GRADE clinical evidence profile below. See also the study selection flow chart in Appendix E, forest plots in Appendix K, GRADE tables in Appendix J, study evidence tables in Appendix H and excluded studies list in Appendix P.

RBC targets

We searched for systematic reviews and randomised controlled trials for addressing effectiveness of different target levels of post-transfusion haemoglobin concentrations for red blood cell transfusion.

- Seven studies which compared haemoglobin threshold levels also reported the target levels of haemoglobin concentrations;[62,121,123,124,170,188,307] these are highlighted and summarised in Table 72below. As outlined earlier, the target levels of haemoglobin concentration are classified into restrictive and liberal and correspond with the restrictive and liberal thresholds of haemoglobin concentration for administration of blood transfusion.
- One study compared target levels of haemoglobin concentrations in patients with advanced gastric cancer who were receiving chemotherapy.[233] No haemoglobin thresholds for transfusion have been reported in this study. However, the only outcome that could be analysed from this study was incidence of acute pulmonary oedema (new cardiac event) and this has been included in the meta-analysis. Other outcomes reported in this study include number of units transfused and quality of life (Karnofsky Performance Scores); these are not reported in an analysable format (mean and standard deviations not reported).
- Only one study was conducted in children.[170]

Evidence from these studies is summarised in the GRADE summary evidence profile (see sections 10.4.1 and 10.4.2). See also the study selection flow chart in Appendix E, GRADE evidence profiles in Appendix J, study evidence tables in Appendix H, forest plots in Appendix K, and excluded studies list in Appendix P.

1 **Table 72: Summary of studies included in the review**

Study	Population (n)	Intervention/comparison	Outcomes	Comments
Blair 1986[24]	Patients with severe upper gastrointestinal haemorrhage n=50 • Liberal group: n=24 • Restrictive group: n=26	• Liberal group received at least 2 units of red blood cells immediately at admission and during their first 24 hours in hospital. • Restrictive group were not transfused red blood cells unless the Hb was less than 8.0 g/dl or shock persisted after initial resuscitation with Haemaccel.	• Blood usage (units) • Mortality	
Bracey 1999[28]	Patients undergoing elective primary coronary artery bypass graft surgery n=428 • Liberal group: n=212 • Restrictive group: n=216	• Liberal group received transfusions at Hb level <9.0 g/dl • Restrictive group received RBC transfusion at a Hb level <8.0 g/dl	• Mortality • Length of hospital stay • Blood usage (units) • Complications • Infection rates • Cardiac events	
Bush 1997[32]	Patients undergoing elective aortic or infrainguinal arterial reconstruction n=99 • Liberal group: n=49 • Restrictive group: n=50	• Liberal group had their Hb concentrations maintained at or above 10.0 g/dl • Restrictive group were transfused only when their Hb concentration fell below 9.0 g/dl	• 30-day mortality, length of ICU stay, length of hospital stay, blood use (units), cardiac events	
Carson 1998[39]	Patients with hip fracture undergoing surgical repair who had post-operative Hb levels <10.0 g/dl n=84 • Liberal group: n=42 • Restrictive group: n=42	• Liberal group received 1 unit of packed RBC at the time of random assignment and as much blood as necessary to keep the Hb level above 10.0 g/dl • Restrictive group received RBC transfusion for symptoms of anaemia or for a Hb level that dropped below 8.0 g/dl	• Mortality, length of hospital stay, blood usage (units), complications, • Pneumonia, stroke, thromboembolism	
Carson 2011[42]	Patients 50 years or older, who are undergoing surgical repair of a hip fracture, with Hb concentrations below 10.0 g/dl within 3 days after surgery and who have clinical evidence for cardiovascular disease or cardiovascular risk factors	• Liberal group - receive packed RBC when haemoglobin level dropped below 10.0 g/dl • Restrictive ('symptomatic strategy') group - receive transfusion if develop symptoms of anaemia or if Hb falls below 8.0 g/dl	• 30 day mortality • Acute coronary syndrome (ACS), in-hospital myocardial Infarction, unstable angina • Pneumonia • Wound infection • Thromboembolism • Stroke or transient ischaemic attack	

Study	Population (n)	Intervention/comparison	Outcomes	Comments
	n=2016			
Carson 2012[41] (Cochrane review)	19 trials involving a total of 6264 patient	The intervention considered was the use of transfusion thresholds ('triggers') as a means of guiding allogeneic and/or autologous red blood cell transfusion.	Primary outcomes • The proportion of patients transfused • Secondary outcomes • The amount of allogeneic and autologous blood transfused • 30 day mortality • Morbidity (non-fatal myocardial infarction, cardiac events) • Pulmonary oedema • Cerebral vascular accident, • Thromboembolism • Infection • Length of hospital stay	
Carson 2013[40]	Patients with acute coronary syndrome or stable angina undergoing catheterisation and a Hb <10 g/dl n=110	Restrictive transfusion group- Patients received blood for symptoms of anaemia or for a Hb of <8 g/dl vs. Liberal transfusion group- Patients received one or more units of blood to raise the Hb level of Hb >10 g/dl	• No. of units transfused • Mortality • MI • Stroke • Congestive heart failure • Pneumonia • Blood stream infection	
Cholette 2011[54]	Infants and children with variations of single ventricle physiology presenting for cavopulmonary connection n=60	Restrictive strategy of Hb <9.0 g/dl Liberal strategy Hb of >13.0 g/dl	• Length of hospital stay • Mortality • No. of patients transfused • No. of units transfused	Children (includes infants)
Colomo 2008[60]	Patients with acute gastrointestinal bleeding and cirrhosis. n=214 • Liberal group: n=105 • Restrictive group: n=109	• Liberal group received packed RBC when Hb level dropped below 9.0 g/dl • Restrictive group received packed RBC when Hb level dropped below 7.0 g/dl	• Mortality • Therapeutic failures, transfusion • Hb concentration • Side effects	
Cooper 2011[62]	Patients with acute myocardial infarction	• Restrictive- transfuse when haematocrit <24% to	• Death at 30 days • Length of hospital	Reports target

Study	Population (n)	Intervention/comparison	Outcomes	Comments
	with anaemia (haematocrit <30%) n=45 Pilot study	maintain 24% to 27% • Liberal –transfuse when haematocrit to maintain 30%-33% <30% • Target range levels of haematocrit compared are 24%-27% (restrictive) vs. 30%-35% (liberal)	stay • No. of units transfused	haemoglobin levels
Degastbakker 2013[81] (PAEDIATRIC)	n=107 Patients with non-cyanotic heart defects between 6 weeks and 6 years of age	Restrictive transfusion group-RBC transfusion if Hb was 8.0 g/dl Liberal transfusion-Hb dropped below 10.8 g/dl	• Length of hospital stay • Total RBC (ml/patient)	
Fan 2014[99]	Patients older than 65 years undergoing total hip replacement surgery n=186	Restrictive (<8 g/dl) vs. Liberal (<10 g/dl) thresholds	• No. of patients transfused • Length of hospital stay • New cardiac events (MI) • Infection (pneumonia)	
Fisher 1956[105]	22 trauma patients were randomly allocated to 1 of 2 groups: • Liberal group: n=10 • Restrictive group: n=12 NB: no demographic data were reported	• Liberal group: the aim was to achieve 100% or more of the red cell volume at the end of resuscitation • Restrictive group: an attempt was made to leave the red cell volume at the end of resuscitation at 70% to 80% of normal	• Blood usage (units), blood loss • Wound healing • Elevated temperature • Number of patients transfused	
Fortune 1987[107]	Patients with acute injury and haemorrhage. n=25 • Liberal group: n=13 • Restrictive group: n=12	• Liberal group had their Hct brought up to 40% slowly over a period of several hours by the infusion of packed red cells • Restrictive group had their Hct maintained close to 30% by the appropriate administration of packed red cells	• RBC consumption (units)	
Foss 2009[108]	Patients with hip fracture n=120 • Liberal group: n=60 • Restrictive group: n=60	• Liberal group received packed RBC when Hb level dropped below 10.0 g/dl • Restrictive group received packed RBC when Hb level dropped below 8.0 g/dl	• Mortality • Length of stay • Cardiac complications • Infectious complications	
Grover 2005[119]	Patients undergoing elective lower limb joint replacement surgery. n=260	• Liberal group received packed RBC when Hb level dropped below 10.0 g/dl • Hb concentration maintained between 10.0 to	• Number of units • Transfused • Length of hospital stay	

Study	Population (n)	Intervention/comparison	Outcomes	Comments
	• Liberal group: n=109 • Restrictive group: n=109	12.0 g/dl • Restrictive group received packed RBC when Hb level dropped below 8.0 g/dl • Hb concentration maintained between 8.0 to 9.5 g/dl	• Adverse events • New infections requiring antibiotic therapy	
Hajjar 2010[121]	Adult patients who underwent cardiac surgery with cardiopulmonary bypass n=502 • Liberal group: n=257 • Restrictive group: n=255	• Liberal group were transfused RBC if the haematocrit was less than 30% at any time from the start of surgery until discharge from the ICU • Restrictive group were transfused if haematocrit values were less than 24% • Above values are both the thresholds as well as targets for blood transfusion	• Primary outcome composite endpoint that included 30-day all-cause mortality and severe morbidity (cardiogenic shock, ARDS or acute renal injury requiring dialysis or haemofiltration). • Cardiac neurologic and infectious complications • Inflammatory complications • ICU and hospital lengths of stay • RBC transfusions	Reports target haemoglobin levels Non-inferiority trial
Hebert 1995[124]	Critically ill patients admitted with Hb values < 9.0 g/dl n=69 • Liberal group: n=36 • Restrictive group: n=33 • Pilot study	• Liberal group were transfused RBC if the Hb level fell to between 10.0 to 10.5 g/dl • Hb level maintained between 10.0 to 12.0 g/dl • Restrictive group were transfused RBC if the Hb level fell to between 7.0 to 7.5 g/dl • Hb level was maintained between 7.0 to 9.0 g/dl	• Mortality • Length of hospital stay and length of ICU stay • Blood usage (units) • Complications	Reports target haemoglobin levels Undertaken to determine feasibility of a larger multicentre trial
Hebert 1999[123]	Critically ill patients who had Hb concentrations < 9.0 g/dl TRICC trial (Transfusion Requirements in Critical Care) n=838 • Liberal group: n=420 • Restrictive group: n=418	• Liberal group were transfused RBC when the Hb concentration fell below 10.0 g/dl • The Hb concentration was maintained between 10.0 to 12.0 g/dl • Restrictive group were transfused RBC if the Hb concentration dropped below 7.0 g/dl • The Hb concentration was maintained between 7.0 to 9.0 g/dl	• Mortality • Length of hospital stay • Length of ICU stay, blood usage (units) • Complications, infection rates, • Cardiac events • Pulmonary oedema • Pneumonia	Reports target haemoglobin levels. Trial also reports actual target levels achieved.

Study	Population (n)	Intervention/comparison	Outcomes	Comments
		• Average targets achieved in each group were: 8.5 g/dl and 10.7 g/dl		
Holst 2014[133]	Patients with septic shock in ICU n=998	Restrictive (<7 g/dl) vs. liberal (<9 g/dl) thresholds	• No. of patients transfused • Mortality at 30 days (primary outcome at 90 days) • New cardiac events (MI) • Serious adverse reaction to blood (allergic reaction, haemolysis, TRALI, TACO)	
Johnson 1992[146]	39 autologous blood donors undergoing elective myocardial revascularisation were randomised to 1 of 2 groups: • Liberal group: n=18; M/F=16/2; mean (SD) age=60.5 (6.9) years • Restrictive group: n=20; M=20; mean (SD) age=58.2 (7.5) years	• Liberal group received blood to achieve a Hct value of 32% • Restrictive (conservative) group received transfusions for a Hct value less than 25%	• Cardiac events • Complications, • Blood use • Number of patients receiving transfusions • Length of ICU stay • Length of hospital stay	
Karam 2011[150]	Sub-group analysis of TRIPICU study (Lacroix 2007) Stabilised critically ill children. Analysis of sub-group of patients with sepsis and transfusion requirements in paediatric intensive care unit.	• Restrictive strategy Hb <7.0 g/dl • Liberal strategy Hb 9.5 g/dl	• Death at 28 days • Length of PICU stay • Number of patients needing transfusion	
Lacroix 2007[170]	Stable, critically ill children with Hb concentrations below 9.5 g/dl n=637 • Liberal group: n=317; mean (SD) age=39.6 (51.9) months • Restrictive group: n=320; mean (SD)	• Liberal group were transfused RBC when the Hb concentration fell below 9.5 g/dl, with a target range of 11.0 to 12.0 g/dl • Restrictive group were transfused RBC if the Hb concentration dropped below 7.0 g/dl, with a target range of 8.5 to 9.5 g/dl	• 28-day mortality • Sepsis • Transfusion reactions • Infections • Length of stay	Reports target haemoglobin levels. Also includes infants and neonates- indirect non-inferiority trial.

Study	Population (n)	Intervention/comparison	Outcomes	Comments
	age=35.8 (46.2) months			
Lotke 1999[181]	152 patients undergoing primary total knee arthroplasty (TKA) were randomly assigned to 1 of 2 groups: • Liberal group: n=65; M/F=19/46; mean age=69.7 years • Restrictive group: n=62; M/F=20/42; mean age=68.7 years	• Liberal group were transfused autologous blood immediately after TKA, beginning in the recovery room post-operatively • Restrictive group were transfused autologous blood when the Hb level had fallen to < 9.0 g/dl	• Complications • Cardiac events • Blood usage (units) • Number of patients transfused	
Markatou 2012[188]	Patients undergoing major abdominal surgery n=58 Open labelled trial	Restrictive (<7.7 g/dl) vs. Liberal (<9.9 g/dl) Thresholds Targets- For restrictive group- Between 7.7 and 9.9 g/dl For liberal group- 10 g/dl or above	• No. of patients transfused • Units of blood transfused(median, range) • Mortality (within 30 days) • Length of hospital stay • Pulmonary complications	Reports target haemoglobin levels.
Nielsen 2012A[216]	n=48 Patients undergoing major spinal surgery	Restrictive 7.3 g/dl Liberal 8.9 g/dl	• Adverse events	
Park 2008[233]	Chemotherapy for gastric cancer (cancer related anaemia)	RBC transfusion to raise and maintain Hb concentration to differing target levels (10 g/dl vs. 12 g/dl)	• Acute pulmonary oedema	Reports target haemoglobin levels
Pinheiro de Almeida 2015[238]	Adult patients with cancer having major abdominal surgery who required post-operative intensive care	Restrictive transfusion strategy versus. Liberal transfusion strategy. The patients in the restrictive and liberal erythrocyte transfusion strategy groups received one erythrocyte unit each time their haemoglobin concentration decreased to less than 7 or 9 g/dl respectively, during their ICU stay. Physicians were instructed to administer transfusions 1 unit at a time and to measure haemoglobin concentration after each transfusion unit. In both	• Mortality at 30 days • Number of patients transfused • Myocardial Infarction, • Congestive Heart failure.	

Study	Population (n)	Intervention/comparison	Outcomes	Comments
		groups, no further units were given if the goal haemoglobin concentration was obtained (7 g/dl for the restrictive strategy and 9g/dl for the liberal strategy).		
Shehata 2012[270]	High risk cardiac patients undergoing cardiac surgery n=100	Restrictive transfusion strategy –RBCs if their Hb concentration was 70 g/litre or less intra-operatively during bypass surgery and 75 g/litre or less post-operatively. Liberal transfusion strategy – RBCs if their Hb concentration was 95 g/litre or less during bypass surgery and less than 100 g/litre post-operatively	• Death • Transfusion reaction • Pneumonia • Post-operative MI • Stroke • Pulmonary embolism • Length of hospital stay • No. of patients transfused	
So-Osman 2010[276]	619 patients undergoing elective orthopaedic hip/knee replacement surgery were randomised to 1 of 2 groups: • Liberal (standard care) group: n=304; M/F=118/186; mean (SD) age=70.3 (9.7) years • Restrictive (new transfusion policy) group: n=299; M/F=84/215; mean (SD) • Age=70.7 (10.2) years	• Liberal group received standard care • Restrictive group were treated using a 'new transfusion policy'	• Red blood cell usage • Length of hospital stay • Hb levels • Mobilisation delay • Post-operative complications	
Villanueva 2013A[307]	Patients with severe acute upper gastrointestinal bleeding. n=921	• Restrictive strategy- Hb threshold for transfusion 7 g/dl • Liberal strategy - Hb threshold for transfusion of 7 to 9 g/dl • Target levels compared are 7-9 g/dl (restrictive) vs. 9-11 g/dl (liberal)	• No. of patients transfused • No. of units transfused • Mortality 45 days • Length of hospital stay • Adverse events (any) • Bacterial infection • Pulmonary oedema • Myocardial infarction	Reports target haemoglobin levels

Study	Population (n)	Intervention/comparison	Outcomes	Comments
Walsh 2013[309]	n=100 Anaemic older critically ill patients requiring prolonged mechanical ventilation.	Restrictive strategy (Hb transfusion trigger <70 g/litre; target Hb range, 71-91 g/litre) Liberal transfusion trigger <90 g/litre; target Hb range, 91-110 g/litre	• Length of hospital stay • Mortality • Number of patients transfused • Quality of life • Adverse events (acute coronary syndrome, thrombotic events)	
Webert 2008[315]	60 adult patients with acute leukaemia were randomly allocated to 1 of 2 groups: • Liberal group: n=31; M/F=14/17; mean (SD) age=45.3 (16.8) years • Restrictive group: n=29; M/F=1811; mean (SD) age=50.8 (15.3) years	• Liberal group were transfused 2 units of RBC when the Hb concentration fell below 12.0 g/dl • Restrictive group were transfused 2 units of RBC if the Hb concentration dropped below 8.0 g/dl, with a target range of 85 to 95 g/dl	• Transfusions	
Zygun 2009[335]	30 patients with severe traumatic brain injury were randomly allocated to 1 of 3 groups: • Liberal group 1: n=10 • Liberal group 2: n=10 • Restrictive group: n=10 NB: Mean (SD) age=39 (15) years, 70% of trial participants were male	• Liberal group 1 were transfused 2 units of RBC when the Hb concentration fell below 9.0 g/dl • Liberal group 2 were transfused 2 units of RBC when the Hb concentration fell below 10.0 g/dl • Restrictive group were transfused 2 units of RBC if the Hb concentration dropped below 8.0 g/dl	• ICU Mortality	

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10.4.1 Summary of the evidence (Summary GRADE profile)- haemoglobin thresholds for blood transfusion

10.4.1.1 Restrictive strategy compared with liberal strategy for blood transfusion (adults)

Table 73: Blood transfusions (adults)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with blood transfusions (adults) (95% CI)
Number of patients needing transfusion	7963 (23 studies)	VERY LOW[a,b] due to risk of bias, inconsistency	RR 0.65 (0.58 to 0.74)	Moderate	
				920 per 1000	322 fewer per 1000 (from 239 fewer to 386 fewer)
Number of patients needing transfusion (sub-groups) - Peri-operative surgical patients	4525 (11 studies)	VERY LOW[a,c,d] due to risk of bias, inconsistency, imprecision	RR 0.61 (0.50 to 0.76)	Moderate	
				878 per 1000	878 per 1000
Number of patients needing transfusion (sub-groups) - Critical care	2203 (5 studies)	VERY LOW[a,d,e] due to risk of bias, inconsistency, imprecision	RR 0.73 (0.64 to 0.84)	Moderate	
				1000 per 1000	1000 per 1000
Number of patients needing transfusion (sub-groups) - Acute blood loss/trauma	1175 (4 studies)	LOW[a,f] due to risk of bias, inconsistency	RR 0.58 (0.46 to 0.74)	Moderate	
				952 per 1000	952 per 1000
Number of patients needing transfusion (sub-groups) - chemotherapy and stem-cell transplants	60 (1 study)	HIGH	RR 0.96 (0.82 to 1.12)	Moderate	
				936 per 1000	936 per 1000
Number of units of blood transfused in those transfused	2143 (10 studies)	MODERATE[a]			The mean number of units of blood transfused in those transfused in the intervention groups was 1.13 lower (1.67 to 0.59 lower)
Number of units of blood transfused in those transfused (sub-groups) - Peri-operative surgical patients	397 (5 studies)	MODERATE[a] due to risk of bias			The mean number of units of blood transfused in those transfused (sub-groups) - peri-operative surgical patients in the intervention groups was 0.55 lower (0.91 to 0.18 lower)
Number of units of blood transfused in those transfused (sub-groups) - Critical care	700 (1 study)	MODERATE[g] due to risk of bias			The mean number of units of blood transfused in those transfused (sub-groups) - critical care in the intervention groups was

					1.72 lower (2.45 to 0.99 lower)
Number of units of blood transfused in those transfused (sub-groups) - Acute blood loss/trauma	936 (3 studies)	MODERATE[a] due to risk of bias			The mean number of units of blood transfused in those transfused (sub-groups) - acute blood loss/trauma in the intervention groups was 2.19 lower (2.58 to 1.8 lower)
Number of units of blood transfused in those transfused (sub-groups) - Acute coronary syndrome (ACS)	110 (1 study)	MODERATE[h] due to risk of bias			The mean number of units of blood transfused in those transfused (sub-groups) - acute coronary syndrome (ACS) in the intervention groups was 1.09 lower (1.49 to 0.69 lower)

(a) Majority of the evidence is from studies at high risk of bias.
(b) Evidence of high heterogeneity with I^2 value of 93%.
(c) I^2=91%.
(d) Confidence interval crosses one default MID.
(e) I^2=83%.
(f) I^2=76%.
(g) Unclear randomisation. No blinding.
(h) Unclear randomisation and allocation concealment

Table 74: **Length of hospital stay (adults)**

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Length of hospital stay (adults) (95% CI)
Hospital length of stay-	5396 (12 studies)	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision			The mean hospital length of stay- subgroups in the intervention groups was 0.52 lower (1.11 lower to 0.06 higher)
Hospital length of stay- subgroups - Peri-operative surgical patients	3624 (9 studies)	MODERATE[a] due to risk of bias			The mean hospital length of stay- subgroups - peri-operative surgical patients in the intervention groups was .01 higher (0.30 lower to 0.32 higher)
Hospital length of stay- subgroups - Critical care	838 (1 study)	MODERATE[d] due to risk of bias			The mean hospital length of stay- subgroups - critical care in the intervention groups was 0.7 lower (3.33 lower to 1.93 higher)
Hospital length of stay- subgroups – ACS (Acute MI)	45 (1 study)	LOW[e,c] due to risk of bias, imprecision			The mean hospital length of stay- subgroups – ACS (acute mi) in the intervention groups was 4.2 lower

					(6.93 to 1.47 lower)
Hospital length of stay- subgroups - Acute blood loss/trauma	889 (1 study)	MODERATE[f] due to risk of bias			The mean hospital length of stay- subgroups - acute blood loss/trauma in the intervention groups was 1.9 lower (3.34 to 0.46 lower)

(a) Majority of the evidence is from studies at high risk of bias.
(b) I^2=55%.
(c) Confidence interval crosses one MID.
(d) Unclear randomisation. No blinding.
(e) Unclear randomisation and allocation concealment.
(f) Unclear blinding.

Table 75: All cause-Mortality at 30 days (adults)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Mortality (adults) (95% CI)
30-day mortality	7604 (20 studies)	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 0.92 (0.74 to 1.14)	Moderate	
				51 per 1000	4 fewer per 1000 (from 13 fewer to 7 more)
All-cause mortality at 30 days (sub-groups) - Perioperative surgical patients	4308 (11 studies)	VERY LOW[a,d] due to risk of bias, imprecision	RR 0.90 (0.66 to 1.23)	Moderate	
				24 per 1000	24 per 1000
All-cause mortality at 30 days (sub-groups) - Critical care	2203 (5 studies)	LOW[a,e] due to risk of bias, imprecision	RR 0.98 (0.73 to 1.31)	Moderate	
				250 per 1000	250 per 1000
All-cause mortality at 30 days (sub-groups) –ACS (Acute MI)	154 (2 studies)	VERY LOW[a,b] due to risk of bias, imprecision	RR 3.85 (0.82 to 18)	Moderate	
				48 per 1000	48 per 1000
All-cause mortality at 30 days (sub-groups) - Acute blood loss/trauma	939 (2 studies)	LOW[a,c] due to risk of bias, imprecision	RR 0.55 (0.34 to 0.89)	Moderate	
				88 per 1000	88 per 1000

(a) Majority of the evidence is from studies at high risk of bias.
(b) Effect sizes on forest plot are not consistent with each other.
(c) Confidence interval crosses one MID.
(d) Confidence interval crosses both default MIDs and line of no effect.

(e) Confidence interval crosses one default MID and line of no effect.

Table 76: New cardiac events (adults)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with New cardiac events (adults) (95% CI)
New Cardiac events (MI, CHF)- sub-total analysis - Myocardial infarction	6393 (15 studies)	VERY LOW[a] due to risk of bias, imprecision	RR 1.13 (0.76 to 1.67)	Moderate	
				18 per 1000	2 more per 1000 (from 4 fewer to 12 more)
New Cardiac events (MI, CHF)- sub-total analysis - Congestive heart failure	4208 (7 studies)	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 1.00 (0.54 to 1.83)	Moderate	
				42 per 1000	0 fewer per 1000 (from 19 fewer to 35 more)

(a) Confidence interval crosses both MIDs.
(b) Majority of the evidence was from studies at high risk of bias.
(c) I^2=61%.

Table 77: Infection - adults

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Infection - adults (95% CI)
Infection (Pneumonia, surgical site infection, septicaemia, UTI, infections not specified) - Pneumonia	3451 (8 studies)	LOW[a,b] due to risk of bias, imprecision	RR 0.9 (0.73 to 1.11)	Moderate	
				41 per 1000	4 fewer per 1000 (from 11 fewer to 5 more)
Infection (Pneumonia, surgical site infection, septicaemia, UTI, infections not specified) - Surgical site/Wound infection	2136 (2 studies)	LOW[a,b] due to risk of bias, imprecision	RR 0.73 (0.52 to 1.01)	Moderate	
				62 per 1000	17 fewer per 1000 (from 30 fewer to 1 more)
Infection (Pneumonia, surgical site infection, septicaemia, UTI, infections not specified) - Septicaemia/ Bacteraemia	229 (2 studies)	LOW[a,b] due to risk of bias, imprecision	RR 1 (0.06 to 15.62)	Moderate	
				8 per 1000	0 fewer per 1000 (from 8 fewer to 117 more)
Infection (Pneumonia, surgical site infection, septicaemia, UTI, infections not specified) - Infection (not specified)	2422 (4 studies)	LOW[a,b] due to risk of bias, imprecision	RR 0.89 (0.74 to 1.07)	Moderate	
				100 per 1000	11 fewer per 1000 (from 26 fewer to 7 more)

(a) Majority of the evidence was from studies at high risk of bias.
(b) Confidence interval crosses one MID.

Table 78: Adverse events (adults)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Adverse events (adults) (95% CI)
All adverse events (as defined by the study)	1914 (3 studies)	LOW[a,b] due to risk of bias, imprecision	RR 0.83 (0.72 to 0.97)	Moderate	
				2 per 1000	0 fewer per 1000 (from 0 fewer to 1 fewer)
Transfusion associated circulatory overload (TACO)	1866 (2 studies)	MODERATE[a] due to risk of bias	RR 0.13 (0.03 to 0.54)	Moderate	
				18 per 1000	16 fewer per 1000 (from 8 fewer to 17 fewer)
Transfusion Related Acute Lung Injury (TRALI)	1866 (2 studies)	MODERATE[a] due to risk of bias	Not estimable		

(a) Majority of the evidence is from studies at high risk of bias.
(b) Confidence interval crosses one MID.

10.4.1.2 Restrictive strategy compared with liberal strategy for blood transfusion (children)

Table 79: Blood transfusion –(children)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Blood transfusion (children) (95% CI)
Total RBC ml/patient	107 (1 study)	MODERATE[a,b] due to risk of bias			The mean total RBC ml/patient in the intervention groups was 73.0 lower (1.0352 to 0.4248 lower)
Number of patients needing transfusion – children	697 (2 studies)	MODERATE[d] due to risk of bias	RR 0.46 (0.41 to 0.52)	Moderate	
				972 per 1000	525 fewer per 1000 (from 467 fewer to 573 fewer)
Number of patients needing transfusion (sub-group)-children - Critical care	637 (1 study)	MODERATE[d] due to risk of bias	RR 0.47 (0.41 to 0.53)	Moderate	
				978 per 1000	978 per 1000
Number of patients needing transfusion (sub-group)-children - Congenital cardiac disease	60 (1 study)	MODERATE[e,f,g] due to risk of bias	RR 0.38 (0.24 to 0.61)	Moderate	
				967 per 1000	967 per 1000
Number of units transfused-children	690 (2 studies)	VERY LOW[e,f] due to risk of bias, inconsistency			The mean number of units transfused-children in the intervention groups was 0.65 lower (0.98 to 0.33 lower)

(a) Unclear sequence generation and unclear blinding.
(b) I^2=97%.
(c) Most information comes from studies with high risk of bias.
(d) Unclear randomisation. No blinding of clinical staff and patients.
(e) Unclear randomisation and allocation concealment.
(f) I^2=93%.
(g) Confidence interval crosses one default MID.

Table 80: All-cause mortality (30 days) (children)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Mortality (children) (95% CI)
All- cause Mortality (30 days)	697 (2 studies)	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.93 (0.46 to 1.87)	Moderate	
				39 per 1000	3 fewer per 1000 (from 21 fewer to 34 more)

(a) Most information is from studies at high risk of bias.
(b) Lacroix 2007- Included infants <1 year.
(c) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect.

Table 81: Length of stay (children)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Length of hospital stay (children) (95% CI)
ICU length of stay	637 (1 study)	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision			The mean ICU length of stay in the intervention groups was 0.4 lower (1.59 lower to 0.79 higher)

(a) Unclear randomisation sequence generation.
(b) Not protocol outcome. Length of hospital stay not reported. Study included infants <1 year.
(c) Confidence interval crosses one default MID and line of no effect.

Table 82: Adverse events (children)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with New cardiac events (children) (95% CI)
Pulmonary oedema	637 (1 study)	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.09 (0.01 to 1.62)	Moderate	
				16 per 1000	15 fewer per 1000 (from 16 fewer to 10 more)

(a) Unclear randomisation sequence generation.
(b) Pulmonary oedema not protocol specified new cardiac event. Study includes children less than 1 year.
(c) Confidence interval crosses both default MIDs and line of no effect.

Table 83: Infection (children)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	*Risk difference with Infection (children) (95% CI)*
Infection (Nosocomial infections)	637 (1 study)	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.82 (0.61 to 1.09)	Moderate	
				249 per 1000	45 fewer per 1000 (from 97 fewer to 22 more)

(a) Unclear randomisation and blinding.
(b) Not specified type of nosocomial infection. Included infants (<1 year).
(c) Confidence interval crosses one default MID and line of no effect.

10.4.2 Summary of the evidence - Target haemoglobin levels for blood transfusion

This section summarises the evidence on haemoglobin target levels for RBC transfusion from those studies that report haemoglobin thresholds for RBC transfusion and are included in the analysis and results presented in section 1.6.1 above. Hence the results are not independent of the results above.

10.4.2.1 Summary GRADE clinical evidence profiles

Restrictive strategy compared with liberal strategy (adults)

Table 84: Blood transfusion (adults)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Blood transfusions (adults) (95% CI)
Number of patients needing transfusion (all studies)	2350 (5 studies)	LOW[a,b] due to risk of bias, inconsistency	RR 0.61 (0.55 to 0.67)	Moderate	
				918 per 1000	358 fewer per 1000 (from 303 fewer to 413 fewer)
Number of units of blood transfused in those transfused	1634 (3 studies)	LOW[a,c] due to risk of bias, inconsistency			The mean number of units of blood transfused in those transfused in the intervention groups was 1.72 lower (2.41 to 1.02 lower)

(a) Majority of the evidence was from studies at high risk of bias.
(b) I^2 value=64%.
(c) I^2 value=68%.

Table 85: Length of hospital stay (adults)

Outcomes	No. of	Quality of the	Relative	Anticipated absolute effects

	Participants (studies) Follow up	evidence (GRADE)	effect (95% CI)	Risk with Control	Risk difference with Length of hospital stay (adults) (95% CI)
Hospital length of stay	1772 (3 studies)	LOW[a,b] due to risk of bias, imprecision			The mean hospital length of stay in the intervention groups was 2.16 lower (3.81 to 0.5 lower)

(a) Majority of the evidence is from studies at high risk of bias.
(b) Confidence interval crosses MID.

Table 86: All-cause mortality at 30 days (adults)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Mortality (adults) (95% CI)
All-cause mortality at 30 days	2395 (6 studies)	LOW[a,b] due to risk of bias, imprecision	RR 0.78 (0.63 to 0.97)	Moderate	
				92 per 1000	20 fewer per 1000 (from 3 fewer to 34 fewer)

(a) Majority of the evidence is from studies at high risk of bias.
(b) Confidence interval crosses one MID.

Table 87: New cardiac events (adults)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with New cardiac events (adults) (95% CI)
New Cardiac events (MI, CHF)- sub-total analysis - Myocardial infarction	838 (1 study)	LOW[a,b] due to risk of bias, imprecision	RR 0.25 (0.07 to 0.88)	Moderate	
				29 per 1000	22 fewer per 1000 (from 3 fewer to 27 fewer)
New Cardiac events (MI, CHF)- sub-total analysis - Congestive heart failure	924 (2 studies)	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.48 (0.3 to 0.78)	Moderate	
				77 per 1000	40 fewer per 1000 (from 17 fewer to 54 fewer)

(a) Majority of the evidence is from studies at high risk of bias.
(b) Confidence interval crosses one MID.
(c) One study reports acute pulmonary oedema which is a surrogate outcome for congestive heart failure.

Table 88: Infection (adults)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Infection - adults (95% CI)
Infection- Pneumonia	920 (2 studies)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.95 (0.73 to 1.2)	Moderate	
				201 per 1000	10 fewer per 1000 (from 54

					fewer to 44 more)
Infection (Pneumonia, surgical site infection, septicaemia, UTI) - Infection (not specified)	502 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.22 (0.74 to 2.01)	Moderate	
				99 per 1000	22 more per 1000 (from 26 fewer to 100 more)

(a) Evidence from study at high risk of bias.
(b) Confidence interval crosses both MIDs.

Table 89: Adverse events (adult)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Adverse events (adults) (95% CI)
All adverse events (as defined by the study)	889 (1 study)	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.84 (0.72 to 0.97)	Moderate	
				481 per 1000	77 fewer per 1000 (from 14 fewer to 135 fewer)

(a) Evidence from study at high risk of bias.
(b) Adverse event not defined in study.
(c) Confidence interval crosses one MID.

Restrictive strategy compared with liberal strategy (children)

Table 90: Blood transfusion (children)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Blood transfusion (children) (95% CI)
Total RBC ml/patient	456 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision			The mean total RBC ml/patient in the intervention groups was 0.2 higher (0.4 lower to 0.8 higher)
Number of patients needing transfusion - children (critical care)	637 (1 study)	MODERATE[a] due to risk of bias	RR 0.47 (0.41 to 0.53)	Moderate	
				978 per 1000	518 fewer per 1000 (from 460 fewer to 577 fewer)

(a) Evidence from study at high risk of bias.
(b) Confidence interval crosses both MIDs.

Table 91: All-cause mortality at 30 days (children)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Mortality (children) (95% CI)

All-cause mortality at 30 days	637 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.99 (0.48 to 2.04)	Moderate	
				44 per 1000	0 fewer per 1000 (from 23 fewer to 46 more)

(a) Evidence from study at high risk of bias.
(b) Confidence interval crosses both MIDs.

Table 92: Length of stay (children)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Length of hospital stay (children) (95% CI)
ICU length of stay	637 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision			The mean ICU length of stay in the intervention groups was 0.4 lower (1.59 lower to 0.79 higher)

(a) Evidence from study at high risk of bias.
(b) Confidence interval crosses both MIDs.

Table 93: Adverse events (children)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with New cardiac events (children) (95% CI)
Pulmonary oedema	637 (1 study)	VERY LOW[a,b,c] due to risk of bias, indirectness, imprecision	RR 0.09 (0.01 to 1.62)	Moderate	
				16 per 1000	15 fewer per 1000 (from 16 fewer to 10 more)

(a) Evidence from study at high risk of bias.
(b) Study reports acute pulmonary oedema which is a surrogate outcome for congestive heart failure.
(c) Confidence interval crosses one MID.

Table 94: Infections (children)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Control	Risk difference with Infection (children) (95% CI)
Infection (Nosocomial infections)	637 (1 study)	LOW[a,b] due to risk of bias, imprecision	RR 0.82 (0.61 to 1.09)	Moderate	
				249 per 1000	45 fewer per 1000 (from 97 fewer to 22 more)

(a) Evidence from study at high risk of bias.
(b) Confidence interval crosses one MID.

10.5 Economic evidence

10.5.1 RBC Thresholds

Published literature

One relevant economic evaluation was identified with the relevant comparison for RBC thresholds and targets and has been included in this review.[309] This is summarised in the economic evidence profile below (Table 95) and the economic evidence tables in Appendix I.

Two economic evaluations relating to this review question were identified but were excluded due to a combination of limited applicability and methodological limitations.[231,331] These are summarised in Appendix Q, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix F.

Table 95: Economic evidence profile: Restrictive versus liberal threshold and target

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Walsh 2013[309] (UK)	Partially applicable[(a)]	Potentially serious limitations[(b)]	Within-trial analysis (RCT) of anaemic older critically ill patients requiring prolonged mechanical ventilation transfused using either a liberal strategy (Hb transfusion trigger ≤90 g/litre; target Hb range, 91–110 g/litre) or a restrictive strategy (Hb transfusion trigger ≤70 g/litre; target Hb range, 71–90 g/litre). RCT included in clinical review. Analysis of individual level resource use, with unit costs applied.	£18,265[(c)]	0.072 life years[(d)]	£253,681 per life year gained	Bootstrapping analysis was used to quantify uncertainty in the ICER but only reported graphically.

(a) Health effects not expressed in terms of QALYs.

(b) Health and resource outcomes based on one RCT of critically ill patients, short follow-up period, cost of strategies and blood transfusion not included in analysis.

(c) 2010 UK pounds. Costs 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.

(d) Mean life years and mean SF-6D from within-trial analysis. QALYs were not calculated but SF-6D utility data were reported, incremental mean difference (liberal–restrictive) at: 60 days: -0.04 (95% CI -0.10 to 0.02) and 180 days: 0.06 (95% CI -0.01 to 0.14).

Unit costs

Relevant unit costs are provided in Appendix N to aid consideration of cost-effectiveness.

10.5.2 RBC Targets

Published literature

One relevant economic evaluation was identified with the relevant comparison for RBC thresholds and targets and has been included in this review.[309] This is summarised in the economic evidence profile above (Table 95) and the economic evidence tables in Appendix I.

See also the economic article selection flow chart in Appendix F.

Unit costs

Relevant unit costs are provided in Appendix N to aid consideration of cost-effectiveness.

10.6 Evidence statements

Clinical

RBC thresholds

Restrictive strategy versus liberal strategy in adults

Thirty RCTs compared restrictive strategies with liberal strategies for blood transfusion in adults. The evidence showed clinically important benefit with restrictive strategies with respect to the number of patients transfused and number of units transfused. The evidence suggested that there may be a benefit with respect to adverse events, and length of hospital stay with the restrictive strategies, but there was considerable uncertainty. No difference was observed with respect to mortality and infection between the groups. The evidence suggested that new cardiac events may be more in patients who received blood transfusions at restrictive thresholds, but there was considerable uncertainty.

The evidence was of low and very low quality. No evidence was identified for quality of life.

Restrictive strategy versus liberal strategy in children

Three RCTs compared restrictive strategy with liberal strategy in children. The evidence showed that there was a clinically important benefit with restrictive strategies in children with respect to the number of patients transfused. The evidence suggested that lower volumes and less number of units may be transfused in children with restrictive strategies, but there was some uncertainty. The evidence suggested that there may be no difference between the groups with respect to mortality at 30 days, ICU length of stay, adverse events and infections (nosocomial infection), however there was considerable uncertainty.

The evidence in children ranged from moderate to very low quality. No evidence was identified for the critical outcome quality of life.

RBC targets

Restrictive strategy versus liberal strategy in adults

Seven RCTs compared restrictive strategy with liberal strategy in adults. The evidence showed clinically important benefit with the use of restrictive targets for blood transfusion for the outcomes of number of patients transfused and number of units transfused. The evidence suggested that there may be a benefit with respect to mortality (all cause at 30 days), new cardiac events, length of hospital stay and adverse events in patients being transfuse to restrictive target levels, but there was some uncertainty. No difference was observed between the groups with respect to incidence of infections (pneumonia).

The evidence was of low and very low quality. No evidence was identified for outcomes quality of life, new cardiac events (MI), new cardiac events (MI) and adverse events.

Restrictive strategy versus liberal strategy in children

One RCT compared restrictive strategy with liberal strategy in children. The evidence showed clinically important benefit for restrictive strategy for the outcome number of patients transfused. The evidence suggested there may be a benefit with the use of restrictive targets with respect to ICU length of stay and pulmonary oedema, however there was considerable uncertainty. The evidence suggested that there may be no difference between groups with respect to the total volume of RBC transfused, mortality and infections but there was some uncertainty.

The evidence ranged from moderate to very low quality. No evidence was identified for the critical outcome quality of life.

Economic

One cost-effectiveness analysis found that, in anaemic, older, critically ill patients requiring prolonged mechanical ventilation, a restrictive red blood cell strategy was more costly and more effective than a liberal red blood cell transfusion strategy (ICER: £253,681 per life year gained). This analysis was assessed as partially applicable with potentially serious limitations.

10.7 Recommendations and link to evidence

Recommendations	13. Use restrictive red blood cell transfusion thresholds for patients who need red blood cell transfusions and who do not have major haemorrhage or acute coronary syndrome.
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, infections (including pneumonia, surgical site infection, UTI and septicaemia/bacteraemia), quality of life, acute and delayed serious adverse events and new cardiac events as the critical outcomes for decision making. Other important outcomes included the number of patients transfused, the number of units transfused and length of stay in hospital.
Trade off between clinical benefits and harms	No evidence was identified to independently evaluate the effect of different thresholds or targets of haemoglobin concentration for blood transfusion because these interventions were linked in most studies. Evidence from the combined review of RBC thresholds and RBC targets comparing restrictive and liberal strategies suggested that the use of restrictive strategies (use of restrictive thresholds and targets) had a positive effect on important outcomes such as number of patients

transfused and number of units transfused. The evidence also suggested benefit for restrictive strategy for mortality (all cause at 30 days), infection (pneumonia), adverse events and length of hospital stay, there was too much uncertainty within the effect estimates to allow confident interpretation of clinical benefit or harm for these outcomes
. The evidence also showed that new cardiac events (MI, CHF) appeared to be higher in the restrictive strategy group; however, this was not considered to be clinically important.

There was evidence from three studies comparing restrictive thresholds with liberal thresholds in children. The evidence showed that there was clinically important benefit for use of restrictive thresholds for number of patients transfused, total RBC ml/patient and number of units transfused per patient. The evidence also showed benefit for use of restrictive thresholds for mortality 30 days, ICU length of stay, new cardiac event (pulmonary oedema) and infection (nosocomial infection), but there was considerable uncertainty in the effect estimates. .

No evidence was identified for the critical outcome quality of life in either adults or children.

No evidence was identified for patients with co-existing ischaemic disease, including chronic cardiovascular disease.One study reported a sub-group analysis of the data in this group, and thiswas used to inform the wider consensus of the GDG on this topic[133].The evidence was deemed to be inconclusive and a research recommendation was made in this area.

There was no clear evidence that using restrictive strategies (use of restrictive thresholds and targets) would harm the general population when considering RBC transfusions.

Based on the evidence above, the GDG recommended the use of restrictive thresholds and targets for RBC transfusion for the majority of patients.

The GDG discussed the evidence with respect to specific subgroups such as patients with acute coronary syndrome and major haemorrhage. The GDG agreed that the safest threshold levels were uncertain for these sub-groups, and might be specific to individual patients.

For patients with acute coronary syndrome the GDG agreed there are physiological reasons that anaemia may be less well tolerated, which include the fact that the heart relies more on increasing coronary blood flow to meet increasing oxygen demands than other organs (which can extract a greater proportion of oxygen from blood if required). An acute coronary syndrome occurs when coronary blood flow cannot meet the heart's oxygen requirement, either because a coronary blood vessel is occluded or when coronary blood flow is insufficient. This can occur in patients with a primary cardiac event, but might also affect patients with chronic coronary disease in whom other factors decrease coronary blood flow, such as shock or hypotension. For these patients the GDG agreed that clinical judgement was needed on an individual patient basis using information about disease severity and cardiovascular status (for example blood pressure and heart rate). Although restrictive strategies may be safe, the actual transfusion threshold and target haemoglobin may need to be higher than used for patients without coronary disease.

The GDG discussed the specific needs of patients with major haemorrhage. It was agreed that in this clinical situation, status changes quickly and unpredictably and clinical judgement in relation to RBC transfusion is needed. In addition, the

	haemoglobin concentration may not reflect the circulating blood volume and the immediate risk to the patient is from hypovolaemia.
Economic considerations	No economic analyses were identified to independently evaluate the effect of different thresholds or targets of haemoglobin concentration for blood transfusion because these interventions were linked. One cost-effectiveness analysis was identified which compared a restrictive RBC transfusion strategy to a liberal transfusion strategy. This analysis found that in anaemic, older, critically ill patients requiring prolonged mechanical ventilation, a restrictive RBC strategy was more costly and more effective than a liberal RBC transfusion strategy (ICER: £253,681 per life year gained). The increased cost of the restrictive threshold strategy compared to the liberal threshold strategy was largely due to an increased intensive care unit and hospital length of stay. Although, this study did not report cost-effectiveness in terms of cost per QALY it suggests that a restrictive threshold may not be cost-effective. The GDG noted that healthcare costs were high and mostly attributable to the ICU admission. The GDG also highlighted that the mortality difference reported could have occurred by chance due to the sample size in the trial. The GDG concluded that it is not possible to extrapolate the findings in this study to other transfusion recipients and therefore decided not to make a recommendation in this subgroup of patients based on this evidence. In this analysis, the higher cost of restrictive strategy was driven by an increased length of stay. However, the GDG noted that the clinical evidence in all other patients receiving transfusion showed a shorter length of stay when using a restrictive strategy compared with a liberal one. No relevant economic evaluations comparing different thresholds or targets of haemoglobin concentration for RBC transfusion in other populations were identified. The cost of RBC transfusion was considered by the GDG. Allogeneic RBC cost £122.09 per unit in England and Wales. It was noted that this cost does not include all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications. The GDG considered these costs and agreed that generally a restrictive strategy for RBC transfusion would be cheaper than a liberal one. Given that it was also concluded that the clinical evidence did not suggest harm from a restrictive strategy it was therefore judged likely to be cost-effective. The GDG considered that for specific subgroups such as in patients with major haemorrhage or acute coronary syndrome it may not be appropriate to use a restrictive threshold, and the economic savings from a restrictive transfusion strategy could be outweighed by the risk to patients of hypovolaemia and low haemoglobin concentration, respectively. Therefore, based on the clinical and economic evidence, the GDG agreed that a restrictive transfusion strategy should be offered to people in the absence of major haemorrhage or acute coronary syndrome.
Quality of evidence	The quality of evidence for all outcomes was low or very low by GRADE criteria for the combined RBC thresholds and RBC targets review This was largely because of risk of bias arising from a lack of allocation concealment, inadequate blinding and serious or very serious imprecision. The GDG also noted that the definition of restrictive and liberal thresholds varied widely between different studies, which made specific recommendations in relation to haemoglobin values difficult. The GDG noted that for most studies the restrictive haemoglobin thresholds were 70 to 80g/L.

	The economic evaluation was assessed as partially applicable with potentially serious limitations.
Other considerations	The recommendation applies to adults and children requiring RBC transfusions. Although trauma patients were outside the scope of this guideline, the review included some studies with trauma patients. This was agreed because the population was not markedly different from this guideline's population, for example, some patients in critical care. The GDG discussed that the recommendation would, however, not be applicable to patients with major haemorrhage and it was important to highlight this in the above recommendation. For patients with cyanotic congenital heart disease, the GDG agreed that the reduced arterial oxygen content increased the risk from a low haemoglobin concentration. The GDG noted that some important patient groups in whom there is a physiological rationale, a higher haemoglobin threshold for transfusion may have clinical benefit such as those with brain injury, acute and chronic cardiovascular disease, but evidence from these groups was of poor quality. It was noted that there are three on-going trials comparing restrictive and liberal threshold strategies, the TRIGGER trial (transfusion in gastrointestinal bleeding), the TITRe2 trial (Transfusion Indication Threshold Reduction on transfusion rates, morbidity and healthcare resource use following cardiac surgery) and the TRIST trial (transfusion of red cell in haematopoietic stem cell transplantation). The GDG also noted that recommending restrictive thresholds may be a sensible way of managing blood resource.

1

Recommendations	**14. When using a restrictive red blood cell transfusion threshold, consider a threshold of 70 g/litre and a haemoglobin concentration target of 70–90 g/litre after transfusion.**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, infections (including pneumonia, surgical site infection, UTI and septicaemia/bacteraemia), quality of life, acute and delayed serious adverse events and new cardiac events as the critical outcomes for decision making. Other important outcomes included the number of patients transfused, the number of units transfused and length of stay in hospital.
Trade off between clinical benefits and harms	The evidence from the combined review comparing restrictive and liberal targets in adults suggested that there was clinically important benefit with the use of restrictive targets for the outcomes number of patients transfused and number of units transfused. The evidence also suggested that there was lower mortality (all cause at 30 days), new cardiac events, length of hospital stay, adverse events and infection (pneumonia) for patients receiving restrictive strategy, but there was some uncertainty in the effect estimates. No evidence was identified for outcomes quality of life, number of units transfused, new cardiac events (MI), new cardiac events (MI) and adverse events. There was evidence from one study comparing restrictive and liberal targets in children. The evidence suggested that there was clinically important benefit with

	the use of restrictive targets for the outcome number of patients transfused. The evidence also suggested benefit for restrictive strategy for the outcomes total RBC ml/patient mortality 30 days, ICU length of stay, new cardiac event (pulmonary oedema) and infection (nosocomial infection), but there was considerable uncertainty within the effect estimates. No evidence was identified for the critical outcome quality of life. The GDG discussed the specific thresholds and target levels for RBC transfusion and based the recommendation on the threshold and target ranges used in the studies. The majority of the studies reported a restrictive haemoglobin threshold of 70 g/litre for blood transfusion and target haemoglobin levels of 70-90 g/litre. Most other studies used a haemoglobin threshold of 80 g/L.
Economic considerations	No economic evidence was identified to independently evaluate the effect of different thresholds or targets of haemoglobin concentration for blood transfusion. The specific threshold and targets outlined for a restrictive strategy are based on those reported in majority of the evidence identified in the clinical review. Economic considerations for a restrictive strategy are described in the LETR above.
Quality of evidence	The quality of evidence for all outcomes was low or very low by GRADE criteria for both the combined RBC thresholds and RBC targets review This was largely because of risk of bias arising from a lack of allocation concealment, inadequate blinding and serious or very serious imprecision. There was also considerable variation within the studies in the levels of haemoglobin concentration used for haemoglobin targets. The economic evaluation was assessed as partially applicable with potentially serious limitations. The GDG agreed that the same recommendations should apply for children as for adults.
Other considerations	The recommendation applies to adults and children requiring RBC transfusions. It was noted that there are three on-going trials comparing restrictive and liberal threshold strategies, the TRIGGER trial (transfusion in gastrointestinal bleeding), the TITRe2 trial (Transfusion Indication Threshold Reduction on transfusion rates, morbidity and healthcare resource use following cardiac surgery) and the TRIST trial (transfusion of red cell in haematopoietic stem cell transplantation).

1

Recommendations	**15. Consider a red blood cell transfusion threshold of 80 g/litre and a haemoglobin concentration target of 80–100 g/litre after transfusion for patients with acute coronary syndrome.**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, infections (including pneumonia, surgical site infection, UTI and septicaemia/bacteraemia), quality of life, acute and delayed serious adverse events and new cardiac events as the critical outcomes for decision making. Other important outcomes included the number of patients transfused, the number of units transfused and length of stay in hospital.
Trade off between clinical benefits and	There was evidence from two studies comparing restrictive strategy with liberal strategy in patients with acute coronary syndrome. Evidence from these studies suggested benefit with the use of liberal thresholds compared with restrictive

harms	thresholds with respect to critical outcomes such as mortality and new cardiac events (myocardial infarctions) but suggested that restrictive thresholds may be better in this subgroup at reducing the number of units of allogeneic blood transfused and the length of stay in hospital. For this group of patients with acute coronary syndrome, the GDG agreed that there are physiological reasons as to why anaemia may be less well tolerated, which include the fact that the heart relies more on increasing coronary blood flow to meet increasing oxygen demands than other organs (which can extract a greater proportion of oxygen from blood if required). An acute coronary syndrome occurs when coronary blood flow cannot meet the heart's oxygen requirement, either because a coronary blood vessel is occluded or when coronary blood flow is insufficient. This can occur in patients with a primary cardiac event, but might also affect patients with chronic coronary disease in whom other factors decrease coronary blood flow, such as shock or hypotension. For these patients the GDG agreed that clinical judgement was needed on an individual patient basis using information about disease severity and cardiovascular status (for example blood pressure and heart rate). Although restrictive strategies may be safe, the actual transfusion threshold and target haemoglobin may need to be higher than used for patients without coronary disease. The GDG agreed to recommend higher threshold levels for this group of patients. Based on the thresholds used in the studies, the GDG recommended a level of 80-100 g/litre as the transfusion threshold for this group. The recommendation was based on the evidence and consensus expert opinion of the GDG members.
Economic considerations	No relevant economic evaluations comparing different thresholds or targets of haemoglobin concentration for RBC transfusion in people with acute coronary syndrome were identified. The cost of RBC transfusion was considered by the GDG. Allogeneic RBC cost £122.09 per unit in England and Wales. It was noted that this cost does not include all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications. The GDG considered that for specific subgroups such as in patients with acute coronary syndrome it may not be appropriate to use the same restrictive thresholds as for patients without acute coronary disease, and the economic savings from a restrictive transfusion strategy may be outweighed by the risk to patients of lower haemoglobin concentrations. The specific threshold and targets outlined for this subgroup of patients are based on those reported in the evidence identified in the clinical review and consensus expert opinion of GDG members.
Quality of evidence	The quality of evidence for all outcomes was low or very low by GRADE criteria. This was largely because of risk of bias arising from a lack of allocation concealment, and serious or very serious imprecision. The GDG considered this evidence was not relevant to children, with the exception of those with cardiac disease that could compromise coronary blood flow or oxygen supply to heart muscle.
Other considerations	The recommendation applies to adults with acute coronary syndrome requiring RBC transfusions. The GDG noted that some important patient groups in whom there is a physiological rationale, a higher haemoglobin threshold for transfusion may have

	clinical benefit such as those with brain injury, acute and chronic cardiovascular disease, but evidence from these groups was limited and of poor quality. The literature suggests that there may be some evidence of harm with the use of restrictive red blood cell thresholds in populations with coronary ischaemia at baseline. In this guideline a level of 80–100 g/litre was used for patients with acute coronary syndrome, but further studies are needed to determine the optimal transfusion threshold for patients with chronic cardiovascular disease. The GDG agreed that further research was required in this area and drafted a research recommendation (see section 10.8).

1

Recommendations	**16. Consider setting individual thresholds and haemoglobin concentration targets for each patient who needs regular blood transfusions for chronic anaemia.**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, infections (including pneumonia, surgical site infection, UTI and septicaemia/bacteraemia), quality of life, acute and delayed serious adverse events and new cardiac events as the critical outcomes for decision making. Other important outcomes included the number of patients transfused, the number of units transfused and length of stay in hospital.
Trade off between clinical benefits and harms	No evidence was identified for this recommendation. The GDG discussed the specific needs of patients who received transfusions for chronic anaemia, including elderly patients. It was agreed that these patients were a separate group who may not benefit from the thresholds and target levels set for the overall population. This was because the severity of anaemia may relate to an individual's level of symptoms such as fatigue and breathlessness, and their quality of life. These patients may need to have specific thresholds and targets set for them individually after clinical assessment. The recommendation was based on the consensus expert opinion of the GDG members.
Economic considerations	No relevant economic evaluations comparing different thresholds or targets of haemoglobin concentration for RBC transfusion people with chronic anaemia were identified. The cost of RBC transfusion was considered by the GDG. Allogeneic RBC cost £122.09 per unit in England and Wales. It was noted that this cost does not include all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications. The GDG considered that for this group of patients who require regular blood transfusion for chronic anaemia, setting individual thresholds and targets after clinical assessment would be current practice and would not have a significant economic impact.
Quality of evidence	No evidence was identified for this recommendation and the recommendation was based on the consensus expert opinion of the GDG members.
Other considerations	The recommendation applies to adults and children requiring RBC transfusions.

10.8 Research Recommendations

3. **Red Blood Cell Transfusion: What is the clinical and cost effectiveness of restrictive compared with liberal red blood cell thresholds and targets for patients with chronic cardiovascular disease?**
   - **Why this is important: The literature suggests that there may be some evidence of harm with the use of restrictive red blood cell thresholds in populations with coronary ischaemia at baseline. In this guideline a level of 80–100 g/litre was used for patients with acute coronary syndrome, but further studies are needed to determine the optimal transfusion threshold for patients with chronic cardiovascular disease.**

11 Red blood cell transfusion: doses

11.1 Review question: What is the clinical- and cost-effectiveness of different doses of red blood cell transfusion?

Population	• Adults • Children • Young people • Exclusions: Patients who are actively bleeding
Intervention	• Low dose or single unit • High dose or multiple units
Comparison	• Low dose (single unit) versus high dose or multiple units
Outcomes	• All-cause mortality at 30 days • Quality of life • New cardiac event (myocardial infarction, cardiac failure) • Length of stay in hospital • Infections (for example, pneumonia) • Number of patients needing transfusions • Number of units transfused/Volume in ml (in children) • Acute and delayed serious adverse events as reported in study (TACO and TRALI, iron overload).
Study designs	• RCTs • Systematic reviews

For full details see review protocol in C.3, Appendix C.

11.2 Clinical evidence

We searched for randomised controlled trials comparing the effectiveness of different doses of red blood cell transfusion.

- No relevant clinical studies were identified for this review.
- One study did not meet the review protocol criteria entirely, but provided supportive evidence for decision making.[276] It evaluated the effectiveness of two transfusion policies in adult patients (>18 years of age) who were scheduled to undergo a total hip replacement or total knee replacement surgery. Patients were classified to receive different dosage of RBC transfusion (1 unit, 1-2 units, 3 units) based on transfusion policies followed in hospitals. The transfusion policies were classified into restrictive and liberal and were developed taking into account patient's age and specific co-morbidities. Results are presented comparing different transfusion policies.

11.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

Relevant unit costs are provided in Appendix N to aid consideration of cost-effectiveness.

11.4 Evidence statements

Clinical

No relevant clinical studies were identified.

Economic

No relevant economic evaluations were identified.

11.5 Recommendations and link to evidence

Recommendations	**17. Consider single-unit red blood cell transfusions for adults (or equivalent volumes, calculated based on body weight, for children or adults who weigh under 50 kg) who do not have active bleeding.**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, infections (including pneumonia, surgical site infection, UTI and septicaemia/bacteraemia), quality of life, acute and delayed serious adverse events and new cardiac events as the critical outcomes for decision making. Other important outcomes included the number of patients transfused, the number of units transfused and length of stay in hospital.
Trade off between clinical benefits and harms	No evidence was identified for this review. The GDG discussed the potential benefits of transfusing single units of RBC rather than multiple units in the first instance. These benefits included a potential reduction in the numbers of units transfused and therefore a potential reduction in transfusion-related adverse events including decreasing the risk of transfusion-associated circulatory overload and would help to make best use of the limited supply of donor blood. There was no specific evidence available for RBC doses in the paediatric population. The GDG felt it reasonable that the equivalent recommendations should apply for children as for adults.
Economic considerations	No relevant economic evaluations comparing different doses of RBC for transfusion were identified. The cost of RBC transfusion was considered by the GDG. Allogeneic RBC cost £122.09 per unit in England and Wales. It was noted that this does not include hospital costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications. The same cost per unit applies for children as it does for adults. If less than one unit is required for transfusion, the full cost of the unit is still incurred as the

	remaining blood cannot be used for another patient. The GDG noted that the potential clinical benefits of transfusing single units of RBC rather than multiple units in the first instance (such as a reduction in the number of units transfused and the potential resultant reduction in transfusion-related adverse events) would be likely to also reduce costs.
Quality of evidence	No studies were identified which met the review protocol criteria. The recommendation was based on the consensus expert opinion of the guideline development group members.
Other considerations	The GDG considered that the recommendation would not be applicable to patients with major haemorrhage where patients have active bleeding and blood loss can be life-threatening.(follow the recommendations in NICE's guideline on Major trauma, currently in development). For children it is likely to require repeated single-unit equivalent transfusions in order to bring their Hb up to the recommended target. A higher volume may be considered (up to a maximum of a single unit) in order to reduce donor exposure.

1

Recommendations	**18. After each single-unit red blood cell transfusion (or equivalent volumes, calculated based on body weight, for children or adults who weigh under 50 kg), clinically reassess and check haemoglobin levels, and give further transfusions if needed.**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, infections (including pneumonia, surgical site infection, UTI and septicaemia/bacteraemia), quality of life, acute and delayed serious adverse events and new cardiac events as the critical outcomes for decision making. Other important outcomes included the number of patients transfused, the number of units transfused and length of stay in hospital.
Trade off between clinical benefits and harms	No evidence was identified for this review. The GDG discussed the potential benefits of monitoring after each transfusion after transfusing single units of RBC. In order to ensure that patients receive the correct dose of RBC, the GDG stressed the importance of reassessing the patient after administering each unit and then transfusing additional single units as required. Patients should therefore not receive too little or too much RBC and there is potential to save blood and therefore reduce the risk of transfusion related adverse events. There is minimal discomfort or inconvenience for the patient in monitoring after transfusion. The GDG felt it reasonable that equivalent recommendations should apply for children as for adults in clinical situations where repeated blood tests are feasible. The patient should be reassessed after each transfusion of red cells (volume calculated by body weight).
Economic considerations	The GDG highlighted that the cost of clinically reassessing and checking haemoglobin levels was negligible and would be offset by savings as a result of transfusing fewer units of RBC.
Quality of evidence	No studies were identified which met the review protocol criteria. The recommendation was based on the consensus expert opinion of the guideline development group members.

Other considerations	The GDG considered that the recommendation would not be applicable to patients with major haemorrhage where patients have active bleeding and blood loss can be life-threatening.((follow the recommendations in NICE's guideline on Major trauma, currently in development).

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12 Platelet transfusion: thresholds and targets

Platelets are blood cells involved in haemostasis. Platelet concentrates are prepared by blood services from whole blood donations or by apheresis of single donors and are the second most commonly used blood component after red cell transfusion (271,000 adult doses were provided in England in 2013/14)[211]. Platelet transfusions are used to treat and prevent bleeding in patients with thrombocytopenia or platelet dysfunction. While the majority of platelet transfusions are administered to patients with primary haematological disorders, they are commonly used in other clinical scenarios, such as critical care and major haemorrhage.

There are still several areas of controversy concerning the use of platelet transfusions, including whether a policy of prophylactic platelet transfusion is superior to a policy of no prophylaxis for the prevention of severe thrombocytopenic bleeding, what platelet count threshold should be used to trigger the transfusion of prophylactic platelets, and what is the optimal platelet dose to prevent thrombocytopenic bleeding.

National audits of the use of platelet transfusions have shown considerable non-compliance with recommendations for platelet count thresholds and platelet dose.

12.1 Review question: What is the clinical- and cost-effectiveness of different target levels of post-transfusion platelet counts?

For full details see review protocol in Appendix C.

Table 96: PICO characteristics of review question

Population	Bleeding and non-bleeding patients receiving platelet transfusion
Intervention(s)	• High target platelet counts as defined by the trial • Low target platelet counts as defined by the trial
Comparison(s)	• High target platelet counts vs. Low target platelet counts

Outcomes	Critical outcomes:
	• All-cause mortality at 30 days
	• Infections (for example, pneumonia).
	• Bleeding
	  ○ Occurrence of bleeding (non-bleeding patients)
	  ○ Cessation of bleeding (bleeding patients)
	• Quality of life.
	• Serious adverse events as defined by studies
	Important outcomes:
	• Length of stay (hospitalisation)
	• Number of patients needing platelet transfusions
	• Number of units transfused (platelets)

Study design	RCTs and systematic reviews

No evidence was found for this question

12.2 Review question: What is the clinical- and cost-effectiveness of platelet transfusion at different platelet count thresholds?

For full details see review protocol in Appendix C.

Table 97: PICO characteristics of review question

Population	Bleeding and non-bleeding patients receiving platelet transfusion
Intervention(s)	**Interventions in bleeding patients:** • Low platelet thresholds for transfusion (as defined by the trial) • High platelet thresholds for transfusion (as defined by the trial) **Interventions in non-bleeding patients:** • Low platelet thresholds for prophylactic transfusion (as defined by the trial) • High platelet thresholds for prophylactic transfusion (as defined by the trial) • No Prophylactic transfusion
Comparison(s)	• Prophylactic platelet transfusions (high/low threshold) vs. No Prophylactic platelet transfusion • Low threshold vs. High threshold (in bleeding and non-bleeding patients)
Outcomes	Critical outcomes: • All-cause mortality at 30 days • Infections (for example, pneumonia). • Bleeding ○ Occurrence of bleeding (non-bleeding patients) ○ Cessation of bleeding (bleeding patients) • Quality of life. • Serious adverse events as defined by studies. Important outcomes: • Length of stay (hospitalisation). • Number of patients needing platelet transfusions. • Number of units transfused (platelets).
Study design	RCTs and Systematic reviews

The GDG was interested in knowing the most clinical and cost-effective platelet count threshold for platelet transfusion.

We looked at 2 broad comparison groups:

- Population: Bleeding patients
  - Comparators: Low threshold versus high threshold (no evidence found)
- Population: Non bleeding patients
  - Comparators:
    - Prophylactic platelet transfusions versus no prophylactic platelet transfusions
    - Low threshold versus high threshold

It was agreed that haematology* and non- haematology patients** (defined below) were clinically very different and the data for each of these patient groups should be reviewed separately. The GDG also wanted to evaluate the data separately for adults and children and the review was thus stratified into eight broad population groups as follows:

Bleeding patients:

- Adults who are haematology patients

- Adults who are non-haematology patients
- Children who are haematology patients
- Children who are non-haematology patients

Non-bleeding patients:

- Adults who are haematology patients
- Adults who are non-haematology patients
- Children who are haematology patients
- Children who are non-haematology patients

Our protocol defines adults as aged 18 years and above, young adults as 16–18 years and children below 16 years of age. We identified a few studies where the population included adults along with adolescents and or children and the data were not reported separately for each of these population groups.

In the comparison of low threshold versus high threshold, there were two studies[86,334] which included children and adults. One included patients above 2 years of age with a median of 45 years[334] and the other had patients with a median age of 33 years[86]. As the data were not reported separately for children and adults in these two studies, we have included these two studies in the adult haematology patients group. One more study[249] included adolescents and adults above 16 years of age; we have included this study in the adult haematology group, as data were not reported separately for adolescents and adults.

For full details see review protocol in Appendix C.

*Haematology patients: patients receiving intensive chemotherapy or haemopoietic stem cell transplant, platelet function disorders, idiopathic thrombocytopenic purpura (ITP), aplastic anaemia, myelodysplasia.

**Non-haematology patients: patients with sepsis, critical care, surgical patients, liver failure, renal failure.

12.3 Clinical evidence

No RCTs or systematic reviews comparing platelet thresholds in bleeding patients were identified.

Seven RCTs were identified and included in the review.[86,125,204,249,283,311,334] All of the studies were in non-bleeding patients and compared either low threshold versus high threshold or prophylactic versus no prophylactic platelet transfusions. These studies are summarised inTable 98 below.

One Cochrane review was identified in our search.[97] However, we have not included this Cochrane review in our evidence review as the outcomes did not entirely match our protocol outcomes; but we have used some data from the Cochrane review where data for individual outcomes were not clearly reported in the papers(We have used data for the following outcomes: number of patients with significant bleeding and number of platelet units transfused per patient from the study[125] in the Cochrane review).

There was a variation in the bleeding scales for assessment of severity bleeding in the studies. The majority of the studies used the WHO grading system (1-4); however, there was one study[334] that used the modified GIMEMA criteria and another[125] used a standardised toxicity scale (no details reported) for assessment of bleeding. We have tried to correlate the bleeding criteria from the other scales to the WHO bleeding criteria while analysing the data.

Evidence from the included studies is summarised in the GRADE clinical evidence profile and clinical evidence summary below (Table 72). See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, GRADE tables in Appendix J and excluded studies list in Appendix Q.

Table 98: Summary of studies included in the review

Study	Population	Intervention/ comparisons	Outcomes	Comments
Diedrich 2005[86]	Adults and children <18 years undergoing an allogeneic haematopoietic stem cell transplant Study design: RCT	Prophylactic platelet transfusion if platelet count <10x10^9/litre vs. prophylactic platelet transfusion platelet count <30x10^9/litre.	• Mortality (all cause) (3 years). • No. of patients with bleeding event. • Transfusion related mortality (3 years). • Bacteraemia.	The WHO grading system for assessment of bleeding. Bacteraemia was defined as the first positive blood culture related to a febrile episode during the first 30 days after transplantation.
Heckman 1997[125]	Patients aged >17 years undergoing induction therapy for acute leukaemia Study design: RCT	Prophylactic platelet transfusion if platelet counts ≤10x10^9/litre vs. prophylactic platelet transfusion if platelet count ≤20x10^9/litre.	• Hospital stay. • Number of patients needing platelet transfusion. • Number of patients with bleeding events. • All-cause mortality. • No. of units transfused per patient. • Adverse event (transfusion reaction).	Severity of bleeding was graded using a standardised toxicity scale. Median values reported for hospital length of stay.
Rebulla 1997[249]	Patients with acute myeloid leukaemia (AML); adolescents and adults (aged 16-70 years); admitted to hospital for 1st course of induction chemotherapy Study design: RCT	Transfusion platelets prophylactically when the platelet count falls below 10^9/litre per cubic millimetre or was 10 to 20x10^9/litre cubic millimetre when the body temperature exceeded 38 degrees, in the presence of fresh minor or major bleeding or if invasive procedures were necessary vs. transfusion platelets prophylactically when the platelet count falls below 20x10^9/litre per	• Mortality (all causes). • Number of patients with major bleeding episodes. • Number of platelet transfusions/ patient.	Severity of haemorrhage was graded on a 8 point scale: 0- no bleeding, 1- petechial or mucosal or retinal bleeding that did not require red blood cell transfusion, 2- melena, haematemesis, haematuria, or haemoptysis, 3- any bleeding that required red blood cell transfusion, 4-

		cubic millimetre.		retinal bleeding accompanied by visual impairment, 5- non fatal cerebral bleeding, 6- fatal cerebral bleeding, 7- non fatal cerebral bleeding. Minor haemorrhage as score of 1 and major haemorrhage as a score of more than 1.
Stanworth 2013[283]	Patients 16 years or older who were receiving chemotherapy or undergoing stem-cell transplantation and who had or were expected to have thrombocytopenia. Study design: RCT	No prophylaxis if the platelet count was less than $10x10^9$ per litre vs. prophylactic transfusion if the platelet count was less than $10x10^9$ per litre.	• Number of patients who had bleeding events. • Number of patients who had major bleeding events. • Number of patients needing platelet transfusion. • Number of units (platelets) transfused/patient. • Hospital length of stay. • Serious adverse events (including sepsis and respiratory deterioration). • Transfusion related serious adverse event (urticarial and angioedema).	The WHO grading system for assessment of bleeding. Non-inferiority trial Median and IQ range values reported for the outcome hospital length of stay
Zumberg 2002[334]	Patients older than 2 years who underwent an allogeneic, matched unrelated donor (MUD), syngeneic, or autologous bone marrow transplant (BMT). Study design: RCT	Patients to receive prophylactic platelet transfusions if their morning platelet counts fell below $10x10^9$/litre vs. patients to receive prophylactic platelet transfusions if their morning platelet counts fell below $20x10^9$/litre.	• All-cause mortality. • Bleeding. • No. of units red blood cells transfused. • Hospital length of stay. • No. of platelet transfusions (prophylactic and therapeutic).	Modified GIMEMA criteria used for assessment of bleeding. The causes of bleeding were primarily muco-cutaneous and genitourinary
Wandt 2012[311]	Patients aged 16-80 years who were undergoing intensive	Prophylactic platelet transfusion when platelet counts were	• Mortality (all cause). • Number of	The WHO grading system for assessment of

	chemotherapy for acute myeloid leukaemia or autologous haemopoietic stem-cell transplantation for haematological cancers. Study design: RCT	$10x10^9$ per litre or lower. vs. Patients to received platelet transfusion when bleeding occurred.	bleeding episodes (grade 2 or higher). • Number of major bleeding episodes (grade 3 and 4). • Duration of hospital stay. • Side effects of transfusion (not defined).	bleeding.
Murphy 1982[204]	Children with previously untreated acute leukaemia. Study design: RCT	The prophylactic group received platelets when the platelet count fell below $20x10^9$/litre per mm^3 irrespective of clinical events versus therapeutic group was transfused only when significant bleeding occurred and not for thrombocytopenia alone.	• Number of patients with bleeding events. • Mortality (all cause). • Mortality from bleeding.	No bleeding scale was stated.

12.3.1 Clinical evidence summary (Summary GRADE profiles):

Table 99: Prophylactic transfusion compared with no prophylactic transfusion - adults who are haematology patients (non-bleeding patients)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylactic transfusion - Adults who are haematology patients	Risk difference with Prophylactic transfusion (95% CI)
Number of patients with bleeding events (WHO grade 2 or higher)	991 (2 studies)	VERY LOW[a,b,c] due to risk of bias, inconsistency, imprecision	RR 0.7 (0.61 to 0.8)	Moderate	
				573 per 1000	172 fewer per 1000 (from 115 fewer to 223 fewer)
Number of patients with major bleeding events (WHO grade 3 or 4)	991 (2 studies)	MODERATE[a] due to risk of bias	RR 0.3 (0.14 to 0.65)	Moderate	
				63 per 1000	44 fewer per 1000 (from 22 fewer to 54 fewer)
Serious adverse events (including sepsis and respiratory deterioration)	598 (1 study)	LOW[c,d] due to risk of bias, imprecision	RR 1.12 (0.6 to 2.07)	Moderate	
				60 per 1000	7 more per 1000 (from 24 fewer to 64 more)
Transfusion related serious adverse event (urticarial and angioedema)	600 (1 study)	VERY LOW[d,e] due to risk of bias, imprecision	RR 3.02 (0.12 to 73.84)	Moderate	
				0 per 1000	-
Number of patients needing platelet transfusion	600 (1 study)	MODERATE[d] due to risk of bias	RR 1.52 (1.37 to 1.69)	Moderate	
				585 per 1000	304 more per 1000 (from 216 more to 404 more)
Number of units (platelets) transfused per patient	600 (1 study)	MODERATE[d] due to risk of bias			The mean number of units (platelets) transfused per patient in the intervention groups was 1.3 higher (0.75 to 1.85 higher)
Mortality (all cause)	391 (1 study)	LOW[e] due to imprecision	RR 0.73 (0.23 to 2.25)	Moderate	
				36 per 1000	10 fewer per 1000 (from 28 fewer to 45 more)
Side effects of transfusion (not specified)	391 (1 study)	VERY LOW[e,f] due to indirectness, imprecision	RR 0.94 (0.57 to 1.56)	Moderate	
				137 per 1000	8 fewer per 1000 (from 59 fewer to 77 more)

(a) Most information is from studies at high risk of bias.
(b) I^2=92%.
(c) Confidence interval crosses one default MID and line of no effect.
(d) Study at high risk of bias.
(e) Confidence interval crosses both default MIDs and line of no effect.
(f) No pre-specified definition of side-effects.

Table 100: Prophylactic transfusion compared with no prophylactic transfusion - children who are haematology patients (non-bleeding patients)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No prophylactic transfusion - Children who are haematology patients	Risk difference with Prophylactic transfusion (95% CI)
Number of patients with major bleeding events (WHO grade 3 or 4)	56 (1 study)	LOW[a,b] due to risk of bias, imprecision	RR 0.55 (0.28 to 1.06)	Moderate	
				524 per 1000	236 fewer per 1000 (from 377 fewer to 31 more)
Mortality (all cause) (3 years)	56 (1 study)	VERY LOW[a,c,d] due to risk of bias, indirectness, imprecision	RR 1.03 (0.48 to 2.2)	Moderate	
				333 per 1000	10 more per 1000 (from 173 fewer to 400 more)
Mortality from bleeding (3 years)	56 (1 study)	VERY LOW[a,d,e] due to risk of bias, indirectness, imprecision	RR 0.3 (0.03 to 3.11)	Moderate	
				95 per 1000	67 fewer per 1000 (from 92 fewer to 200 more)

(a) Study is at high risk of bias.
(b) Confidence interval crosses one default MID and line of no effect.
(c) Mortality assessed at 3 years, our protocol outcome was mortality at 30 days.
(d) Confidence interval crosses both default MIDs and line of no effect.
(e) Mortality assessed at 3 years, our protocol outcome was mortality at 30 days.

Table 101: Low platelet thresholds compared with high platelet thresholds - adults who are haematology patients (non-bleeding patients)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with High platelet thresholds - Adults who are haematology patients	Risk difference with Low platelet thresholds (95% CI)
Mortality (all cause)	658 (4 studies)	LOW[a,b] due to risk of bias, imprecision	RR 1.14 (0.9 to 1.45)	Moderate	
				233 per 1000	33 more per 1000 (from 23 fewer to 105 more)
Mortality (all cause) -	333	LOW[a,c]	RR 1.17	Moderate	

Patients undergoing chemotherapy	(2 studies)	due to risk of bias, inconsistency	(0.85 to 1.6)	391 per 1000	66 more per 1000 (from 59 fewer to 235 more)
Mortality (all cause) - Patients undergoing stem cell transplant	325 (2 studies)	LOW[a,b] due to risk of bias, imprecision	RR 1.12 (0.78 to 1.6)	Moderate	
				226 per 1000	27 more per 1000 (from 50 fewer to 136 more)
Number of patients with bleeding events (WHO grade 2 or higher)	238 (2 studies)	LOW[a,d] due to risk of bias, indirectness	RR 0.97 (0.91 to 1.04)	Moderate	
				975 per 1000	29 fewer per 1000 (from 88 fewer to 39 more)
Number of patients with major bleeding events (WHO grade 3 or 4)	652 (4 studies)	VERY LOW[a,b,e,f] due to risk of bias, inconsistency, indirectness, imprecision	RR 1.17 (0.84 to 1.64)	Moderate	
				172 per 1000	29 more per 1000 (from 28 fewer to 110 more)
Number of patients with major bleeding events (WHO grade 3 or 4) - Patients undergoing chemotherapy	333 (2 studies)	VERY LOW[a,b,g,h] due to risk of bias, inconsistency, indirectness, imprecision	RR 1.41 (0.95 to 2.1)	Moderate	
				185 per 1000	76 more per 1000 (from 9 fewer to 203 more)
Number of patients with major bleeding events (WHO grade 3 or 4)- Patients undergoing stem cell transplant	319 (2 studies)	VERY LOW[a,d,i] due to risk of bias, indirectness, imprecision	RR 0.76 (0.4 to 1.45)	Moderate	
				117 per 1000	28 fewer per 1000 (from 70 fewer to 53 more)
Infections (Bacteraemia)	166 (1 study)	LOW[b,j] due to risk of bias, imprecision	RR 1.14 (0.76 to 1.7)	Moderate	
				345 per 1000	48 more per 1000 (from 83 fewer to 242 more)
Adverse events	78 (1 study)	LOW[b,j] due to risk of bias, imprecision	RR 0.07 (0 to 1.09)	Moderate	
				195 per 1000	181 fewer per 1000 (from 195 fewer to 18 more)
Number of units (platelets) transfused per patient	492 (3 studies)	MODERATE[a] due to risk of bias			The mean number of units (platelets) transfused per patient in the intervention groups was 1.96 lower (3.03 to 0.89 lower)
Number of units (platelets) transfused per patient - Patients undergoing chemotherapy	333 (2 studies)	MODERATE[a] due to risk of bias			The mean number of units (platelets) transfused per patient - patients undergoing chemotherapy in the intervention groups

					was 2.09 lower (3.2 to 0.99 lower)
Number of units (platelets) transfused per patient - Patients undergoing stem cell transplant	159 (1 study)	MODERATE[a] due to risk of bias			The mean number of units (platelets) transfused per patient - patients undergoing stem cell transplant in the intervention groups was 0.2 higher (4.27 lower to 4.67 higher)

(a) Most information is from studies at high risk of bias.
(b) Confidence interval crosses one default MID and line of no effect.
(c) I^2=66%.
(d) Zumberg 2002 assigned bleeding scores based on modified GIMEMA criteria.
(e) I^2=54%.
(f) Heckman 1997 did not use WHO bleeding criteria, but used a standardised toxicity scale (no details reported). Zumberg 2002 assigned bleeding scores based on modified GIMEMA criteria.
(g) I^2=75%.
(h) Heckman 1997 used a standardised toxicity scale to assess severity of bleeding.
(i) Confidence interval crosses both default MIDs and line of no effect.
(j) Study at high risk of bias.

12.4 Economic evidence

Published literature

One economic evaluation was identified comparing prophylactic platelet transfusion to no prophylactic transfusion and has been included in this review.[35] This is summarised in the economic evidence profile below (Table 102) and the economic evidence tables in Appendix I.

One economic evaluation relating to this review question was identified but was excluded due to a combination of limited applicability and methodological limitations.[261] This is summarised in Appendix Q, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix F.

Table 102: Economic evidence profile: Prophylactic versus no prophylactic platelet transfusion

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost-effectiveness	Uncertainty
Campbell 2014[34] (UK NHS)	Partially applicable[(a)]	Potentially serious limitations[(b)]	Within-trial analysis (RCT) of patients 16 years or older who were receiving chemotherapy or undergoing stem-cell transplantation and who had or were expected to have thrombocytopenia receiving: 1. Prophylactic platelet transfusion if the platelet count <10x10^9 per litre 2. No prophylactic transfusion if the platelet count <10x10^9 per litre Analysis of individual level resource use, with unit costs applied.	saves £801[(c)]	See clinical review (Stanworth 2013) and economic evidence table in Appendix I.	n/a	Bootstrapping analysis was used to quantify uncertainty in the costs (95% CI: -£1479 to -£113). Subgroup analyses of costs conducted looking at autologous haematopoietic stem cell transplantation (HSCT) patients and chemotherapy/allogeneic HSCT patient separately. 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.

(a) Health effects not expressed as QALYs.

(b) Health and resource outcomes based on one of two RCTs comparing prophylaxis to no prophylaxis included in the clinical review (Stanworth 2013), 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.

(c) Cost components included: 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 medications, serious adverse event-related investigation and medications and serious adverse event-related ICU ward stay.

Unit costs

Relevant unit costs are provided in Appendix N to aid consideration of cost-effectiveness.

12.5 Evidence statements

Clinical

Prophylactic platelet transfusion versus no prophylactic platelet transfusion in adult haematology patients

Two RCTs compared prophylactic platelet transfusion with no prophylactic platelet transfusion in adult haematology patients. The evidence suggested that there was a clinically important benefit for patients receiving prophylactic platelet transfusion for the outcome of number of patients with major bleeding events (WHO grade 3 or 4). The evidence suggested that there may be fewer patients with bleeding events (WHO grade 2 or higher) and lower mortality in patients receiving prophylactic platelet transfusions, but there was some uncertainty. No difference was observed between groups with respect to side effects of transfusion and serious adverse events, including sepsis and respiratory deterioration, but there was considerable uncertainty. The evidence suggested that transfusion-related serious adverse events (urticarial and angioedema) and number of units (platelets) transfused per patient may be higher in patients receiving prophylactic platelet transfusion, but there was considerable uncertainty. The evidence showed that higher numbers of patients needed platelet transfusions when receiving prophylactic platelet transfusion; this difference was considered to be clinically important. The quality of the evidence ranged from moderate to very low quality.

No evidence was identified for the critical outcomes of infections (for example, pneumonia) and quality of life and for length of stay in hospital.

Prophylactic platelet transfusion versus no prophylactic platelet transfusion in children (haematology patients)

One RCT compared prophylactic platelet transfusions with no prophylactic platelet transfusions in paediatric haematology patients. The evidence suggested that there were fewer number of patients with major bleeding events (WHO grade 3 or 4), and less mortality from bleeding (3 years) in patients receiving prophylactic platelet transfusion, but there was some uncertainty. There was no important difference between the groups for all-cause mortality (3 years). The quality of evidence was of low or very low quality.

No evidence was identified for the critical outcomes of infections, quality of life and serious adverse events, or for the important outcomes of number of patients needing platelet transfusions, number of units of platelets transfused and length of stay in hospital.

Low platelet threshold versus high platelet thresholds (adult haematology patients)

Four RCTs compared low platelet thresholds with high platelet thresholds for transfusion in adult haematology patients. The evidence suggested there were fewer adverse events and less number of units transfused (platelets) per patient in patients receiving platelet transfusion at lower thresholds, but there was some uncertainty. There was no difference between the groups for the outcomes of mortality (all cause), number of patients with bleeding events (WHO grade 2 or 3), number of patients with major bleeding events (WHO grade 3 or 4) and infections (bacteraemia) but there was some uncertainty. The evidence ranged from moderate to very low quality.

No evidence was identified for the critical outcome of quality of life or the important outcomes of number of patients needing platelet transfusions and length of stay in hospital.

Economic

One cost-consequence analysis found that prophylactic platelet transfusion was more costly than no prophylactic platelet transfusion (£801 more per patient) and had 0.21 fewer units of red blood cell transfused per patient, 2% fewer with major bleeds (WHO grade 3 or 4) and 8.4% fewer with bleeds (WHO grade 2 or above), but had 1.31 more units of platelets transfused per patient, mean additional haematology ward stay of 0.5 days and 1% fewer serious adverse events. This was assessed as partially applicable with potentially serious limitations.

12.6 Recommendations and link to evidence

Recommendations	**Patients with thrombocytopenia who are bleeding** **19. Offer platelet transfusions to patients with thrombocytopenia who have clinically significant bleeding (World Health Organization [WHO] grade 2) and a platelet count below $30x10^9$ per litre.** **20. Use higher platelet thresholds (up to a maximum of $100x10^9$ per litre) for patients with thrombocytopenia and either of the following:** • **severe bleeding (WHO grades 3 and 4)** • **bleeding in critical sites, such as the central nervous system (including eyes).**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (occurrence of bleeding in non-bleeding patients and cessation of bleeding in bleeding patients; bleeding defined as WHO grade 2 and above), infections (for example, pneumonia), quality of life and serious adverse events as the critical outcomes for decision making. Other important outcomes included the number of patients needing platelet transfusions, the number of units of platelets transfused and length of stay in hospital.
Trade off between clinical benefits and harms	No evidence was identified to evaluate the effect of different threshold or target platelet counts for blood transfusion in patients who were bleeding. This was true for both haematology and non-haematology patients. The GDG drew on its knowledge and experience and agreed that patients who were bleeding and were thrombocytopenic with a platelet count of less than $30x10^9$/litre should be offered platelet transfusions. It was agreed that, clinically, this was an appropriate level at which the maintenance of platelet counts would outweigh any negative effects of not administering platelet transfusions such as continued or increased bleeding and increased risk of mortality and adverse events. In patients who had severe bleeding (WHO grade 3 and 4) or patients who were bleeding in critical sites, the GDG advocated a more cautious approach and recommended a higher platelet count for transfusion as the risk of mortality and complications of bleeding was higher in this group. As there was a lack of evidence

	for a specific threshold level in this group, the recommendation allows for clinical judgement to select a suitable level between 30x10^9/litre and 100x10^9/litre depending on the clinical circumstances The GDG agreed that the same consensus recommendations should apply for children as for adults in the absence of specific evidence that children with thrombocytopenia and bleeding should be treated differently from adults.
Economic considerations	No relevant economic evaluations comparing different thresholds or targets of platelet counts for platelet transfusion were identified for this population. The cost of platelet transfusion was considered by the GDG. Allogeneic platelets cost £208.09 per unit in England and Wales. It was noted that this cost does not include all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests. One US study (Riley 2012)[251] was identified which reported the additional costs associated with platelet transfusion:£56 per transfusion. The GDG discussed this estimate and felt that it may underestimate the additional costs associated with platelet transfusion. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications. For bleeding patients with thrombocytopenia, the GDG considered that the cost of transfusing platelets at a threshold of 30x10^9/litre was offset by avoiding the negative costly outcomes that would result from not transfusing these patients, such as further bleeding leading to lengthier more expensive hospitalisation (for example, ICU) and mortality. In patients with severe bleeding or bleeding in critical sites, the GDG agreed a higher threshold is justifiable as there is a greater risk of mortality and complications due to bleeding in this group.
Quality of evidence	No studies were identified which met the review protocol criteria. The recommendations for platelet transfusion for patients who were bleeding and were thrombocytopenic were based on the consensus expert opinion of the GDG members. There was no specific evidence available for the use of platelets in the paediatric population.
Other considerations	The recommendations apply to adults and children requiring platelet transfusions.

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Recommendations	**<u>Patients who are not bleeding or having invasive procedures or surgery</u>** **21. Offer prophylactic platelet transfusions to patients with a platelet count below 10x10^9 per litre who are not bleeding or having invasive procedures or surgery, unless they have:** • **chronic bone marrow failure** • **autoimmune thrombocytopenia** • **heparin-induced thrombocytopenia** • **thrombotic thrombocytopenic purpura.**

Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (occurrence of bleeding in non-bleeding patients and cessation of bleeding in bleeding patients; bleeding defined as WHO grade 2 and above), infections (for example, pneumonia), quality of life and serious adverse events as the critical outcomes for decision making. Other important outcomes included the number of patients needing platelet transfusions, the number of units of platelets transfused and length of stay in hospital.
Trade off between clinical benefits and harms	Evidence for platelet transfusion at different platelet count thresholds was available for non-bleeding haematology patients (adults and children). No evidence was identified in non-haematology patients. No evidence was identified to evaluate the effect of different target levels of post-transfusion platelet counts in patients who were not bleeding and were not due to undergo invasive procedures or surgery. Evidence from two studies of platelet thresholds comparing prophylactic transfusion with no-prophylactic transfusion in adult haematology patients showed that there was clinical benefit from the use of prophylactic transfusion with respect to critical outcomes such as number of patients with bleeding events (WHO grade 2 or higher) and number of patients with major bleeding events (WHO grade 3 or 4). The evidence suggested that there was lower mortality (30 days) and side effects of transfusion in patients receiving prophylactic platelet transfusion, but there was some uncertainty within the effect estimates. The evidence suggested higher transfusion-related serious adverse events (urticarial and angioedema) and number of units (platelets) transfused per patient in patients receiving prophylactic platelet transfusion, but there was some uncertainty in the effect estimates. The evidence showed a higher number of patients needing platelet transfusion in patients receiving prophylactic platelet transfusion; this difference was considered to be clinically important. There was no important difference in effect between the groups for serious adverse events (including sepsis and respiratory deterioration). Evidence from one study comparing prophylactic transfusion with no-prophylactic transfusion in paediatric haematology patients showed that there were fewer number of patients with major bleeding events (WHO grade 3 or 4) and mortality from bleeding (3 years) in patients receiving prophylactic platelet transfusion, but there was some uncertainty. There was no important difference between the groups for all-cause mortality (3 years). No evidence was identified for the critical outcomes of infections, quality of life and serious adverse events, or for the important outcomes of number of patients needing platelet transfusions, number of units of platelets transfused and length of stay in hospital. Evidence from fours studies comparing low platelet threshold with high platelet threshold in adults haematology patients showed that there was benefit with the use of a low threshold with respect to number of units of platelets transfused per patient and adverse events, but there was some uncertainty. There was no important difference between the groups for the outcomes mortality (all cause), number of patients with bleeding events (WHO grade 2 or 3), number of patients with major bleeding events (WHO grade 3 or 4) and infections (bacteraemia); but there was some uncertainty in the effect estimates .

	No evidence was identified for the critical outcome of quality of life or the important outcomes of number of patients needing platelet transfusions and length of stay in hospital. Based on the evidence above and the expert consensus opinion of the GDG members, the GDG recommended the use of prophylactic transfusion for non-bleeding patients who were not undergoing invasive procedures or surgery. The GDG discussed the specific platelet count level for transfusion and recommended prophylactic platelet transfusions at a platelet count threshold less than $10x10^9$/litre in patients who were not bleeding and were not undergoing invasive procedures or surgery; this patient group primarily includes haematology patients undergoing intensive chemotherapy and/or haemopoietic stem cell transplantation. The level of platelet count of less than $10x10^9$/litre selected as the threshold for prophylactic platelet transfusions in this patient group was based on the evidence for this threshold provided by the identified studies. The GDG agreed that the same recommendations should apply for children as for adults on the basis of the combined evidence for both adults and children and the lack of specific evidence that children should be treated differently in this situation. .
Economic considerations	One economic evaluation comparing prophylactic to no prophylactic platelet transfusion was identified. This UK cost-consequence analysis found that in adult non-bleeding haematology patients, prophylactic platelet transfusion was more expensive than no prophylactic platelet transfusion. This analysis was based on an RCT by Stanworth 2013 which was included in the clinical evidence. Of note, this study was one of two RCTs identified in the clinical review comparing prophylaxis to no prophylaxis and therefore did not reflect the full body of evidence. Stanworth 2013 showed that there was clinical benefit from the use of prophylactic transfusion with respect to two of the critical outcomes: number of patients with bleeding events (WHO grade 2 or higher) and number of patients with major bleeding events (WHO grade 3 or 4). For other critical outcomes, differences between the two interventions were considered by the GDG to be clinically unimportant. Sensitivity analyses conducted as part of the economic evaluation indicated that when uncertainty in the inputs was explored, the conclusion regarding prophylaxis being more costly than no prophylaxis became less certain. This study was assessed as partially applicable with potentially serious limitations. The GDG considered this economic evaluation provided insufficient economic evidence to recommend a change in current practice, that is, to recommend no prophylaxis transfusion in this population. No relevant economic evaluations comparing different thresholds or targets of platelet counts for platelet transfusion were identified in children. In addition, the cost of platelet transfusion was considered by the GDG. Allogeneic platelets cost £208.09 per unit in England and Wales. It was noted that this cost does not include all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests. One US study (Riley 2012)[251] was identified which reported that the additional costs associated with platelet transfusion were £56 per transfusion. The GDG discussed this estimate and felt that it may underestimate the additional costs associated with platelet transfusion. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications.

	Based on the clinical evidence, the GDG recommended prophylactic transfusions of platelets for non-bleeding patients not undergoing invasive procedures or surgery. The GDG considered that the cost of prophylactic transfusion of platelets was likely to be outweighed by the savings as a result of reducing the number of people experiencing bleeding events which may lead to lengthier, more expensive hospitalisation (for example, ICU) and the need for RBC transfusion. Based on the clinical evidence, the GDG recommended a low platelet count threshold of $10x10^9$/litre was appropriate for these patients.
Quality of evidence	The quality of evidence for most of the outcomes was low or very low by GRADE criteria. This was largely due to risk of bias arising from a lack of allocation concealment, inadequate blinding, serious or very serious imprecision and indirectness of population and outcomes. The recommendation was based on this evidence and the consensus expert opinion of the GDG members. There was no specific evidence available for the use of platelets in the paediatric population.
Other considerations	The recommendations apply to adults and children requiring platelet transfusions. The GDG noted that consideration should be given to raising the platelet threshold in the presence of anti-platelet medications. The GDG does not recommend increasing the threshold for prophylactic platelet transfusions in haematology patients with fever or being administered antibiotics. Although no evidence was identified in children which met the protocol criteria, the GDG noted that in a post-hoc analysis of an RCT of prophylactic platelet transfusions for patients with treatment-induced thrombocytopenia paediatric patients were at a higher risk of bleeding. However this was over a wide range of platelet counts and the excess bleeding risk may have been due to factors other than platelet counts (Josephson et al 2012).

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Recommendations	**<u>Patients who are having invasive procedures or surgery</u>** **22. Consider prophylactic platelet transfusions to raise the platelet count above 50x109 per litre in patients who are having invasive procedures or surgery** **23. Consider a higher threshold (for example 50–75x10^9 per litre) in patients with a high risk of bleeding who are having invasive procedures or surgery after taking into account:** • **the specific procedure the patient is having** • **the cause of the thrombocytopenia** • **whether the patient's platelet count is falling** • **any coexisting causes of abnormal haemostasis.** **24. Consider prophylactic platelet transfusions to raise the platelet count above 100x10^9 per litre in patients having surgery in critical sites, such as the central nervous system (including the posterior segment of the eyes).**

Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (occurrence of bleeding in non-bleeding patients and cessation of bleeding in bleeding patients; bleeding defined as WHO grade 2 and above), infections (for example, pneumonia), quality of life and serious adverse events as the critical outcomes for decision making. Other important outcomes included the number of patients needing platelet transfusions, the number of units of platelets transfused and length of stay in hospital.
Trade off between clinical benefits and harms	No direct evidence was identified to evaluate the effect of different post-transfusion platelet counts in patients who were not bleeding and were undergoing invasive procedures and surgery. The recommendations for prophylactic platelet transfusions in patients who were undergoing invasive procedures or surgery were based on indirect evidence from the review evaluating platelet counts in prophylactic platelet transfusions in patients who were not undergoing invasive procedures or surgery and the consensus expert opinion of the GDG members. The GDG considered it likely that there would be benefits from giving prophylactic platelets in reducing the risk of bleeding and likelihood of requiring a transfusion for these patients. The increase in target platelet count took into account the following: • the specific nature of the invasive procedure or surgery and the risks associated with it • the site at which the procedure was undertaken. It was agreed that these patients may need a more cautious approach if there are additional factors likely to increase the risk of bleeding, such as anti-platelet medication, and they will need to have specific thresholds and targets set for them individually after clinical assessment. Particular caution is advised if the platelet count is falling or there is a co-existing coagulation abnormality. Guidance from the Obstetric Anaesthetists Association (2013) suggests no increased risk of vertebral canal haematoma with central neuroaxial blockade in immune thrombocytopenia (ITP) or gestational thrombocytopenia (GTP) if platelet count is >75 x10^9/l and expert anaesthetists might perform central neuroaxial blockade providing the platelet count is >50 x10^9/l and stable. If the procedure was at a critical site, the GDG agreed that the target platelet counts would have to be even higher to outweigh the risks as any bleeding from these sites was associated with higher risk of adverse events and recommended a target platelet count of 100x10^9/litre for surgery in critical sites such as the central nervous system (including the posterior segment of the eyes) and lungs. There was no specific evidence available for the use of platelets in the paediatric population. The GDG agreed that in general the same recommendations should apply for children as for adults as there was no specific evidence available suggesting that children should be treated differently. However, it was noted that lower thresholds than 50 x10^9/l may be considered for paediatric lumbar puncture procedures that are simple and likely to be uncomplicated, for example in children who have acute leukaemia and are stable.
Economic considerations	No relevant economic evaluations comparing different thresholds or targets of platelet counts for platelet transfusion were identified in this population. The cost of platelet transfusion was considered by the GDG. Allogeneic platelets cost £208.09 per unit in England and Wales. It was noted that this cost does not include

	all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests. One US study (Riley 2012)[251] was identified which reported that the additional costs associated with platelet transfusion were £56 per transfusion. The GDG discussed this estimate and felt that it may underestimate the additional costs associated with platelet transfusion. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications. Based on the expert consensus opinion of the GDG members and indirect evidence, the GDG recommended a higher threshold for prophylactic platelet transfusions depending on the type of procedure or surgery due to the increased risk of bleeding, mortality and adverse events. The GDG considered that the cost of transfusing platelets for these people was likely to be offset by avoiding the negative costly outcomes that would result from not transfusing them, such as increased risk of bleeding leading to lengthier, more expensive hospitalisation (for example, ICU), adverse events and mortality.
Quality of evidence	The recommendations for prophylactic platelet transfusions in patients who were undergoing invasive procedures or surgery were based on indirect evidence and the consensus expert opinion of the GDG members. The quality of the indirect evidence for most of the outcomes was low or very low by GRADE criteria. This was largely due to risk of bias arising from a lack of allocation concealment, inadequate blinding, serious or very serious imprecision and indirectness of population and outcomes. There was no specific evidence available for the use of platelets in the paediatric population.
Other considerations	The recommendations apply to adults and children requiring platelet transfusions.

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Recommendations	**25. Do not routinely offer prophylactic platelet transfusions to patients with any of the following:** • **chronic bone marrow failure** • **autoimmune thrombocytopenia** • **heparin-induced thrombocytopenia** • **thrombotic thrombocytopenic purpura.** **26. Do not offer prophylactic platelet transfusions to patients having procedures with a low risk of bleeding, such as adults having central venous cannulation or any patients having bone marrow aspiration and trephine biopsy.**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (occurrence of bleeding in non-bleeding patients and cessation of bleeding in bleeding patients; bleeding defined as WHO grade 2 and above), infections (for example, pneumonia), quality of life and serious adverse events as the critical outcomes for decision making. Other important outcomes included the number of patients needing platelet transfusions, the number of units of platelets transfused and length of stay in hospital.
Trade off between clinical benefits and	No studies were identified which met the review protocol criteria. The recommendation was based on the consensus expert opinion of the GDG

harms	members. Based on consensus, the GDG recommended not to routinely offer platelets for patients with chronic bone marrow failure, autoimmune thrombocytopenia, heparin-induced thrombocytopenia or thrombotic thrombocytopenic purpura. Whilst platelet transfusions may reduce bleeding and need for transfusion in these patients, the reasons for not recommending platelets in these groups are lack of evidence of clinical effectiveness, the availability of alternative treatments and the potential for adverse effects. The exceptions to this are in the case of major bleeding where alternative measures have been ineffective or have not yet time to produce clinical benefit. The GDG considered that patients undergoing procedures at low risk of bleeding, for example central venous cannulation in adults, and patients undergoing bone marrow aspiration and biopsy should not receive platelet transfusions because of the low risk of bleeding and the potential for complications of transfusion. There was no specific evidence available for the use of platelets in the paediatric population. The GDG agreed that in general the same consensus recommendations should apply for children as for adults in the absence of specific evidence that children should be treated differently from adults. However the assessment of bleeding risk for procedures such as central venous cannulation may be different in small children compared to adults. .
Economic considerations	No relevant economic evaluations comparing different thresholds or targets of platelet counts for platelet transfusion were identified in these populations. The cost of platelet transfusion was considered by the GDG. Allogeneic platelets cost £208.09 per unit in England and Wales. It was noted that this cost does not include all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests. One US study (Riley 2012)[251] was identified which reported that the additional costs associated with platelet transfusion were £56 per transfusion. The GDG discussed this estimate and felt that it may be an underestimate of the additional costs associated with platelet transfusion. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications. The GDG considered that the lack of clinical effectiveness and the potential infectious and immunological risks from receiving a transfusion did not justify the additional cost of transfusing platelets in these populations.
Quality of evidence	No studies were identified which met the review protocol criteria The recommendation was based on the consensus expert opinion of the GDG members.
Other considerations	The recommendations apply to adults and children requiring platelet transfusion.

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13 Platelet transfusion: doses

Platelets are blood cells involved in haemostasis. Platelet concentrates are prepared by blood services from whole blood donations or by apheresis of single donors and are the second most commonly used blood component after red cell transfusion (271,000 adult doses were provided in England in 2013/14)[211]. Platelet transfusions are used to treat and prevent bleeding in patients with thrombocytopenia or platelet dysfunction. While the majority of platelet transfusions are administered to patients with primary haematological disorders, they are commonly used in other clinical scenarios, such as critical care and major haemorrhage.

There are still several areas of controversy concerning the use of platelet transfusions, including whether a policy of prophylactic platelet transfusion is superior to a policy of no prophylaxis for the prevention of severe thrombocytopenic bleeding, what platelet count threshold should be used to trigger the transfusion of prophylactic platelets, and what is the optimal platelet dose to prevent thrombocytopenic bleeding.

National audits of the use of platelet transfusions have shown considerable non-compliance with recommendations for platelet count thresholds and platelet dose.

13.1 Review question: What is the clinical- and cost-effectiveness of different doses of platelet transfusion?

For full details see review protocol in Appendix C.

Table 103: PICO characteristics of review question

Population	• Adults • Children • Exclusions: Patients who are actively bleeding
Intervention(s)	• Low dose or single unit as defined by the trial • High dose or multiple units as defined by the trial
Comparison(s)	• Low dose (single unit) vs. High dose or multiple units
Outcomes	• All-cause mortality at 30 days • Quality of life • Length of stay (hospitalisation) • Infections (for example, pneumonia) • Number of patients needing transfusions • Number of units transfused • Bleeding • Serious adverse events
Study design	• RCTs • Systematic reviews • Large cohort studies

The GDG was interested to know the most clinical and cost-effective dose for platelet transfusions.

Strata

It was acknowledged that that there are differences between haematology and non-haematology patients, adults and children, and patients who are actively bleeding and not actively bleeding.

The review was thus stratified into broad population groups as follows:

Prophylactic transfusions

- Adults who are haematology patients and not bleeding
- Adults who are non-haematology patients and not bleeding
- Children who are haematology patients and not bleeding
- Children who are non-haematology patients and not bleeding

Therapeutic transfusions

- Adults who are haematology patients and bleeding
- Adults who are non-haematology patients and bleeding
- Children who are haematology patients and bleeding
- Children who are non-haematology patients and bleeding

Outcome- Bleeding

The outcome of bleeding to be assessed in this review was defined as that equivalent to WHO grade 2 and above this grade. WHO defines bleeding as grade 2 if there is mild blood loss.

A modified WHO scale defines grade 2 bleeding as epistaxis or oral bleeding for 30 minutes or more (total duration in the prior 24 hours), haematoma, melena, haemoptysis, purpura of 1-inch diameter or more, retinal haemorrhage without visual impairment or blood in cerebrospinal fluid after non-traumatic lumbar puncture.

For full details and definitions of haematology and non-haematology patients, see review protocol in Appendix C.

13.2 Clinical evidence

We searched for randomised trials comparing the effectiveness of low dose platelet transfusions, medium dose platelet transfusions and high dose platelet transfusions.

No systematic reviews or studies were identified which evaluated dosage in therapeutic platelet transfusions.

One Cochrane review was identified which evaluated the effectiveness of different doses of prophylactic platelet transfusions.[97] However, the outcomes and subgroups in this review differed from those outlined in this review's protocol and the analysis has been carried out again taking this into account.

Five studies were included in the review (Heddle 2009,[126] Klumpp 1999,[166] Sensebe 2005,[265] Slichter 2010,[274] Tinmouth 2004;[292] these are summarised in Table 104 below. Of these, one study was not designed to assess the effect of platelet dose on incidence of haemorrhage or overall survival.[166] This study was not analysed as part of this review.

All studies were in patients receiving prophylactic platelet transfusions (studies excluded patients who had bleeding greater than WHO grade 2).

1 **Table 104: Summary of studies included in the review**

Study	Population	Intervention/ Comparison	Outcomes	Comments
Estcourt 2012[97] (Cochrane review)	Patients receiving prophylactic platelet transfusions	Comparison of different doses	• Significant bleeding • All-cause mortality • Infections	Adapted for this review
Heddle 2009[126]	Thrombocytopenic adults were randomised when they required their first study prophylactic platelet transfusion. Subgroup: Prophylactic transfusions. Exclusions: Evidence of WHO grade 2 bleeding or greater at study assessment. Multicentre study (Canada, Norway, US) n=122 (127 randomised) Study design: RCT	Standard dose: 300 to 600x10^9 platelets /product Low dose: 150 to <300x10^9 platelets/ product	• Occurrence of WHO grade 2 or higher bleed • Platelet transfusion requirements • Red blood cell transfusion requirements (SD not reported, but mean difference per thrombocytopenic day reported)	Non-inferiority study
Klumpp 1999[166]	Patients undergoing haematopoietic progenitor cell transplantation. Crossover study. Exclusion: Existence or development of bleeding that required therapeutic platelet transfusion. n=46	Low dose: 3.1x10^{11} platelets (range 2.3-3.5x10^{11}) High dose: 5.0x10^{11} platelets (range 4.5-6.1x10^{11})	None from protocol	Not designed to assess effect of platelet dose on incidence of haemorrhage or overall survival. Not analysed.
Sensebe 2005[265]	PROBE study. Patients with acute leukaemia undergoing first line treatment or autologous haematopoietic stem cell transplantation. Randomised open label study. Multicentre centre study in France. n=101 Study design: RCT	Single dose: 0.5x10^{11}/10 kg Double dose: 1.0x10^{11}/10 kg	WHO grade 2 or 3 haemorrhages (analysed). Number of transfusions (reported in median, range). Total number of platelets transfused (only mean reported, no SD). Mortality (reported but unclear from which arm).	
Slichter 2010[274]	PLADO trial. Thrombocytopenic patients (haematology patients, all ages included, median 30 years). Subgroup: Prophylactic transfusions at platelet thresholds ≤10000 platelets/microliter.	Doses compared (platelets per square meter of body surface area) Low dose: 1.1 x 10^{11}	• Occurrence of WHO grade 2 or higher bleed (including data for subgroups in protocol) • Platelet transfusion requirements • Red blood cell	• Number of platelet units not analysed as total number of units reported and median with range reported; mean and SD not reported; added to summary of evidence

Study	Population	Intervention/ Comparison	Outcomes	Comments
	Patients also received platelet transfusions for acute bleeding or in association with an invasive procedure. Exclusions: • Evidence of WHO grade 2 bleeding or greater at study assessment • Patients receiving anti-thrombotic drugs n=1272 (1351 enrolled) Study design: RCT	Medium dose: 2.2 x 10^{11} High dose: 4.4 x 10^{11}	transfusion requirements (SD not reported, but Mean difference per thrombocytopenic day reported). • Serious adverse events • Mortality	
Tinmouth 2004[292]	Patients with acute leukaemia and undergoing chemotherapy (n=34) or undergoing autologous peripheral blood progenitor cell transplantation (n=77) randomised to receive prophylactic platelet transfusions if platelet count lower than 10 x 10^9/litre. Adults (>16 years of age). Exclusions: Patients who had active bleeding. Patients receiving anti-coagulants, anti-platelet agents and anti-fibrinolytic agents. n=111 Study design: RCT	Low dose: 3 whole blood derived platelet units. Standard dose: 5 whole blood derived platelet units.	• Major bleeding events (WHO grade 2 or higher). • Number of prophylactic platelet transfusion episodes. • Number of platelet units transfused. • Number of RBC transfusion episodes. • Number of RBC units transfused.	• Phase II study. • Stopping criteria to identify high probability of equivalence or moderately high probability of non-equivalence. • Information on protocol subgroups (acute leukaemia, autologous transplant). • Number of platelet units not analysed as total number of units reported and median with range reported; mean and SD not reported; added to summary of evidence.

There was considerable variation in the reporting of units of platelet dose across the studies. Although doses were classified as low, medium or high in the studies, due to the variation in the dose units reported, there were differences in what the patients actually received in terms of number of platelets.

To standardise the doses and analyse them to their nearest groups, the doses were classified based on the standard dosage of platelets used in clinical practice in the UK. The standard UK dosage of platelets per bag is 2.4x10^{11} platelets per unit or bag.[212] The average body surface area for a man is 1.9 m^2 and 1.6 m^2 for a woman. The standard dose of platelets in UK clinical practice equates to a platelet dose between the low and medium dose as reported in the Slichter et al. 2010 study (between 1.1x10^{11} to 2.2x10^{11} per square metre of body surface area per transfusion).[274] Doses reported in other studies were also equated to this standard dose and the classification is presented below (see Table 105).

Table 105: Platelet dose classification

Study	Dose and units as reported in study	Dose group as reported in study	Dose group as analysed in clinical evidence

			review
Slichter 2010[274]	$1.1x10^{11}$ platelets per square metre of body surface area per transfusion	Low dose	LOW
Heddle 2009[126]	$1.5\text{-}3.0x10^{11}$platelets/product	Low dose	LOW
Slichter 2010[274]	$2.2x10^{11}$ platelets per square metre of body surface area per transfusion	Medium dose	MEDIUM/STANDARD
Heddle 2009[126]	3.0-6.0 x 10^{11} platelets/product	Standard dose	MEDIUM
Slichter 2010[274]	4.4 x 10^{11} platelets per square metre of body surface area per transfusion	High dose	HIGH
Sensebe 2005[265]	0.5 x 10^{11}/10 kg	Single dose	MEDIUM/STANDARD
Sensebe 2005[265]	1.0 x 10^{11}/10 kg	Double dose	HIGH
Tinmouth 2004[292]	3 platelet units	3 units	LOW
Tinmouth 2004[292]	5 platelet units	5 units	MEDIUM/STANDARD

Evidence from the above studies is summarised in the GRADE clinical evidence summary tables below (Table 106-Table 108). See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, GRADE tables in Appendix J and excluded studies list in Appendix P.

13.2.1 Clinical evidence summary (summary GRADE profiles)

Table 106: Clinical evidence summary- Low dose versus medium dose

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medium dose	Risk difference with Low dose (95% CI)
Number of patients with bleeding (WHO grade 2 and above)	1070 (3 studies)	MODERATE[a] due to risk of bias	RR 1.04 (0.95 to 1.13)	Moderate	
				492 per 1000	20 more per 1000 (from 25 fewer to 64 more)
Mortality at 30 days	1070 (3 studies)	VERY LOW[a,b] due to risk of bias, imprecision	RR 2.04 (0.7 to 5.93)	Moderate	
				10 per 1000	10 more per 1000 (from 3 fewer to 49 more)
Infections	840 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.01 (0.3 to 3.48)	Moderate	
				12 per 1000	0 more per 1000 (from 8 fewer to 30 more)
Serious adverse events	840 (1 study)	LOW[a,c] due to risk of bias, imprecision	RR 1.31 (0.81 to 2.13)	Moderate	
				64 per 1000	20 more per 1000 (from 12 fewer to 72 more)

(a) Majority of the evidence was from one study where a significant percentage of patients in each group did not receive transfusions within the assigned dose range.
(b) Confidence interval crosses both MIDs.
(c) Confidence interval crosses one MID.

Table 107: Clinical evidence summary- High dose versus medium dose

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Medium dose	Risk difference with High dose (95% CI)
Number of patients with bleeding (WHO grade 2 and above)	951 (2 studies)	MODERATE[a] due to risk of bias	RR 1.02 (0.93 to 1.11)	Moderate	
				366 per 1000	7 more per 1000 (from 26 fewer to 40 more)
Mortality at 30 days	855 (2 studies)	VERY LOW[a,b] due to risk of bias, imprecision	RR 1.71 (0.51 to 5.81)	Moderate	
				10 per 1000	7 more per 1000 (from 5 fewer to 48 more)
Infections	855 (1 study)	VERY LOW[a,b] due to risk of	RR 1.37 (0.44 to	Moderate	
				12 per 1000	4 more per 1000

		bias, imprecision	4.29)		(from 7 fewer to 39 more)
Serious adverse event	855 (1 study)	LOW[a,c] due to risk of bias, imprecision	RR 1.31 (0.81 to 2.11)	Moderate	
				64 per 1000	20 more per 1000 (from 12 fewer to 71 more)

(a) Majority of the evidence was from one study where a significant percentage of patients in each group did not receive transfusions within the assigned dose range.
(b) Confidence interval crosses both MIDs.
(c) Confidence interval crosses one MID.

Table 108: Clinical evidence summary-Low dose versus high dose

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with High dose	Risk difference with Low dose (95% CI)
Number of patients with bleeding (WHO grade 2 and above)	849 (1 study)	LOW[a,b] due to risk of bias, imprecision	RR 1.05 (0.78 to 1.42)	Moderate	
				162 per 1000	8 more per 1000 (from 36 fewer to 68 more)
Mortality at 30 days	849 (1 study)	VERY LOW[a,c] due to risk of bias, imprecision	RR 1.33 (0.5 to 3.54)	Moderate	
				16 per 1000	5 more per 1000 (from 8 fewer to 41 more)
Infections	849 (1 study)	VERY LOW[a,c] due to risk of bias, imprecision	RR 0.74 (0.24 to 2.31)	Moderate	
				16 per 1000	4 fewer per 1000 (from 12 fewer to 21 more)
Serious adverse event	849 (1 study)	VERY LOW[a,c] due to risk of bias, imprecision	RR 1.01 (0.65 to 1.57)	Moderate	
				83 per 1000	1 more per 1000 (from 29 fewer to 47 more)

(a) Majority of the evidence was from one study where a significant percentage of patients in each group did not receive transfusions within the assigned dose range.
(b) Confidence interval crosses one MID.
(c) Confidence interval crosses both MIDs.

13.2.2 Clinical evidence (data not reported in analysable format)

Table 109: Number of platelet transfused

Study	Low dose	Medium dose	High dose
Number of platelet transfusions per patient			
Slichter 2010 (Median, IQR)	5 (3-9)	3 (2-6)	3 (2-6)
Tinmouth 2004 (Median, range)	3 (0-49)	5 (0-110)	-
Total number of platelets transfused			
Slichter 2010 (Median, IQR)	$9.25x10^{11}$ ($4.91x10^{11}$ to $17.91x10^{11}$)	$11.25x10^{11}$ ($6.99x10^{11}$ to $22.76x10^{11}$)	$19.63x10^{11}$ ($10.61x10^{11}$ to $37.44x10^{11}$)

IQR: Interquartile range

13.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

One economic evaluation relating to this review question was identified but was excluded due to a combination of limited applicability and methodological limitations.[251] This is summarised in Appendix Q, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix F.

Unit costs

Relevant unit costs are provided in Appendix N to aid consideration of cost-effectiveness.

13.4 Evidence statements

Clinical

Low platelet dose versus medium platelet dose

Three RCTs compared low dose platelet transfusions with medium dose platelet transfusions. The evidence showed that there was no important difference between low platelet dose and medium platelet dose with respect to number of patients with bleeding (WHO Grade 2 and above). The evidence suggested that mortality and serious adverse events were higher in patients receiving low dose platelet transfusion and that there was no difference between the low dose and medium dose with respect to infections but there was considerable uncertainty. The evidence ranged from moderate to very low quality.

No evidence was identified for the critical outcome quality of life and important outcomes such as number of patients needing platelet transfusions, number of platelet units transfused and length of stay in hospital.

High platelet dose versus medium platelet dose

Two RCTs compared high dose with medium dose for platelet transfusion. The evidence showed that there was no important difference between the groups for the outcome number of patients with bleeding (WHO Grade 2 and above). The evidence suggested that mortality, infections, and serious adverse events were higher in patients receiving high dose platelet transfusion, but there was considerable uncertainty. The quality of the evidence ranged from moderate to very low quality.

No evidence was identified for the critical outcome quality of life, and important outcomes such as number of patients needing platelet transfusions, number of platelet units transfused and length of stay in hospital.

Low platelet dose versus high platelet dose

One RCT compared low dose with high dose for platelet transfusion. The evidence suggested that mortality was higher and infections were fewer in patients receiving low dose platelet transfusion, however there was considerable uncertainty. The evidence suggested that there was no important difference between the groups for the outcomes number of patients with bleeding and serious adverse events, but there was considerable uncertainty. The evidence ranged from low to very low quality.

No evidence was identified for the critical outcome quality of life, and important outcomes such as number of patients needing platelet transfusions, number of platelet units transfused and length of stay in hospital.

Economic

No relevant economic evaluations were identified.

13.5 Recommendations and link to evidence

Recommendations	27. Do not routinely give more than a single dose of platelets in a transfusion.
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (the number of patients with bleeding that was WHO grade 2 and above or equivalent), infections (for example, pneumonia), quality of life and serious adverse events as the critical outcomes for decision making. Other important outcomes included the number of patients needing platelet transfusions, the number of platelet units transfused and length of stay in hospital.
Trade off between clinical benefits and harms	The GDG noted that one unit of platelets in England and Wales is equivalent to a dose midway between the low and medium doses described in the clinical evidence reviewed. Evidence from three RCTs comparing low dose with medium dose for platelet transfusion suggested benefit for patients receiving low dose platelet transfusion with respect to mortality and serious adverse events; but there was considerable uncertainty. The evidence showed that there was no important difference in effects between low platelet dose and medium platelet dose for the outcomes number of patients with bleeding and infections, but there was some uncertainty. No evidence was identified for the critical outcome quality of life and important outcomes such as number of patients needing platelet transfusions, number of platelet units transfused and length of stay in hospital. Evidence from two RCTs comparing high dose with medium dose for platelet transfusion suggested benefit for medium dose with respect to mortality, infections, and serious adverse events, but there was considerable uncertainty in the effect estimates. The evidence showed that there was no important difference in effects between the groups for the outcome number of patients with bleeding. No evidence was identified for the critical outcome quality of life, and important outcomes such as number of patients needing platelet transfusions, number of platelet units transfused and length of stay in hospital. Evidence from one RCT comparing low dose with high dose for platelet transfusion suggested benefit for high dose with respect to mortality, however there was some uncertainty. The evidence suggested that there were fewer infections in patients receiving low dose platelet transfusion, but there was some uncertainty. The evidence suggested that there was no important difference in effects between the groups for the outcomes number of patients with bleeding and serious adverse events, but there was some uncertainty. The evidence was generally of very low quality. No evidence was identified for the critical outcome quality of life, and important outcomes such as number of patients needing platelet transfusions, number of platelet units transfused and length of stay in hospital. 'Based on the lack of evidence of benefit for medium and high dose over

	single dose platelets, the potential for harm from increased donor exposure and the additional costs, the GDG recommended a single dose of platelets per transfusion. It was agreed that limiting the dosage of platelets to a single dose in a transfusion would help save resources and minimise exposure to donor blood. The GDG agreed thatin general the same recommendations should apply for children as for adults in the absence of evidence that children should be treated differently from adults.
Economic considerations	No relevant economic evaluations comparing different doses of platelets for transfusion were identified. The cost of platelets transfusion was considered by the GDG. Allogeneic platelets cost £208.09 per unit in England and Wales. It was noted that this cost does not include all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests. One US study (Riley 2012)[251] was identified which reported that the additional costs associated with platelet transfusion were £56 per transfusion. The GDG discussed this estimate and felt that it may underestimate the additional costs of platelet transfusion. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications. Higher doses (more units) will be associated with higher costs. Based on this and the clinical evidence considerations, the GDG recommended a single unit of platelets per transfusion.
Quality of evidence	The quality of evidence was moderate for the critical outcome of number of patients who had bleeding above WHO grade 2 or equivalent for low dose compared with medium dose and high dose compared with medium dose. The quality of evidence was low for the same outcome when low dose was compared with high dose. The quality of evidence was very low for other critical outcomes (all-cause mortality at 30 days, infections, serious adverse events) for all comparisons in the review. There was no specific evidence available for children.
Other considerations	An adult dose (or unit) of platelets is prepared either by pooling platelets from the buffy coats of 4 whole blood donations or by apheresis of a single donor; the platelet content is approximately 3 x 10^{11}/unit and the volume is approximately 300ml for a unit of pooled buffy coat platelets and 200ml for a unit of apheresis platelets. The recommendation applies to adults and children requiring platelet transfusions. The GDG noted that the dose range for children is usually 10-20ml/kg up to the maximum adult dose. The GDG considered dosing of platelets in platelet function disorders, such as thrombocytopenia, and agreed that higher doses 'e.g. a dose of 2 adult units may be considered in the presence of bleeding or as prophylaxis in advance of major surgery' Tests for platelet dysfunction and other disorders of haemostasis may be carried out as adjuncts to measuring platelet count and are helpful in diagnosis and management. Some patients may have poor response to platelet transfusion and this should be

	investigated and managed appropriately. Although no evidence was identified in non-haematology patients, the GDG was confident in extrapolating the evidence to this population and the recommendation applies to both haematology and non-haematology patients.

1

Recommendations	**28. Only consider giving more than a single dose of platelets in a transfusion for patients with severe thrombocytopenia and bleeding in a critical site, such as the central nervous system (including eyes).**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (the number of patients with bleeding that was WHO grade 2 and above or equivalent), infections (for example, pneumonia), quality of life and serious adverse events as the critical outcomes for decision making. Other important outcomes included the number of patients needing platelet transfusions, the number of platelet units transfused and length of stay in hospital.
Trade off between clinical benefits and harms	The GDG noted that one unit of platelets in England and Wales is equivalent to a dose midway between the low and medium doses described in the clinical evidence reviewed. No clinical evidence was identified for any specific group who require higher doses of platelet transfusion. The GDG considered specific requirements for patients who had severe thrombocytopenia and bleeding in a critical site and agreed that higher doses of platelet transfusions may be needed to provide timely and effective haemostasis. Based on the above rationale and economic considerations, the GDG recommended that higher doses of platelet transfusions, whilst not the standard treatment, may be considered in patients with severe thrombocytopenia and bleeding from a critical site. The GDG agreed that in general the same recommendations should apply for children as for adults in the absence of specific evidence that children should be treated differently from adults, while acknowledging that the precise volume of platelets transfused to children will partly take into account optimal utilisation of the platelet unit in order to minimise wastage and donor exposure (see Other considerations).
Economic considerations	No relevant economic evaluations comparing different doses of platelets for transfusion were identified. The cost of platelet transfusion was considered by the GDG. Allogeneic platelets cost £208.09 per unit in England and Wales. It was noted that this cost does not include all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests. One US study (Riley 2012)[251] was identified which reported that the additional costs associated with platelet transfusion were £56 per transfusion. The GDG discussed this estimate and felt that it may underestimate the additional costs associated with platelet transfusion. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications.

	In patients with severe thrombocytopenia and bleeding in a critical site the GDG made a consensus recommendation to consider transfusing more than one unit per transfusion. The GDG considered that the cost of transfusing additional units in these patients was outweighed by the savings as a result of preventing further bleeding and complications.
Quality of evidence	No studies were identified which met the review protocol criteria. The recommendation for consideration of higher doses of platelet transfusion for severely thrombocytopenic patients and patients who were bleeding from critical sites was based on the consensus expert opinion of the GDG members. Although there was no specific evidence available for the paediatric population, the GDG agreed that the same recommendations should apply for children as for adults.
Other considerations	The protocol for the clinical evidence review set to evaluate the evidence for both haematology and non-haematology populations. Although no evidence was identified in non-haematology patients, the GDG was confident in extrapolating the evidence to this population and the recommendation is applicable to both haematology and non-haematology patients. The GDG noted that the dose range for children is usually 10-20ml/kg up to the maximum adult dose, taking into account aspects including maximal utilisation of the platelet unit and the volume clinically appropriate to transfuse to the patient. . The GDG considered dosing of platelets in platelet function disorders and agreed that higher doses may be required in these cases. Tests for platelet dysfunction and coagulopathies may be carried out as adjuncts to measuring platelet count and are helpful in diagnosis and management. The GDG also considered that some patients may have poor response to platelet transfusion and this should be investigated and managed appropriately. The GDG discussed specific considerations with respect to investigations and platelet dosing in patients receiving antiplatelet drugs and patients who have co-existing coagulopathies.

1

Recommendations	**29. Clinically reassess the patient's condition and check their platelet count after each platelet transfusion, and give further doses if still needed.**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (the number of patients with bleeding that was WHO grade 2 and above or equivalent), infections (for example, pneumonia), quality of life and serious adverse events as the critical outcomes for decision making. Other important outcomes included the number of patients needing platelet transfusions, the number of platelet units transfused and length of stay in hospital.
Trade off between clinical benefits and harms	No clinical evidence was identified for monitoring of platelet counts after each transfusion. The recommendation was based on the consensus expert opinion of the GDG members. It was agreed that there would be minimal discomfort or harms for patients to be reassessed and it was beneficial to check platelet counts after each transfusion to determine the effectiveness of transfusions and potentially avoid further unnecessary transfusions. Based on the above rationale and economic considerations, the GDG

	recommended checking platelet counts after each transfusion. There was no specific evidence available for the paediatric population. The GDG agreed that the same recommendations should apply for children as for adults in order to assess the effectiveness of platelet transfusion..
Economic considerations	The GDG highlighted that the cost of clinically reassessing and checking platelet count was negligible and would be offset by savings as a result of transfusing fewer units of platelets.
Quality of evidence	No studies were identified which met the review protocol criteria. The recommendation for the assessment of platelet counts after each platelet transfusion was based on the consensus expert opinion of the GDG members.
Other considerations	The GDG discussed the importance of monitoring and recommended assessment of platelet count after each platelet transfusion to evaluate response to platelet therapy and guide a further course of treatment. Although no evidence was identified in non-haematology patients, the GDG was confident in extrapolating the evidence to this population and the recommendation is applicable to both haematology and non-haematology patients. Tests for platelet dysfunction and coagulopathies may be carried out as adjuncts to measuring platelet count and are helpful in diagnosis and management. The GDG highlighted the importance of availability of point of care testing to provide evidence for the urgent need for platelet transfusion in clinical settings such as critical care and major surgery. The GDG also considered that some patients may have poor response to platelet transfusion and this should be investigated and managed appropriately. The GDG noted that it was important to check platelet counts after administration of each platelet dose and the recommendation applies to all patients receiving platelet transfusions.

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14 Fresh Frozen Plasma transfusion: thresholds and targets

Fresh frozen plasma (FFP) is either produced from whole blood or obtained by apheresis and rapidly frozen after production to maintain the activity of labile coagulation factors. FFP can be stored at 25°C or below for up to 36 months with rapid thawing at 37°C when needed. After thawing, FFP should be transfused as soon as possible but if delay is unavoidable, it can be stored for up to 4 hours at 22±2°C or 24 hours if stored at 4±2°C. The dose in adults is 15 ml/kg in adults. In the UK, FFP is sourced, as far as possible, from male donors in order to minimize the risk of passive transfer of donor white cell antibodies that can cause transfusion-related acute lung injury (TRALI).

In the UK, FFP for use in patients born after 1996 is sourced from countries with a low risk of vCJD and is pathogen inactivated using methylene blue to reduce the baseline risk of viral transmission.

There is a lack of good evidence to support the clinical use of FFP with largely empirical use in many clinical settings. FFP transfusion is indicated in patients with coagulopathy in the context of major haemorrhage and acute disseminated intravascular coagulation (DIC) in the presence of bleeding. It can also be used to treat inherited single coagulation factor deficiencies if the appropriate factor concentrates are not available. However, FFP should not be used for reversal of oral anticoagulation where the use of prothrombin complex concentrate is indicated. While prophylactic FFP is commonly used in liver disease, many studies show the lack of evidence of clinical benefit in this setting. Audits show that a large proportion of the FFP used in the UK is inappropriate, exposing patients to unnecessary risks.

14.1 Review question: What is the clinical- and cost-effectiveness of transfusions of fresh frozen plasma (FFP) to treat and prevent bleeding?

For full details see review protocol in Appendix C.

Table 110: PICO characteristics of review questions

Population	• Adults who are bleeding • Adults receiving prophylaxis and undergoing procedures • Adults receiving prophylaxis and not undergoing procedures • Children who are bleeding • Children receiving prophylaxis and undergoing procedures • Children receiving prophylaxis and not undergoing procedures

Intervention(s)	• FFP transfusions at different levels of International Normalised Ratio (INR) levels/range of INR levels
	  ○ International normalized ratio (INR) ≤1.5
	  ○ INR 1.6- 2.0
	  ○ INR 2.1 – 2.5
	  ○ INR ≥2.6
	• FFP transfusions based on different levels of prothrombin ration (PT)
	• FFP transfusions based on different levels of activated partial thromboplastin time (APTT)

Comparison(s)	

	• FFP transfusions at different levels of International Normalised Ratio (INR) levels/range of INR levels will be compared to one another. • Transfusions of FFP will also be compared to no transfusion of FFP at each of the above INR levels. • FFP transfusions based on different levels of prothrombin ration (PT) will be compared to one another. • FFP transfusions based on different levels of activated partial thromboplastin time (APTT) will be compared to one another.
Outcomes	Critical outcomes: • Occurrence of bleeding (WHO grade 2 and above or equivalent) • 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 Important outcomes: • Number of patients needing red cell transfusions • Number or volume of red cells transfused • Length of stay (hospitalisation) • Correction of abnormal coagulation test
Study design	• RCTs • Systematic reviews • Observational studies

14.2 Review question: What is the clinical- and cost-effectiveness of different target levels of post-transfusion haemostasis tests with the use of fresh frozen plasma (FFP) for prophylactic transfusions?

For full details see review protocol in Appendix C.

Table 111: PICO characteristics of review question

Population	• Adults who are bleeding • Adults receiving prophylaxis and undergoing procedures • Adults receiving prophylaxis and not undergoing procedures • Children who are bleeding • Children receiving prophylaxis and undergoing procedures • Children receiving prophylaxis and not undergoing procedures
Intervention(s)	FFP transfusion to achieve the following target INR levels will be compared to one another: • FFP transfusion to high target levels of INR (as defined by trial) • FFP transfusion to low target levels of INR (as defined by trial) •
Comparison(s)	• FFP transfusion to achieve high target INR levels will be compared with FFP

	transfusion to achieve low target INR levels.
Outcomes	Critical outcomes: • Occurrence of bleeding (WHO grade 2 and above or equivalent) • 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 Important outcomes: • Number of patients needing red cell transfusions • Number or volume of red cells transfused • Length of stay (hospitalisation) • Correction of abnormal coagulation test
Study design	• RCTs • Systematic reviews • Observational studies

14.3 Clinical evidence

We have combined the questions for FFP thresholds and FFP targets in one review. We searched for systematic reviews, randomised controlled trials and observational studies addressing the two clinical questions: effectiveness of transfusions of fresh frozen plasma (FFP) to treat and prevent bleeding and effectiveness of different target levels of post-transfusion haemostasis tests with the use of fresh frozen plasma FFP for prophylactic transfusions.

Four studies, three RCTs[189,218,294] comparing FFP with no FFP and one multicentre prospective cohort study (2 papers) comparing different INR ranges were included in the review.[282,310] This review includes 3 comparisons: Therapeutic FFP vs. No FFP (Noddeland 2002); Prophylactic FFP vs. No FFP (Matsumoto 2007, Trimble 2007); FFP transfusion at different INR ranges (Walsh 2010).

One Cochrane review [149] was included in the review; this review aimed to determine whether the use of a restrictive versus a liberal plasma transfusion threshold affected mortality or morbidity in critically ill patients, and also to assess the clinical effects of different plasma transfusion thresholds in critically ill patients. However, no RCTs were identified or included in the Cochrane review that evaluated plasma transfusion strategies according to predetermined coagulation test thresholds.

One large cohort study[90] comparing therapeutic FFP transfusion with no FFP transfusion was considered for inclusion. The study aimed to assess the relationship between therapeutic transfusion of FFP and 30 day mortality in cardiac surgery patients suffering from excessive bleeding.

These are summarised in Table 72 below.

The table includes references Octaplas and Uniplas which are specific preparations of FFP.

The data for the review could not be pooled due to variation in the study designs, populations groups and comparisons across the studies. The results have been presented per study, but quality assessment was done per outcome as in GRADE applying the criteria of assessment of risk of bias, indirectness and imprecision. Evidence from the included studies is summarised in the modified GRADE clinical evidence profile below (Table 113). The data for some of the outcomes was not reported in an analysable format, for example, no confidence intervals were reported for the change in INR. However, the GDG felt that it was useful to still present the raw data and a modified GRADE

approach was undertaken to assess the quality of the evidence in the absence of being able to asses imprecision. See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, and excluded studies list in Appendix P.

Table 112: Summary of studies included in the review

Study	Population, no. of patients, study design, setting	Intervention/ comparison	Outcomes	Comments
Matsumoto 2007[189]	RCT n=43 Setting: Japan 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.	Prophylactic FFP vs. no FFP	No relevant outcomes reported	Aim of the study: To evaluate whether or not the infusion of FFP could prevent the occurrence of VOD in high risk patients who had undergone SCT
Noddeland 2002[218]	Prospective parallel group randomised controlled trial Setting: Norway n=84 Adult patients scheduled for elective open heart surgery. Exclusion criteria: unstable angina pectoris, hypersensitivity to blood products, exposure to viral hepatitis during the last 6 months, suspected drug abuse, participation in other clinical studies or pregnancy.	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 plasma)	• 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	Aim of the study: To compare the effect of Uniplas and Octaplas in open heart surgery

Study	Population, no. of patients, study design, setting	Intervention/ comparison	Outcomes	Comments
Trimble 1964[294]	RCT Setting: Canada n=51 Patients undergoing open-heart surgery Included both adults and children	Prophylactic FFP vs. No FFP FFP I unit (250 cc) and 2 units (500 cc) for adults was administered.	• Post-operative bleeding (chest drainage in first 24 hours)	Study aimed to establish whether the routine use of fresh frozen plasma would measurably decrease post-operative bleeding after open heart surgery. Data reported separately for adults and children
Walsh 2010/Stanworth 2011[282,310]	Prospective multiple centre observational cohort study Setting: UK n=1,923 Inclusion of all patients sequentially admitted to 29 adult UK general ICUs over 8 weeks	FFP transfusion at different INR levels (threshold)	• Mortality • Clinically significant bleeding recorded on same day as FFP transfusion • Change of INR following FFP transfusion • Median length of hospital stay	• Critically ill patients with prolonged prothrombin time Strata: • Adults who are bleeding • Adults receiving prophylaxis and undergoing procedures • Adults receiving prophylaxis and not undergoing procedures
Karam 2013[149]	Cochrane Systematic review 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. No RCTs were identified that evaluated plasma transfusion strategies according to predetermined coagulation test thresholds.	Two plasma transfusion strategies, using a restrictive and a liberal threshold of at least one coagulation test,	• 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.	• Critically ill patients
Doussau	Prospective cohort	Therapeutic FFP transfusion vs. no	• Mortality (30 days)	Study aimed to assess relationship

Study	Population, no. of patients, study design, setting	Intervention/ comparison	Outcomes	Comments
2014[90]	study n=967 (n=562 transfused with FFP and n=405 not transfused with FFP) Recruited from 15 French centres All adult patients undergoing on-pump cardiac surgery and exhibiting peri-operative excessive bleeding complications until 48 hours after surgery were eligible. Patients who received a preventive FFP transfusion were excluded	FFP	• Adverse events	between therapeutic transfusion of FFP and 30 day mortality in cardiac surgery patients suffering from excessive bleeding. Study does not define adverse events.

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Table 113: Modified GRADE profile: FFP transfusion versus No FFP transfusion

Quality assessment								
Study	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Effect size**	**Quality**	**Importance**
Mortality (all-cause) at 30 days-								
Walsh 2010[310]/ Stanworth 2011[282]	Prospective cohort study Comparison: INR >1.5 vs. INR <1.5	Serious[a]	Not applicable	Very serious[b]	No imprecision	ICU mortality (30 days): RR: 2.95 (2.96 to 3.54)	VERY LOW	Critical
Length of hospital stay								
Walsh 2010[310]/ Stanworth 2011[282]	Prospective cohort study Comparison: INR >1.5 vs. INR <1.5	Serious[a]	Not applicable	Serious[b]	Not applicable	(Median length of ICU stay, (Q1,Q3)) Admissions with INR >1.5: 3.0 (1.1, 8.1) days Admissions with normal INR test: 1.8 (0.8, 4.3) days	VERY LOW	Important
Change in INR								
Walsh 2010[310]/ Stanworth 2011[282]	Prospective cohort study Comparison: INR >1.5 vs. INR <1.5	Serious[a]	Not applicable	Serious[b]	Not applicable	Median change in INR (pre to post-transfusion INR changes): INR 1 to <1.5: -0.1 INR 1.6 to 2.5: -0.4 INR 2.6 to 3.5: -1.0 INR >3.5: -2.5	VERY LOW	Important
Activated clotting time (ACTT) – Baseline (mean ±SD) seconds								
Noddeland	RCT	Not serious	Not applicable	Serious[c]	Not	Group 1 (n=25): Uniplas (blood	MODERATE	

2002 [218]	Comparison: Therapeutic FFP transfusion vs. no FFP				applicable	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 (all ABO blood groups):135.13±11.64 Group 4 (n=29): control (No FFP. all ABO blood groups):132.27±16.83		
Activated clotting time (ACTT) – After surgery [mean ±SD] seconds								
Noddeland 2002 [218]	RCT Comparison: Therapeutic FFP transfusion vs. no FFP	Not serious	Not applicable	Serious[c]	Not applicable	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 (all ABO blood groups): 111.40±11.03 Group 4 (n=29): control (No FFP . all ABO blood groups): 115.65±11.27 P=NS	MODERATE	
Activated partial thromboplastin time (APTT)-baseline [mean ±SD] seconds								
Noddeland 2002 [218]	RCT Comparison: Therapeutic FFP transfusion vs. no FFP	Not serious	Not applicable	Serious[c]	Not applicable	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 (all ABO blood groups): 28.38±8.15 Group 4 (n=29): control (No FFP	MODERATE	

						. all ABO blood groups):37.19±30.20		
Activated partial thromboplastin time (APTT)-After surgery (mean ±SD) seconds								
Noddeland 2002 [218]	RCT Comparison: Therapeutic FFP transfusion vs. no FFP	Not serious	Not applicable	Serious[c]	Not applicable	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 (all ABO blood groups):36.88±5.28 Group 4 (n=29): control (No FFP, all ABO blood groups):37.69±5.06 P=ns Note: APTT values were moderately elevated after termination of operation of all 4 groups	MODERATE	
No. of patients needing RBC transfusion								
Noddeland 2002 [218]	RCT Comparison: Therapeutic FFP transfusion vs. no FFP	Not serious	Not applicable	Serious[3]	Not applicable	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 (all ABO blood groups) : 13 Group 4 (n=29): control (No FFP, all ABO blood groups):14	MODERATE	
No. of units (RBC) transfused (median , range)								
Noddeland	RCT	Not serious	Not applicable	Serious[3]	Not	Group 1 (n=25): Uniplas (blood	MODERATE	

2002 [218]	Comparison: Therapeutic FFP transfusion vs. no FFP				applicable	groups A,B or AB): 4 (1-14) Group 2 (n=11): Uniplas (blood group O): 5 (1-15) Group 3 (n=19): Octaplas (all ABO blood groups) :4 (2-7) Group 4 (n=29): control (No FFP, all ABO blood groups): 2 (1-5)		
Post-operative bleeding rates from chest drainage (mean ±SD) ml								
Noddeland 2002 [218]	RCT Comparison: Therapeutic FFP transfusion vs. no FFP	Not serious	Not applicable	Serious[3]	Not applicable	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 (all ABO blood groups):993±693 Group 4 (n=29): control (No FFP, all ABO blood groups): 625±181	MODERATE	
Trimble 1964 [294]	RCT Comparison: Prophylactic FFP transfusion vs. no FFP transfusion					Chest drainage first 24 hours (cc) in Children (under 15 years of age) [mean, range] 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] FFP (n=15): 400 (90 to 900) No FFP: 500 (75 to 3,700)	MODERATE	
Quality of life								
No evidence available								Critical
Infections								

No evidence available								Critical
Serious adverse events								
No evidence available								Critical

(a) Observational study and is therefore more prone to selection bias
(b) Critically ill patients
(c) Patients scheduled for elective open heart surgery

Table 114: Modified GRADE profile: Therapeutic FFP transfusion versus No FFP transfusion (cohort study)

Quality assessment						Effect size	Quality	Importance
Study	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**			
Mortality (all-cause) at 30 days-								
Doussau 2014 [90]	Prospective Cohort study n=967 (n=562 transfused with FFP and n=405 not transfused with FFP) FFP vs. no FFP	Serious[a]	Not applicable	No	No	RR 3.02 [1.91 to 4.78][b] **Absolute risk difference** 105 more per 1000 (from 47 more to 196 more)	LOW	Critical
Doussau 2014 [90]	Prospective Cohort study n=967 (n=562 transfused with FFP and n=405 not transfused with FFP)	Serious[a]	Not applicable	No[d]	Very serious[c]	RR 6.49 [0.35 to 120.21]	VERY LOW	Critical

Quality assessment						Effect size	Quality	Importance
Study	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**			
	Therapeutic FFP transfusion vs. no FFP transfusion							

(a) Observational study and is therefore more prone to selection bias.

(b) Other factors significantly associated with 30 day mortality in the univariate analysis were intra-operative haemorrhage (versus 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 (as reported in the paper Doussau 2014).

(c) Confidence interval crosses both default MIDs (0.75 and 1.25) and line of no effect.

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14.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

One economic evaluation relating to the FFP threshold review question was identified but was excluded due to a combination of limited applicability and methodological limitations.[261] This is summarised in Appendix Q, with reasons for exclusion given.

See also the economic article selection flow chart in Appendix F.

Unit costs

Relevant unit costs are provided in Appendix N to aid consideration of cost-effectiveness.

14.5 Evidence statements

Clinical

Prophylactic FFP transfusion versus No prophylactic FFP transfusion

One RCT compared prophylactic FFP transfusion with no prophylactic FFP transfusion. The evidence showed that chest drainage at first 24 hours (cc) in adults and children was found to be lower in the prophylactic FFP group compared with no prophylactic FFP, but there was some uncertainty

The evidence ranged from moderate to very low quality.

No evidence was identified for the critical outcomes such as all-cause mortality at 30 days, infections, quality of life and serious adverse events, and important outcomes such as number of patients needing RBC transfusions, the number of units of RBC transfused, correction of abnormal coagulation tests and length of stay in hospital.

Therapeutic FFP transfusion versus No therapeutic FFP transfusion

One RCT and one cohort study compared therapeutic FFP versus no therapeutic FFP. The evidence suggested that fewer numbers of units (RBC) transfused in patients receiving therapeutic FFP transfusion. The evidence showed that blood loss was higher in patients receiving therapeutic FFP transfusion compared with no therapeutic FFP transfusion, but there was considerable uncertainty

There was no important difference in effects between the groups for the following outcomes number of patients needing RBC transfusion, activated partial thromboplastin time (APTT) (seconds) (before and after surgery) and activated clotting time (ACTT) (seconds) (before and after surgery).

The evidence ranged from moderate to very low quality.

No evidence was identified for the critical outcomes such as all-cause mortality at 30 days, bleeding, infections, quality of life and serious adverse events; and important outcomes such as length of stay in hospital.

FFP transfusion at different INR ranges- Admissions with INR greater than 1.5 versus admissions with normal INR test

One cohort study compared FFP transfusion for patients with admissions with INR greater than 1.5 versus patients with admissions with normal INR test. The evidence showed that mortality (all-cause at 30 days) and length of hospital stay was higher in patients with admissions with INR greater than 1.5; this difference was considered to be clinically important. The evidence showed that 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 less than 1.5, 1.6 to 2.5, 2.6 to 3.5 and more than 3.5, respectively); this difference was considered to be clinically important.

The evidence was of very low quality.

No evidence was identified for the critical outcomes such bleeding, infection, quality of life and serious adverse events , and important outcomes such as number of patients needing RBC transfusions and the number of units of RBC transfused.

Economic

No relevant economic evaluations were identified.

14.6 Recommendations and link to evidence

Recommendations	**30. Only consider fresh frozen plasma transfusion for patients with clinically significant bleeding but without major haemorrhage if they have abnormal coagulation test results (for example, prothrombin time ratio or activated partial thromboplastin time ratio above 1.5).**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (occurrence of bleeding in non-bleeding patients and cessation of bleeding in bleeding patients; bleeding defined as WHO grade 2 and above), infections (including pneumonia, surgical site infection, UTI and septicaemia/bacteraemia), quality of life and serious adverse events as the critical outcomes for decision making. Other important outcomes included the number of patients needing RBC transfusions, the number of units of RBC transfused, correction of abnormal coagulation tests and length of stay in hospital.
Trade off between clinical benefits and harms	There was evidence from one RCT comparing therapeutic FFP transfusion with no FFP transfusion, which showed that there were fewer units of RBC transfused in the group with no FFP transfusion when compared with the groups receiving FFP transfusion. The evidence also suggested that blood loss was higher in patients receiving Therapeutic FFP transfusion compared with no therapeutic FFP transfusion; but there was considerable uncertainty There was no evidence of difference in effect between the groups receiving FFP transfusion and no FFP transfusion for important outcomes such as activated clotting time (ACT), activated partial thromboplastin time (APTT) and number of patients needing RBC transfusion. There was also evidence from one of two large multicentre prospective cohort studies (Walsh 2010, Stanworth 2011, Doussau 2014). [310, 282, 90] The study, Walsh 2010, compared the effect of FFP transfusion at different INR ranges and the independent association of mortality with INR levels. The study reported lower mortality at 30 days in patients who were admitted to the hospital with INR less than 1.5 as compared with patients who were admitted with INR greater than 1.5.

	The median reductions in INR were greater when the pre-FFP transfusion INR values were higher. There was no evidence of difference in effects between the patients admitted with INR greater than 1.5 and INR less than 1.5 for length of hospital stay. The study, Doussau 2014, compared therapeutic FFP transfusion with no FFP transfusion to assess 30 day mortality in cardiac surgery patients suffering from excessive bleeding. The study showed that there was higher mortality and adverse events in the group receiving therapeutic FFP transfusion compared to the group receiving no FFP transfusion. However, the study reported a number of other factors which were found to be significantly associated with 30 day mortality in the univariate analysis. After fitting a model adjusted for all potential confounders, no association was found between FFP transfusion and 30 day mortality. There was no evidence available for the outcomes quality of life, infections, serious adverse events and adverse events related to the transfusion and length of hospital stay. The GDG recommended that FFP should be considered for situations where a patient has clinically significant bleeding and abnormal coagulation test results. In this case, the benefits of potentially reducing bleeding are likely to outweigh the risks of serious adverse events. Major haemorrhage is outside the scope of this guideline. There was no specific evidence available for the for the use of FFP in the paediatric population. The GDG agreed that the same recommendations should apply for children as for adults in the absence of evidence that children with bleeding and abnormal coagulation tests should be treated differently with FFP compared to adults.
Economic considerations	No relevant economic evaluations comparing different thresholds or targets for FFP transfusion were identified. The costs of FFP and Octaplas® transfusion were considered by the GDG. Clinical FFP (UK sourced) costs £28 per unit in England and Wales and Octaplas® costs £53 per 200 ml bag. For patients born on or after 1st January 1996 FFP is sourced from countries with a low risk of vCJD. Either Octaplas® or methylene blue FFP (MBFFP) both pathogen inactivated, are used for these recipients. The cost of MBFFP (non-UK sourced) is £177 per unit in England and Wales. It was noted that these costs do not include all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications. For bleeding patients with abnormal coagulation tests the GDG considered that the cost of transfusing FFP was likely to be offset by avoiding the negative costly outcomes that could result from not transfusing these patients. The negative outcomes potentially include further bleeding leading to lengthier and more complex (and more costly) hospitalisation (for example, ICU) and mortality. There was no specific evidence available for the use of FFP in the paediatric population. The GDG agreed that the same recommendations should apply for children as for adults.
Quality of evidence	The quality of evidence from 1 RCT was very low due to the indirectness of the interventions/population, risk of bias arising from a lack of allocation concealment and inadequate blinding. The quality of evidence from the two cohort studies was

	very low due to the indirectness of the population, and to the risk of bias arising from selection bias related to the design of the observational study. There was no specific evidence available for children. The recommendation was based on the indirect evidence and consensus opinion of the GDG members.
Other considerations	The recommendations apply to adults and children requiring FFP transfusions. The GDG noted that the recommendation may not be applicable to patients with major haemorrhage. For such patients please refer to other appropriate guidance (for example, follow the recommendations in NICE's guideline on Major trauma, currently in development).

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Recommendations	**31. Do not offer fresh frozen plasma transfusions to correct abnormal coagulation in patients who:** • **are not bleeding and** • **are not having invasive procedures or surgery with a risk of clinically significant bleeding.**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (occurrence of bleeding in non-bleeding patients and cessation of bleeding in bleeding patients; bleeding defined as WHO grade 2 and above), infections (including pneumonia, surgical site infection, UTI and septicaemia/bacteraemia), quality of life and serious adverse events as the critical outcomes for decision making. Other important outcomes included the number of patients needing RBC transfusions, the number of units of RBC transfused, correction of abnormal coagulation tests and length of stay in hospital.
Trade off between clinical benefits and harms	No evidence was identified on the effectiveness of FFP transfusions in non-bleeding patients. In patients who have abnormal coagulation test results but are not bleeding and are not having invasive procedures or surgery with a risk of clinically significant bleeding, the GDG considered a more cautious approach and recommended not offering FFP transfusion as there is no evidence of benefit and a risk of complications associated with transfusion, for example, transfusion associated circulatory overload (TACO). There was no specific evidence available for the indications for prophylactic FFP transfusion in the paediatric population. The GDG agreed that the same recommendations should apply for children as for adults in the absence of evidence that children with abnormal coagulation tests should be treated differently with FFP compared to adults.
Economic considerations	No relevant economic evaluations comparing different thresholds or targets for FFP transfusion were identified. The costs of FFP and Octaplas® transfusion were considered by the GDG. Clinical FFP (UK sourced) costs £28 per unit in England and Wales and Octaplas® costs £53 per 200 ml bag. For patients born on or after 1st January 1996 FFP is sourced from countries with a low risk of vCJD. Either Octaplas® or methylene blue FFP (MBFFP) both pathogen inactivated, are used for these recipients. The cost of MBFFP (non-UK sourced) is £177 per unit in England and Wales. It was noted that these costs do not include all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused.

	Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications. The GDG considered that the lack of clinical effectiveness and the potential infectious and immunological risks from receiving a transfusion did not justify the additional cost of transfusing fresh frozen plasma in these populations. There was no specific evidence available for the use of prophylactic FFP transfusion in the paediatric population. The GDG agreed that the same recommendations should apply for children as for adults.
Quality of evidence	No evidence was identified for the use of FFP for prophylactic transfusions in adults. The recommendations were based on the consensus expert opinion of the GDG members. There was no specific evidence available for children.
Other considerations	The recommendation applies to adults and children requiring FFP transfusions.

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Recommendations	**32. Consider prophylactic fresh frozen plasma transfusions for patients with abnormal coagulation who are having invasive procedures or surgery with a risk of clinically significant bleeding.**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (occurrence of bleeding in non-bleeding patients and cessation of bleeding in bleeding patients; bleeding defined as WHO grade 2 and above), infections (including pneumonia, surgical site infection, UTI and septicaemia/bacteraemia), quality of life and serious adverse events as the critical outcomes for decision making. Other important outcomes included the number of patients needing RBC transfusions, the number of units of RBC transfused, correction of abnormal coagulation tests and length of stay in hospital.
Trade off between clinical benefits and harms	There was evidence from two RCTs comparing prophylactic FFP transfusion with no FFP transfusion. There was no evidence of a difference in effect between the groups receiving prophylactic FFP transfusion and no FFP transfusion for critical outcomes such as bleeding. There was no evidence available from the studies for the following outcomes: mortality, quality of life, infections, serious adverse events and adverse events related to the transfusion, length of hospital stay and abnormal coagulation tests. The GDG drew on its knowledge and experience to make this recommendation based on the consensus expert opinion of its members. It agreed that prophylactic FFP transfusion should be considered for patients having surgery or invasive procedures with a risk of clinically significant bleeding and abnormal coagulation test results. However, given the lack of evidence of benefit and the potential risks of transfusion, prophylactic FFP should be reserved for patients at high risk of clinically significant bleeding (including bleeding at critical sites). There was no specific evidence available for the indications for prophylactic FFP transfusion in the paediatric population. The GDG agreed that the same recommendations should apply for children as for adults in the absence of evidence that children with abnormal coagulation tests having invasive procedures or surgery at risk of bleeding should be treated differently with FFP compared to adults.

Economic considerations	No relevant economic evaluations comparing different thresholds or targets for FFP transfusion were identified. The costs of FFP and Octaplas® transfusion were considered by the GDG. Clinical FFP (UK sourced) costs £28 per unit in England and Wales and Octaplas® costs £53 per 200 ml bag. For patients born on or after 1st January 1996 FFP is sourced from countries with a low risk of vCJD. Either Octaplas® or methylene blue FFP (MBFFP) both pathogen inactivated, are used for these recipients. The cost of MBFFP (non-UK sourced) is £177 per unit in England and Wales. It was noted that these costs do not include all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications. For patients having surgery or invasive procedures with a risk of clinically significant bleeding and where there are abnormal coagulation test results, the GDG considered that the cost of transfusing FFP was likely to be offset by avoiding the negative costly outcomes that would result from not transfusing these patients. The negative outcomes potentially include bleeding leading to lengthier and more complex (and more costly) hospitalisation (for example, ICU) and mortality. There was no specific evidence available for the use of prophylactic FFP transfusion in the paediatric population. The GDG agreed that the same recommendations should apply for children as for adults.
Quality of evidence	The quality of evidence was very low due to the indirectness of the interventions/population, the risk of bias arising from a lack of allocation concealment and inadequate blinding. The recommendations were based on indirect evidence and the consensus expert opinion of the GDG members. There was no specific evidence available for children.
Other considerations	The GDG noted that the risk of bleeding depends on the patient's clinical condition and that of the procedure itself. Surgeons may also attribute a particular level of bleeding risk to certain procedures based on their experience and expertise. The recommendations apply to adults and children requiring FFP transfusions.

15 Fresh Frozen Plasma transfusion: doses

Please see the thresholds and targets chapter for introductory text.

15.1 Review question: What is the clinical- and cost-effectiveness of different doses of FFP?

For full details see review protocol in Appendix C.

Table 115: PICO characteristics of review question

Population	• Adults who are bleeding • Adults receiving prophylaxis and undergoing procedures • Adults receiving prophylaxis and not undergoing procedures • Children who are bleeding • Children receiving prophylaxis and undergoing procedures • Children receiving prophylaxis and not undergoing procedures
Intervention(s)	• Standard dose FFP as reported by trial • High dose FFP as reported by trial
Comparison(s)	Standard dose vs. high dose
Outcomes	Critical outcomes: • Occurrence of bleeding (WHO grade 2 and above or equivalent) • 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 Important outcomes: • Number of patients needing red cell transfusions • Number or volume of red cells transfused. • Length of stay (hospitalisation) • Correction of abnormal coagulation test
Study design	• RCTs • Systematic reviews • Observational studies

15.2 Clinical evidence

We searched for systematic reviews, randomised controlled trials and observational studies addressing effectiveness of different doses of fresh frozen plasma (FFP) for transfusion.

No RCTs were identified for the review. One retrospective cohort study met our inclusion criteria and was included in the review;[55]this is summarised in Table 72 below.

The study compared a standard dose and high dose doses of FFP to assess whether this resulted in correction of coagulation test results. The population included critically patients who were bleeding or about to undergo procedure.

The study reported the following outcomes: correction of coagulation abnormalities (prothrombin time [PT] and activated partial thromboplastin time [APTT]). No clinical outcomes were reported.

The data for some of the outcomes was not reported in an analysable format. However, the GDG felt that it was useful to still present the raw data and a modified GRADE approach was undertaken to assess the quality of the evidence in the absence of being able to asses imprecision. . The results have been presented per study, but quality assessment done per outcome using a modified GRADE approach.

Evidence from the included study is summarised in the modified GRADE profile below (Table 113). See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, and excluded studies list in Appendix P.

Table 116: Summary of studies included in the review

Study	Population , study design, n, setting	Intervention/comparison	Outcomes	Comments
Chowdhury 2004[55]	Retrospective cohort study Setting: UK n=22 Patients in ICU who are bleeding or about to undergo an invasive procedure. Group 1 (standard dose): (n=10) The median volume of FFP given according to body weight was 12.2 ml/kg (range 5.6 -22.1 ml/kg). The median dose of FFP infused was 1.0 litre (range 0.5 to 1.5 litres). Group 2 (high dose): (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)	FFP Transfusion at dose according to guidelines (standard dose) vs. FFP transfusion at higher dose	Correction of coagulation abnormalities (PT, APTT)	• Critically ill patients Strata: • Adults receiving prophylaxis and undergoing procedures

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Table 117: Modified GRADE profile: FFP standard dose versus FFP high dose

Quality assessment						Effect size	Quality	Importance
Study	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**			
Pre-transfusion PT (seconds)								
Chowdhury 2004 [55]	Retrospective cohort study	Serious[a]	No serious inconsistency	Serious[b]	Not applicable	Group 1 (standard dose): 22.8 (17-222) seconds Group 2 (high dose): 24 (17-44) seconds	VERY LOW	Important
Pre-transfusion aPTT (seconds)								
Chowdhury 2004 [55]	Retrospective cohort study	Serious[a]	No serious inconsistency	Serious[b]	Not applicable	Group 1 (standard dose): 46.4 (30-223) seconds Group 2(high dose): 41 (28-198) seconds	VERY LOW	Important
Post-transfusion PT (seconds)								
Chowdhury 2004 [55]	Retrospective cohort study	Serious[a]	No serious inconsistency	Serious[b]	Not applicable	Group 1(standard dose): 19 (15-36) seconds Group 2(high dose): 16 (14-20) seconds	VERY LOW	Important
Post-transfusion aPTT (seconds)								
Chowdhury 2004 [55]	Retrospective cohort study	Serious[a]	No serious inconsistency	Serious[b]	Not applicable	Group 1(standard dose): 37 (30-158) seconds Group 2(high dose): 30* (24-45) seconds * significant difference when comparing groups 1 and 2 post-transfusion ($p<0.05$)	VERY LOW	Important
Bleeding								

No evidence available								
Adverse events related to transfusion								
No evidence available								
Pre-transfusion INR								
No evidence available								
Mortality (all cause)								
No evidence available								
Length of hospital stay								
No evidence available								
Number of patients needing RBC transfusion								
No evidence available								
Number of RBC units or volume of RBC transfused.								
No evidence available								
Quality of life								
No evidence available								
Infections								
No evidence available								
Serious adverse events								
No evidence available								

(a) This study uses a retrospective cohort design and is therefore more prone to selection bias and it does not include sufficient numbers of participants, n=22.
(b) Critically ill patients

15.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

Relevant unit costs are provided in Appendix N to aid consideration of cost-effectiveness.

15.4 Evidence statements

Clinical

Standard dose FFP versus high dose FFP

One RCT compared standard dose FFP with high dose FFP. The evidence suggested that post-transfusion aPTT was lower in high dose FFP group compared with standard dose FFP group.

There was no important difference in effects between the groups for the outcomes pre-transfusion PT (seconds), post-transfusion PT (seconds) and pre-transfusion aPTT (seconds).

The evidence was of very low quality.

No evidence was identified for the critical outcomes, such as all-cause mortality at 30 days, bleeding, infections, quality of life and serious adverse events, and important outcomes such as the number of patients needing RBC transfusions, and the number of units of RBC transfused.

Economic

No relevant economic evaluations were identified.

15.5 Recommendations and link to evidence

Recommendations	33. Use a dose of at least 15 ml/kg when giving fresh frozen plasma transfusions.
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (occurrence of bleeding in non-bleeding patients and cessation of bleeding in bleeding patients; bleeding defined as WHO grade 2 and above), infections (including pneumonia, surgical site infection, UTI and septicaemia/bacteraemia), quality of life and serious adverse events as the critical outcomes for decision making. Other important outcomes included the number of patients needing RBC transfusions, the number of units of RBC transfused, correction of abnormal coagulation tests and length of stay in hospital.
Trade off between clinical benefits and harms	There was no evidence from randomised studies for this review. However, there was evidence from one very small observational study. The evidence suggested that there may be some benefit from high dose FFP

	compared with standard dose FFP with respect to one important outcome, post-transfusion APTT, but this evidence was of very low quality. There was evidence of no difference in effect between standard dose and high dose for the outcomes evaluating pre-transfusion and post-transfusion PT (prothrombin time) and pre-transfusion activated partial thromboplastin time (APTT); this evidence was also of very low quality. There was no evidence for any clinical outcomes. The evidence for the comparison of standard dose with high dose FFP was inconclusive. The GDG noted that standard dose in clinical practice is equivalent to 15 ml/kg which was slightly higher than the standard dose (12 ml/kg) described in the clinical evidence reviewed. Based on the above evidence and consensus opinion, the GDG recommended use of FFP dose of at least 15 ml/kg to increase the likelihood of providing a sufficient quantity of coagulation factors to reduce bleeding. There was no specific evidence available for dose of FFP transfusion in the paediatric population. The GDG felt it reasonable that the same recommendations should apply for children as for adults.
Economic considerations	No relevant economic evaluations comparing different doses for FFP transfusion were identified. The costs of FFP and Octaplas® transfusion were considered by the GDG. Clinical FFP (UK sourced) costs £28 per unit in England and Wales and Octaplas® costs £53 per 200 ml bag. For patients born on or after 1st January 1996 FFP is sourced from countries with a low risk of vCJD. Either Octaplas® or methylene blue FFP (MBFFP) both pathogen inactivated, are used for these recipients. The cost of MBFFP (non-UK sourced) is £177 per unit in England and Wales. It was noted that these costs do not include all costs associated with a transfusion such as staff time, disposables, storage, wastage and laboratory tests. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications. Based on the clinical evidence, consensus expert opinion of GDG members and the cost of FFP transfusion, the GDG agreed to recommend the standard dose used in clinical practice: at least 15 ml/kg per transfusion.
Quality of evidence	The quality of evidence for all outcomes was very low by GRADE criteria. The recommendation was based on very low quality evidence and the consensus expert opinion of the GDG members.
Other considerations	The GDG discussed issues with dosing of FFP in current clinical practice and noted that in their experience, FFP tends to be administered in sub-therapeutic doses. The GDG was keen to make a recommendation highlighting the need for administering FFP at the right dose and therefore recommended a dose of at least 15 ml/kg. The GDG noted that in order to reduce the risk of transfusion-associated circulatory overload (TACO) special consideration needs to be given for obese patients and patients receiving high volume of fluids, as this dose may be inappropriate in these situations. For patients born on or after 1st January 1996, non-UK plasma from countries with a low risk of variant Creutzfeldt-Jakob disease is used,[190] and it has additional pathogen inactivation steps (methylene-blue or solvent detergent treatment) to reduce the risk of viral transfusion transmission due to differences in baseline viral activity levels between countries.

	The recommendations apply to adults and children requiring FFP transfusions.

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Recommendations	**34. Clinically reassess the patient's condition and repeat the coagulation tests after fresh frozen plasma transfusion, and give further doses if needed.**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (occurrence of bleeding in non-bleeding patients and cessation of bleeding in bleeding patients; bleeding defined as WHO grade 2 and above), infections (including pneumonia, surgical site infection, UTI and septicaemia/bacteraemia), quality of life and serious adverse events as the critical outcomes for decision making. Other important outcomes included the number of patients needing RBC transfusions, the number of units of RBC transfused, correction of abnormal coagulation tests and length of stay in hospital.
Trade off between clinical benefits and harms	No evidence was identified for this recommendation. The GDG discussed that although coagulation test abnormalities are poor predictors of bleeding, it was important to measure the coagulation screen to assess the presence and severity of a coagulopathy before transfusion, and to reduce unnecessary transfusions and their associated risks. The GDG agreed that the patient's clinical condition (including their bleeding risk, or evidence of side effects such as volume overload) and coagulation tests should be repeated after transfusion, so as to guide the need for any further FFP transfusions. The recommendations were based on the consensus expert opinion of the GDG members There was no specific evidence available for the paediatric population. The GDG agreed that the same recommendations should apply for children as for adults in order to guide the need for any further FFP transfusions. .
Economic considerations	The GDG noted that the cost of clinically reassessing and repeating coagulation tests was negligible and would be offset by savings as a result of transfusing fewer units of FFP.
Quality of evidence	No evidence was identified for this recommendation. The recommendations were based on the consensus expert opinion of the GDG members
Other considerations	Risks for using FFP are similar to those with other blood components, including allergic transfusion reactions, transfusion associated circulatory overload (TACO) and transfusion related acute lung injury (TRALI). The risk of TRALI has been significantly reduced by the selection of plasma for FFP from male donors in the UK. Recipients born on or after Jan 1st 1996 (including all children) receives pathogen inactivated imported FFP. Pathogen inactivation of FFP reduces coagulation factor activity but both Octaplas and MBFFP are widely used in many countries and there is no clear evidence of impact of pathogen inactivation on clinical efficacy. The recommendations apply to adults and children requiring FFP transfusions.

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16 Cryoprecipitate: thresholds and targets

Cryoprecipitate is prepared from the cryoglobulin fraction obtained by thawing fresh frozen plasma. After removal of the supernatant, the precipitate, containing Factor VIII:C, von Willebrand factor (VWF), fibrinogen, fibronectin and factor XIII is refrozen in approximately 30 ml of plasma. This can be stored at -25°C or below for up to 36 months. After thawing, it should be infused as soon as possible though it can be stored at ambient temperature for up to 4 hours. Each unit should contain a minimum of 70 IU of factor VIII:C and 140 mg of fibrinogen. A standard adult dose of cryoprecipitate is 10 units available in the UK as pools of 5 single units.

Cryoprecipitate is used as a source of fibrinogen in acquired hypofibrinogenaemia, which may be seen, for example, with major haemorrhage or disseminated intravascular coagulation. Fibrinogen concentrate is available in the UK but only licensed for use in congenital hypofibrinogenaemia. Cryoprecipitate must not be used for replacement of coagulation factors in inherited conditions such as haemophilia or von Willebrand's disease, since specific factor concentrates are available.

16.1 Review question: What is the clinical- and cost-effectiveness of transfusions of cryoprecipitate to treat and prevent bleeding?

For full details see review protocol in Appendix C.

Table 118: PICO characteristics of review questions

Population	• Adults who are bleeding • Adults receiving prophylaxis and undergoing procedures • Children who are bleeding • Children receiving prophylaxis and undergoing procedures
Intervention(s)	• Low thresholds (fibrinogen levels) for transfusion ○ ≤1 g/litre ○ As defined by trial - PT or APTT time as reported in trial (>1.5 times the control) • High thresholds (fibrinogen levels) for transfusion ○ >1 g/litre ○ As defined by trial • PT or APTT time as reported in trial (>2 times of control)
Comparison(s)	All thresholds compared with one another
Outcomes	Critical outcomes: • Occurrence of bleeding (WHO grade 2 and above or equivalent)- prophylactic • 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 Important outcomes: • Number of patients needing red cell transfusions • Number or volume of red cells transfused • Length of stay (hospitalisation) • Correction of abnormal coagulation test
Study design	• RCTs

	• Systematic reviews • Cohort studies >1000 patients

16.2 Review question: What is the clinical- and cost-effectiveness of different target levels of post-transfusion haemostasis tests with the use of cryoprecipitate for prophylactic transfusions?

For full details see review protocol in Appendix C.

Table 119: PICO characteristics of review question

Population	• Adults who are bleeding • Adults receiving prophylaxis and undergoing procedures • Adults receiving prophylaxis and not undergoing procedures • Children who are bleeding • Children receiving prophylaxis and undergoing procedures • Children receiving prophylaxis and not undergoing procedures
Intervention(s)	• Low target levels as defined by trial • High target levels as defined by trial
Comparison(s)	• High target levels vs. low target levels
Outcomes	Critical outcomes: • Occurrence of bleeding (WHO grade 2 and above or equivalent)- prophylactic • 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. Important outcomes: • Number of patients needing red cell transfusions • Number or volume of red cells transfused • Length of stay (hospitalisation) • Correction of abnormal coagulation test
Study design	• RCTs • Systematic reviews • Cohort studies >1000 patients

16.3 Clinical evidence

We searched for systematic reviews, randomised controlled trials and observational studies addressing the two clinical questions: 'What is the clinical- and cost-effectiveness of transfusions of cryoprecipitate to treat and prevent bleeding?' and 'What is the clinical- and cost-effectiveness of different target levels of post-transfusion haemostasis tests with the use of cryoprecipitate for prophylactic transfusions?'

We did not identify any study entirely meeting our protocol criteria. However, we identified a large observational study assessing the efficacy of cryoprecipitate in patients with major trauma,[132] which

we have included in our evidence review (indirect population). We also identified a small prospective cohort study (n=13) which assessed the efficacy of cryoprecipitate use in treating bleeding in patients undergoing cardiac surgery; [176] however, we did not include this study in our review as this did not meet our protocol criteria of including cohort studies with more than 1000 patients.

In our search, we also identified a Cochrane review which assessed the benefits and harms of fibrinogen concentrate.[319] This Cochrane review assessed the benefits and harms of fibrinogen concentrate compared with placebo or usual treatment for bleeding patients. But we did not consider inclusion of this Cochrane review in our evidence review as fibrinogen concentrate was not included as one of the blood products to be covered in our scope.

Evidence from the included studies is summarised in the modified GRADE clinical evidence profile below (Table 113). See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, and excluded studies list in Appendix P.

Table 120: Summary of studies included in the review

Study	Population, No. of patients, study design, setting	Intervention/ comparison	Outcomes	Comments
Holcomb 2013[132]	Prospective Observational Multicentre Major Trauma Transfusion (PROMMTT) study. The PROMMT study enrolled 1,245 adult trauma patients from 10 US Level 1 trauma centres during July 2009 to October 2010. n=1238 n=359 patients received cryoprecipitate; n=879 did not receive cryoprecipitate. Inclusion criteria: Patients were eligible if they required the highest level of trauma activation, were age 16 or older and were transfused at least one unit of RBCs in the first 6 hours after admission.	Cryoprecipitate versus no cryoprecipitate Among patients who received cryoprecipitate, the median number of units infused by 24 hours was 10 (interquartile range, 10-20). One dose of cryoprecipitate was defined as 10 U	• Mortality 30 days • Number of units of RBC transfused	This paper is a secondary analysis of 1238 of 1245 of the PROMMT study patients

Table 121: Modified GRADE profile: Cryoprecipitate versus no cryoprecipitate

Quality assessment						Effect size	Quality	Importance
Study	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**			
Mortality (all-cause) at 30 days								
Holcomb 2013 [132]	Prospective Cohort study n=1245 Comparison: Cryoprecipitate vs. no cryoprecipitate	Serious[a]	Not applicable	Serious[b]	No imprecision	RR 1.43 (1.14 to 1.78) Absolute effect: 80 more per 1000 (from 26 more to 144 more)	VERY LOW	Critical
Number of RBC units transfused (24 hours)								
Holcomb 2013 [132]	Prospective Cohort study n=1245 Comparison: Cryoprecipitate vs. no cryoprecipitate	Serious[a]	Not applicable	Serious[b]	Not applicable	(median, IQR) No cryoprecipitate (n=879): 4 (2-7) Cryoprecipitate (n=359) :7 (4-17) p<0.001	VERY LOW	Important

(a) Observational study and is therefore more prone to selection bias
(b) Patients with major trauma

16.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

Relevant unit costs are provided in Appendix N to aid consideration of cost-effectiveness.

16.5 Evidence statements

Clinical

One large prospective cohort study assessed the efficacy of cryoprecipitate in patients with major trauma. The evidence showed mortality (all-cause) at 30 days and number of RBC units transfused (24 hours) to be higher in patients receiving cryoprecipitate transfusion compared with patients not receiving cryoprecipitate transfusion. The evidence was of very low quality.

No evidence was identified for the critical outcomes such as bleeding (occurrence of bleeding in non-bleeding patients and cessation of bleeding in bleeding patients; bleeding defined as WHO grade 2 and above), infections, quality of life, serious adverse events, adverse events related to transfusion, or for the important outcomes such as number of patients needing RBC transfusions, the number of units of RBC transfused, correction of abnormal coagulation tests and length of stay in hospital.

Economic

No relevant economic evaluations were identified.

16.6 Recommendations and link to evidence

Recommendations	**35. Consider cryoprecipitate transfusions for patients without major haemorrhage who have:** • **clinically significant bleeding and** • **a fibrinogen level below 1.5 g/litre.**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (occurrence of bleeding in non-bleeding patients and cessation of bleeding in bleeding patients; bleeding defined as WHO grade 2 and above), infections (for example, pneumonia, surgical site infection, UTI and septicaemia/bacteraemia), quality of life, serious adverse events and adverse events related to transfusion as the critical outcomes for decision making. Other important outcomes included the number of patients needing RBC transfusions, the number of units of RBC transfused, correction of abnormal coagulation tests and length of stay in hospital.
Trade-off between	No direct evidence relating to the use of cryoprecipitate transfusion at any specific

clinical benefits and harms	fibrinogen level was identified for this recommendation. There was indirect evidence (indirect population) from one large multicentre prospective cohort study which compared the efficacy of cryoprecipitate administration in patients with major trauma.[132] The study reported that mortality at 30 days appeared to be higher in patients receiving cryoprecipitate transfusion compared with patients not receiving cryoprecipitate transfusions and the number of units of RBC transfused appeared to be higher in patients receiving cryoprecipitate transfusion compared with patients not receiving cryoprecipitate transfusion. Although the study reported adverse events associated with the use of cryoprecipitate, the GDG noted that it had a high risk of bias and the findings are likely to be specific to the trauma population and agreed that these cannot be extrapolated to this review population as the population was too indirect. Major trauma is excluded from the scope of this guidance - for guidance specific to this topic, follow the recommendations in NICE's guideline on Major trauma, currently in development. The GDG discussed that, despite the lack of evidence, cryoprecipitate should be considered for the treatment of acquired fibrinogen deficiency when there is active bleeding. The potential benefit of reducing bleeding and preventing further deterioration is likely to outweigh the risk of adverse effects of transfusion. In many such clinical settings there may be other multiple clotting factor deficiencies and accordingly initial treatment with FFP should be given. Whilst FFP does contain fibrinogen, the volume needed to be transfused per adult dose is relatively large (at least 15 ml/kg plasma). Cryoprecipitate contains fibrinogen in a more concentrated form with a lower total volume transfused per dose. Accordingly, in patients needing fibrinogen replacement, in particular if on-going low fibrinogen levels after FFP transfusion or where fibrinogen levels are dropping rapidly, cryoprecipitate therapy is indicated. The risks of cryoprecipitate therapy are as those stated earlier in relation to potential adverse events of transfusing blood and components. The donor exposure depends on the component transfused. Accordingly, each unit of red cells exposes the patient to one donor per red cell unit transfused, FFP to approximately 4 to 6 donors per adult dose (of 4 to 6 units FFP), but the standard adult cryoprecipitate dose of 10 units (in 2 pools of 5 units each in the UK) results in a donor exposure of 10 donors per adult dose. Cryoprecipitate delivers a high dose of fibrinogen in a small fluid volume, compared with therapeutic doses of FFP, so the GDG agreed that cryoprecipitate may be considered as initial treatment when fibrinogen replacement in a small volume is desirable for example to minimise the risk of TACO. The GDG noted that cryoprecipitate transfusion may reduce the risk of transfusion-associated circulatory overload (TACO) compared to FFP transfusion. There was no specific evidence available for the indications for cryoprecipitate transfusion in the paediatric population. The GDG agreed that the same recommendations should apply for children as for adults in the absence of evidence that indications for cryoprecipitate in children with bleeding and low fibrinogen are different compared to adults. However there are specific recommendations for dosage and type of component for children (see recommendation number 38). This recommendation was based on the indirect evidence and consensus expert opinion of the GDG members.
Economic considerations	No relevant economic evaluations comparing different thresholds or targets for cryoprecipitate were identified. The cost of cryoprecipitate was considered by the GDG. Pooled cryoprecipitate costs £181 per pool in England and Wales, where one pool of cryoprecipitate is derived from 5 units of donated blood. For patients born after 1st January 1996, methylene blue cryoprecipitate is required. The cost of methylene blue cryoprecipitate-pooled (non-UK sourced) is £1,080 per pool where

	one pool of methylene blue cryoprecipitate is derived from 6 units of donated blood. It was noted that this figure does not include all costs associated with a transfusion such as staff time, disposables, and storage, wastage and laboratory tests. No direct estimates for the additional cost of transfusing cryoprecipitate were identified. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications.. Based on consensus expert opinion of the GDG members, the GDG considered that, for patients with clinically significant bleeding with abnormal coagulation who have been treated with FFP and have a fibrinogen level below 1.5 g/litre, the cost of transfusing cryoprecipitate was likely to be offset by avoiding the negative costly outcomes that would result from not transfusing these patients. The potential negative outcomes include possible further bleeding leading to potentially lengthier and more complex (and costly) hospitalisation (for example, ICU), and mortality.
Quality of evidence	No direct evidence was identified for the use of cryoprecipitate. The quality of evidence from 1 cohort study was very low due to the indirectness of the population and risk of bias arising from selection bias related to the design of the observational study. The recommendation was based on the indirect evidence and consensus expert opinion of the GDG members.
Other considerations	The GDG discussed findings from studies which did not meet the protocol criteria to inform the consensus recommendation. One small prospective cohort study (n=13) assessed the efficacy of cryoprecipitate use in treating bleeding in patients undergoing cardiac surgery[175] and was excluded as it did not meet our protocol criteria for inclusion of cohort studies (n<1000 patients). The study reported that fibrinogen levels (mg/dl), APTT (seconds) and INR appeared to be lower after cryoprecipitate transfusion. One Cochrane review on the use of fibrinogen concentrate[319] was identified and reported the following findings, though there was considerable uncertainty with respect to all of them: Mortality and incidence of allogeneic blood transfusion appeared to be lower in patients receiving fibrinogen concentrate compared with patients not receiving it. Length of hospital stay (days) appeared to be longer in patients receiving fibrinogen concentrate compared with patients not receiving it. Adverse events such as thrombotic episodes (arterial and venous graft occlusion, pulmonary embolus, deep venous thrombosis) did not appear to be different in patients receiving fibrinogen concentrate and patients not receiving it. Fibrinogen concentrate was not considered as an intervention in the scope of this guideline. The level of fibrinogen of 1.5 g/litre as a threshold for considering cryoprecipitate transfusion in bleeding patients was consensus based, and for some patients with acquired fibrinogen deficiency and bleeding that is not severe (for example, with disseminated intravascular coagulation (DIC)) a fibrinogen threshold of 1.0 g/litre may be more appropriate. The GDG also noted that methylene blue cryoprecipitate was introduced by NHSBT for treatment of children and young adults as part of the vCJD risk reduction strategy,[213] and as for FFP is now provided for all patients born on or after 1st Jan 1996. Each pool of Methylene Blue contains 6 units of Cryoprecipitate . The GDG noted that there were no on-going trials of cryoprecipitate that were of interest in the guideline population defined in the review protocol.

	The same recommendations apply to adults and children.

1
2

Recommendations	**36. Do not offer cryoprecipitate transfusions to correct the fibrinogen level in patients who:** • **are not bleeding and** • **are not having invasive procedures or surgery with a risk of clinically significant bleeding.**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (occurrence of bleeding in non-bleeding patients and cessation of bleeding in bleeding patients; bleeding defined as WHO grade 2 and above), infections (for example, pneumonia, surgical site infection, UTI and septicaemia/bacteraemia), quality of life, serious adverse events and adverse events related to transfusion as the critical outcomes for decision making. Other important outcomes included the number of patients needing RBC transfusions, the number of units of RBC transfused, correction of abnormal coagulation tests and length of stay in hospital.
Trade-off between clinical benefits and harms	No evidence was identified for this recommendation. The recommendation was based on the consensus expert opinion of the GDG members. The GDG considered that cryoprecipitate may reduce the risk of bleeding and the risks of having a transfusion in patients with abnormal coagulation but there was no evidence for this. In patients who have low fibrinogen levels but are not bleeding and are not having invasive procedures or surgery with a risk of clinically significant bleeding, the GDG considered a cautious approach and recommended not offering cryoprecipitate transfusion as there is no evidence of benefit and a risk of complications of transfusion. The risks of cryoprecipitate therapy are as those stated earlier in relation to potential adverse events of transfusing blood and components. The donor exposure depends on the component transfused. Accordingly, each unit of red cells exposes the patient to one donor per red cell unit transfused, FFP to approximately 4 to 6 donors per adult dose (of 4 to 6 units FFP), but the standard adult cryoprecipitate dose of 10 units (in 2 pools of 5 units each in the UK) results in a donor exposure of 10 donors per adult dose. The GDG felt, therefore, that the overall benefit was not great enough to recommend the use of cryoprecipitate in these patients. There was no specific evidence available for the use of cryoprecipitate transfusion in the paediatric population. The GDG agreed that the same consensus recommendations should apply for children as for adults in the absence of evidence that indications for cryoprecipitate in children with bleeding and low fibrinogen are different compared to adults. However there are specific recommendations for dosage and type of component for children (see recommendation number 38).
Economic considerations	No relevant economic evaluations comparing different thresholds or targets for cryoprecipitate were identified. The cost of cryoprecipitate was considered by the GDG. Pooled cryoprecipitate costs £181 per pool in England and Wales, where one pool of cryoprecipitate is derived from five units of donated blood. For patients born after 1st January 1996 methylene blue cryoprecipitate is required. The cost of methylene blue cryoprecipitate-pooled (non-UK sourced) is £1,080 per pool where one pool of methylene blue cryoprecipitate is derived from six units of donated blood. It was noted that this figure does not include all costs associated with a transfusion such as staff time, disposables, and storage, wastage and laboratory tests. No direct estimates for the additional cost of transfusing cryoprecipitate were identified. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay

	or with the management of transfusion-related complications. Based on consensus expert opinion, the GDG considered that, given the lack of evidence of benefit from cryoprecipitate transfusion in patients with abnormal coagulation and the potential infectious and immunological risks from receiving a transfusion, the cost of transfusing cryoprecipitate was not justified.
Quality of evidence	No evidence was identified which met the review protocol criteria. The recommendation was based on the consensus expert opinion of the GDG members.
Other considerations	The GDG discussed findings from studies which did not entirely meet the protocol criteria to inform the consensus recommendation. One large multicentre prospective cohort study assessed the efficacy of cryoprecipitate in patients with major trauma.[132] The study reported that mortality at 30 days appeared to be higher in patients receiving cryoprecipitate transfusion compared with patients not receiving cryoprecipitate transfusions and the number of units of RBC transfused appeared to be higher in patients receiving cryoprecipitate transfusion compared with patients not receiving cryoprecipitate transfusion. Although the study reported harm associated with the use of cryoprecipitate, the GDG noted that the studies were at high risk of bias and the findings are likely to be specific to the trauma population and therefore the findings cannot be extrapolated to this review population. Major trauma is excluded from the scope of this guidance- for guidance specific to this topic, follow the recommendations in NICE's guideline on Major trauma, currently in development. Another small prospective cohort study (n=13) assessed the efficacy of cryoprecipitate use in treating bleeding in patients undergoing cardiac surgery[176] and was excluded as it did not meet our protocol criteria for inclusion of cohort studies (n<1000 patients).The study reported that fibrinogen level (mg/dl) and APTT (seconds) and INR appeared to be lower after cryoprecipitate transfusion. One Cochrane review on the use of fibrinogen concentrate[319] was identified and reported the following findings: Mortality and incidence of allogeneic blood transfusion appeared to be lower in patients receiving fibrinogen concentrate compared with patients not receiving concentrate. Length of hospital stay (days) appeared to be longer in patients receiving fibrinogen concentrate compared with patients not receiving concentrate. Adverse events such as thrombotic episodes (arterial and venous graft occlusion, pulmonary embolus, deep venous thrombosis) did not appear to be different in patients receiving fibrinogen concentrate and patients not receiving fibrinogen concentrate. There was considerable uncertainty with respect to all the findings. Although it acts on the same pathway as fresh frozen plasma, cryoprecipitate and prothrombin complex concentrates, fibrinogen concentrate was not considered as an intervention in the scope of the guidance. The GDG also noted that methylene blue cryoprecipitate was introduced by NHSBT for treatment of children as part of the vCJD risk reduction strategy [213] and as for FFP is now provided for all patients born on or after 1st Jan 1996. Each pool of Methylene Blue contains 6 units of . The GDG noted that there were no on-going trials of cryoprecipitate in the guideline population of interest. The same recommendations apply to adults and children.

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Recommendations	37. Consider prophylactic cryoprecipitate transfusions for patients with a fibrinogen level below 1.0 g/litre who are having invasive procedures or surgery with a risk of clinically significant bleeding.
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (occurrence of bleeding in non-bleeding patients and cessation of bleeding in bleeding patients; bleeding defined as WHO grade 2 and above), infections (for example, pneumonia, surgical site infection, UTI and septicaemia/bacteraemia), quality of life, serious adverse events and adverse events related to transfusion as the critical outcomes for decision making. Other important outcomes included the number of patients needing RBC transfusions, the number of units of RBC transfused, correction of abnormal coagulation tests and length of stay in hospital.
Trade-off between clinical benefits and harms	No evidence was identified for use of cryoprecipitate transfusion in patients having surgery or invasive procedures with a risk of clinically significant bleeding and where there is a low fibrinogen level less than 1.0 g/litre. No evidence was identified on the use of cryoprecipitate transfusion at any specific fibrinogen level. The recommendation was based on the consensus expert opinion of the GDG members. The GDG drew on its knowledge and experience and agreed that prophylactic cryoprecipitate transfusion should be considered for patients having surgery or invasive procedures with a risk of clinically significant bleeding and abnormal coagulation test results. The lower threshold fibrinogen concentration of 1.0 g/litre (compared to 1.5 g/litre for bleeding patients) was chosen in view of the lack of evidence and as this is a commonly used dose in clinical practice. There was no specific evidence available for the use of cryoprecipitate transfusion in the paediatric population. T. The GDG agreed that the same consensus recommendations should apply for children as for adults in the absence of evidence that indications for cryoprecipitate in children with bleeding and low fibrinogen are different compared to adults.
Economic considerations	No relevant economic evaluations comparing different thresholds or targets for cryoprecipitate were identified. The cost of cryoprecipitate was considered by the GDG. Pooled cryoprecipitate costs £181 per pool in England and Wales, where one pool of cryoprecipitate is derived from five units of donated blood. For patients born after 1st January 1996 methylene blue cryoprecipitate is required. The cost of methylene blue cryoprecipitate-pooled (non-UK sourced) is £1,080 per pool where one pool of methylene blue cryoprecipitate is derived from six units of donated blood. It was noted that these figures do not include all costs associated with a transfusion such as staff time, disposables, and storage, wastage and laboratory tests. No direct estimates for the additional cost of transfusing cryoprecipitate were identified. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications. Based on consensus expert opinion, the GDG considered that for patients having surgery or invasive procedures with a risk of clinically significant bleeding and where there is a low fibrinogen level of less than 1.0 g/litre, the cost of transfusing cryoprecipitate was likely to be offset by avoiding the negative costly outcomes that would result from not transfusing these patients. The negative outcomes include possible bleeding leading to lengthier and more complex (and more costly) hospitalisation (for example, ICU) and mortality.
Quality of evidence	No evidence was identified which met the review protocol criteria. The recommendation was based on the consensus expert opinion of the GDG members.
Other considerations	The GDG agreed that as cryoprecipitate delivers a high dose of fibrinogen in a small fluid volume, relative to FFP, it may be considered as initial treatment when

	fibrinogen replacement in a small volume is desirable. The GDG noted that a cryoprecipitate transfusion may reduce the risk of TACO (transfusion-associated circulatory overload) more than a FFP transfusion. The GDG discussed that infectious and immunological risks with cryoprecipitate transfusion were similar to other blood products, but as cryoprecipitate is pooled (1 pool comes from 5 units of blood), this increased the risk of number of donor exposures. The GDG agreed that, although transfusion therapy with either FFP or cryoprecipitate is usually indicated if fibrinogen levels are less than 1.0 g/litre and bleeding is present, FFP transfusion should be given first instead of cryoprecipitate in order to address the multiple coagulation factor deficiencies. The same recommendations apply for adults and children. The GDG also noted that methylene blue cryoprecipitate was introduced by NHSBT for treatment of children and young adults as part of the vCJD risk reduction strategy,[213] and is now provided for all patients born on or after 1st Jan 1996. Each pool of Methylene Blue Cryoprecipitate contains is 6 units of cryoprecipitate.

1
2

17 Cryoprecipitate: doses

See introductory text in Cryoprecipitate, thresholds and targets section.

17.1 Review question: What is the clinical- and cost-effectiveness of different doses of cryoprecipitate for transfusion?

For full details see review protocol in Appendix C.

Table 122: PICO characteristics of review question

Population	• Adults who are bleeding • Adults receiving prophylaxis and undergoing procedures • Children who are bleeding • Children receiving prophylaxis and undergoing procedures
Intervention(s)	• Standard adult dose (where 1 dose of cryoprecipitate will increase fibrinogen count by about 1 g/litre) • High dose (adults) • Dose in children: 10-15 ml/kg
Comparison(s)	Standard dose vs. High dose
Outcomes	Critical outcomes: • Occurrence of bleeding (WHO grade 2 and above or equivalent) • 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. Important outcomes: • Number of patients needing red cell transfusions • Number of red cell units or volume transfused • Length of stay (hospitalisation) • Correction of abnormal coagulation test.
Study design	• RCTs • Systematic reviews • Observational studies

17.2 Clinical evidence

We searched for systematic reviews, randomised controlled trials and observational studies addressing effectiveness of different doses of cryoprecipitate for transfusion.

No studies were found which met the criteria set in the review protocol. See the study selection flow chart in Appendix E and excluded studies list in Appendix P.

NHSBT Portfolio of Blood Components and Guidance for their Clinical Use

Cryoprecipitate Dose

A single unit contains a mean of approximately 400-460mg fibrinogen. The adult therapeutic dose is 2 pools of 5, or one unit per 5-10 kg body weight, dependent on the degree of fibrinogen deficiency. For older children the typical dose is 5-10 ml/kg.

Response should be monitored by repeat coagulation tests.

GRADE profile (standard dose versus high dose)

There are no GRADE tables for this review.

17.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

Relevant unit costs are provided in Appendix N to aid consideration of cost-effectiveness.

17.4 Evidence statements

Clinical

No relevant clinical evidence was identified for this question.

Economic

No relevant economic evaluations were identified.

17.5 Recommendations and link to evidence

Recommendations	38. Use an adult dose of 2 pools when giving cryoprecipitate transfusions (for children, use 5–10 ml/kg up to a maximum of 2 pools).
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (occurrence of bleeding in non-bleeding patients and cessation of bleeding in bleeding patients; bleeding defined as WHO grade 2 and above), infections (for example, pneumonia, surgical site infection, UTI and septicaemia/bacteraemia), quality of life, serious adverse events and adverse events related to transfusion as the critical outcomes for decision making. Other important outcomes included the number of patients needing RBC transfusions, the number of units of RBC transfused, correction of abnormal coagulation tests and length of stay in hospital.
Trade-off between	No evidence was identified for the use of an appropriate dose of cryoprecipitate

clinical benefits and harms	transfusions. The recommendation was based on consensus expert opinion of the GDG members. Giving a dose that is too low may result in bleeding not being prevented and further adverse outcomes related to this, such as mortality. Giving a higher dose increases the risks from the product itself, such as increased infectious and immunological risks from the transfusion. Moreover, as cryoprecipitate is a pooled product, the donor exposure is higher than transfusion with any other product. The GDG discussed current standard practice in the NHS (which is to give 2 pools for adults) and decided that there was no reason to recommend a higher or lower dose than this for adults. The GDG agreed that coagulation tests need to be repeated to check whether further doses are required and to reduce the possibility of over prescribing. There was no specific evidence available for the paediatric population. The GDG agreed that equivalent recommendations should apply for children as for adults, with the dose adjusted to take account of the weight of the child.
Economic considerations	No relevant economic evaluations comparing different thresholds or targets for cryoprecipitate were identified. The cost of cryoprecipitate was considered by the GDG. Pooled cryoprecipitate costs £181 per pool in England and Wales, where one pool of cryoprecipitate is derived from five units of donated blood. For patients born after 1st January 1996 methylene blue cryoprecipitate is required. The cost of methylene blue cryoprecipitate-pooled (non-UK sourced) is £1,080 per pool where one pool of methylene blue cryoprecipitate is derived from six units of donated blood. It was noted that these costs do not include all costs associated with a transfusion such as staff time, disposables, and storage, wastage and laboratory tests. No direct estimates for the additional cost of transfusing cryoprecipitate were identified. As part of the health economic model developed in this guideline, the additional cost associated with transfusion was estimated to be £70 per first unit transfused. Of note this estimate does not include costs associated with hospital stay or with the management of transfusion-related complications. Based on consensus expert opinion of the GDG members and the cost of cryoprecipitate, the GDG agreed to recommend the standard dose used in current clinical practice, two pools per transfusion for adults.
Quality of evidence	No evidence was identified which met the review protocol criteria for the use of an appropriate dose of cryoprecipitate transfusions. The recommendation was based on the consensus expert opinion of the GDG members.
Other considerations	The GDG based their recommendation on consensus expert opinion of the GDG members and their prior knowledge of information on doses and on fibrinogen in cryoprecipitate units. Fibrinogen levels are lower in methylene blue than in standard cryoprecipitate but both are within UK specifications. .

1

2

Recommendations	**39. Clinically reassess the patient's condition, repeat the fibrinogen level measurement and give further doses if needed.**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (occurrence of bleeding in non-bleeding patients and cessation of bleeding in bleeding patients; bleeding defined as WHO grade 2 and above), infections (for example, pneumonia, surgical site infection, UTI and septicaemia/bacteraemia), quality of life, serious adverse events and adverse events related to transfusion as the critical outcomes for decision making. Other important outcomes included the number of patients needing RBC transfusions, the number of units of RBC transfused, correction of

	abnormal coagulation tests and length of stay in hospital.
Trade-off between clinical benefits and harms	No evidence was identified for this recommendation. The GDG discussed that it was important to measure the fibrinogen level to assess the presence and severity of hypofibrinogenaemia before transfusion, and to reduce unnecessary transfusions and their associated risks. The GDG agreed that the patient's clinical condition (including their bleeding risk, or evidence of side effects) and fibrinogen level should be repeated after transfusion, so as to guide the need for any further cryoprecipitate transfusions. The recommendation was based on consensus expert opinion of the GDG members. There was no specific evidence available for the paediatric population. The GDG agreed that the same recommendations should apply for children as for adults in order to assess the effectiveness of cryoprecipitate transfusion. .
Economic considerations	The GDG noted that the cost of clinically reassessing and repeating coagulation tests was negligible and would be likely to be offset by savings as a result of transfusing fewer units of cryoprecipitate.
Quality of evidence	No evidence was identified which met the review protocol criteria for the use of an appropriate dose of cryoprecipitate transfusions. The recommendation was based on the consensus expert opinion of the GDG members.
Other considerations	The GDG based its recommendation on consensus expert opinion of the GDG members. The same recommendations apply to adults and children. Fibrinogen levels are lower in methylene blue than in standard cryoprecipitate but both are within UK specifications.

1

18 Prothrombin Complex Concentrates: thresholds and targets

Patients on oral anticoagulants, such as warfarin, have low levels of the vitamin K-dependent clotting factors (II, VII, IX & X). Emergency reversal requires replacement of these factors either when major bleeding occurs (for example, in the brain or gut) or, if urgent surgery is needed.

Prothrombin complex concentrates (PCC) are produced from pooled plasma with additional viral inactivation steps undertaken. PCC containing all these four clotting factors (the so-called '4-factor PCCs', such as octaplex and beriplex) are licensed in the UK for the emergency reversal of oral anticoagulation. PCCs reverse the coagulopathy in this setting more rapidly with lower infusion volumes needed than FFP.

18.1 Review question: What is the clinical- and cost-effectiveness of transfusions of prothrombin complex concentrates (PCC) to treat and prevent bleeding?

For full details see review protocol in Appendix C.

Table 1: PICO characteristics of review question- PCC threshold

Population	• Adults who are bleeding
	• Adults receiving prophylaxis and undergoing procedures
	  ○ Patients on Vitamin K antagonists
	  ○ Patients on novel anticoagulants
	• Children who are bleeding
	• Children receiving prophylaxis and undergoing procedures
	  ○ Children on Vitamin K antagonists
	• Children on novel anticoagulants

Intervention(s)	• In patients receiving Vitamin K antagonists, PCC transfusions at the following International normalised ratio (INR) levels will be compared with one another: • INR ≤1.5 • INR 1.6- 2.0 • INR 2.1 – 2.5 • INR ≥2.6 • In patients receiving novel anticoagulants, PCC transfusion at high and low threshold levels of the following coagulation tests will be compared with one another: • Prothrombin time ratio (PT) • Activated Partial Thromboplastin time (APTT)
Comparison(s)	• PCC transfusions at different INR/PT/APTT thresholds will be compared with one another.
Outcomes	• 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 at end of follow-up • Infections (for example, pneumonia) • Serious adverse events • Adverse events related to the transfusion • Number of patients needing red cell transfusions

	• Number or volume of red cells transfused • Length of stay (hospitalisation) • Correction of abnormal coagulation test
Study design	• RCTs • Systematic reviews • Large Cohort studies

18.2 Review question: What is the clinical- and cost-effectiveness of different target levels of post-transfusion haemostasis tests with the use of prothrombin complex concentrates (PCC) for prophylactic transfusions?

For full details see review protocol in Appendix C.

Table 2: PICO characteristics of review question- PCC targets

Population	• Adults who are bleeding • Adults receiving prophylaxis and undergoing procedures ○ Patients on Vitamin K antagonists ○ Patients on novel anticoagulants • Children who are bleeding • Children receiving prophylaxis and undergoing procedures ○ Children on Vitamin K antagonists • Children on novel anticoagulants
Intervention(s)	In patients receiving Vitamin K antagonists, the interventions are • PCC transfusion to achieve low target levels of INR (as defined by trial) • PCC transfusion to achieve high target levels of INR (as defined by trial) PCC transfusions to achieve low target levels of INR will be compared with PCC transfusions to achieve high target levels of INR. In patients receiving novel anticoagulants, the interventions are • PCC transfusion to achieve low target levels of PT/APTT (as defined by trial) • PCC transfusion to achieve high target levels of PT/APTT (as defined by trial)
Comparison(s)	PCC transfusions to achieve low target levels of PT/APTT will be compared with PCC transfusions to achieve high target levels of PT/APTT.
Outcomes	• 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 at end of follow-up • Infections (for example, pneumonia) • Serious adverse events • Adverse events related to the transfusion • Number of patients needing red cell transfusions • Number or volume of red cells transfused • Length of stay (hospitalisation) • Correction of abnormal coagulation test
Study design	• RCTs • Systematic reviews

- Large cohort studies

18.3 Clinical evidence

We searched for systematic reviews, randomised controlled trials and observational studies addressing the review clinical questions: What is the clinical- and cost-effectiveness of transfusions of prothrombin complex concentrates (PCC) to treat and prevent bleeding? and What is the clinical- and cost-effectiveness of different target levels of post-transfusion haemostasis tests with the use of prothrombin complex concentrates (PCC) for prophylactic transfusions?

No studies were found which met the criteria set in the review protocol. See the study selection flow chart in Appendix E and excluded studies list in Appendix P.

18.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

Relevant unit costs are provided in Appendix N to aid consideration of cost-effectiveness.

18.5 Evidence statements

Clinical

No relevant clinical evidence was identified.

Economic

No relevant economic evaluations were identified.

18.6 Recommendations and link to evidence

Recommendations	**40. Offer immediate prothrombin complex concentrate transfusions for the emergency reversal of warfarin anticoagulation in patients with either:** • **severe bleeding or** • **head injury with suspected intra-cerebral haemorrhage.** **41. For guidance on reversing anticoagulation treatment in people who have a stroke and a primary intracerebral haemorrhage, see**

	recommendation 1.4.2.8 in the NICE guideline on the initial diagnosis and management of stroke.
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (cessation of bleeding in bleeding patients), infections (for example, pneumonia), quality of life, serious adverse events and adverse events related to transfusion as the critical outcomes for decision making. Other important outcomes included length of stay (hospitalisation), number of patients needing red blood transfusions, number of units of red blood cells transfused and correction of abnormal coagulation tests. For major bleeding, follow the recommendations in NICE's guideline on Major trauma, this guideline is currently in development, project details can be found at: https://www.nice.org.uk/guidance/indevelopment/gid-cgwave0642 . For PCC for bleeding, follow the recommendation in NICE's guideline on Acute upper gastrointestinal bleeding: management (2012), CG 141. For PCC, follow recommendation 1.4.2.8 in NICE's guideline on Stroke (2008), CG 68.
Trade off between clinical benefits and harms	No evidence was identified for this recommendation. The recommendations were based on the consensus expert opinion of the GDG members. In making the recommendation, the GDG took into consideration the clinical evidence from the PCC dose review along with the consensus opinion of the GDG. The evidence from studies on PCC dosage suggested that PCC was effective in immediate correction of INR; however, the effect of PCC on other clinical outcomes was not conclusive. The GDG discussed the potential benefits of having a PCC transfusion to reduce blood loss, and consequently improve prognosis in terms of both morbidity and mortality. The GDG agreed that one of the major advantages of PCC in the emergency correction of over anti-coagulation was the speed at which correction of INR was achieved. The GDG considered findings from studies which did not meet the protocol criteria entirely, but provided evidence of the speed of INR correction with PCC administration (for details, please refer to the 'other considerations' section. The risks in having a PCC transfusion, including thrombotic events, were also discussed. The GDG agreed that overall, the benefit of INR correction with PCC outweighed the risk of thrombotic complications (assessed from the same studies, please refer to the 'other considerations' section) and recommended the use of PCC transfusion for emergency reversal of warfarin anticoagulation. The GDG also took into consideration that there were no alternative treatment options to PCC which would provide correction of coagulation as rapidly in patients on warfarin with major bleeding. The opinion of the GDG was that PCC should be offered to patients with major bleeding and for patients with head injury suspected of having intra cerebral haemorrhage. The GDG was unanimous in its decision to recommend the use of PCC. There was no specific evidence available for the use of PCC transfusion in the paediatric population. The GDG agreed that the same recommendations should

	apply for children as for adults, as PCC are used for children and the risks and benefits would be likely to be the same in this situation as for adults. .
Economic considerations	No relevant economic evaluations comparing different thresholds or targets for PCC were identified. The cost of PCC was considered by the GDG: beriplex and octaplex cost £255 and £245 per 500 IU vial, respectively. Based on consensus expert opinion, the GDG considered that, for emergency reversal of anti-coagulation with warfarin in people with major bleeding or with head injury suspected of having intra cerebral haemorrhage, the cost of transfusing PCC was likely to be offset by avoiding the negative costly outcomes that would result from not transfusing these patients. The potential negative outcomes include further bleeding leading to lengthier and more complex (and costly) hospitalisation (for example, ICU), adverse events and mortality.
Quality of evidence	No evidence was identified for this recommendation. The recommendation was based on the consensus expert opinion of the GDG members. The GDG drew on its knowledge and experience and agreed that PCC should be offered for patients with major bleeding and for patients with head injury suspected of having intra cerebral haemorrhage. Whilst there was no evidence that met our inclusion criteria and this recommendation would usually have been worded to say "Consider PCC", in this emergency situation the GDG felt that treatment needed to be given immediately and therefore a stronger "Offer" recommendation was more appropriate.
Other considerations	The recommendation applies to adults and children requiring PCC transfusions. The GDG also took into consideration findings of 3 cohort studies: Pabinger 2008, Leal Noval 2013 and Dowlatshahi 2012[229, 174, 91] which did not meet the protocol criteria to inform the consensus recommendations. A small multi-centre single arm prospective observational study by Pabinger et al. (n=44)[229]assessed the efficacy of and safety of stratified Beriplex dosing in rapidly normalising elevated INR and achieving haemorrhage control : The study reported that: At 30 minutes post-infusion, INR declined to ≤1.3 in 40 patients (93%). In the remaining three patients, INR was 1.4 at this time point. Median INR declined to 1.2 at 30 minutes from 3.2 at baseline. Throughout the 48h observation period INR remained stable, with the median value fluctuating between 1.2 and 1.3 at all post-infusion time points. In 25 patients (58%), adverse events occurred, including 2 suspected thromboembolic complications. In six patients the adverse events were classified as serious and three of these patients died as a result. One serious adverse event was categorised as possibly related to PCC administration, while all other serious and non-serious adverse events were judged to be unrelated. The single possibly related serious adverse event was a suspected pulmonary embolism in a 70 year old man who entered the study requiring reversal of phenprocoumon anticoagulation to control acute bleeding resulting from perforation of stomach cancer. A retrospective single centre study by Leal-Noval et al. [174] (n=142) evaluated the laboratory and clinical efficacy of PCC, as assessed by its capacity of returning INR to normal and decreasing bleeding and transfusion requirements, in patients with or without vitamin K antagonists treatment (). Most patients (69%) received PCC for reversing the anticoagulant effects of vitamin K antagonists. The median dose was 1200 (900-1500) IU per patient (15 IU/kg). The study reported that: After PCC infusion, mean INR value decreased significantly from 4±3 to 1.7±1.2. Similar reductions were observed for aPTT values. Patients treated for excessively

	elevated INR (INR ≥4) and aPTT values (aPTT ≥ 68 s) showed the highest decrements. Patients who reached a post-infusion INR less than 1.4 (n=88) had lower mortality than patients who remained with an INR at least 1.4 (n=54) (crude mortality rate 33 vs. 55.6% respectively; p<0.001). Reduction or arrest of bleeding was observed in 75 out of 142 patients (52.8%) after PCC infusion. Overall mortality during hospitalisation was higher amongst vitamin K antagonist patients, and around 30% of all the deaths were considered as bleeding related. A study by Dowlatshahi [91] reported the data from a prospective multi-centre registry to monitor use of PCC therapy in Canada (n=141). Patients were treated with median Octaplex dose of 1000 IU (interquartile range, 500; based on Factor IX equivalence). Patients with intra-parenchymal haemorrhage had an in-hospital mortality rate of 42.3%. ; in hospital mortality was 42.3%. INR correction <1.5 was achieved in 71.8% at 1 hour and in 76.4% at 6 hours. There were 3 confirmed thrombotic complications within 7 days of therapy (2%). The total 30-day thrombotic event rate was 5%. Vitamin K needs to be administered in addition to PCC for patients with major bleeding or suspected intra-cerebral haemorrhage because it increases the levels of coagulation factors whose production is reduced by warfarin.

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Recommendations	**42. Consider immediate prothrombin complex concentrate transfusions to reverse warfarin anticoagulation in patients having emergency surgery, depending on the level of anticoagulation and the bleeding risk.**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (cessation of bleeding in bleeding patients), infections (for example, pneumonia), quality of life, serious adverse events and adverse events related to transfusion as the critical outcomes for decision making. Other important outcomes included length of stay (hospitalisation), number of patients needing red blood transfusions, number of units of red blood cells transfused and correction of abnormal coagulation tests.For major bleeding, follow the recommendations in NICE's guideline on Major trauma, currently in development. For PCC for bleeding, follow the recommendation in NICE's guideline on Acute upper gastrointestinal bleeding: management (2012), CG 141. For PCC, follow recommendation 1.4.2.8 in NICE's guideline on Stroke (2008), CG 68.
Trade off between clinical benefits and harms	No evidence was identified for this recommendation. The recommendations were based on the consensus expert opinion of the GDG members. In making the recommendation, the GDG noted the lack of evidence and took into consideration the clinical evidence data from the PCC dose review along with the consensus opinion of the GDG. The evidence from studies on PCC dosage suggested that PCC was effective in immediate correction of INR; however, the effect of PCC on other clinical outcomes was not conclusive. The GDG discussed the potential benefits of PCC, especially in patients without

	major bleeding, where rapid anticoagulant reversal may be required prior to emergency surgery. The GDG noted that the rapid onset of action of PCC made them ideal for anticoagulant reversal in an emergency situation. Weighing up the potential adverse effects of PCC for example, thromboembolic events against the risk of bleeding, the opinion of the GDG was that PCC should be considered for patients undergoing emergency surgery. The level of anticoagulation and the risk of bleeding for the individual patient should be taken into account. The GDG was unanimous in its decision. There was no specific evidence available for the paediatric population for this recommendation. The GDG agreed that the same recommendations should apply for children as for adults, as PCC are used for children and the risks and benefits would be likely to be the same in this situation as for adults..
Economic considerations	No relevant economic evaluations comparing different thresholds or targets for PCC were identified. The cost of PCC was considered by the GDG: beriplex and octaplex cost £255 and £245 per 500 IU vial, respectively. Based on consensus expert opinion, the GDG considered that, in an emergency situation where immediate reversal of anti-coagulation with warfarin is required in people undergoing emergency surgery, the cost of transfusing PCC was likely to be offset by avoiding the negative costly outcomes that would result from not transfusing these patients. The potential negative outcomes include further bleeding leading to lengthier and more complex (and costly) hospitalisation (for example, ICU), adverse events and mortality.
Quality of evidence	No evidence was identified for this recommendation. The recommendation was based on the consensus expert opinion of the GDG members. The GDG drew on its knowledge and experience and agreed that PCC should be considered for immediate reversal of anti-coagulation with warfarin in people undergoing emergency surgery.
Other considerations	The recommendation applies to adults and children requiring PCC transfusions. The GDG also took into consideration findings of 3 cohort studies (Pabinger 2008, Leal- Noval 2013, Dowlatshahi 2012) [229, 174, 91] which did not meet the protocol criteria to inform the consensus recommendations. A small multi-centre single arm prospective observational study by Pabinger et al. (n=44) [229] assessed the efficacy of and safety of stratified Beriplex dosing in rapidly normalising elevated INR and achieving haemorrhage control. The study reported that: At 30 minutes post-infusion, INR declined to ≤1.3 in 40 patients (93%). In the remaining three patients, INR was 1.4 at this time point. Median INR declined to 1.2 at 30 minutes from 3.2 at baseline. Throughout the 48h observation period INR remained stable, with the median value fluctuating between 1.2 and 1.3 at all post-infusion time points. In 25 patients (58%), adverse events occurred, including 2 suspected thromboembolic complications. In six patients the adverse events were classified as serious and three of these patients died as a result. One serious adverse event was categorised as possibly related to PCC administration, while all other serious and non-serious adverse events were judged to be unrelated. The single possibly related serious adverse event was a suspected pulmonary embolism in a 70-year-old man who entered the study requiring reversal of phenprocoumon anticoagulation to control acute bleeding resulting from perforation of stomach cancer. A retrospective single centre study by Leal-Noval et al. [174] (n=142) evaluated the

	laboratory and clinical efficacy of PCC, as assessed by its capacity of returning INR to the norm and decreasing bleeding and transfusion requirements, in patients with or without vitamin K antagonists treatment. Most patients (69%) received PCC for reversing the anticoagulant effects of vitamin K antagonists. The median dose was 1200 (900-1500) IU per patient (15 IU/kg). The study reported that: After PCC infusion, mean INR value decreased significantly from 4±3 to 1.7±1.2. Similar reductions were observed for aPTT values. Patients treated for excessively elevated INR (INR ≥4) and aPTT values (aPTT ≥ 68 s) showed the highest decrements. Patients who reached a post-infusion INR less than 1.4 (n=88) had lower mortality than patients who remained with an INR at least 1.4 (n=54) (crude mortality rate 33 versus 55.6% respectively; p<0.001). Reduction or arrest of bleeding was observed in 75 out of 142 patients (52.8%) after PCC infusion. Overall mortality during hospitalisation was higher amongst vitamin K antagonist patients, and around 30% of all the deaths were considered as bleeding related. A study by Dowlatshahi [91] reported the data from a prospective multi-centre registry to monitor use of PCC therapy in Canada (n=141). Patients were treated with median Octaplex dose of 1000 IU (interquartile range, 500; based on Factor IX equivalence). Patients with intra-parenchymal haemorrhage had an in-hospital mortality rate of 42.3%. In hospital mortality was 42.3%. INR correction <1.5 was achieved in 71.8% at 1 hour and in 76.4% at 6 hours. There were 3 confirmed thrombotic complications within 7 days of therapy (2%). The total 30-day thrombotic event rate was 5%. The GDG wished to note that vitamin K needs to be administered with PCC for warfarin reversal.

Recommendations	**43. Monitor the international normalised ratio (INR) to confirm that warfarin anticoagulation has been adequately reversed, and consider further prothrombin complex concentrate.**
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (cessation of bleeding in bleeding patients), infections (for example, pneumonia), quality of life , serious adverse events and adverse events related to transfusion as the critical outcomes for decision making. Other important outcomes included length of stay (hospitalisation), number of patients needing red blood transfusions, number of units of red blood cells transfused and correction of abnormal coagulation tests. For major bleeding, follow the recommendations in NICE's guideline on Major

	trauma, currently in development. For PCC for bleeding, follow the recommendation in NICE's guideline on Acute upper gastrointestinal bleeding: management (2012), CG 141. For PCC, follow recommendation 1.4.2.8 in NICE's guideline on Stroke (2008), CG 68.
Trade off between clinical benefits and harms	No evidence was identified for this recommendation. The recommendation was based on the consensus expert opinion of the GDG members. The GDG discussed the potential benefits of PCC transfusion and monitoring after each transfusion; and the monitoring to include INR tests to confirm adequate reversal of anti-coagulation with warfarin. If there is no adequate reversal of INR, additional doses of PCC could be given as required. The GDG also discussed that PCC dosing may often be determined by INR and it could influence future treatments. It is inconvenient for the patient to undergo monitoring for INR levels as it is and invasive test and is required to be done regularly; however, it was felt that the importance of getting the dose right and therefore reducing the risk of bleeding or of unnecessary administration of PCC (for example, thromboembolic events) means that monitoring is worthwhile. There was no specific evidence available for the paediatric population. The GDG agreed that the same recommendations should apply for children as for adults in order to ensure effectiveness of PCC treatment. .
Economic considerations	The GDG noted that the cost of monitoring INR to confirm adequate reversal of anti-coagulation with warfarin was negligible and would be offset by savings as a result of transfusing less PCC.
Quality of evidence	No evidence was identified for this recommendation. The recommendation was based on the consensus expert opinion of the GDG members. There was no specific evidence available for the paediatric population
Other considerations	The recommendation applies to adults and children requiring PCC transfusions.

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19 Prothrombin Complex Concentrates: doses

Please see detailed introduction in section 18.

19.1 Review question: What is the clinical- and cost-effectiveness of different doses of prothrombin complex concentrates (PCC) for transfusion?

For full details see review protocol in Appendix C.

Table 123: PICO characteristics of review question

Population	• Adults who are bleeding
	• Adults receiving prophylaxis and undergoing procedures
	  ○ Patients on Vitamin K antagonists
	  ○ Patients on novel anticoagulants
	• Children who are bleeding
	• Children receiving prophylaxis and undergoing procedures
	  ○ Children on Vitamin K antagonists
	• Children on novel anticoagulants

Intervention(s)	• Low dose PCC for transfusion (as defined by the trial) • High dose PCC for transfusion (as defined by the trial)
Comparison(s)	High dose of PCC for transfusion will be compared with low dose of PCC for transfusion.
Outcomes	• 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 at end of follow-up • Infections (for example, pneumonia) • Serious adverse events • Adverse events related to the transfusion • Number of patients needing red cell transfusions • Number or volume of red cells transfused • Length of stay (hospitalisation) • Correction of abnormal coagulation test
Study design	• RCTs • Systematic reviews • Large cohort studies

19.2 Clinical evidence

We searched for systematic reviews, randomised controlled trials and observational studies addressing the clinical question: What is the clinical- and cost-effectiveness of different doses of prothrombin complex concentrates (PCC) for transfusion?

Three studies were included in the review: [160,162,301] these are summarised in Table 124 below.

The data for the review could not be pooled due to variation in the study designs and different dosing regimens across the studies. The results have been presented per study, and quality assessment done per outcome using the GRADE approach.

Evidence from these studies is summarised in the GRADE clinical evidence profile and clinical evidence summary below (Table 125;Table 126;Table 127). See also the study selection flow chart in Appendix E, study evidence tables in Appendix H, forest plots in Appendix K, GRADE tables in Appendix J and excluded studies list in Appendix P.

Table 124: Summary of studies included in the review

Study	Population	Intervention/ comparison	Outcomes	Comments
Kerebel 2013[160] Multicentre RCT n=59 France	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.	• 25 IU /kg body weight of 4-factor PCC (low dose) (octaplex) • 40 IU /kg body weight of 4-factor PCC (high dose) (octaplex)	• Mortality at 30 days • Patients with at least one adverse event • Patients with at least one serious adverse event • Patients with at least one thrombotic event	
Vannart 2006[301] RCT n=93 The Netherlands	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.	• Standard dose: single dose of 20 ml of PCC (corresponding with a dose of 500 IU FIX or about 7IU FIX/kg) (n=47) • Individualised dosing regimen: Dose taking into account the target INR* and the body weight of the patient n=46) *Target INR of 1.5 was set for major bleeding e.g. in the digestive tract or the CNS and urgent surgical interventions. (33/46) *Target INR of 2.1 was set for small	• Number of patients reaching target INR, at 15 minutes after the first dosage of PCC • Serious adverse events	

Study	Population	Intervention/ comparison	Outcomes	Comments
		urgent interventions, and for minor bleedings such as epistaxis or haematuria (13/46) Mean weight: 72.5 kg Baseline INR: 4.7 (mean) Mean dose for patients in the individualised dosing regimen: • 50 ml (target INR 2.1) • 80 ml (Target INR 1.5)		
Khorsand 2012[162] Two-Cohort study n=240	Patients were eligible for inclusion if reversal of vitamin K antagonist (VTA) treatment with prothrombin complex concentrate (PCC) was indicated for major or clinically relevant, non-intracranial bleeding.	• Low Fixed dose PCC- median PCC dosage per patient 1040 IU FIX (range 260-1560) (Cofact) vs. • 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.	• Number of patients achieving target INR at 15 minutes after PCC infusion (INR<2) • Deep Vein thrombosis (DVT) • All-cause mortality	

19.2.1 Summary of the evidence

Table 125Low dose PCC (25 IU/kg) compared with high dose PCC (40 IU/kg) (RCT)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with High dose (40 IU/kg) (RCT)	Risk difference with Low dose (25 IU/kg) (95% CI)
Mortality	59 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.69 (0.22 to 2.19)	Moderate	
				200 per 1000	62 fewer per 1000 (from 156 fewer to 238 more)
Patients with at least one adverse event	59 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.99 (0.79 to 1.25)	Moderate	
				833 per 1000	8 fewer per 1000 (from 175 fewer to 208 more)
Patients with at least one serious adverse event	59 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 0.95 (0.5 to 1.8)	Moderate	
				400 per 1000	20 fewer per 1000 (from 200 fewer to 320 more)
Patients with at least one thrombotic event	58 (1 study)	VERY LOW[a,b] due to risk of bias, imprecision	RR 1 (0.15 to 6.63)	Moderate	
				69 per 1000	0 fewer per 1000 (from 59 fewer to 388 more)
Target INR (<1.2) achieved	59 (1 study)	LOW[a,c] due to risk of bias, imprecision	RR 0.58 (0.37 to 0.92)	Moderate	
				767 per 1000	322 fewer per 1000 (from 61 fewer to 483 fewer)

(a) Allocation concealment not reported. Open label study.
(b) Confidence interval crosses both default MIDs and line of no effect.
(c) Confidence interval crosses one default MID.

Table 126: Modified GRADE profile: Low Fixed dose PCC (1040 IU FIX) compared with variable dose PCC (cohort study)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with variable dose (cohort study)	Risk difference with Fixed dose (1040 IU) (95% CI)
Target INR reached	240 (1 study)	VERY LOW[a] due to risk of bias	RR 0.98 (0.89 to 1.07)	Moderate	
				892 per 1000	18 fewer per 1000 (from 98 fewer to 62 more)
Deep vein	240	VERY LOW[a,b]	RR 0.46	Moderate	

thrombosis	(1 study)	due to risk of bias, imprecision	(0.02 to 11.12)	7 per 1000	4 fewer per 1000 (from 7 fewer to 71 more)
Mortality (all cause)	240 (1 study)	VERY LOW[a,c] due to risk of bias, imprecision	RR 0.54 (0.31 to 0.94)	Moderate	
				259 per 1000	119 fewer per 1000 (from 16 fewer to 179 fewer)

(a) Observational study and is therefore more prone to selection bias.
(b) Confidence interval crosses both default MIDs and line of no effect.
(c) Confidence interval crosses one default MID.

Table 127: Standard dose PCC (500 IU FIX/7 IU FIX/kg) compared with individualised dosing regimen of PCC (RCT)

Outcomes	No. of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Individualised dosing regimen [RCT]	Risk difference with Standard dose (500 IU FIX/7 IU/kg) (95% CI)
Target INR at 15 minutes after the first dosage of PCC	93 (1 study)	MODERATE[a] due to risk of bias	RR 0.48 (0.34 to 0.68)	Moderate	
				891 per 1000	463 fewer per 1000 (from 285 fewer to 588 fewer)
Serious adverse events	94 (1 study)	LOW[a,b] due to risk of bias, imprecision	RR 1 (0.15 to 6.81)	Moderate	
				43 per 1000	0 fewer per 1000 (from 37 fewer to 250 more)

Allocation concealment not reported. Open label study.
(b) Confidence interval crosses both default MIDs and line of no effect.

19.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

Relevant unit costs are provided in Appendix N to aid consideration of cost-effectiveness.

19.4 Evidence statements

Clinical

Low dose PCC versus high dose PCC

One RCT compared low dose PCC with high dose PCC. The evidence suggested that there was lower mortality in patients receiving low dose PCC, but there was considerable uncertainty. There was no difference of effect between patients receiving low dose PCC and high dose PCC with respect to the number of patients with at least one adverse event, number of patients with at least one serious adverse event and number of patients with at least one thrombotic event. The evidence suggested that low dose PCC may be clinically effective with respect to number of patients achieving target INR (<1.2), but there was some uncertainty. The evidence ranged from low to very low quality.

No evidence was identified for the critical outcomes such as bleeding (cessation of bleeding in bleeding patients), infections, quality of life; and important outcomes such as length of stay, number of patients needing red blood transfusions, number of units of red blood cells transfused.

Low fixed dose PCC versus variable dose regimen PCC

One cohort study compared low fixed dose PCC with variable dose regimen PCC. The evidence suggested that there may be lower mortality and less number of patients with deep vein thrombosis with low fixed dose PCC , but there was considerable uncertainty. No clinically important differences were observed between the groups with respect to achievement of target INR levels (<1.5). All evidence was of very low quality.

No evidence was identified for the critical outcomes such as bleeding (cessation of bleeding in bleeding patients), infections, quality of life, serious adverse events, and important outcomes, such as length of hospital stay, number of patients needing red blood transfusions, number of units of red blood cells transfused.

Standard dose PCC versus individualised dosing regimen PCC

One RCT compared standard dose PCC with individualised dosing regimen PCC. The evidence showed a clinically important benefit with standard dose PCC with respect to achievement of target INR at 15 minutes after the first dosage of PCC. No difference was observed between the groups with respect to serious adverse events, but there was considerable uncertainty. The evidence was of low and moderate quality.

No evidence was identified for the critical outcomes, such as all-cause mortality at 30 days, bleeding (cessation of bleeding in bleeding patients), infections (for example, pneumonia), quality of life; and important outcomes such as length of stay (hospitalisation), number of patients needing red blood transfusions, and number of units of red blood cells transfused

Economic

No relevant economic evaluations were identified.

19.5 Recommendations and link to evidence

Recommendations	No recommendations made
Relative values of different outcomes	The GDG considered all-cause mortality at 30 days, bleeding (cessation of bleeding in bleeding patients), infections (for example, pneumonia), quality of life, serious adverse events and adverse events related to transfusion as the critical outcomes for decision making. Other important outcomes included length of stay (hospitalisation), number of patients needing red blood transfusions, number of units of red blood cells transfused and correction of abnormal coagulation tests. The GDG was aware that NICE had produced guidance on Upper Gastrointestinal Bleeding and Stroke which provided recommendations on PCC and were happy to refer patients to those guidelines. Additionally, NICE was in the process of developing guidance on major bleeding in its Trauma guideline.
Trade off between clinical benefits and harms	Evidence from one RCT comparing low dose PCC with high dose PCC showed that there was lower mortality in patients receiving low dose PCC, but there was some uncertainty within the effect estimate. The evidence suggested that there was no important difference of effect between patients receiving low dose PCC and high dose PCC for the outcomes patients with at least one adverse event, patients with at least one serious adverse event and patients with at least one thrombotic event. The evidence showed clinically important benefit for low dose PCC for the outcome number of patients achieving target INR (<1.2). No evidence was identified for the critical outcomes such as bleeding (cessation of bleeding in bleeding patients), infections, quality of life; and important outcomes such as length of stay, number of patients needing red blood transfusions, number of units of red blood cells transfused. Evidence from one cohort study comparing low fixed dose PCC with variable dose regimen PCC showed clinically important benefit for low fixed dose PCC for the outcome mortality (in-hospital). The evidence suggested that there were fewer patients with deep vein thrombosis in patients receiving low fixed dose PCC, but there was considerable uncertainty. There was no important difference between the groups for the outcome number of patients achieving target INR (<1.5). No evidence was identified for the critical outcomes such as bleeding (cessation of bleeding in bleeding patients), infections, quality of life, serious adverse events, and important outcomes, such as length of hospital stay, number of patients needing red

<table>
<tr><td></td><td>blood transfusions, number of units of red blood cells transfused.

Evidence from one RCT comparing standard dose PCC with individualised dosing regimen PCC suggested that there was no important difference between the groups for the outcome serious adverse events. The evidence showed clinically important benefit for standard dose PCC for the outcome, target INR achieved at 15 minutes after the first dosage of PCC. No evidence was identified for the critical outcomes, such as all-cause mortality at 30 days, bleeding (cessation of bleeding in bleeding patients), infections (for example, pneumonia), quality of life; and important outcomes such as length of stay (hospitalisation), number of patients needing red blood transfusions, and number of units of red blood cells transfused

The GDG agreed not to make any recommendations on PCC dosage as the evidence was very weak and the majority of the evidence (2 studies) used the product Co-fact, which is not licenced to be used in the UK. The GDG were not comfortable in making a consensus based recommendation on the specific dose of PCC to be administered in the absence of good quality evidence.

There was no specific evidence available in the paediatric population for this recommendation. The GDG agreed that, as for adults, no recommendation should be made for children.</td></tr>
<tr><td>Economic considerations</td><td>No relevant economic evidence was identified for this review.</td></tr>
<tr><td>Quality of evidence</td><td>The quality of evidence from the 2 RCTS was very low due to risk of bias arising from a lack of allocation concealment and inadequate blinding.

The quality of evidence from one cohort study was very low as it was an observational study and therefore is more prone to selection bias. There was no specific evidence available for children.
.</td></tr>
<tr><td>Other considerations</td><td>Although no recommendations were drafted regarding the doses of PCC to be administered, the GDG discussed the standard dose of PCC used in clinical practice and agreed that prescribers should follow the summary of product characteristics (SPC) when prescribing PCC. The GDG noted the following based on the SPC:
The dose of PCC will depend on the INR before treatment.
Octaplex SpC can be prescribed (based on SPC) for normalisation of INR (≤ 1.2 within 1 hour) at different initial INR levels as follows:
<table>
<tr><td>Initial INR</td><td>2– 2.5</td><td>2.5 – 3</td><td>3 – 3.5</td><td>> 3.5</td></tr>
<tr><td>Approximate dose*
(ml Octaplex/kg body weight)</td><td>0.9 –1.3</td><td>1.3 – 1.6</td><td>1.6 – 1.9</td><td>> 1.9</td></tr>
</table>
*The single dose should not exceed 3.000 IU (120 ml Octaplex).

Beriplex can be prescribed (based on SPC) as follows:
<table>
<tr><td>Pre-treatment INR</td><td>2.0 – 3.9</td><td>4.0 – 6.0</td><td>> 6.0</td></tr>
<tr><td>Approximate Beriplex dose ml/kg body weight</td><td>1</td><td>1.4</td><td>2</td></tr>
<tr><td>Approximate Beriplex dose IU (Factor</td><td>25</td><td>35</td><td>50</td></tr>
</table></td></tr>
</table>

	IX)/kg body weight Dose is based on body weight up to but not exceeding 100 kg. For patients weighing more than 100 kg, the maximum single dose (IU of Factor IX) should therefore not exceed 2500 IU for an INR of 2.0 – 3.9, 3500 IU for an INR of 4.0 – 6.0 and 5000 IU for an INR of > 6.0.

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20 Patient information

Most patients, when facing any kind of medical or surgical procedure, expect to know what it involves before it is undertaken. This includes: why it may be necessary; how it will be carried out; what its implications are; and whether there are any feasible alternatives. Blood transfusion is no different.

The United Kingdom is fortunate for there is no lack of information about blood transfusion. Clinical staff have access to guidance on explaining transfusion to patients and carers. There is a suite of information leaflets, including ones written for children, which hospitals can order free of charge or download. The problem is that this material does not seem to reach most patients. Nor are all patients satisfied with the verbal explanations of transfusion given to them by doctors and nurses. Indeed, some patients would like to ask clinicians more questions but feel they shouldn't.

Some blood transfusions are not planned, of course, and are carried out in an emergency. In this case, there may be no opportunity to explain to patients or carers beforehand what is being done, or why. In such cases the patient or carers must be given comprehensive information. For many years, there has been guidance to clinicians that they should give post-transfusion information to such patients, encompassing advice about the implications of the transfusion they have received. To inspire confidence and aid treatment and recovery – and to avoid the opposite – the quality of communication is the key.

20.1 Review question: What is the information and support patients under consideration for a blood transfusion and their family members or carers would value and how would they prefer to receive it?

For full details see review protocol in Appendix C.

Table 128: PICO characteristics of review question

Population and setting	Adults and children under consideration for a blood transfusion and their family members and carers. All settings relevant to the NHS will be considered.
Objective	To consider people's experience and preferences for information requirements on blood transfusion
Review strategy	• Study designs to be considered: ○ Qualitative studies (interviews, focus groups, observations) ○ Surveys • Population size and directness: ○ No limitations on sample size ○ Studies with indirect populations will not be considered for example, people receiving IV fluids • Setting: ○ Any setting where people receive blood transfusions relevant to the NHS • Appraisal of methodological quality ○ The methodological quality of each study will be assessed using NICE checklists and the quality of the evidence will be assessed by a modified GRADE approach for each outcome • Data synthesis ○ Thematic analysis of the data will be conducted and findings presented

20.2 Clinical evidence

20.2.1 Methods

We searched for qualitative studies exploring patients' and carers' perceptions of their experiences of receiving blood transfusion as well as the information and support they wanted to receive.

Seven qualitative studies were included in the review.[3,46,65,78,106,109,203]These are summarised in Table 129below. Key findings from these studies are summarised in the evidence summary below (see Table 129). See also the study selection flow chart in Appendix E, study evidence tables in Appendix H , and excluded studies list in Appendix P.

The aim of all the studies was to explore people's experiences of receiving a blood transfusion, as well as information and support that they found helpful in their experience of receiving a blood transfusion. Some studies explored patients' views on consent for receiving a blood transfusion and what information was provided to them prior to obtaining consent. A variety of qualitative methodologies were used to inform the research including interviews and surveys (see Table 129). Two studies used one-to-one interviews as their data-collection method, while the remaining 5 studies were surveys.

The critical appraisal of the studies included was done using the NICE checklist for qualitative studies. A thematic analysis was conducted on the findings from the different studies and observations from patients receiving transfusion were grouped under various emerging themes. The quality of evidence was assessed for each theme based on a modified GRADE approach of assessing the limitations of the evidence (as a proxy for risk of bias assessment), applicability of the study (as a proxy for indirectness) and the coherence of findings (as a proxy for inconsistency) across the studies contributing to that theme. No assessment of imprecision was undertaken as these are qualitative data and therefore a summative quantitative assessment was not considered applicable here.

20.2.2 Summary of studies included in the review

Table 129: Summary of included studies

Study	Design	Population (n)	Research aim	Comments
Qualitative studies (for example, 1:1 interviews, focus groups, partner interviews, semi-structured interviews focus groups)				
Adams et al. 2011[3]	Semi-structured interviews	Adults who had received a blood transfusion over the five week study period (n=21)	To develop a more robust understanding of patients' experience of preparing for and receiving a blood transfusion	
Fitzgerald et al. 1999[106]	Interviews	People who were able and willing to describe their experience of receiving a blood transfusion (n=19)	To develop a description of patients' experiences of the blood transfusion process	No information on when the interview was conducted (how long after the transfusion)
Surveys				
Chan et al. 2005[46]	Patient self-administered survey	Adult patients who had received red cell transfusion within the study period (3 months) (n=344)	To gain insight into the barriers for effective communication of transfusion information	No information on validation or piloting of survey. Survey had no open ended questions

Court et al. 2011[65]	Patient administered survey questionnaire.	Adult patients whose blood was cross-matched over a 2 month period, whether they received a transfusion or not. (n=164)	To evaluate patient perceptions of blood transfusion and what the patient remembers of the consent process	
Davis et al. 2012[78]	Cross sectional survey	Patients who received blood transfusions (one off transfusions and regular transfusion recipients). (n=110)	To investigate patients' attitudes towards information they were provided with about transfusion and consenting to a transfusion	Researcher helped patients fill out survey- may have introduced bias (researcher bias, interviewer bias)
Friedman et al. 2012[109]	Bedside survey with interviews	Adult inpatients who had received with RBC transfusion within the preceding 3 days. (n=45)	To evaluate patient's understanding of the principles of blood transfusion as well as proper collection of patients consent	Choice of answers was fixed in the survey interview and the questions were leading
Murphy et al. 1997[202]	Survey	Patients who had been transfused during current admission and were sufficiently well to answer a questionnaire. (n=51)	To study patients' attitudes to receiving information about blood transfusion or written consent before transfusion	No information on validation or piloting of survey

20.2.3 Evidence

Table 130: Themes and sub themes

Main theme	Sub-themes
Paternalism and decision making- trust in health care professionals	Trust Involvement
Information received	Understanding of information received Satisfaction with content of information Variation in information received
Mode of information delivery	Preference for written information
Risk perception/concern	No sub-themes

Table 131: Evidence summary: Summary of people's experiences of blood transfusion in relation to information provision

Themes/Sub-themes	No. of studies	Design	Sample size	Summary of findings per theme	Comments on overall quality assessment
Theme: Paternalism and decision making					
Sub-theme: Trust	2	1 (semi-structured interviews) + 1 (survey)	21 (interviews)+ 164 (surveys)	• Patients rarely questioned physicians' decisions to transfuse and trusted them to make the right decision for them (interviews) • Patients accepted that the doctor knew best and did not query it.	Very low quality based on limitations of studies. Evidence is applicable to target population and setting. Observations are coherent across all studies.
Sub-theme: Involvement	2	2 (surveys)	164+110	• Some patients wanted to have more involvement in the decision making process but were afraid to ask in case they were seen as awkward patients. • Many patients were just told they needed a transfusion and said that there was no time to ask questions. One patient reported that he could have a full discussion about risks and benefits of transfusion only because he kept asking questions.	Very low quality based on limitations in studies. Evidence is applicable to target population and setting. Observations are coherent across all studies.
Theme: Information received					
Sub-theme: Understanding of information received	7	2 (interviews) 5 (surveys)	21+19 (interviews) 344+164+110 + 45+51 (surveys)	• Patients reported that although information was given to them before blood transfusion, this was not adequate especially regarding their clinical status and transfusion procedures. • 80% of patients in one survey recalled having a discussion and signing a consent form for transfusion. • 59.1% of patients in another survey said they were informed they may need a transfusion. 86.7% said that they were explained the reason for	Very low quality based on limitations in studies. Evidence is applicable to target population and setting. Observations are not coherent across all

Themes/Sub-themes	No. of studies	Design	Sample size	Summary of findings per theme	Comments on overall quality assessment
				the transfusion. 67% said they were informed of the benefits of transfusion and 27.8% said they were informed of the risks of transfusion. • 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. • 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. 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 if 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). • 31% of patients reported receiving any information before transfusion; the rest of 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). • 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. (interviews)	studies.
Sub-theme: Satisfaction with	6	5 (survey)	344+164+110	• 62% of patients felt that the discussion was completely understandable; Only 35% of patients indicated that that they felt	Very low quality based

Themes/Sub-themes	No. of studies	Design	Sample size	Summary of findings per theme	Comments on overall quality assessment
content of information		1(interview)	+45+51 (survey) 19(interviews)	better informed and more comfortable with the decision to accept blood as a result of the written consent process. • 59.8% of patients felt that they had received sufficient information and 61.9% of patents were completely satisfied with the information they received. • The majority said they were satisfied with the information that was provided. Some patients reported that they would have liked to have been given more information. 'I was extremely concerned with the lack of information.' Patients receiving one-off transfusion appeared less satisfied with the information provided than those receiving regular transfusions • 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. • 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) (interviews) • 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.	on limitations in studies. Evidence is applicable to target population and setting. Observations are not coherent across all studies.
Sub-theme: Variation in	1	1 (interview)	19	• Participants reported receiving some information about risks; advice on this was wide-ranging from reassurance that it was a safe procedure to	Low quality evidence based on limitations in

Themes/Sub-themes	No. of studies	Design	Sample size	Summary of findings per theme	Comments on overall quality assessment
information received				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.	study. Evidence is applicable to target population and setting.
Theme: Mode of information delivery					
Sub-theme: Preference for written information	6	5 (surveys) 1 (interview)	344+164+110 +45+51 (surveys) 19 (interviews)	• 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) • 58.8% were explained verbally what the transfusion involves. 26.8% of patients 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. Patients preferred to receive written information in the form of a leaflet and felt that this would have been helpful. • Only one patient said they were given the NHS leaflet 'receiving a blood transfusion'. • 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 patients were aware of the guide. Patients also indicated that they would like to receive the Transfusion Health Guide. Patients also wanted more information in layperson terminology.	Very low quality based on limitations in studies. Evidence is applicable to target population and setting. Observations were slightly incoherent across studies.

Themes/Sub-themes	No. of studies	Design	Sample size	Summary of findings per theme	Comments on overall quality assessment
				• 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 (interviews). • 53% of patients indicated that they would have found it helpful to have been provided with written information about blood transfusion.	
Theme: Risk perception/concern					
No sub-theme	4	2 (semi-structured interviews) 2 (survey)	21+19 (interviews) 344+164 (surveys)	• Patients had concerns about blood safety, disease transmission, screening and testing of blood and administration of the transfusion (interviews). • 77% felt that the risk of blood products was less than that of surgery or anaesthetic. • 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. • 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 (interviews).	Very low quality based on limitations in studies. Evidence is applicable to target population and setting. Observations were coherent across studies.

20.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix F.

Unit costs

Relevant unit costs are provided in Appendix N to aid consideration of cost-effectiveness.

20.4 Narrative summary

Theme: Paternalism and decision making

- Findings from one interview and one survey indicated that patients trusted healthcare professionals to make the right decision for them regarding blood transfusions. However, evidence from two surveys also indicated that patients would like to be more involved in the decision making process but were afraid to ask in case they were viewed as awkward. The evidence was of very low quality.

Theme: Information received

- **Understanding of the information received:** Evidence from 2 interviews and 5 surveys indicated that, in the majority of cases, consent was taken with factual information being given prior to obtaining consent; this information was perceived to be inadequate, with some patients not knowing the reason for transfusion. People who received regular transfusions had better understanding of the information regarding transfusion. The evidence was of very low quality.
- **Satisfaction with content of information:** Evidence from 1 interview and 5 surveys showed that the majority of patients felt satisfied with the information they received; some patients would have liked to have received more information and time to think before giving consent for transfusion. Patients also felt that any additional information on risks and benefits of transfusion would be helpful in coming to a decision. The evidence was of very low quality.
- **Variation in information received:** One qualitative study with interviews from patients receiving transfusion found that advice and information about risks of transfusion was wide-ranging and varied. Information ranged 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.

Theme: Mode of information delivery

- **Preference for written information:** Evidence from 1 interview and 5 surveys indicated that patients felt they would have found it helpful to have been provided with written information about blood transfusion. Written information was not always provided to patients and there was variation in awareness that written information was available. One study also showed a positive correlation indicating recipients receiving written information felt better informed and more comfortable with their decision to receive blood. The evidence was of very low quality.

Theme: Risk perception/concern

- Evidence from 2 interviews and 2 surveys showed that patients had concerns about blood safety, disease transmission, screening and testing of blood and administration of the transfusion. Patients mentioned the risk of HIV infection from blood transfusion but also rationalised verbally

that the risk was infinitesimal and that the consequence of not being transfused far outweighed the possibility of infection or that it did not matter. The slight risk of infection was accepted as unavoidable.

Economic

No relevant economic evaluations were identified.

20.5 Recommendations and link to evidence

Recommendations	**44. Provide verbal and written information to patients who may have or who have had a transfusion, and their family members or carers (as appropriate), explaining:** • **the reason for the transfusion** • **the risks and benefits** • **the transfusion process** • **any transfusion needs specific to them** • **any alternatives that are available, and how they might reduce their need for a transfusion** • **the implications of having a transfusion, such as no longer being able to donate blood** • **that they are encouraged to ask questions.** **45. Document discussions in the patient's notes.**
Relative values of different outcomes	The GDG agreed that outcomes which highlighted patients' experience and information needs regarding blood transfusions were vital to this review. These outcomes include the information that patients would value (i.e. want or find useful), patients' preference for type of information, patient/carer satisfaction and health related quality of life in patients receiving transfusions (HRQoL). The outcomes were explored using a qualitative review approach.
Trade off between clinical benefits and harms	The evidence suggested that patients had limited understanding of many aspects of transfusion; however, they did want to be part of an informed decision making process. The evidence also showed that patients were reassured by provision of written information. The GDG agreed that it was important to provide patients with information they required and to provide it in a format suitable to them as it would help them be more comfortable with receiving a transfusion or make informed choices (some may choose not to receive a transfusion). Patients should also be encouraged to ask questions. The GDG also agreed that it was important to document the information provided and any subsequent discussion in the patient's notes, as it would benefit both the patient and the clinician. No clinical harms or adverse effects of providing information were found in the literature or noted by the GDG.
Economic considerations	No relevant economic evaluations were identified. The GDG considered that although this recommendation may have cost implications as a result of additional health care professional time and additional resource requirements (for example, where information does not already exist in a suitable format), this is an essential part of good patient care to ensure patients are adequately informed. The GDG

	noted that good quality information, in a number of different formats, was accessible from NHSBT free of charge.
Quality of evidence	A qualitative review was conducted. The quality of evidence ranged from low to very low; this was due to limitations in studies, risk of bias and lack of generalisability of findings. The recommendations were based on the evidence and the consensus opinion of the GDG members.
Other considerations	The GDG noted that good quality information for patients regarding transfusion was available. The national information leaflets from NHSBT[f] were considered to be a good source of information. However, it was recognised that delivering such information presented a major challenge in that it often failed to reach the patients concerned. The GDG agreed that information for patients should be 'appropriate', that is, it should be tailored to their specific needs. The content and format of information should take into account: • age of the patient (for example, different style of presentation for children) • literacy (verbal or visual information can be provided for patients who may not be able to read) • language (information can be provided in languages other than English, taking into account the diversity of the population) • mental capacity • special transfusion needs or individual transfusion requirements (for example, the need for irradiated blood). No evidence regarding provision of information to children was identified; the GDG extrapolated from the evidence from adults and agreed the recommendations should apply to both adults and children. However, the format of information provided to children should take into account their age. The GDG noted that currently, NHSBT does provide information in booklets which are specific to children of different ages. The GDG noted that patients should be provided with information regarding alternatives to blood transfusion such as cell salvage and tranexamic acid in order to make a more informed decision regarding blood transfusion. The GDG also noted that information could be made available online for people who preferred to access it; patients could be directed to specific websites providing reliable information on blood transfusion. The GDG agreed that information provided to patients should be given at an appropriate time; the provision of information should also allow the patient to think through it, ask questions and be a part of the decision-making process. Based on the evidence which ranged from low to very low quality and consensus opinion, the GDG recommended providing information on transfusion to patients in a format that was tailored their requirements. There was emphasis on documenting these discussions and relaying of information regarding transfusion to primary care providers.

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[f] NHSBT leaflets are free and may be ordered directly from the distribution hub operated by access 24 from: https://ww3.access-24.co.uk/Login.aspx?ReturnUrl=%2fWebSite%2fStock%2fHome%2fStock.aspx. The NHSBT patient information leaflets can be found at http://hospital.blood.co.uk/patient-services/patient-blood-management-resources/patient-information-leaflets/. More information on: Why you might need a blood transfusion, the risks and benefits and how will you feel during a blood transfusion is available at: http://hospital.blood.co.uk/media/27165/inf64_will-i-need-a-blood-transfusion.pdf

Recommendations	**46. Provide the patient and their GP with copies of the discharge summary or other written communication that explains:** • **the details of any transfusions they had** • **the reasons for the transfusion** • **any adverse events.**
Relative values of different outcomes	The GDG agreed that outcomes which highlighted patients' experience and information needs regarding blood transfusions were vital to this review. These outcomes include the information that patients would value (i.e. want or find useful), patients' preference for type of information, patient/carer satisfaction and health related quality of life in patients receiving transfusions (HRQoL). The outcomes were explored using a qualitative review approach.
Trade off between clinical benefits and harms	The evidence suggested that patients had limited understanding of many aspects of transfusion; however, they did want to be part of an informed decision-making process. The evidence also showed that patients were reassured by provision of written information. The GDG agreed that it was important to provide patients with information they required and to provide it in a format suitable to them as it would help them be more comfortable with receiving a transfusion or make informed choices (some may choose not to receive a transfusion). No clinical harms or adverse effects of providing information were found in the literature or noted by the GDG. The GDG noted that the minimal time needed to add information regarding patients' transfusion to discharge summary or via written communication (letter/email) to patients' GPs was greatly outweighed by the benefits of doing this; for example, this would help patients to understand the reasons for transfusion and discourage them from donating blood. In the long term, this will save time for both patients and health professionals.
Economic considerations	No relevant economic evaluations were identified. The GDG considered that although this recommendation may have cost implications as a result of additional health care professional time where this is currently not done this is an essential part of good patient care to ensure patients are adequately informed.
Quality of evidence	A qualitative review was conducted. The quality of evidence ranged from low to very low; this was due to limitations in studies, risk of bias and lack of generalisability of findings. The recommendations were based on the evidence and the consensus opinion of the GDG members.
Other considerations	The GDG noted that good quality information for patients regarding transfusion was available. The national information leaflets from NHSBT[g] were considered to be a very good source of information. However, it was recognised that delivering such information presented a major challenge (in that it often failed to reach the patients concerned). The GDG acknowledged noted that information should be provided to patients and/or their carers if appropriate, for example, to parents of people receiving transfusions or carers of people with reduced capacity. No evidence regarding provision of information to children was identified; the GDG extrapolated from the evidence from adults and agreed the recommendations should apply to both adults and children.

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[g] NHSBT leaflets are free and may be ordered directly from the distribution hub operated by access 24 from: https://ww3.access-24.co.uk/Login.aspx?ReturnUrl=%2fWebSite%2fStock%2fHome%2fStock.aspx. The NHSBT patient information leaflets can be found at http://hospital.blood.co.uk/patient-services/patient-blood-management-resources/patient-information-leaflets/. More information on: Why you might need a blood transfusion, the risks and benefits and how will you feel during a blood transfusion is available at: http://hospital.blood.co.uk/media/27165/inf64_will-i-need-a-blood-transfusion.pdf

21 Acronyms and abbreviations

Acronym or abbreviation	Description
ACT	Activated clotting time
APTT	Activated partial thromboplastin time
ATR	Acute transfusion reactions
BCSH	British Committee for Standards in Haematology
CABG	Coronary artery bypass grafting
CDS	Clinical Decision Support
CPOE	Computerised physician order entry system
DIC	Disseminated intravascular coagulation
DVT	Deep vein thrombosis
EIS	Electronic identification system
Electronic UPI	Unique patient identification
EPO	Erythropoietin
ERBI	Electronic Remote Blood Issue
FID	Functional Iron Deficiency
FFP	Fresh Frozen Plasma
GIMEMA	Italian Group for Haematological Diseases in Adults
Hb	Haemoglobin
HSCT	Hematopoietic stem cell transplantation
ICS	Intra-operative cell salvage
ICU	Intensive Care Unit
INR	International normalised ratio
I-TRAC	Transfusion, blood tracking system
MBFFP	Methylene blue Fresh Frozen Plasma
NHSBT	National Health Service Blood and Transplant
OAT	Oral anticoagulant therapy
PCC	Prothrombin Complex Concentrates
PCS	Post-operative cell salvage
PROMMTT	Prospective Observational Multicentre Major Trauma Transfusion
RBC	Red blood cell
RFID	Radiofrequency identification
SAVR	Surgical Aortic Valve Replacement
SCT	Stem Cell Transplantation
SHOT	Serious Hazards of Transfusion
TACO	Transfusion associated circulatory overload
TKA	Total Knee Arthroplasty
TRALI	Transfusion related acute lung injury
TXA	Tranexamic acid
Uniplas	Universal Fresh Frozen Plasma
UTI	Urinary Tract Infection
vCJD	Variant Creutzfeldt-Jakob disease
VENO	Veno occlusive disease

Acronym or abbreviation	Description
WHO	World Health Organisation
CRASH-2	Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage

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22 Glossary

22.1 Methodology glossary

Term	Definition
Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
Algorithm (in guidelines)	A flow chart of the clinical decision pathway described in the guideline, where decision points are represented with boxes, linked with arrows.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm.
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Base case analysis	In an economic evaluation, this is the main analysis based on the most plausible estimate of each input. In contrast, see Sensitivity analysis.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Bayesian analysis	A method of statistics, where a statistic is estimated by combining established information or belief (the 'prior') with new evidence (the 'likelihood') to give a revised estimate (the 'posterior').
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Influences on a study that can make the results look better or worse than they really are (Bias can even make it look as if a treatment works when it does not). Bias can occur by chance, deliberately or as a result of systematic errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias. A single-blinded study is one in which patients do not know which study group they are in (for example, whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers and doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.

Term	Definition
Case–control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition. For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinician	A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also observational study.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concordance	This is a recent term whose meaning has changed. It was initially applied to the consultation process in which doctor and patient agree therapeutic decisions that incorporate their respective views, but now includes patient support in medicine taking as well as prescribing communication. Concordance reflects social values but does not address medicine-taking and may not lead to improved adherence.
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect

Term	Definition
	of the test or treatment – often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any effects due to the treatment.
Cost–benefit analysis (CBA)	Cost–benefit analysis is one of the tools used to carry out an economic evaluation. The costs and benefits are measured using the same monetary units (for example, pounds sterling) to see whether the benefits exceed the costs.
Cost–consequences analysis (CCA)	Cost–consequences analysis is one of the tools used to carry out an economic evaluation. This compares the costs (such as treatment and hospital care) and the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost–benefit analysis or cost-effectiveness analysis, it does not attempt to summarise outcomes in a single measure (like the quality-adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out.
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life-years gained (that is, the number of years by which life is extended as a result of the intervention).
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost–utility analysis (CUA)	Cost–utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.
Credible interval (CrI)	The Bayesian equivalent of a confidence interval.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Deterministic analysis	In economic evaluation, this is an analysis that uses a point estimate for each input. In contrast, see Probabilistic analysis.

Term	Definition
Diagnostic odds ratio	The diagnostic odds ratio is a measure of the effectiveness of a diagnostic test. It is defined as the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease.
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Disutility	The loss of quality of life associated with having a disease or condition. See Utility
Dominance	A health economics term. When comparing tests or treatments, an option that is both less effective and costs more is said to be 'dominated' by the alternative.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	An economic evaluation is used to assess the cost-effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits – health effects – relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost–benefit analysis, cost–consequences analysis, cost-effectiveness analysis, cost–minimisation analysis and cost–utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant).
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality of life. It provides a single index value for health status.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower

Term	Definition
	cost per unit of effect, when both are compared with a do-nothing alternative, then Option A is said to have extended dominance over Option B. Option A is therefore more cost-effective and should be preferred, other things remaining equal.
Extrapolation	An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Generalisability	The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Harms	Adverse effects of an intervention.
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality of life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment. Intention-to-treat analyses are often

Term	Definition
	used to assess clinical effectiveness because they mirror actual practice: that is, not everyone complies with treatment and the treatment people receive may be changed according to how they respond to it.
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Intra-operative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.
Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity).
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Logistic regression or Logit model	In statistics, logistic regression is a type of analysis used for predicting the outcome of a binary dependent variable based on one or more predictor variables. It can be used to estimate the log of the odds (known as the 'logit').
Loss to follow-up	A patient, or the proportion of patients, actively participating in a clinical trial at the beginning, but whom the researchers were unable to trace or contact by the point of follow-up in the trial
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Multivariate model	A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable.
Net monetary benefit (NMB)	The value in monetary terms of an intervention net of its cost. The NMB can be calculated for a given cost-effectiveness threshold. If the threshold is £20,000 per QALY gained then the NMB for an intervention is calculated as: (£20,000 × mean QALYs) − mean cost. The most preferable option (that is, the most clinically effective option to have an ICER below the threshold selected) will be the treatment with the highest NMB.
Network meta-analysis	A network meta-analysis is a method for simultaneously comparing multiple treatments in a single meta-analysis.
Number needed to treat (NNT)	The average number of patients who need to be treated to get a positive outcome. For example, if the NNT is 4, then 4 patients would have to be treated to ensure 1 of them gets better. The closer the NNT is to 1, the better the treatment. For example, if you give a stroke prevention drug to 20 people before 1 stroke is prevented, the number needed to treat is 20. See also number needed to harm, absolute risk reduction.

Term	Definition
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups – in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, relative risk, risk ratio.
Opportunity cost	The loss of other healthcare programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant. For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
Peri-operative	The period from admission through surgery until discharge, encompassing the pre-operative and post-operative periods.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what

Term	Definition
	effect the experimental treatment has had – over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Polypharmacy	The use or prescription of multiple medications.
Posterior distribution	In Bayesian statistics this is the probability distribution for a statistic based after combining established information or belief (the prior) with new evidence (the likelihood).
Post-operative	Pertaining to the period after patients leave the operating theatre, following surgery.
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Pre-operative	The period before surgery commences.
Pre-test probability	In diagnostic tests: the proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Prevalence	See Pre-test probability.
Prior distribution	In Bayesian statistics, this is the probability distribution for a statistic based on previous evidence or belief.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Probabilistic analysis	In economic evaluation, this is an analysis that uses a probability distribution for each input. In contrast, see Deterministic analysis.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.
Quality of life	See ‘Health-related quality of life’.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality of life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality of life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it

Term	Definition
	could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the relative risk is 1. If the first group had a relative risk of 2, subjects in that group would be twice as likely to have the event happen. A relative risk of less than one means the outcome is less likely in the first group. Relative risk is sometimes referred to as risk ratio.
Reporting bias	See 'Publication bias'.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	Selection bias occurs if: a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or b) There are differences between groups of participants in a study in terms of how likely they are to get better.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive result in people who don't have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months

Term	Definition
	pregnant, but would probably also include those who are 5 and 7 months pregnant. If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative'). Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
Specificity	The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases. See related term 'Sensitivity'. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	An organisation with an interest in a topic that NICE is developing a clinical guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be: • manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
State transition model	See Markov model
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Transition probability	In a state transition model (Markov model), this is the probability of moving

Term	Definition
	from one health state to another over a specific period of time.
Treatment allocation	Assigning a participant to a particular arm of a trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost–utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).

22.2 Clinical Glossary

Term	Definition
Active bleeding	Also known as or related to haemorrhage, loss of blood, bleeding (finding), haemorrhage, bleeding
Allogeneic	From another member of the same species
Antifibrinolytics	Antifibrinolytics inhibit the activation of plasminogen to plasmin, prevent the break-up of fibrin and maintain clot stability. They are used to prevent excessive bleeding.
Autologous	Obtained from the same individual.
Allogenic	A transplant where the donated material comes from different (although often related) individuals than the recipients.
Anaemia	A condition where a lack of iron in the body leads to a reduction in the number of red blood cells.
Aplastic anaemia	Inability of stem cells to generate mature blood cells, resulting in deficiency of red blood cells, white blood cells and platelets
Arthroplasty	Surgical repair of a joint
Autoimmune thrombocytopenia	A disorder of low blood platelet counts in which platelets are destroyed by antibodies produced by the immune system.
Bacteraemia	The presence of bacteria in the blood.
Cell salvage	Cell salvage is a process that collects blood from an operating site. This blood is then processed in a cell salvage machine and given back to the patient. This type of blood transfusion where the patient receives their own blood back is called autologous transfusion.
Cryoprecipitate	A source of fibrinogen, vital to blood clotting.
Erythropoietin	A glycoprotein hormone that controls erythropoiesis, or red blood cell production.
Fibrinogen	A glycoprotein that helps in the formation of blood clots.
Fibrinolysis	A process within the body that prevents blood clots that occur naturally from growing and causing problems.
Fresh frozen plasma	The remaining serum of human blood that is frozen after the cellular component has been removed for blood transfusion.
Functional Iron Deficiency	An inadequate iron supply to the bone marrow in the presence of storage iron in reticuloendothelial cells. Seen in patients with renal failure who require parenteral iron therapy to respond to administered erythropoietin to correct anaemia.
Genitourinary	The organ system of the reproductive organs and the urinary system.

Term	Definition
Haematemesis	The vomiting of blood.
Haematuria	The presence of red blood cells (erythrocytes) in the urine.
Haemoglobin	The iron-containing oxygen-transport metalloprotein in red blood cells.
Haemolysis	The rupturing of erythrocytes (red blood cells) and the release of their contents (cytoplasm) into surrounding fluid.
Haemopoietic stem cell transplant	Intravenous infusion of autologous or allogeneic stem cells collected from the bone marrow, peripheral blood or umbilical cord blood to replenish haematopoietic function in patients whose bone marrow or immune system is damaged or ineffective.
Haemoptysis	Haemoptysis is the coughing of blood originating from the respiratory tract below the level of the larynx.
Haemostatic	Retarding or stopping the flow of blood within the blood vessels.
Haemostasis	A process which causes bleeding to stop, meaning to keep blood within a damaged blood vessel
International normalised ratio (INR)	A laboratory test measure of blood coagulation, based on prothrombin time.
Iron deficiency anaemia	A condition where a lack of iron in the body leads to a reduction in the number of red blood cells.
Myelodysplasia	Ineffective production of red blood cells, white blood cells and platelets.
Myocardial infarction	Heart attack.
Nosocomial infections	Infections occurring within 48 hours of hospital admission, 3 days of discharge or 30 days of an operation.
Platelets	Blood cells whose function (along with coagulation factors) is to stop bleeding.
Pulmonary oedema	An excess collection of watery fluid in the lungs.
Septicaemia	Septicaemia (another name for blood poisoning) refers to invasion of bacteria into the bloodstream and this occurs as part of sepsis.
Severe bleeding	Bleeding which includes blood gushing or spraying from the wound and not clotting.
Thrombocytopenic	A disorder in which there is a relative decrease of thrombocytes, commonly known as platelets, present in the blood.
Thromboembolism	Formation in a blood vessel of a clot (thrombus) that breaks loose and is carried by the blood stream to plug another vessel.
Thrombosis	The formation of a blood clot inside a blood vessel, obstructing the flow of blood through the circulatory system.
Thrombotic thrombocytopenic purpura	A rare disorder of the blood-coagulation system, causing extensive microscopic clots to form in the small blood vessels throughout the body.
Tranexamic acid	An antifibrinolytic agent which promotes blood clotting.
Variant Creutzfeldt-Jakob disease	A rare, degenerative, fatal brain disorder.
Vascular	The body's network of blood vessels.
WHO Grade 1	Grade 1 petechial (broken capillary blood vessels) bleeding.
WHO Grade 2	Grade 2 mild blood loss (clinically significant).
WHO Grade 3	Grade 3 gross blood loss, requires transfusion (severe).
WHO Grade 4	Grade 4 debilitating blood loss, retinal or cerebral, associated with fatality.

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