

Transfusion

Blood transfusion

Clinical guideline

Appendices O-R

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Final version

*Commissioned by the National Institute for
Health and Care Excellence*

Disclaimer

Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and, where appropriate, their guardian or carer.

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Contents

Appendices O-R	767
Appendix O: Research recommendations.....	768
Appendix P: Excluded clinical studies	777
Appendix Q: Excluded economic studies	794
Appendix R: NICE technical team	798
References	799

Appendices O-R

Appendix O: Research recommendations

O.1 Red blood cell thresholds and targets

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.

Criteria for selecting high-priority research recommendations:

<p>PICO question</p>	<p>Population: Patients with chronic cardiovascular disease in whom a decision is made to transfuse red cells.</p> <p>Intervention and Comparison: ‘Liberal’ and ‘restrictive’ transfusion triggers for red cell transfusion based on the pre-transfusion haemoglobin concentration (possibly 10g/dl for the ‘liberal transfusion strategy’ and 8g/dl for ‘restrictive’).</p> <p>Outcomes: Primary outcome: RBC use from randomisation to hospital discharge (proportion of patients receiving red cell transfusion and number of units of red cells/transfused patient).</p> <p>Secondary outcomes</p> <ol style="list-style-type: none"> 1. Use of non-RBC blood products post-randomisation (FFP; cryoprecipitate; platelets) 2. Mortality (hospital; 90 days) 3. HRQoL (90 days) 4. ICU and hospital length of stay
<p>Importance to patients or the population</p>	<p>The research could be used to formulate evidence-based guidance for clinical staff that in turn will assist in reducing donor exposure to patients by giving specific transfusion triggers for clinical staff. By promoting a consistent approach nationally this would improve patient safety and allow benchmarking of patient outcomes.</p>
<p>Relevance to NICE guidance</p>	<p>The results would ensure that implementation of specific red blood cell thresholds based on evidence allowing improved clinical and cost effectiveness.</p>
<p>Relevance to the NHS</p>	<p>The study would provide evidence to guide clinicians on use of either high or low red cell thresholds across the NHS. It would also assist in showing which threshold best supports patient safety and best outcomes. More optimum use of blood products would ensure these are available for those in whom greatest clinical benefit occurs.</p> <p>Variation in clinical practice and patient care in relation to blood product transfusion will be reduced.</p>

Transfusion
Appendices O-R

National priorities	-
Current evidence base	The overall quality of current clinical evidence was very low in being inconsistent with each paper aiming for specific haemoglobin targets. There was high risk of bias found.
Study design	<p>Randomised Controlled Trial in patients with chronic cardiovascular disease. Patients randomised to low thresholds vs. high thresholds for red cell transfusions.</p> <p>Studies of specific patients groups such as surgical and medical should be collated and analysed, areas of research could include patients who have undergone similar surgical procedures or the same underlying medical conditions. A comparison should be undertaken by randomly selecting low/high thresholds targets and reviewing outcomes e.g. hospital stay, complications etc. Work to specific guideline for each group.</p>
Economic considerations	If the findings show low haemoglobin thresholds and targets are effective this will mean financial savings of 1 or 2 units of red cells per patient.
Feasibility	<p>This research should be completed within a reasonable timescale.</p> <p>May have to consider ethical issues if using high and low thresholds most of the research papers used specific target haemoglobins for their patient groups.</p>
Equalities	No specific equality issues identified
Importance	None.

O.2 Electronic Decision Support

What is the clinical and cost effectiveness of electronic decision support systems 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.

PICO question	<p>Population: Patients in whom a request for red cells or other blood products is made</p> <p>Intervention: Electronic decision support system specific to blood transfusion</p> <p>Comparison: Existing blood transfusion request procedures (excluding electronic decision support systems)</p> <p>Outcomes: Inappropriate blood transfusion; overall rates of blood transfusion; mortality; hospital length of stay; quality of life; pretransfusion haemoglobin level (for red cell transfusion), pretransfusion platelet count (for platelet transfusion), coagulation results (for plasma and coagulation factor transfusion)</p>
Importance to patients or the population	Reduction in inappropriate blood transfusion will reduce risk to patients, and improve clinical outcomes. Reduction in overall use of blood products will reduce costs to the NHS, and increase availability for the population. Cost-effective systems will reduce cost to the NHS as well as improve patient outcomes.
Relevance to NICE guidance	The results would ensure that implementation of electronic decision support was based on evidence of clinical and cost effectiveness.
Relevance to the NHS	<p>The study would provide evidence to guide whether the electronic decision support systems for blood transfusion should be introduced across the NHS. The benefits for patients and the health service in terms of improved outcomes and safer use of blood products would result in more optimum use of blood products and greater consistency between individual patients and clinicians. More optimum use of blood products would ensure these are available for those in whom greatest clinical benefit occurs.</p> <p>Variation in clinical practice and patient care in relation to blood product transfusion will be reduced.</p>
National priorities	-
Current evidence base	The overall quality of current clinical evidence was very low. No evidence relating to quality of life or the impact on pretransfusion haemoglobin, platelet, or coagulation

Transfusion
 Appendices O-R

	tests was identified. No evidence concerning the cost effectiveness of electronic decision support systems was identified.
Study design	A variety of study designs may be appropriate. These could include parallel group randomised trials, cluster randomised trials, or other forms of evaluation. Studies should include all patients in whom blood transfusions occur, and may need to specifically account for important subgroups, for example urgent versus non-urgent transfusions, transfusions of red cells or platelets or plasma, and specific NHS settings.
Economic considerations	An electronic decision support system would be implemented at hospital/blood bank level. Economic evaluations need to account for an institution level perspective in addition to an individual patient perspective. Cost effectiveness analysis needs to acknowledge that subsequent implementation would require investment within multiple institutions within the NHS.
Feasibility	This research should be completed within a reasonable timescale. There are technical issues over trial design but it is unlikely there would be ethical problems. Specific consideration of the consent procedures required is relevant, as individual patient consent is unlikely to be feasible.
Equalities	No specific equality issues identified
Other comments	None.

O.3 Post-operative cell salvage following cardiac surgery

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 components, clinical outcomes and quality of life.

PICO	<p>Population: Patients undergoing coronary artery bypass surgery and/or valvular surgery Patients in whom overall perioperative blood loss is expected to be >500mL Patients considered to be at risk of significant post-operative blood loss based on pre-operative and/or intraoperative factors</p> <p>Intervention: The intervention is a device, namely the use of a post-operative cell salvage system that collects shed blood from post-operative chest drains, washes, and haemoconcentrates the RBCs, and re-infuses via a venous cannula. All patients should receive intraoperative interventions to minimise blood loss and RBC transfusion according to NICE guidance, namely the use of tranexamic acid and, for selected cases, intraoperative cell salvage. All patients will receive RBC transfusions during the post-operative ICU period according to a protocol consistent with recommendations in the NICE guidance The intervention groups will receive post-operative cell salvage from chest drains, with re-infusion following RBC processing until bleeding has stopped or a clinical decision to discontinue post-operative cell salvage is made</p> <p>Comparator: All patients should receive intraoperative interventions to minimise blood loss and RBC transfusion according to NICE guidance, namely the use of tranexamic acid and, for selected cases, intraoperative cell salvage. All patients will receive RBC transfusions during the post-operative ICU period according to a protocol consistent with recommendations in the NICE guidance The comparator group will NOT receive post-operative cell salvage from chest drains.</p> <p>Outcomes: Primary outcome: RBC use from randomization to hospital discharge</p> <p>Secondary outcomes Haemoglobin concentration at ICU discharge Use of non-RBC blood products post-randomization (FFP; cryoprecipitate; platelets) Reoperation rate</p>
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	<p>Mortality (hospital; 90 days) HRQoL (90 days) ICU and hospital length of stay A cost-effectiveness analysis should be incorporated.</p>
Study Design	<p>To define the at risk population a systematic review of available literature to define risk factors for post-operative risk of bleeding should be undertaken</p> <p>If necessary, new research to define the at risk population, for example to develop a risk score, should inform the RCT design</p> <p>The main trial should be a randomized parallel group design, with concealment of outcome assessors for the outcomes if feasible</p>
Timeframe	No specific timeframe
Importance to patients or the population	<p>Cardiac surgery utilises a high proportion of the UK blood supply. Wide variation in blood use remains between individual patients, surgeons, and hospitals. RBC transfusion has been associated with adverse outcomes in cardiac surgery, but it is uncertain whether this association is causative. NICE guidance will recommend tranexamic acid is offered to all patients undergoing cardiac surgery in whom blood loss is expected to be greater than 500 mLs. The consideration of intraoperative cell salvage for cases in whom large blood losses are expected will also be recommended based on clinical judgement. Some patients continue to lose blood from chest drains post-operatively, and a small proportion has major blood losses, which may require reoperation. Post-operative cell salvage could reduce RBC requirements, and/or improve post-operative haemoglobin concentration in patients, and may reduce other complications in patients who suffer major bleeding (for example: coagulopathy, hypothermia). These benefits may reduce complications, ICU and hospital length of stay, RBC and other blood product use, and HRQoL.</p>
Relevance to NICE guidance	<p>The NICE systematic review suggested that post-operative cell salvage may be clinically and cost-effective. However, the GDG recognised this was based on a small number of studies, and in patients in whom other recommended therapies, for example tranexamic acid, may not have been used.</p> <p>Post-operative salvage is available, but evidence to guide whether and when it should be used is weak.</p> <p>This question is of medium interest and it will inform the use of an available therapy and enable future updates to provide recommendations for this technology</p>
Relevance to the NHS	<p>If post-operative cell salvage is clinically and cost-effective, its implementation would benefit patients and the NHS, through reduced cost and reducing use of RBCs.</p> <p>Cardiac surgery is a costly and high volume procedure in the NHS.</p> <p>High quality evidence would enable business plans to be developed to support the introduction of post-operative cell salvage in an equitable</p>

	manner to patients undergoing cardiac surgery
National priorities	-
Current evidence base	<p>The NICE systematic review found possible benefit from post-operative cell salvage, but problems with the evidence base were:</p> <ul style="list-style-type: none"> • The quality of the evidence was low • The evidence was not obtained in patient groups in whom other NICE guidance was implemented, namely the use of tranexamic acid, intraoperative cell salvage, and the use of restrictive transfusion triggers • The target population was not clearly defined
Equality	-
Feasibility	<p>This research is feasible within the NHS; the sample size is likely to be achievable within a high volume surgery, and there are no particular ethical issues.</p> <p>If post-operative cell salvage is shown to be cost-effective the cost of a trial is likely to be justified given the volume of this type of surgery each year. If a trial finds no benefit, it will provide high quality evidence that existing use of post-operative cell salvage should be reviewed.</p>
Other comments	It is likely that a manufacturer of post-operative cell salvage equipment would provide the excess treatment costs for a trial.

O.4 Fresh frozen plasma for patients with abnormal haemostasis who are having invasive procedures or surgery

What dose of fresh frozen plasma is most clinically effective at preventing bleeding in patients with abnormal haemostasis who are having invasive procedures or surgery?

Why this is important

Audits have shown that fresh frozen plasma is widely used for non-bleeding patients in the intensive care unit (ICU) and many other clinical settings. There is a large variation in dose and no real evidence base to guide practice. Fresh frozen plasma transfusions may cause adverse outcomes in people who are critically ill, including transfusion-related acute lung injury, transfusion-related circulatory overload, multi-organ failure and an increased risk of infections.

A multicentre study (2011)⁴²⁵ of ICUs in the UK showed that 12.7% of patients admitted to the ICU received fresh frozen plasma. The median dose was 10.8 ml/kg, but doses varied widely (range 2.4–41.1 ml/kg). This study showed that a high proportion of fresh frozen plasma transfusions had unproven clinical benefit.^{312,426,433}

Better evidence from clinical trials could significantly alter how fresh frozen plasma is used, and in particular ensure that clinically effective doses are given to patients.

<p>PICO</p>	<p>Population</p> <p>Patients with abnormal coagulation (either defined by lab testing and/or near patient global tests of haemostasis) undergoing planned surgery or interventional procedure such as venous and/or arterial cannulation, drain insertion.</p> <p>The clinician in charge of the patient has decided to correct the coagulation abnormality with FFP transfusion.</p> <p>The coagulation abnormalities for inclusion and list of procedures require clear definition</p> <p>Either gender; age >18years</p> <p>Exclusion criteria : patients with active acute bleeding; patients undergoing procedures involving certain critical sites such as the central nervous system.</p> <p>Intervention:</p> <p>Several potential designs are possible.</p> <p>Research is needed to compare the clinical effectiveness and safety of current consensus-based doses of FFP (for example 15ml/kg) versus a higher dose more likely to correct coagulation abnormalities (for example 30ml/kg)</p> <p>Comparator:</p> <p>As above: current consensus-based doses (for example 15ml/kg) versus a higher dose more likely to correct coagulation abnormalities (for example 30ml/kg)</p> <p>Coagulation abnormalities as defined by POCT viscoelastometric techniques together with laboratory based coagulation testing where latter results available</p> <p>Outcome:</p> <p>Primary outcome</p> <p>This should be a measure of bleeding complications. This could use a composite measure, for example including bleeding at the site of intervention/surgery and/or the requirement for red cell transfusions to correct blood loss.</p> <p>Secondary outcomes</p> <p>These could include:</p> <p>Coagulation parameters pre and post administration for either FFP dose and correction achieved</p> <p>Number of transfused red cell units associated with the procedure</p> <p>Length of ICU stay (if ICU-based study) and hospital stay.</p> <p>Transfusion related adverse events, specifically TRALI and TACO.</p> <p>Other adverse events - acute renal failure, sepsis, and allergic complications.</p> <p>Early and late mortality.</p> <p>Costs of blood and components transfused</p>
<p>Study Design</p>	<p>The trial is likely to have short recruitment windows and be undertaken under urgent/emergency situations. Several study designs could be considered:</p> <p>A pragmatic design with the population based in part on the responsible clinician’s decision to correct coagulopathy using FFP transfusion will be relevant to NHS practice, reflect current variation in decision-making, and include the “uncertainty principle” in enrolment.</p> <p>Parallel group randomised controlled study of two or three FFP doses</p> <p>Cluster randomised trial of ICUs or hospitals where a specific transfusion policy is applied during the trial. Cross over designs could be considered.</p>

Transfusion
Appendices O-R

Importance to patients or the population	<p>Many patients currently receive FFP for prophylaxis with much variation in dose. The risk of this practice, in the absence of any proven clinical benefit, is potentially significant.</p> <p>Evidence based guidance, based on high quality research is likely to improve guidance on the optimum dose of FFP needed to prevent bleeding . Key critical outcomes include mortality, infection, and altered length of stay.</p> <p>As about 15% of all ICU patients receive FFP, the impact on a population level is potentially high.</p>
Relevance to NICE guidance	<p>High.</p> <p>The current NICE guidance does not have a practice recommendation around the dose of FFP for prophylaxis because the quality of evidence was very low. This is an important gap that needs to be addressed to guide clinical practice.</p>
Relevance to the NHS	<p>The result of this study would influence management of patients on ICU and in other areas who have coagulation abnormalities needing FFP transfusion prior to surgery or intervention. Evidence based administration of FFP could decrease adverse events and improve patient outcomes and this also has a potential to reduce health care costs</p>
National priorities	-
Current evidence base	Lack of high quality studies in particular randomised controlled trials.
Equality	-
Feasibility	This research is feasible , for example through the NIHR critical care network.
Other comments	-

Appendix P: Excluded clinical studies

P.1 Erythropoietin and iron

Study	Exclusion reason
Adamson 1996 ⁶	Systematic review: literature search not sufficiently rigorous. Systematic review: methods are not adequate/unclear
Andrews 1997 ¹⁹	Not review population. Non-anaemic patients
Atabek 1995 ²⁶	Incorrect study design
Beris 2008 ³⁷	Systematic review: study designs inappropriate
Bhandal 2006 ⁴¹	Non -surgical patients
Braga 1998 ⁵⁵	Letter to the editor
Breymann 1996 ⁵⁷	Includes patients with vaginal delivery and c-section.
Cherian 2013 ⁸⁸	Systematic review- checked references
Chua 2014 ⁹⁸	Abstract
Corwin 2002 ¹⁰⁹	Intensive care patients not about transfusion during surgery
Corwin 2004 ¹⁰⁷	Systematic review: study designs inappropriate
Corwin 2007 ¹⁰⁸	Intensive care patients. not about transfusion in surgery
Cuenca 2007 ¹¹⁴	Incorrect study design
Del campo 1982 ¹²³	Incorrect study design
Duh 2008 ¹³²	Systematic review is not relevant to review question or unclear PICO
Froessler 2012 ¹⁵⁴	Systematic review- checked references
Froessler 2013 ¹⁵³	Systematic review- checked references
Goodnough 1994 ¹⁷³	Incorrect population of interest- autologous blood donors
Jaspers 2014 ²²⁰	EPO after allogeneic haematopoietic cell transplantation
Jeong 2014 ²²¹	Incorrect study design
Krafft 2011 ²⁴⁷	Postpartum women. Mentions but does not stratify between spontaneous. caesarean and operative vaginal deliveries
Keating 2015 ²³³	Narrative review
Lee 2014 ²⁵⁶	Incorrect study design
Lin 2013 ²⁶⁶	Systematic review- checked references
Maclaren 2004 ²⁸¹	Systematic review is not relevant to review question or unclear PICO
Mercuriali 1994 ²⁹⁴	Incorrect population (autologous blood donation)
Monk 1999 ³⁰⁰	Inappropriate comparison. Incorrect interventions
Moonen 2008 ³⁰¹	Incorrect interventions
Mudge 2009 ³⁰⁹	Incorrect population of interest- kidney transplant patients
Mudge 2012 ³¹⁰	Incorrect population of interest- kidney transplant patients
Munoz 2006 ³¹⁶	Incorrect study design
Munoz 2008 ³¹⁴	Systematic review: study designs inappropriate; methods are not adequate/unclear
Pajoumand 2004 ³⁴⁴	Systematic review is not relevant to review question or unclear PICO
Pfeffer 2009 ³⁵⁵	No surgery patients
Pieracci 2009 ³⁵⁷	Intensive care patients. not about transfusion during surgery
Reim 2014 ³⁶⁹	Study protocol

Rowlands 2013 ³⁷⁷	Study protocol
Shimpo 1994 ³⁹⁶	In Japanese
Singh 2006 ⁴⁰¹	No surgery patients
Sowade 1998 ⁴¹⁹	Systematic review is not relevant to review question or unclear PICO
Tran 2014 ⁴⁵²	Narrative review - checked references
Van loo 1996 ⁴⁶⁵	Incorrect population of interest- kidney transplant patients
Walpoth 1996 ⁴⁷⁶	Incorrect interventions
Watanabe 1992 ⁴⁸⁸	Autologous blood donation
Weber 2005 ⁴⁹¹	Allogeneic and autologous blood transfusion. Unable to clearly separate results between autologous and allogeneic transfusions.
Yang 2011 ⁵⁰⁷	Systematic review: literature search not sufficiently rigorous
Yazicioglu 2001 ⁵¹⁰	Incorrect population of interest- autologous blood donors

P.2 Alternatives

Study	Exclusion reason
Abdullah 2012 ⁴	Conference abstract
Adler ma 2011 ⁷	Incorrect interventions- systematic review
Aggarwal 2012 ⁸	Does not meet the inclusion criteria
Alipour 2013 ¹⁰	No outcomes of interest
Allanki 2009 ¹¹	Abstract
Almeida 2013 ¹²	Non-randomized prospective cohort study
Alshryda 2011 ¹⁴	Incorrect interventions- systematic review
Alshryda 2014 ¹⁵	Meta-analysis
Aluri 2012 ¹⁶	Abstract
Antinolfi 2010 ²⁰	Conference abstract
Antonopoulou 2013 ²¹	Abstract
Aoki 2012 ²³	Incorrect study design
Badeaux 2014 ²⁸	Systematic review of IV TXA in patients undergoing spine surgery. All references checked.
Baldus 2010 ³⁰	Incorrect study design
Barbara 2010 ³¹	Abstract
Basta 2012 ³²	Systematic review: methods are not adequate/unclear
Bhavana 2013 ⁴²	Abstract
Blatsoukas 2010 ⁴⁷	Not RCT
Boenigk 2011 ⁴⁸	Conference abstract
Borisov 2011 ⁵¹	Conference abstract
Bouali 2011 ⁵²	Conference abstract
Bracey 2009 ⁵³	Conference abstract
Briganti 2011 ⁵⁸	Conference abstract
Cacheux 2012 ⁶⁴	Conference abstract
Campbell 2012 ⁶⁷	Cell salvage plus heparin vs blood returned unprocessed

Transfusion
Appendices O-R

Cavolli 2011 ⁸¹	Abstract
Celebi 2006 ⁸²	Incorrect interventions
Chan 2013 ⁸³	Systematic review: methods are not adequate/unclear
Chen 2008 ⁸⁵	No relevant outcomes reported
Chen 2013 ⁸⁷	Systematic review: methods are not adequate/unclear
Chen 2013 ⁸⁶	Objective/outcomes of the study not relevant
Cheriyana 2013 ⁸⁹	Meta-analysis
Cholette 2011 ⁹²	Abstract
Cholette 2012 ⁹³	Abstract
Cholette 2013 ⁹⁴	Mean age of patients around 4 months
Christabel 2014 ⁹⁶	No relevant outcomes reported
Chu 2013 ⁹⁷	Non-randomised study
Crash-2 collaborators 2011 ¹⁰²	Population out of scope (trauma)
Dadure 2011 ¹¹⁶	Incorrect age group
Dalmau 2000 ¹¹⁷	Not review population
Damgaard 2010 ¹¹⁸	No relevant outcomes reported
Dhariwal 2014 ¹²⁷	Systematic review of use of ICS in caesarean section. Only one RCT was included in this review and this study is included in our evidence review.
Duran 2003 ¹³³	Not in English
Elgafy 2010 ¹³⁸	Systematic review: study designs inappropriate
Espahbod 2014 ¹³⁹	Meta-analysis
Faraoni 2011 ¹⁴³	Conference abstract
Faraoni 2012 ¹⁴⁵	Paediatric cardiac surgery - does not include all types of sur
Faraoni 2014 A ¹⁴⁴	Systematic review- does not meet our protocol criteria entirely
Fu 2013 ¹⁵⁵	Total knee arthroplasty - does not include all types of sur
Gandhi 2013 ¹⁵⁸	Total knee and hip arthroplasty -does not include all types of surgeries
Garg 2012 ¹⁵⁹	Conference abstract
Gautam 2011 ¹⁶⁰	Incorrect study design
Gautam 2013 ¹⁶¹	Systematic review: study designs inappropriate. Incorrect study design
Gill 2008 ¹⁶⁵	Spine surgery -no other surgeries included
Golab 2008 ¹⁶⁸	Incorrect age group
Gomez 2012 ¹⁷⁰	Conference abstract
Goobie 2011 ¹⁷¹	Incorrect age group
Gourlay 2013 ¹⁷⁷	Abstract
Goz 2013 ¹⁷⁸	Abstract
Grassin-delyle 2013 ¹⁷⁹	Incorrect interventions
Grundsell 1984 ¹⁸⁵	Does not meet inclusion criteria
Guay 2006 ¹⁸⁶	Incorrect age group

Transfusion
Appendices O-R

Gurusamy 2011 ¹⁸⁹	Incorrect population
Haien 2013 ¹⁹⁰	Systematic review: methods are not adequate/unclear
Halder 2013 ¹⁹¹	Incorrect study design
Hashimoto 2007 ¹⁹³	Cell salvage compared to autologous blood transfusion
Hassani 2012 ¹⁹⁴	Paper not in English
Hoelscher 2011 ²⁰¹	Conference abstract
Hogan 2014 ²⁰²	Abstract
Huang 2014 ²⁰⁶	Meta-analysis
Huet 1999 ²⁰⁷	Systematic review: methods are not adequate/unclear
Hutton 2012 ²⁰⁹	Conference abstract
Hutton 2012 ²⁰⁸	Systematic review: methods are not adequate/unclear
Ipema 2012 ²¹³	Systematic review: study designs inappropriate
Jahanshahi 2014 ²¹⁷	No outcomes of interest
Jairath 2014 ²¹⁸	Abstract
Jimenez-yuste 2002 ²²²	Incorrect interventions
Kashefi 2012 ²³⁰	Paper not in English
Kaste 1979 ²³¹	Use of TXA subarachnoid haemorrhage -not relevant population
Kelley 2014 ²³⁴	Retrospective case control study
Kim2014A ²⁴⁰	Systematic review
Klinck 1993 ²⁴¹	Conference abstract
Konig 2013 ²⁴⁵	Non-randomised study
Kristensen 1992 ²⁴⁸	Excluded from Cochrane review for insufficient data
Kumar 2014 ²⁴⁹	Systematic review- includes non-randomised studies
Leelahanon 2002 ²⁵⁹	Conference abstract
Li 2013 ²⁶³	Meta-analysis
Li 2014 ²⁶²	Meta-analysis of autologous blood transfusion drainage vs. no drainage in patients undergoing primary THA. All references checked.
Lian 2011 ²⁶⁴	Not in English
Lin 2011 ²⁶⁸	Incorrect study design
Liu 2010 ²⁶⁹	Not in English
Lundin 2013 ²⁷⁵	Abstract
Ma 2010 ²⁷⁹	Abstract
Macgillivray 2011 ²⁸⁰	Inappropriate comparison
Maniar 2012 ²⁸⁴	Control group not part of randomisation
Markar 2012 ²⁸⁵	Systematic review: methods are not adequate/unclear
Martinez-sanz 2011 ²⁸⁷	Conference abstract
Mason 2011 ²⁸⁹	Incorrect study design
Matkovic 2010 ²⁹⁰	Abstract
Meybohm 2013 ²⁹⁶	Systematic review: study designs inappropriate

Transfusion
Appendices O-R

Miao 2014 ²⁹⁷	Single-center, retrospective study
Moguilevitch 2011 ²⁹⁸	Abstract
Molloy 2007 ²⁹⁹	Incorrect interventions
Moore 2011 ³⁰²	Abstract
Morales 2013 ³⁰³	Abstract
Moret 2006 ³⁰⁴	Conference abstract
Morgenschweis 2011 ³⁰⁶	Abstract
Munoz 2013 ³¹⁷	Retrospective review
Munoz 2014 ³¹⁵	Before and after cohort study
Ngaage 2010 ³²⁷	Systematic review: study designs inappropriate. Incorrect interventions
Nicolai 2004 ³²⁹	Inappropriate comparison
Offierski 2013 ³³⁵	Conference abstract
Oishi 1997 ³³⁷	Inappropriate comparison
Ozal 2002 ³⁴⁰	Incorrect interventions
Panteli2013 ³⁴⁸	Systematic review- check references
Patel 2014 ³⁵²	Incorrect interventions
Peitsidid 2014 ³⁵⁴	Systematic of TXA in patients with menorrhagia due to uterine fibroids (Incorrect population)
Proctor 2011 ³⁵⁸	Conference abstract
Prokopchuk-gauk 2012 ³⁵⁹	Conference abstract
Pundir 2013 ³⁶⁰	Systematic review
Risch 2000 ³⁷³	Not in English
Rybo 1972 ³⁷⁸	Not relevant surgery- conization
Sasanuma 2011 ³⁸²	Incorrect interventions
Schouten 2009 ³⁸⁷	Inappropriate comparison
Shantikumar 2011 ³⁹²	Systematic review: methods are not adequate/unclear
Shen 2013 ³⁹⁴	Abstract
Shimizu 2011 ³⁹⁵	Upto 40% of children in both groups less than 1 year of age
Shulman 1998 ³⁹⁸	Inappropriate comparison
Silva 2013 ³⁹⁹	Retrospective cross-sectional study
Sinclair 2009 ⁴⁰⁰	Systematic review: methods are not adequate/unclear
Singh 2010 ⁴⁰³	Incorrect study design
Song 2013 ⁴¹⁸	Craniosystosis -no other surgeries included
Song 2013 ⁴¹⁷	Orthognathic surgeries- other types of surgeries not included
So-Osman 2014 A ⁴¹⁴	Reports combined results for (ICS+PCS)+PCS as AUTO group; does not meet protocol
So-Osman 2014B ⁴¹¹	Abstract
Specchiulli 2011 ⁴²⁰	Conference abstract
Sukeik 2011 ⁴³⁵	Orthognathic surgery- not all surgeries included
Sun 2008 ⁴³⁶	Systematic review: methods are not adequate/unclear

Taj 2014 ⁴³⁷	No outcomes of interest
Tan2013 ⁴³⁸	Meta-analysis
Thomassen 2011 ⁴⁴²	Abstract
Toda 2013 ⁴⁴⁹	Conference abstract
Vacharaksa 2002 ⁴⁶¹	Incorrect interventions
Vela 2012 ⁴⁶⁸	Conference abstract
Wang 2009 ⁴⁸³	Systematic review: methods are not adequate/unclear
Wardrop 2012 ⁴⁸⁵	Conference abstract
Washington 2009 ⁴⁸⁷	Abstract
Waters 2012 ⁴⁹⁰	Systematic review: methods are not adequate/unclear
Weltert 2013 ⁴⁹³	Inappropriate comparison
Williams 2009 ⁵⁰²	Abstract
Yagi 2012 ⁵⁰⁴	Incorrect study design
Yang 2012 ⁵⁰⁸	Systematic review: methods are not adequate/unclear
Yang 2013 ⁵⁰⁵	Systematic review: methods are not adequate/unclear
Yassen 1993 ⁵⁰⁹	Not review population
Yutthakasemsunt2013 ⁵¹²	Incorrect population- non-surgical patients with traumatic brain injury
Zaporozhan 2013 ⁵¹⁵	Conference abstract
Zhang 2012 ⁵¹⁶	Systematic review: methods are not adequate/unclear
Zhang 2014 ⁵¹⁷	Systematic review of TXA in patients undergoing TKA. Checked references.
Zhaohui 2014 ⁵¹⁹	Incorrect comparisons- TXA +epinephrine vs. Epinephrine
Zhaoyu 2014 ⁵¹⁸	Meta-analysis of TXA in patients undergoing primary TKA. All references checked.
Zheng 2000 ⁵²⁰	Conference abstract
Zhou 2013 ⁵²¹	Systematic review: methods are not adequate/unclear
Zhu 2010 ⁵²²	Conference abstract

P.3 Red blood cells RBC Targets

Study	Exclusion reason
Alvarez 2001 ¹⁷	Review article
Bellomo 2001 ³⁵	Abstract
Berns 2010 ³⁸	Incorrect study design. Narrative review
Bracey 1999 ⁵⁴	Incorrect interventions
Carson 1998 ⁷³	Narrative review
Carson 1998 ⁷⁴	Incorrect interventions. Inappropriate comparison
Carson 2002 ⁷⁷	Systematic review conducted in 2002 (all relevant references noted)
Carson 2011 ⁷⁸	Incorrect interventions

Transfusion
Appendices O-R

Carson 2012 ⁷⁶	clinical practice guideline
Carson 2013 ⁷⁵	Incorrect interventions
Colomo 2008 ¹⁰³	Incorrect interventions
De gast-bakker 2013 ¹²²	Incorrect interventions
Foss 2009 ¹⁵⁰	Incorrect interventions
Grover 2006 ¹⁸⁴	Incorrect interventions
Hardy 2003 ¹⁹²	Narrative review
Hebert 2000 ¹⁹⁶	Review article
Hogshire 2013 ²⁰³	Literature review
Holst 2013 ²⁰⁵	Incorrect interventions
Jairath 2013 ²¹⁹	Incorrect interventions
Johnson 1992 ²²⁴	Incorrect interventions
Karam 2011 ²²⁸	Incorrect interventions
Kennedy 2002 ²³⁵	Incorrect interventions
Lum 1997 ²⁷⁴	Incorrect study design
Napolitano 2004 ³²⁵	Narrative review
Nielsen 2012 ³³⁰	Incorrect interventions
O'hara 1999 ³³⁴	Review of medical records. Incorrect study design
Palmieri 2007 ³⁴⁵	Incorrect study design
Parker 2013 ³⁴⁹	Incorrect interventions
Rosland 2014 ³⁷⁴	Cohort study
Rouette 2010 ³⁷⁶	Incorrect interventions
Shehata 2012 ³⁹³	Incorrect interventions
Singh 2008 ⁴⁰²	Incorrect study design. Critical review
So-osman 2010 ⁴¹²	Incorrect interventions
So-osman 2013 ⁴¹³	Incorrect interventions
Strippoli giovanni 2006 ⁴³⁴	Only includes patients with chronic kidney disease
Tay 2011 ⁴³⁹	Protocol for study
Valeri 1998 ⁴⁶⁴	Article
Vichinsky 1995 ⁴⁷¹	Patients with haemoglobinopathies
Viele 1994 ⁴⁷²	Literature review
Wali 2003 ⁴⁷⁵	Patients with haemoglobinopathies
Walsh 2013 ⁴⁷⁸	Incorrect interventions
Wang 2013 ⁴⁸⁴	Includes only upper GI bleeding
Webert 2008 ⁴⁹²	Incorrect interventions
Whyte 2011 ⁴⁹⁶	Infants

Willems 2010 ⁵⁰⁰	Sub group analysis of cardiac surgery patients in TRIPICU study (Lacroix 2007 which has been included)
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P.4 RBC Doses

Study	Exclusion reason
Arslan 2004 ²⁵	Incorrect interventions
Carson 2013 ⁷⁵	Incorrect interventions
Cooper 2011 ¹⁰⁵	Incorrect interventions
Lightdale 2012 ²⁶⁵	Incorrect study design
Parker 2013 ³⁴⁹	Incorrect interventions
Shehata 2012 ³⁹³	Incorrect interventions
Slight 2008 ⁴⁰⁷	Incorrect interventions
Smith 2013 ⁴⁰⁹	Review- checked references
Walsh 2013 ⁴⁷⁸	Incorrect interventions
Wang 2013 ⁴⁸⁴	Incorrect interventions

P.5 Platelets

P.5.1 Platelet thresholds and targets

Study	Exclusion reason
Callow 2002 ⁶⁵	Incorrect study design
Cameron 2007 ⁶⁶	Incorrect study design
Goodnough 2002 ¹⁷²	Abstract
Heddle 2009 ¹⁹⁸	Incorrect interventions
Khan Assir 2013 ²³⁷	Incorrect interventions
Klumpp 1999 ²⁴³	Incorrect interventions
Nevo 2007 ³²⁶	Incorrect study design
Razzaghi 2012 ³⁶⁶	Only includes patients with upper GI bleeding
Rebulla 1996 ³⁶⁷	conference abstract
Sensebe 2005 ³⁸⁹	Incorrect interventions
Solomon 1978 ⁴¹⁶	Incorrect interventions
Stanworth 2004 ⁴²³	This Cochrane review has been updated in 2012
Tinmouth 2002 ⁴⁴⁶	Incorrect interventions
Tinmouth 2004 ⁴⁴⁷	Incorrect interventions
Wandt 1995 ⁴⁸⁰	Incorrect study design. conference abstract
Wandt 1998 ⁴⁷⁹	Incorrect study design
Wandt 2009 ⁴⁸¹	conference abstract
Zahur-ur-rehman 2002 ⁵¹³	Incorrect interventions

Platelet targets

Study	Exclusion reason
Callow 2002 ⁶⁵	Incorrect interventions
Cameron 2007 ⁶⁶	Incorrect interventions
Diedrich 2005 ¹²⁸	Incorrect interventions
Estcourt 2012 ¹⁴¹	Incorrect interventions

Goodnough 2002 ¹⁷²	Incorrect interventions
Heckman 1997 ¹⁹⁷	Incorrect interventions
Heddle 2009 ¹⁹⁸	Incorrect interventions
Khan Assir 2013 ²³⁷	Incorrect interventions
Klumpp 1999 ²⁴³	Incorrect interventions
Nevo 2007 ³²⁶	Incorrect interventions
Razzaghi 2012 ³⁶⁶	Incorrect interventions
Rebulla 1996 ³⁶⁷	Incorrect interventions
Rebulla 1997 ³⁶⁸	Incorrect interventions
Sensebe 2005 ³⁸⁹	Incorrect interventions
Stanworth 2004 ⁴²³	Incorrect interventions
Stanworth 2010 ⁴²⁸	Incorrect interventions
Stanworth 2013 ⁴²⁹	Incorrect interventions
Tinmouth 2002 ⁴⁴⁶	Incorrect interventions
Tinmouth 2004 ⁴⁴⁷	Incorrect interventions
Wandt 1995 ⁴⁸⁰	Incorrect interventions
Wandt 1998 ⁴⁷⁹	Incorrect interventions
Wandt 2009 ⁴⁸¹	Incorrect interventions
Wandt 2012 ⁴⁸²	Incorrect interventions
Zahur-ur-rehman 2002 ⁵¹³	Incorrect interventions
Zumberg 2002 ⁵²⁵	Incorrect interventions

P.5.2 Platelet doses

Study	Exclusion reason
Ackerman 2000 ⁵	Incorrect interventions
Cid 2007 ⁹⁹	Systematic review: methods are not adequate/unclear
Estcourt 2014 ¹⁴²	Protocol for Cochrane review
Herman 1995 ¹⁹⁹	Abstract
Josephson 2009 ²²⁵	Abstract
Kaufman 2015 ²³²	Secondary analysis of PLADO study. The study examined the frequency of transfusion related adverse events (TRAE) and whether the risk of TRAEs varied depending on the platelet characteristics.
Klumpp 1995 ²⁴²	Abstract
Klumpp 1999 ²⁴³	Crossover study
Lu 2011 ²⁷²	Abstract
Lu 2013 ²⁷³	Abstract
Murphy 2003 ³²⁰	Inappropriate comparison. not randomised to compare platelet doses
Murphy 2006 ³²¹	Inappropriate comparison. not randomised to compare platelet dose
Norol 1995 ³³²	Abstract
Pedrazzoli 1997 ³⁵³	Abstract
Sahin 2013 ³⁷⁹	Abstract
Schiffer 1976 ³⁸⁴	Incorrect interventions
Schiffer 1976 ³⁸⁵	Incorrect interventions

Slichter 2005 ⁴⁰⁶	Incorrect interventions
Slichter 2006 ⁴⁰⁵	Narrative paper; background and rationale for PLADO trial
Slichter 2009 ⁴⁰⁴	Abstract
Stanworth 2004 ⁴²³	Systematic review; updated in 2012 (Estcourt 2012)
Steffens 2002 ⁴³¹	Inappropriate comparison
Tinmouth 2002 ⁴⁴⁶	Abstract
Tinmouth 2003 ⁴⁴⁸	Systematic review: methods are not adequate/unclear
Triulzi 2009 ⁴⁵⁵	Abstract
Triulzi 2012 ⁴⁵⁶	Secondary analysis of Slichter 2010; outcomes not relevant to protocol
Van rhenen 2003 ⁴⁶⁶	Incorrect interventions
Wandt 2009 ⁴⁸¹	Abstract

P.6 FFP

P.6.1 FFP thresholds and targets

Study	Exclusion reason
Casbard 2004 ⁷⁹	Systematic review is not relevant to review question or unclear PICO
Dara 2005 ¹¹⁹	Incorrect study design
Doussau 2014 ¹³⁰	Incorrect interventions
Levy 2011 ²⁶¹	Conference abstract
Muller 2011 ³¹³	Incorrect interventions
Stanworth 2004 ⁴²¹	Systematic review is not relevant to review question or unclear PICO
Stanworth 2006 ⁴²²	Narrative review
Stanworth 2007 ⁴²⁴	Systematic review is not relevant to review question or unclear PICO
Stanworth 2011 ⁴²⁶	Incorrect study design
Tinmouth 2008 ⁴⁴⁵	Conference abstract
Williamson 1999 ⁵⁰³	Incorrect interventions

P.6.2 FFP doses

Study	Exclusion reason
Abdel-wahab 2006 ³	Incorrect interventions
Anwar 2012 ²²	conference abstract
Besandre 2012 ⁴⁰	Conference abstract. Full paper not published so far.
Boldt 1989 ⁵⁰	Not in English
Carino 2009 ⁷¹	conference abstract
Casbard 2004 ⁷⁹	Systematic review is not relevant to review question or unclear PICO
Despotis 1994 ¹²⁶	Incorrect interventions
Dzik 2004 ¹³⁶	Narrative review
Khan 2007 ²³⁸	Incorrect interventions
Labarinas 2013 ²⁵¹	Literature review

Lauzier 2007 ²⁵⁴	Inappropriate comparison. Incorrect interventions
Lerner 2000 ²⁶⁰	Incorrect interventions
Levy 2011 ²⁶¹	Incorrect interventions. conference abstract
Matsumoto 2007 ²⁹¹	Incorrect interventions. Inappropriate comparison
Motta 2014 ³⁰⁸	Neonates
Muller 2011 ³¹³	Study protocol
Noddeland 2002 ³³¹	Incorrect interventions. Inappropriate comparison
Puronen 2009 ³⁶¹	Incorrect interventions. conference abstract
Sezik 2014 ³⁹⁰	Incorrect study design.
Stanworth 2004 ⁴²¹	Not relevant comparisons. References noted. Incorrect interventions
Stanworth 2006 ⁴²²	Literature review
Stanworth 2007 ⁴²⁴	Review article
Stanworth 2007 ⁴²⁷	Literature review
Tollofsrud 2003 ⁴⁵¹	Inappropriate comparison. Incorrect interventions
Trimble 1964 ⁴⁵³	Incorrect interventions. Inappropriate comparison
Tripodi 2012 ⁴⁵⁴	Incorrect study design
Urwylar 2009 ⁴⁶⁰	Study protocol
Verghese 2008 ⁴⁶⁹	Narrative review
Walsh 2011 ⁴⁷⁷	Conference abstract. Study included
White 2011 ⁴⁹⁵	conference abstract
Willems 2014 ⁵⁰¹	Incorrect interventions
Williamson 1999 ⁵⁰³	Incorrect interventions
Yang 2012 ⁵⁰⁶	Not all comparisons relevant. One study reference identified.
Youssef 2003 ⁵¹¹	Incorrect interventions. Inappropriate comparison

P.7 Cryoprecipitate

P.7.1 Cryoprecipitate thresholds and targets

Study	Exclusion reason
Abbott 2009 ²	Inappropriate comparison
Fenger-eriksen 2009 ¹⁴⁷	Incorrect interventions
French 2003 ¹⁵¹	Incorrect interventions. Inappropriate comparison
Galas 2012 ¹⁵⁶	Inappropriate comparison. conference abstract
Goldenberg 2006 ¹⁶⁹	Review article
Hesselvik 1987 ²⁰⁰	Not review population
Hwang 1991 ²¹¹	Not review population
Iyengar 2013 ²¹⁶	Incorrect interventions
Karlsson 2009 ²²⁹	Incorrect interventions
Ketchum 2006 ²³⁶	Review article
Koustousov 2012 ²⁴⁶	Incorrect interventions. conference abstract
Lang 1993 ²⁵²	Incorrect interventions. Inappropriate comparison
Lee 2014 ²⁵⁸	cohort study <1000 patients
Stevens 1986 ⁴³²	Not review population

Teitel 2011 ⁴⁴⁰	Incorrect interventions
Tinegate 2011 ⁴⁴⁴	Survey
Warmuth 2012 ⁴⁸⁶	Systematic review is not relevant to review question or unclear PICO. Relevant papers ordered
Wikkelsø 2013 ⁴⁹⁹	Incorrect interventions
Zakout 2009 ⁵¹⁴	conference abstract

P.7.2 Cryoprecipitate doses

Study	Exclusion reason
Abbott 2009 ²	Inappropriate comparison. Incorrect interventions
Fenger-eriksen 2009 ¹⁴⁷	Incorrect interventions
French 2003 ¹⁵¹	Incorrect interventions. Inappropriate comparison
Galas 2012 ¹⁵⁶	Incorrect interventions. Inappropriate comparison
Goldenberg 2006 ¹⁶⁹	Incorrect interventions. Inappropriate comparison
Hesselvik 1987 ²⁰⁰	Incorrect interventions. Inappropriate comparison
Holcomb 2013 ²⁰⁴	Incorrect interventions. Inappropriate comparison
Hwang 1991 ²¹¹	Incorrect interventions. Inappropriate comparison
Iyengar 2013 ²¹⁶	Incorrect interventions
Karlsson 2009 ²²⁹	Incorrect interventions
Ketchum 2006 ⁶⁶	Incorrect interventions
Koustousov 2012 ²⁴⁶	Incorrect interventions. Inappropriate comparison
Lang 1993 ²⁵²	Incorrect interventions. Inappropriate comparison
Lee 2014 ²⁵⁸	Incorrect interventions
Stevens 1986 ⁴³²	Incorrect interventions. Inappropriate comparison
Teitel 2011 ⁴⁴⁰	Inappropriate comparison. conference abstract
Warmuth 2012 ⁴⁸⁶	Incorrect interventions. Inappropriate comparison
Wikkelsø 2013 ⁴⁹⁹	Incorrect interventions. Inappropriate comparison

P.8 PCC

P.8.1 PCC thresholds and targets

Study	Exclusion reason
Arshad 2013 ²⁴	Protocol for study- for follow up
Awad 2013 ²⁷	Review
Bechtel 2011 ³³	Review. Not directly relevant to review question
Bershad 2010 ³⁹	Literature review
Cabral 2013 ⁶³	Retrospective case series review of 30 patients; not information on thresholds/targets
Chong 2010 ⁹⁵	Case series of 7 patients; evaluates PCC + FFP
Desmettre 2012 ¹²⁵	Paper not available
Eerenberg 2011 ¹³⁷	Healthy volunteer study; comparisons not relevant
Dowlathshahi 2012 ¹³¹	Canadian registry. n=141. Does not compared PCC transfusion at different thresholds/target levels

Huynh 2014 ²¹⁰	n=44. Small retrospective study
Johansen 2013 ²²³	Protocol for Cochrane review on PCC for peri-operative reversal of Vitamin K antagonist
Junagade 2007 ²²⁶	Abstract
Knight 2009 ²⁴⁴	Systematic review on efficacy of r FactorVIIa and aPCC
Leal-noval 2013 ²⁵⁵	Do not report number of patients in allocated to low (15 IU/kg) and high dose groups (25 IU/kg)
Lin 2013 ²⁶⁷	Systematic review of PCCs and fibrinogen concentrates (FIBCs) in combination
Lusher 1980 ²⁷⁸	RCT evaluating efficacy of 2 PCC preparations with placebo; does not evaluate INR thresholds or targets-wrong comparison
Lusher 1983 ²⁷⁷	Compares 2 different types of PCCs, not relevant comparison
Lusher 1984 ²⁷⁶	Narrative review of PCC and Factor VIII inhibitors
Mai 2013 ²⁸³	Abstract
Otite 2013 ³³⁹	Abstract
Pabinger 2008 ³⁴¹	44 patients, no control arm, prospective study
Pabinger 2010 ³⁴²	Evaluates impact of speed of PCC infusion
Patanwala 2011 ³⁵¹	Systematic review- relevant papers ordered
Solbeck 2012 ⁴¹⁵	Systematic review- checked references
Staudinger 1999 ⁴³⁰	Cohort study, n=16.
Varga 2013 ⁴⁶⁷	Retrospective case series on efficacy of PCC dose; to include if RCTs included of every low quality/ do not provide helpful evidence; Info for other considerations
Valentino 2009 ⁴⁶³	Abstract
Voils 2012 ⁴⁷⁴	Systematic review- relevant references noted

P.8.2 PCC doses

Study	Exclusion reason
Bershad 2010 ³⁹	Literature review
Cabral 2013 ⁶³	No comparison groups
Chong 2010 ⁹⁵	Case series of 7 patients; evaluates PCC + FFP
Desmettre 2012 ¹²⁵	Paper not available
Eerenberg 2011 ¹³⁷	Healthy volunteer study; comparisons not relevant
Huynh 2014 ²¹⁰	Small retrospective study, n=44.
Knight 2009 ²⁴⁴	Systematic review on efficacy of Factor VII and PCC
Leal-Noval 2013 ²⁵⁵	Does not report number of patients in allocated to low (15 IU/kg) and high dose groups (25 IU/kg)
Lusher 1980 ²⁷⁸	RCT evaluating efficacy of 2 PCC preparations with placebo; dose not evaluate INR thresholds or targets-wrong comparison
Lusher 1983 ²⁷⁷	Compares 2 different types of PCCs, not relevant comparison
Lusher 1984 ²⁷⁶	Narrative review of PCC and Factor VIII inhibitors
Pabinger 2008 ³⁴¹	Does not report outcomes/results according to the different doses of PCC
Pabinger 2010 ³⁴²	Evaluates impact of speed of PCC infusion

Varga 2013 ⁴⁶⁷	Retrospective case series on efficacy of PCC dose
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P.9 Monitoring for acute reactions

None

P.10 Electronic decision support

Reference	Reason for exclusion
Choi 2014 ⁹¹	Abstract
Cotterell 2013 ¹¹⁰	Systematic review
Estcourt 2013 ¹⁴⁰	Abstract
Goodnough 2013 ¹⁷⁴	Abstract
Rao 2013 ³⁶⁴	Abstract
Morris 2011 ³⁰⁷	Abstract
Mascotti 2009 ²⁸⁸	Abstract
Kuo 2011 ²⁵⁰	Abstract
Gregurek 2010 ¹⁸²	Abstract
Gregurek 2009 ¹⁸¹	Abstract
Goddard 2010 ¹⁶⁷	Abstract
Rothschild 2004 ³⁷⁵	Abstract
Uriz 2011 ⁴⁵⁹	Intervention does not match protocol (for patient identification)
Alves 2002 ¹⁸	Population does not match protocol (In neonates)
Schnurr 2010 ³⁸⁶	Intervention does not match protocol
Febr 2011 ¹⁴⁶	Abstract
Guerra 2010 ¹⁸⁷	Abstract
Martinez 2011 ²⁸⁶	Abstract
McCroy 2010 ²⁹³	Abstract
Waters 2012 ⁴⁸⁹	Abstract
Zijlker 2013 ⁵²³	Abstract
Shojania 2009 ³⁹⁷	Review (not relevant comparisons)
Philcox 1987 ³⁵⁶	Incorrect intervention
Palo 2006 ³⁴⁶	Intervention does not match protocol(database system to manage blood component use in hospital)
Morgan 1973 ³⁰⁵	Intervention does not match protocol(computer controlled automated transfusion, not for decision support)

P.11 Electronic patient identification

Study	Exclusion reason
Aandahl 2007 ¹	Incorrect interventions. Narrative review
Baele 1994 ²⁹	Incorrect interventions
Brewer 1977 ⁵⁶	Incorrect interventions. Narrative paper
Burrows 2009 ⁶⁰	Incorrect interventions. Evaluates inaccessibility of identification bands in operating theatre
Clark 1984 ¹⁰⁰	Narrative paper

Study	Exclusion reason
Clifford 2013 ¹⁰¹	Incorrect interventions
Cottrell 2013 ¹¹⁰	Audit of transfusion practice. Incorrect interventions
Davis 2012 ¹²¹	Incorrect interventions
Dzik 2003 ¹³⁵	Review
Dzik 2007 ¹³⁴	Narrative paper
Finlay 2005 ¹⁴⁸	Incorrect interventions
Galusha 2003 ¹⁵⁷	Narrative paper
Goodnough 2009 ¹⁷⁶	Incorrect interventions
Goodnough 2012 ¹⁷⁵	Incorrect interventions. Narrative paper
Green 2008 ¹⁸⁰	Inappropriate comparison. Narrative paper
Grimm 2010 ¹⁸³	Inappropriate comparison. Survey; no co-relation presented between patient identification by electronic methods and inappropriate transfusions
Gumpeni 2006 ¹⁸⁸	Narrative paper
Ibojie 2000 ²¹²	Incorrect interventions
Mercuriali 1996 ²⁹⁵	Incorrect interventions (only non-electronic patient identification)
Murphy 2007 ³¹⁹	Incorrect interventions
Novis 2003 ³³³	Incorrect interventions
Ohsaka 2009 ³³⁶	Incorrect interventions
Pagliari 2006 ³⁴³	narrative review
Quillen 2006 ³⁶²	Incorrect interventions
Renner 1993 ³⁷⁰	Incorrect interventions
Rentas 1999 ³⁷¹	Incorrect interventions
Sandler 2007 ³⁸⁰	Wrong comparison (only evaluates if RFID system can be implemented, does not evaluate prevention of errors)
Schulmeister 2008 ³⁸⁸	Narrative paper
Smith 2011 ⁴¹⁰	Incorrect interventions
Thomas 2004 ⁴⁴¹	Incorrect interventions. Narrative paper
Tiehen 1998 ⁴⁴³	Narrative paper
Valenstein 2004 ⁴⁶²	Review, not systematic
Wenz 1991 ⁴⁹⁴	Incorrect interventions (only non-electronic patient identification)
Wickham 2006 ⁴⁹⁸	Inappropriate comparison
Wickham 2006 ⁴⁹⁷	Abstract

P.12 Patient information

Reference	Reason for exclusion
Benson 1996 ³⁶	Evaluates patients views regarding receiving home transfusions
Bielby 2013 ⁴³	Abstract
Bishop 2009 ⁴⁵	Abstract
Bishop 2010 ⁴⁶	Does not address review question; no information on patients views regarding info
Burgess 2006 ⁵⁹	Audit results and recommendations for practice
Busby 2012 ⁶²	Abstract
Busby 2013 ⁶¹	Abstract

Transfusion
Appendices O-R

Reference	Reason for exclusion
Cankovic 2009 ⁶⁹	Abstract
Cankovic 2011 ⁷⁰	Abstract
Carruther 2001 ⁷²	Audit and survey of hospital practices regarding consent; patients views not reported
Cassidy 2013 ⁸⁰	Abstract
Cong 2009 ¹⁰⁴	Abstract
Corkery2013 ¹⁰⁶	Abstract
Court2010 ¹¹²	Abstract
Court2012 ¹¹¹	Abstract
Davis2012 ¹²¹	Survey to assess patients willingness to participate in transfusion related behaviours related to identity checking and administration of blood
Friedman2011 ¹⁵²	Abstract
Islam2011 ²¹⁵	Abstract
Khan2012 ²³⁹	Evaluates use of a clinician tool to aid patient counselling before blood transfusion
Latreille2010 ²⁵³	Abstract
Lee2003 ²⁵⁷	Evaluates people's perception of the risk of blood transfusion in comparison to other hazards (for example, pesticides, caffeine); wrong objective
Lowe2001 ²⁷⁰	Evaluates perception of risk of blood transfusion with respect to receiving own blood/blood substitutes
Mahapatra2013 ²⁸²	Abstract
Mccarthy2001 ²⁹²	Abstract
Muhammad2014 ³¹¹	Abstract
Naim2011a ³²⁴	Abstract
Naim2011b ³²³	Abstract
Naim2012 ³²²	Abstract
Ngo2013 ³²⁸	Qualitative Systematic review
Orme2013 ³³⁸	Evaluates experiences of patients' experience of living with anaemia and receiving transfusion at a day hospice; does not look at what information people want
Tolich2010 ⁴⁵⁰	Abstract
Twiss2011 ⁴⁵⁸	Abstract
Vetter2014 ⁴⁷⁰	Survey of patients perception of risk of blood transfusion and associated patients characteristics; no reporting of what info people may want

P.12.1 RBC Thresholds

Study	Exclusion reason
Carson 2012 ⁷⁶	Clinical practice guideline
Chatterjee 2013 ⁸⁴	Systematic review: literature search not sufficiently rigorous
Chirico 2011 ⁹⁰	Pre-term infants
Curley 2014 ¹¹⁵	Systematic review- checked references
Desjardins 2012 ¹²⁴	Systematic review: study designs inappropriate
Fischer 2010 ¹⁴⁹	Incorrect interventions
Gauvin 2010 ¹⁶²	Analytic cohort analysis
Hearnshaw 2010 ¹⁹⁵	Incorrect study design
Holst 2013 ²⁰⁵	Protocol- TRISS trial
Jairath 2013 ²¹⁹	Protocol
Kahan 2013 ²²⁷	Statistical analysis plan- TRIGGER trial
Lightdale 2012 ²⁶⁵	Incorrect study design
Parker 2013 ³⁴⁹	Incorrect interventions. Inappropriate comparison
Parker 2014 ³⁵⁰	Systematic review- checked references
Rouette 2010 ³⁷⁶	Sub group analysis of surgery patients in TRIPICU study- we are only updating the Cochrane review (that is, including studies after 2011)
Shah 2015 ³⁹¹	Review article
So-Osman 2010 ⁴¹²	Incorrect interventions
So-Osman 2013 ⁴¹³	Post-hoc analysis
Tay 2011 ⁴³⁹	Protocol -TRIST trial
Wang 2013 ⁴⁸⁴	Includes only upper GI bleeding
Whyte 2011 ⁴⁹⁶	Low birth-weight infants
Willems 2010 ⁵⁰⁰	Sub group analysis of cardiac surgery patients in TRIPICU study (Lacroix 2007 which has been included)

Appendix Q: Excluded economic studies

Q.1 Erythropoietin and iron

Reference	Reason for exclusion
Bedair 2015 ³⁴	This US within trial (prospective cohort) cost consequence analysis of erythropoietin was assessed as partially applicable with potentially serious limitations. The GDG judged the three cost utility analyses (two UK and one USA) and one German cost consequence analysis, were of greater applicability and methodological quality, and therefore this study was selectively excluded.

Q.2 Alternatives to blood transfusion

Reference	Reason for exclusion
Murphy 2005 ³¹⁸	This UK cost–consequence analysis of cell salvage was assessed as partially applicable with potentially serious limitations. However, the GDG judged that the available UK cost–utility analysis ¹²⁰ was of greater applicability and methodological quality, and therefore this study was selectively excluded.
Crotty 2006 ¹¹³	This UK cost–comparison of cell salvage was assessed as partially applicable with very serious limitations. The GDG judged that the available UK cost–utility analysis ¹²⁰ was of greater applicability and methodological quality, and therefore this study was selectively excluded.
Savvidou 2009 ³⁸³	This Greek cost–consequence analysis of cell salvage was assessed as partially applicable with potentially limitations. The GDG judged that the available UK cost–utility analysis ¹²⁰ was of greater applicability and methodological quality, and therefore this study was selectively excluded.
Boese 2011 ⁴⁹	This US cost–consequence analysis of cell salvage was assessed as partially applicable with very serious limitations. The GDG judged that the available UK cost–utility analysis ¹²⁰ was of greater applicability and methodological quality, and therefore this study was selectively excluded.
Dobosz 2012 ¹²⁹	This Polish cost–consequence analysis of cell salvage was assessed as partially applicable with potentially limitations. The GDG judged that the available UK cost–utility analysis ¹²⁰ was of greater applicability and methodological quality, and therefore this study was selectively excluded.
Rao 2012 ³⁶⁵	This US cost–comparison of cell salvage was assessed as partially applicable with very serious limitations. The GDG judged that the available UK cost–utility analysis ¹²⁰ was of greater applicability and methodological quality, and therefore this study was selectively excluded.
Canan 2013 ⁶⁸	This US cost–utility analysis of cell salvage was assessed as not applicable with very serious limitations: QALYs estimated from expert opinion, time frame and discounting unclear, patient perspective taken, and very high unit cost of allogeneic blood which is not representative of current UK unit costs. Therefore this study was excluded.

Reference	Reason for exclusion
Munoz 2013 ³¹⁷	This Spanish cost-consequence analysis of cell salvage was assessed as partially applicable with potentially limitations. The GDG judged that the available UK cost-utility analysis ¹²⁰ was of greater applicability and methodological quality, and therefore this study was selectively excluded.
Albright 2014 ⁹	This US comparative cost analysis of cell salvage was assessed as partially applicable and with potentially serious limitations. The GDG judged that the available UK cost-utility analysis ¹²⁰ was of greater applicability and methodological quality, and therefore this study was selectively excluded.
Bilgili 2014 ⁴⁴	This Turkish cost-consequence analysis of cell salvage was assessed as partially applicable with very serious limitations. Health outcome not expressed as QALYs. No information provided on how the total costs were estimated. Effectiveness data from a retrospective study and therefore not included in the clinical review. Therefore this study was excluded.
Munoz 2014 ³¹⁵	This Spanish cost-consequence analysis of cell salvage was assessed as partially applicable with potentially limitations. The GDG judged that the available UK cost-utility analysis ¹²⁰ was of greater applicability and methodological quality, and therefore this study was selectively excluded.
Lozano 2008 ²⁷¹	This Spanish within trial (retrospective observational) cost consequence analysis of tranexamic acid was assessed as partially applicable with potentially serious limitations. This study was selectively excluded as it was superseded by two recent UK cost consequence analyses ^{13,363} , both of which were within-trial analyses of RCTs that are included in clinical review and therefore more applicable to the UK NHS context.
Gill 2009 ¹⁶⁴	This US within trial (RCT) cost consequence analysis of tranexamic acid was assessed as partially applicable with potentially serious limitations. This study was selectively excluded as it was superseded by two recent UK cost consequence analyses ^{13,363} , both of which were within-trial analyses of RCTs that are included in clinical review and therefore more applicable to the UK NHS context.
Irisson 2012 ²¹⁴	This French within trial (retrospective cohort) cost consequence analysis of tranexamic acid was assessed as partially applicable with potentially serious limitations. This study was selectively excluded as it was superseded by two recent UK cost consequence analyses ^{13,363} , both of which were within-trial analyses of RCTs that are included in clinical review and therefore more applicable to the UK NHS context.
Panchmatia 2012 ³⁴⁷	This UK within trial (prospective cohort) cost consequence analysis of tranexamic acid was assessed as partially applicable with potentially serious limitations. This study was selectively excluded as it was superseded by two recent UK cost consequence analyses ^{13,363} , both of which were within-trial analyses of RCTs that are included in clinical review and therefore more applicable to the UK NHS context.
Gillette 2013 ¹⁶⁶	This US within trial (retrospective cohort) cost consequence analysis of tranexamic acid was assessed as partially applicable with potentially serious limitations. This study was selectively excluded as it was superseded by two recent UK cost consequence analyses ^{13,363} , both of which were within-trial analyses of RCTs that are included in clinical review and therefore more applicable to the UK NHS context.

Reference	Reason for exclusion
Slover 2014 ⁴⁰⁸	This US cost-effectiveness analysis (decision tree) was assessed as partially applicable with very serious limitations. Relative treatment effects were not reported or referenced in this analysis. This study was selectively excluded as it was superseded by two recent UK cost consequence analyses ^{13,363} , both of which were within-trial analyses of RCTs that are included in clinical review and therefore more applicable to the UK NHS context.
Vigna-Taglianti 2014 ⁴⁷³	This Italian within trial (before and after study with regression analysis) cost consequence analysis of tranexamic acid was assessed as partially applicable with potentially serious limitations. This study was selectively excluded as it was superseded by two recent UK cost consequence analyses ^{13,363} , both of which were within-trial analyses of RCTs that are included in clinical review and therefore more applicable to the UK NHS context.
Tuttle 2014 ⁴⁵⁷	This US within trial (retrospective cohort) cost consequence analysis of tranexamic acid was assessed as partially applicable with potentially serious limitations. This study was selectively excluded as it was superseded by two recent UK cost consequence analyses ^{13,363} , both of which were within-trial analyses of RCTs that are included in clinical review and therefore more applicable to the UK NHS context.
George 2015 ¹⁶³	This UK within trial (retrospective cohort) cost consequence analysis of tranexamic acid was assessed as partially applicable with potentially serious limitations. This study was selectively excluded as it was superseded by two recent UK cost consequence analyses ^{13,363} , both of which were within-trial analyses of RCTs that are included in clinical review and therefore more applicable to the UK NHS context.

Q.3 Red blood cells

Reference	Reason for exclusion
Palmieri 2007 ³⁴⁵	This study was assessed as partially applicable with very serious limitations. Based on a before and after study that was excluded from the clinical review. Savings are a product of blood usage and cost of a unit of blood (US cost). Therefore this study was excluded.
Zilberberg 2007 ⁵²⁴	This study was assessed as partially applicable with very serious limitations. Savings are a product of blood usage and cost of a unit of blood (US cost). Therefore this study was excluded.

Q.4 Platelets

Q.4.1 Platelet thresholds and targets

Reference	Reason for exclusion
Sarode 2010 ³⁸¹	This study was assessed as partially applicable with very serious limitations. Based on a before and after study that was excluded from the clinical review protocol. Not all costs are included and source of unit costs unclear (appears to be based on a US hospital). Therefore this study was excluded.

Q.4.2 Platelet dose

Reference	Reason for exclusion
Riley 2012 ³⁷²	This study was assessed as partially applicable with very serious limitations. Based on platelet doses that are not UK standard doses.

Reference	Reason for exclusion
	Assumes same health outcomes for all doses and unit costs are from a US perspective. Therefore this study was excluded.

Q.5 Fresh frozen plasma

Q.5.1 Fresh frozen plasma thresholds and targets

Reference	Reason for exclusion
Sarode 2010 ³⁸¹	This study was assessed as partially applicable with very serious limitations. Based on a before and after study that was excluded from the clinical review protocol. Not all costs are included and source of unit costs unclear (appears to be based on a US hospital). Therefore this study was excluded.

Appendix R: NICE technical team

Name	Role
Sharon Summers-Ma	Guideline Lead
Martin Allaby	Clinical Advisor
Beth Shaw	Technical Lead
Bhash Naidoo	Health Economist
Louise Shires	Guideline Commissioning Manager
Joy Carvill	Guideline Coordinator
James Hall	Editor

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Transfusion
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