NICE National Institute for Health and Care Excellence

Surveillance proposal consultation document

2019 surveillance of blood transfusion (NICE guideline NG24)

Surveillance proposal

We propose to not update the guideline on blood transfusion.

Reasons for the proposal to not update the guideline

Whilst there was new evidence across a number of areas, including red blood cells, platelets and cryoprecipitate, the evidence did not impact on guideline recommendations. Evidence generally supported existing recommendations or did not provide a sufficiently strong case for update due to uncertainty in trial results or unclear benefits of interventions.

For further details and a summary of all evidence identified in surveillance, see appendix A below.

Overview of 2019 surveillance methods

NICE's surveillance team checked whether recommendations in blood transfusion (NICE guideline NG24) remain up to date.

The surveillance process consisted of:

- Feedback from topic experts via a questionnaire.
- A search for new or updated Cochrane reviews.
- Examining related NICE guidance and quality standards and NIHR signals.
- A search for ongoing research.
- Examining the NICE event tracker for relevant ongoing and published events.
- Literature searches to identify relevant evidence.
- Assessing the new evidence against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.
- Consulting on the proposal with stakeholders (this document).

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Evidence considered in surveillance

Search and selection strategy

We searched for new evidence related to the whole guideline.

We found 128 studies in a search for randomised controlled trials (RCTs) and systematic reviews published between 29 January 2015 and 30 September 2019.

See appendix A below for details of all evidence considered, and references.

Selecting relevant studies

Due to the volume of evidence available, only Cochrane reviews and RCTs with a sample size of at least 100 patients were included. The exception to this was for section 1.5 on Cryoprecipitate where we included 1 non-Cochrane systematic review as no evidence was available from RCTs.

Ongoing research

We checked for relevant ongoing research; of the ongoing studies identified, 3 studies were assessed as having the potential to change recommendations. Therefore, we plan to check the publication status regularly and evaluate the impact of the results on current recommendations as quickly as possible. These studies are:

- Pre-operative iron used as blood sparing technique in orthopaedic surgery (total hip replacement and total knee replacement surgery, elective and no revision surgery). ISRCTN75321849
- Two cluster RCTs to evaluate feedback in blood transfusion audits. ISRCTN15490813
- Early cryoprecipitate in major trauma haemorrhage: CRYOSTAT-2. ISRCTN14998314

Intelligence gathered during surveillance

Views of topic experts

We considered the views of topic experts who were recruited to the NICE Centre for Guidelines Expert Advisers Panel to represent their specialty. For this surveillance review, topic experts completed a questionnaire about developments in evidence, policy and services related to the guideline.

We sent questionnaires to 15 topic experts and received 3 responses. Topic experts had expertise in critical care, intensive care, and paediatric intensive care.

Two out of 3 experts felt the guideline should be updated. Experts acknowledged the breadth of scope of the transfusion guideline, which makes identifying update areas difficult, but did suggest that there has been new research around red blood cells and cell salvage in caesarean section.

Implementation of the guideline

The uptake of recommendations has been variable. Some recommendation are well implemented such as recommendation 1.2.2, the proportion of people in hospices who had a pre-transfusion haemoglobin above 70g/L (82% at December 2016); and recommendation 1.3.9, the proportion of prophylactic platelet transfusions in adult haematology patients which were single units (94% at July 2017).

Some recommendations were poorly implemented such as recommendation 1.2.2, proportion of adult haematology patients who were anaemic and had no additional risk factors who were transfused when their haemoglobin was 70g/litre or lower (24% at July 2017); and recommendation 1.2.3, proportion of adult haematology patients who were anaemic and had cardiovascular disease who were transfused when their haemoglobin was 80g/litre or lower. (44% at July 2017). It is unclear why these recommendations were poorly implemented.

Equalities

No equalities issues were identified during the surveillance process.

Overall surveillance proposal

After considering all evidence and other intelligence and the impact on current recommendations, we propose that no update is necessary.

Appendix A: Summary of evidence from surveillance

2019 surveillance of blood transfusion (2015) NICE guideline NG24

Summary of evidence from surveillance

Studies identified in searches are summarised from the information presented in their abstracts.

Feedback from topic experts who advised us on the approach to this surveillance review, was considered alongside the evidence to reach a view on the need to update each section of the guideline.

1.1 Alternatives to blood transfusion for patients having surgery

Recommendations in this section of the guideline

Erythropoietin

1.1.1 Do not offer erythropoietin to reduce the need for blood transfusion in patients having surgery, unless:

- the patient has anaemia and meets the criteria for blood transfusion, but declines it because of religious beliefs or other reasons or
- the appropriate blood type is not available because of the patient's red cell antibodies.

Surveillance proposal

This section of the guideline should not be updated.

Erythropoietin

2019 surveillance summary

One RCT (1) (n=100 patients) of combined iron therapy and erythropoietin, versus placebo, for anaemic patients undergoing transcatheter aortic valve implantation found no significant difference in the rate of 30-day red cell transfusion, number of red cells transfused, 30-day mortality, stroke, acute kidney injury and new-onset atrial fibrillation.

One RCT (2) (n=600 patients) of human recombinant erythropoietin or control given 2 days before cardiac surgery found that erythropoietin significantly decreased patients requiring red blood cell transfusion and number of units transfused. There was no significant difference in all-cause mortality or adverse events.

One RCT (3) of ferric carboxymaltose with or without erythropoietin in the perioperative period of heart failure (n=306 patients) found no significant differences in the number of red blood cell transfusions per patient, survival, quality of life, or adverse events. The authors reported improvements in patients recovering from post-operative anaemia 60 days after discharge.

Intelligence gathering

There was no intelligence relevant to this section of the guideline.

Impact statement

The evidence from 3 RCTs generally found no clear benefit of erythropoietin in cardiovascular surgery. At the time of guideline development, the clinical evidence base for erythropoietin was mixed with both benefits and harms associated with its use; in particular increased mortality and thrombotic complications. Erythropoietin was also not considered cost-effective. No new evidence was identified through surveillance to conflict with this view and as such the recommendations will not be updated.

New evidence is unlikely to change guideline recommendations.

Intravenous and oral iron

1.1.2 Offer oral iron before and after surgery to patients with iron-deficiency anaemia.

1.1.3 Consider intravenous iron before or after surgery for patients who:

- have iron-deficiency anaemia and cannot tolerate or absorb oral iron, or are unable to adhere to oral iron treatment (see the NICE guideline on medicines adherence)
- are diagnosed with functional iron deficiency
- are diagnosed with iron-deficiency anaemia, and the interval between the diagnosis of anaemia and surgery is predicted to be too short for oral iron to be effective.

1.1.4 For guidance on managing anaemia in patients with chronic kidney disease, see the NICE guideline on anaemia management in chronic kidney disease.

Surveillance proposal

This section of the guideline should not be updated. An editorial amendment will be made to recommendation 1.1.3 to highlight the Medicines and Healthcare products Regulatory Agency (MHRA) warning on intravenous iron: Intravenous iron and serious hypersensitivity reactions: strengthened recommendations.

Intravenous and oral iron

2019 surveillance summary

A Cochrane review (4) (3 RCTs; n=114 patients) of iron therapy for pre-operative anaemia found no significant reduction in the proportion of patients who received an allogeneic blood transfusion compared to those receiving no iron therapy. Intravenous iron was potentially more effective than oral iron, but analysis was hampered by small sample size.

One RCT (5) (n=116 patients) of pre-operative oral versus intravenous iron in anaemic patients with colorectal cancer found no significant difference in volume of blood transfused, or number of transfused patients. Intravenous iron was associated with significantly fewer anaemic patients at time of surgery, and higher haemoglobin levels post-surgery, compared with oral iron.

One RCT (1) (n=100 patients) of combined iron therapy and erythropoietin, versus placebo, for anaemic patients undergoing transcatheter aortic valve implantation found no significant difference in the rate of 30-day red cell transfusion, number of red cells transfused, 30-day mortality, stroke, acute kidney injury and new-onset atrial fibrillation.

One RCT (6) of a single dose of intravenous 1000 mg ferric carboxymaltose post-operatively versus control anaemic patients undergoing elective surgery was identified (n=201 patients). Compared with control, ferric carboxymaltose was associated with significantly improved haemoglobin, serum iron, iron saturation, and serum ferritin at 4 weeks, as well as reduced transfused blood units.

One RCT (7) of intravenous iron versus oral iron in patients after cardiovascular surgery (n=150 patients) found a significantly improved ferritin concentration at 7 and 14 days, and had their anaemia corrected or achieved haemoglobin increments of >20g/L. There were no significant differences in other outcomes, including rates of blood transfusion, death, post-operative hospital stay >10 days, and poor wound healing.

Intelligence gathering

Clinical feedback indicated that there is a MHRA safety warning on intravenous iron: Intravenous iron and serious hypersensitivity reactions: strengthened recommendations..

Impact statement

Evidence from a Cochrane review and 4 RCTs found that both oral and intravenous iron therapy may be effective in improving haemoglobin levels, although this may not translate into reduced need for blood transfusions. At the time of guideline development, the clinical evidence base for iron therapy was weak but indicated that oral and intravenous iron may both be clinically effective. However, the committee considered that when used in appropriate patients oral iron was likely to be cost-effective compared to intravenous iron, and patients may have a preference for oral. As such, the committee recommended oral over intravenous iron as the first line option. However, the guideline committee also used their judgement to identify groups where intravenous iron may be suitable. There is no new

evidence identified through the surveillance review that conflicts with this and as such the recommendations will not be updated.

Clinical feedback indicated that there is a MHRA safety warning on intravenous iron: Intravenous iron and serious hypersensitivity reactions: strengthened recommendations. An editorial amendment will be made to recommendation 1.1.3 to highlight the MHRA warning.

New evidence is unlikely to change guideline recommendations.

Cell salvage and tranexamic acid

1.1.5 Offer tranexamic acid to adults undergoing surgery who are expected to have at least moderate blood loss (greater than 500 ml).

1.1.6 Consider tranexamic acid for children undergoing surgery who are expected to have at least moderate blood loss (greater than 10% blood volume).

1.1.7 Do not routinely use cell salvage without tranexamic acid.

1.1.8 Consider intra-operative cell salvage with tranexamic acid for patients who are expected to lose a very high volume of blood (for example in cardiac and complex vascular surgery, major obstetric procedures, and pelvic reconstruction and scoliosis surgery).

Surveillance proposal

This section of the guideline should not be updated.

Cell salvage

2019 surveillance summary

One RCT (8) (n=110 patients) of intra-operative cell salvage, versus no cell salvage, on blood coagulation in high-bleeding-risk patients undergoing cardiac surgery with cardiopulmonary bypass found that cell salvage was associated with significantly increased incidence of heparin residual, total impairment of blood coagulation at the end of surgery, and incidence of excessive bleeding.

One RCT (9) (n=150 patients) of intra-operative cell salvage, versus no cell salvage, in high-bleeding-risk cardiac surgery with cardiopulmonary bypass found that cell salvage patients had significantly lower proportion and quantity of perioperative allogeneic red blood cell transfusions. Compared with control, cell salvage patients had a significantly increased incidence of post-operative excessive bleeding, and incidence of residual heparin and total impairment of blood coagulative function in the 24 hours after surgery. Cell salvage was also associated with a significant decrease in costs of allogeneic red blood transfusion and total allogeneic blood transfusion, but increased costs of total blood transfusion compared with control.

One RCT (10) (n=110 patients) of intraoperative cell salvage, or no cell salvage, in scoliosis patients undergoing primary posterior spinal fusion with segmental spinal instrumentation found that cell salvage patients had significantly lower perioperative allogenic blood transfusion rate and intraoperative red blood cell transfusion requirement.

One HTA (11) included an RCT (12) (n=3038 women) and economic analysis (13) of intraoperative cell salvage, versus usual care without cell salvage during caesarean section in women at risk of haemorrhage. The trial found that compared with control, cell salvage did not have a significant effect on blood transfusions but increased the risk of foetal maternal haemorrhage in rhesus D (RhD)-negative women with RhD-positive babies. There were reportedly no other significant differences in secondary outcomes. Subgroup analysis indicated no significant different in transfusions rates among women receiving an elective caesarean section and a borderline significant reduction in transfusions in women receiving emergency caesarean section with cell salvage compared with no cell salvage. Economic analysis indicated that there is uncertainty around the cost effectiveness of cell salvage for women undergoing caesarean section.

Intelligence gathering

A topic expert highlighted that cell salvage is covered in the guideline but there has been recent work on cell salvage therapy in caesarean section, and highlighted the HTA (11) on cell salvage in caesarean section. There is also an NIHR signal related to the HTA (11) on cell salvage in caesarean section.

Impact statement

Cell salvage

At the time of guideline development, the evidence base and economic modelling indicated that tranexamic acid or the combination of cell salvage with tranexamic acid was more likely to be cost-effective than cell salvage alone. As such the committee developed 2 recommendations. Recommendation 1.1.7 states: do not routinely use cell salvage without tranexamic acid. Recommendation 1.1.8 advises: consider intra-operative cell salvage with tranexamic acid for patients who are expected to lose a very high volume of blood (for example in cardiac and complex vascular surgery, major obstetric procedures, and pelvic reconstruction and scoliosis surgery).

Evidence from 3 RCTs was identified. Two RCTs of cell salvage therapy in cardiac surgery found that cell salvage may be associated with an increase in post-operative excessive bleeding, residual heparin and total impairment of blood coagulative function in the 24 hours after surgery. One RCT found that in spinal fusion patients cell salvage had lower red blood cell transfusion requirements, compared with no cell salvage. Evidence from 1 HTA was highlighted by a topic expert (which included an RCT and economic analysis and was the subject of an NIHR signal) and found no significant difference in the need for donor blood transfusion with cell salvage, compared with no cell salvage, in women undergoing caesarean

section. The cost effectiveness of cell salvage was uncertain. The NIHR signal concluded that cell salvage does not have a role in the routine care of women undergoing caesarean section.

This new evidence generally supports the view that cell salvage should not be used alone and does not contradict the advice to consider intra-operative cell salvage with tranexamic acid for patients who are expected to lose a very high volume of blood. As such, the recommendations will not be updated.

New evidence is unlikely to change guideline recommendations.

Tranexamic acid

2019 surveillance summary

There were 69 RCTs and Cochrane reviews (70 publications) that looked at the effectiveness of tranexamic acid (TXA) based on doses, routes or combinations of TXA, or versus control or an active comparator. The RCTs are described below under the relevant subheading. For ease of interpretation where there are more than 10 RCTs, trials have been further grouped by whether they showed a significant decrease in blood loss or not.

TXA versus control/placebo (25 RCTs)

Significantly reduced blood loss (TXA versus control; 23 RCTs)

One RCT (14) of topical TXA cardiac bath versus cardiac bath after open heart surgery (n=100 patients) found significantly less blood loss at 48 hours and fewer units of transfused blood in the TXA cardiac bath group.

One RCT (15) (n=400 patients) of 0.1% TXA in irrigant fluid, versus placebo during percutaneous nephrolithotomy found significantly lower total blood loss, blood transfusions, operative time, complication rate, amount of irrigant fluid used and hospital stay with the TXA group. There were no reported adverse events.

One RCT (16) of TXA versus placebo in head and neck cancer surgery patients (n=240 patients) found that TXA significantly reduced post-operative blood loss but there was no significant difference in intraoperative blood loss or transfusions. Incidence of wound complications was similar.

One RCT (17) of 3-dose intravenous TXA or placebo in patients with trochanteric fractures (n=176 patients) found significantly less perioperative blood loss, obvious blood loss, hidden blood loss, blood transfusions, and shorter hospital stay in the TXA group.

One RCT (18) of intravenous TXA versus topical TXA versus placebo in patients undergoing posterior lumbar interbody fusion (n=150 patients) found that the post-operative drainage volume, number of blood transfusions, length of hospital stay, and extubation time significantly favoured TXA administration compared with placebo. There was no significant difference between groups in terms of visual analogue scale, prothrombin time, and fibrinogen content.

One RCT (19) of intravenous TXA versus placebo in adolescents undergoing idiopathic scoliosis surgery (n=111 patients) found that the TXA group had significantly less intraoperative blood loss, intraoperative bleeding per hour, per fused spinal level, and post-operative bleeding. No patients in the TXA group needed a transfusion. There were no perioperative adverse events.

One RCT (20) of intravenous TXA versus control for myomectomy (n=132 patients) found significantly reduced blood loss, transfusion needs, haemoglobin and haematocrit compared to control.

One RCT (21) of topical TXA versus control for intertrochanteric fractures (n=200 patients) found that TXA significantly reduced transfusion requirements. There was no significant difference in late complications and overall mortality rate between groups.

One RCT (22) of topical TXA versus fibrin sealant versus control in patients with hip fracture (n=158 patients) found no significant differences in blood loss collected in drains or transfusion rate. There were no complications or adverse effects.

One RCT (23) of intravenous TXA versus control in elderly patients with intertrochanteric fractures (n=100 patients) found significantly less blood loss, hidden blood loss and intraoperative blood loss with TXA. There was no significant difference in post-operative blood loss, transfusions or complications including deep vein thrombosis, pulmonary embolism and infections or myocardial infarction.

One RCT (24) of intravenous TXA versus placebo for the fixation of intertrochanteric fractures (n=100 patients) found significantly improved post-operative haemoglobin and fewer blood transfusions with TXA.

There were 12 RCTs (25,26,27–34,35,36) in patients undergoing knee, hip or shoulder replacement which found that TXA reduced blood loss and transfusions compared with control/placebo.

No significant difference in blood loss (2 studies)

A Cochrane review (37) (1 RCT; n=100 patients) of TXA versus control for reducing blood loss associated with cytoreductive surgery in women with advanced ovarian cancer found no significant difference in total estimated blood loss, re-operation rate, readmission rate or thrombotic events.

One RCT (38) of intravenous TXA versus placebo for patients undergoing percutaneous nephrolithotomy (n=132 patients) found no significant difference in blood loss or haemoglobin drop.

TXA route of administration, dose and combined use in hip and knee surgery

There were 23 RCTs looking at the different routes of administering TXA in patients undergoing hip or knee surgery (43,44,45,46–52,53–62,63–66); 8 RCTs looking at doses of TXA in patients undergoing hip or knee surgery (63–71); and 5 RCTs of combined TXA (for example topical combined with intravenous) in patients undergoing hip or knee arthroplasty.

(72–76) The evidence indicated some significant reductions in blood loss and transfusion requirements for combined TXA, and certain doses and routes of administration. However, NICE is currently developing a guideline on joint replacement (primary): hip, knee and shoulder (expected publication date: March 2020), which includes recommendations on TXA for primary hip, knee and shoulder replacement and as such these studies are not considered further here.

TXA versus epsilon-aminocaproic acid (3 RCTs)

One RCT (77) (n=194 patients) of epsilon-aminocaproic acid versus TXA in patients undergoing total knee arthroplasty found significantly less blood loss, although no transfusions were required in either group. There were no significant differences in length of hospital stay, the change serum creatinine level, or post-operative complications.

One RCT (78) (n=235 patients) of TXA versus epsilon-aminocaproic acid in patients undergoing knee and hip arthroplasty was identified. In knee arthroplasty patients, there was significantly increased blood loss and total drainage with epsilon-aminocaproic acid compared with TXA. There were no significant differences in hip arthroplasty patients across outcomes. No patients required transfusion.

One RCT (79) of epsilon-aminocaproic acid versus TXA in patients undergoing cardiac surgery (n=114 patients) found that epsilon-aminocaproic acid had significantly fewer transfusions intra-operatively to 24 hours compared with TXA. There was no significant difference on chest drainage, and adverse events.

TXA versus epinephrine (3 RCTs)

One RCT (80) TXA alone versus TXA plus intravenous low dose intravenous epinephrine versus TXA plus topical diluted epinephrine in patients undergoing primary knee arthroplasty (n=179 patients) was identified. The trial found significantly less total blood loss and transfusions with TXA plus intravenous low dose intravenous epinephrine compared with other groups. There were no significant differences in the incidence of thromboembolic complications, wound score, or range of motion between the 3 groups.

One RCT (81) of topical TXA plus diluted epinephrine versus topical TXA in patients undergoing total knee arthroplasty (n=100 patients), and 1 RCT (82) in patients undergoing total hip arthroplasty (n=107) found that TXA plus epinephrine significantly reduced total blood loss, hidden blood loss and transfusion rate, compared with topical TXA alone. There was no significant difference in thromboembolic and hemodynamic complications between groups.

TXA with hydroxyethyl starch plus lactate priming solution (1 RCT)

One RCT (83) of hydroxyethyl starch plus lactate priming solution with or without TXA versus ringer solution with or without TXA in patients undergoing coronary artery bypass graft (n=132 patients) found that hydroxyethyl starch plus lactate priming solution with TXA significantly reduced blood loss, post-operative 24 hour drainage loss and blood product transfusions compared with other groups. The haemoglobin and haematocrit values at 12 and

24 hours after surgery were significantly increased with hydroxyethyl starch plus lactate priming solution with TXA versus other groups. There was no significant difference in platelet concentrations between groups.

Intelligence gathering

A topic expert agreed that TXA is adequately covered in the guideline.

Impact statements

At the time of guideline development, the evidence base and economic modelling indicated that TXA or the combination of cell salvage with TXA was more likely to be cost-effective than cell salvage alone. As such the committee developed 2 recommendations. Recommendation 1.1.5 states: Offer tranexamic acid to adults undergoing surgery who are expected to have at least moderate blood loss (greater than 500 ml). Recommendation 1.1.6 advises: consider tranexamic acid for children undergoing surgery who are expected to have at least moderate blood loss (greater than 10% blood volume).

TXA versus control/placebo

Evidence from 25 RCTs found that TXA patients generally had significantly reduced blood loss and transfusion requirements, compared with control, without increasing complications. The effect was consistent across oral TXA, intraarticular TXA and intravenous TXA. This new surveillance evidence is consistent with the evidence included in the original guideline and is in line with guideline recommendations suggesting offering tranexamic acid in adults undergoing surgery expected to have moderate blood loss. As such the recommendations will not be updated.

TXA route of administration, doses and combined use in hip and knee replacement

Evidence from 36 RCTs looking at routes of administration, doses and combined use of TXA (for example topical plus intravenous TXA) in hip and knee replacement patients found some significant reductions in blood loss for combined TXA, and certain doses and routes of administration. Currently this guideline does not provide advice on route of administration, dose or combined us of TXA. However, NICE is currently developing a guideline on joint replacement (primary): hip, knee and shoulder (expected publication date: March 2020), which includes recommendations on route, dose and combined use of tranexamic acid for primary hip, knee and shoulder replacement and as such these studies are not considered further here. However, an editorial amendment will be made to recommendation 1.1.5 to highlight the new guideline on joint replacement (primary): hip, knee and shoulder providing advice on tranexamic acid in primary hip, knee and shoulder replacement.

TXA versus epsilon-aminocaproic acid

Evidence from 3 RCTs found unclear benefits in terms of blood loss between TXA and epsilon-aminocaproic acid in patients undergoing knee surgery or heart surgery. Epsilon-aminocaproic acid is not currently covered in the guideline and this new evidence does not

provide a strong case for inclusion as the evidence does not provide a clear benefit of epsilon-aminocaproic acid compared with TXA.

TXA versus epinephrine

Evidence from 3 RCTs found that TXA plus epinephrine significantly reduced blood loss compared with TXA alone in patients undergoing knee or hip arthroplasty. The combination of TXA and epinephrine is not currently covered in the guideline. This new surveillance evidence is from 3 relatively small non-UK trials, which may not be generalisable to UK clinical practice. As such the recommendations will not be updated until further research is available on the role of epinephrine combined with TXA.

TXA with hydroxyethyl starch plus lactate priming solution

Evidence from 1 RCT found that hydroxyethyl starch plus lactate priming solution with TXA significantly reduced blood loss in patients undergoing coronary artery bypass graft. Currently the guideline recommendations do not include the addition of hydroxyethyl starch plus lactate priming solution to TXA. This new surveillance evidence is specific to patients undergoing coronary artery bypass graft and is based on only 1 small trial. As such, this new evidence does not warrant inclusion in the guideline.

New evidence is unlikely to change guideline recommendations.

1.2 Red blood cells

Recommendations in this section of the guideline

Thresholds and targets

1.2.1 Use restrictive red blood cell transfusion thresholds for patients who need red blood cell transfusions and who do not:

- have major haemorrhage or
- have acute coronary syndrome or
- need regular blood transfusions for chronic anaemia.

1.2.2 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.

1.2.3 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.

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

Doses

1.2.5 Consider single-unit red blood cell transfusions for adults (or equivalent volumes calculated based on body weight for children or adults with low body weight) who do not have active bleeding.

1.2.6 After each single-unit red blood cell transfusion (or equivalent volumes calculated based on body weight for children or adults with low body weight), clinically reassess and check haemoglobin levels, and give further transfusions if needed.

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

Please note that to aid comparison to the guideline recommendations, units for thresholds have been converted from g/decilitre to g/litre, as needed.

Thresholds in cardiovascular conditions – cardiac surgery

One RCT (84,85) (n=5,243 participants) of restrictive threshold (<75 g/litre) or liberal red cell transfusion (threshold <95g/litre in operating room or intensive care unit, or <85 g/litre in non-intensive care unit ward) for cardiac surgery found no significant difference in the composite outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis by hospital discharge or by day 28. Compared with a liberal strategy, restrictive blood cell transfusion had significantly lower red cell transfusions. Six month outcomes showed that a restrictive strategy was non-inferior to a liberal strategy in the composite outcome of death from any cause, myocardial infarction, stroke, or new-onset renal failure with dialysis. There were reportedly no significant differences in the secondary outcomes.

One large UK RCT (86) (87) of a restrictive threshold (post-operative haemoglobin <75 g/litre) versus a liberal threshold (post-operative haemoglobin <90 g/litre) for red blood cell transfusion after cardiac surgery (n=2,003 patients) found no significant difference in the composite outcome of any serious infectious or ischaemic event during the 3 months after randomisation or the majority of secondary outcomes. However, a restrictive threshold was associated with significantly increased risk of mortality (4.2% versus 2.6%) compared with liberal transfusions. There was little difference in cost between groups, although the restrictive group was associated with £182 reduced cost at 3 months owing to less red blood cells transfusions. A cost effectiveness analysis (88) related to the RCT found no clear difference in the cost effectiveness of restrictive versus liberal transfusions after cardiac surgery.

One RCT (89) of a transfusion haematocrit trigger of 24% versus 28% (n=722 adults undergoing coronary artery bypass grafting or valve surgery) was stopped early as the trial found no significant difference in the composite outcome of post-operative morbidities and mortality, but a significantly reduced use of red blood cells with the 24% haematocrit trigger.

Thresholds in chronic cardiovascular conditions

One large RCT (90) of either liberal transfusion (maintain haemoglobin level at 100 g/litre or higher) or restrictive transfusion (transfused when haemoglobin lower than 80 g/litre) in elderly patients with a history or risk factors for cardiac disease (n=2,016 patients) found no significant difference in 3-year mortality between the groups. The underlying causes of death was reported as not differing between groups.

An NIHR signal highlighted a systematic review (91) (11 trials; n=3,033 patients) looking at restrictive (< 80 g/litre) versus liberal (> 80 g/litre) transfusion strategies in patients with cardiovascular disease in a non-cardiac surgery setting, which found that a restrictive threshold was associated with a significantly increased risk of acute coronary syndrome. The review authors deemed that the new findings suggest that people with non-acute cardiovascular disease may also benefit from being managed with liberal thresholds.

Thresholds in non-cardiovascular conditions

One Cochrane review (92) (31 trials; n=12, 587 participants) of restrictive versus liberal red blood cell transfusion thresholds for all conditions found that transfusing at a restrictive haemoglobin concentration (70 g/litre to 80 g/litre) decreased red blood cell transfusion by 43% across a broad range of clinical specialties. There was no significant difference in 30-day mortality or morbidity. The review was not able to assess the effectiveness of restrictive transfusions in specific sub-populations, including acute coronary syndrome, brain injury, stroke, cancer and bone marrow failure.

One Cochrane review (93) (6 trials; n=2,722 participants) of restrictive (usually 80 g/litre) versus liberal blood cell transfusion in patients undergoing hip fracture surgery found no significant difference in mortality, functional recovery or post-operative morbidity. There was evidence of a significantly lower risk of myocardial infarction in the liberal compared with the restrictive transfusion threshold group, but the evidence was deemed very low quality by review authors.

One Cochrane review (94) (3 completed RCTs and 1 non-randomised study; n=240 participants) evaluated restrictive versus liberal red blood cell transfusions for people with haematological cancer treated with intensive chemotherapy and/or radiotherapy, with or without haematopoietic stem cell therapy. A restrictive red blood cell transfusion policy significantly reduced the number of transfusions per participant, but had no clear effect on mortality at 30 to 100 days, bleeding, or hospital stay. The evidence was mainly in adults with acute leukaemia.

One Cochrane review (95) (1 trial; n=13 participants) of restrictive versus liberal red blood cell transfusion policies in patients with aplastic anaemia, myelodysplasia, and other congenital bone marrow failure conditions was found. The trial was deemed too small to find a difference in number of red cell transfusions received or all-cause mortality.

One RCT (96) of restrictive (transfusion trigger ≤70 g/litre) versus liberal (transfusion trigger <100 g/litre) transfusion strategies (n=180 critically ill children) found significantly improved

cardiac output, perfusion index and lactate at the end of the transfusion period with liberal transfusions.

One RCT (97) of a restrictive threshold (haemoglobin <70g/litre) versus a liberal threshold (<9 g/litre) (n=998 patients with septic shock) found no significant difference in mortality at 1-year or health related quality of life at 1-year.

One RCT (98) of a liberal threshold (haemoglobin <90 g/litre) versus restrictive threshold (haemoglobin <70 g/litre) in cancer patients with septic shock (n=300 patients) found no significant difference in mortality at 28 days, or length of ICU or hospital stay. The liberal threshold group received significantly more red blood cell units and mortality was significantly lower, compared with the restrictive threshold.

One RCT (99) of a restrictive threshold (haemoglobin<75 g/litre) versus a liberal threshold (transfuse if haemoglobin<95 g/litre in the operating room or intensive care unit, or if haemoglobin <85 g/litre on the non-intensive care ward) in patients undergoing cardiac surgery (n=4,531 patients) found that restrictive threshold patients had significantly fewer transfusions than liberal threshold patients. There was no significant difference in acute kidney injury.

One RCT (100)(101) of a restrictive threshold (haemoglobin<70 g/litre) versus a liberal threshold (haemoglobin <100 g/litre) in patients with massive burns or major burns (n=345 patients) found that restrictive threshold patients received significantly less blood for both major and massive burns. The restrictive group had significantly fewer ventilator days, intensive care days and length of stay in patients with massive burns but there was no difference with major burns.

One RCT (102) of a restrictive threshold (haemoglobin <97 g/litre) versus a liberal threshold (haemoglobin <11.3g/litre) in the frail elderly after hip fracture (n=157 patients) found no significant difference in quality of life and recovery of daily activities.

One RCT (103)(104)(105) of a restrictive threshold (haemoglobin <97 g/litre) versus a liberal threshold (haemoglobin <113g/litre) in the frail elderly after hip fracture (n=284 patients) found no significant difference in recovery from physical disabilities, mortality, infection rate, or quality of life. In nursing home residents, the 90-day mortality rate was significantly lower following the liberal strategy compared with the restrictive strategy. There was no significant difference in infections with the liberal strategy.

One large RCT (106) of a restrictive threshold (haemoglobin <70 g/litre) versus a liberal threshold (haemoglobin <100 g/litre) in patients in intensive care (n=998 patients) found no significant difference in 90 day mortality. Patients in the restrictive threshold group had significantly less red blood cell transfusions but more temporary protocol suspensions.

Intelligence gathering

During the standard topic expert feedback sought across the entire guideline, a topic expert thought that the paediatric population may be better served with a specific section within this guideline, but acknowledged that there is little evidence to support practice. The expert

also stated that from his experience the following thresholds were clinical practice in the paediatric population: a transfusion threshold of 70 g/litre is accepted but may be higher (90 g/litre) in children with cyanotic heart disease, as well as in other scenarios.

Topic expert feedback was also sought specifically on the NIHR signal and how this might be influencing clinical practice. Feedback from a topic expert indicates that in clinical practice most patients with a chronic cardiovascular condition are managed with a restrictive threshold, unless there are clinical signs of damage such as chest pain, ECG or lactate. The expert also went on to say that in practice most patients with a chronic disease contemplating a transfusion would be having an acute episode of something so the lines become blurred between chronic and acute. The expert also highlighted that in the NIHR signal systematic review there was no difference in mortality or hospital stay.

Impact statements

Thresholds in cardiovascular conditions – cardiac surgery

At the time of guideline development, the evidence base was lacking for red blood cell thresholds in cardiovascular conditions and the guideline committee used their judgement to develop recommendation 1.2.3 which states: 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.

Evidence from 3 RCTs (including 2 RCTs with sample size >2000 patients) in patients undergoing cardiac surgery found that restrictive thresholds were associated with significantly lower red cell transfusions. One trial found a significantly increased risk of death after cardiac surgery with restrictive thresholds. Two trials found no significant difference in composite outcomes composed of morbidity and mortality.

This new evidence appears to generally support the view that higher thresholds should be used in acute coronary conditions, such as cardiac surgery. As such, no update to the guideline recommendations appears warranted.

New evidence is unlikely to change guideline recommendations.

Thresholds in chronic cardiovascular conditions

At the time of guideline development there was no evidence on red blood cell thresholds in chronic cardiovascular conditions and the committee did not make any recommendations specifically addressing patients with chronic cardiovascular conditions. However, the committee deemed this a priority for research and developed a research recommendation asking what is the clinical and cost effectiveness of restrictive compared with liberal red blood cell thresholds and targets for patients with chronic cardiovascular disease?

Evidence from a systematic review in patients with cardiovascular disease not undergoing cardiac surgery found that a restrictive strategy may increase the risk of acute coronary

syndrome. This systematic review was also the subject of an NIHR signal. However, a large RCT in elderly patients with cardiovascular risk factors found no significant benefit of liberal transfusions.

Currently the guideline does not provide specific advice on chronic cardiovascular conditions but suggests using 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 or need regular blood transfusions for chronic anaemia. The guideline recommends a restrictive red blood cell transfusion threshold of 70 g/litre and a liberal red blood cell transfusion threshold of 80 g/litre. However, the haemoglobin concentration targets in the guideline overlap, with restrictive being 70–90 g/litre after transfusion and liberal being 80–100 g/litre after transfusion.

Topic expert feedback indicates that in clinical practice most patients with a chronic condition are managed with a restrictive threshold, unless there are clinical signs of damage such as chest pain, ECG or lactate. The expert also went on to say that in practice most patients with a chronic disease contemplating a transfusion would be having an acute episode of something so the lines become blurred between chronic and acute. The expert also highlighted that in the systematic review there was no difference in mortality or hospital stay. This could in theory make the significant results in acute coronary syndrome a simple case of chance. Furthermore, the cost effectiveness of a liberal threshold in chronic cardiovascular patients is unknown. As such it does not appear warranted to update the guideline recommendations until further research confirms the benefits of a liberal threshold in chronic cardiovascular patients.

New evidence is unlikely to change guideline recommendations.

Thresholds in non-cardiovascular conditions

At the time of guideline development, the evidence base indicated that restrictive red blood transfusions were suitable for the majority of patients. As such, recommendation 1.2.1 was developed which states: use restrictive red blood cell transfusion thresholds for patients who need red blood cell transfusions and who do not have major haemorrhage, acute coronary syndrome or need regular blood transfusions for chronic anaemia. Recommendation 1.2.2 provided clarity around thresholds stating: 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.

Evidence from 4 Cochrane reviews and 8 RCTs found that, compared with liberal transfusion, restrictive transfusions generally decreased red blood cell transfusions without increasing mortality or adverse events across a range of non-cardiovascular populations. The new evidence is in line with previous evidence and current guideline recommendations 1.2.1 and 1.2.2. As such, no update to the guideline recommendations appears warranted.

A topic expert also indicated that the paediatric population may be better served with a specific section within this guideline, but acknowledged that there is little evidence to

support practice. There was no new evidence that would address this issue and as such the guideline will not be updated.

New evidence is unlikely to change guideline recommendations.

1.3 Platelets

Recommendations in this section of the guideline

Thresholds and targets

Patients with thrombocytopenia who are bleeding

1.3.1 Offer platelet transfusions to patients with thrombocytopenia who have clinically significant bleeding (World Health Organization [WHO] grade 2) and a platelet count below 30×10^9 per litre.

1.3.2 Use higher platelet thresholds (up to a maximum of 100×10^9 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

1.3.3 Offer prophylactic platelet transfusions to patients with a platelet count below 10×10^9 per litre who are not bleeding or having invasive procedures or surgery, and who do not have any of the following conditions:

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

Patients who are having invasive procedures or surgery

1.3.4 Consider prophylactic platelet transfusions to raise the platelet count above 50×10^9 per litre in patients who are having invasive procedures or surgery.

1.3.5 Consider a higher threshold (for example $50–75\times10^9$ per litre) for 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.

1.3.6 Consider prophylactic platelet transfusions to raise the platelet count above 100×10^9 per litre in patients having surgery in critical sites, such as the central nervous system (including the posterior segment of the eyes).

When prophylactic platelet transfusions are not indicated

1.3.7 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.

1.3.8 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.

Doses

1.3.9 Do not routinely transfuse more than a single dose of platelets.

1.3.10 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).

1.3.11 Reassess the patient's clinical condition and check their platelet count after each platelet transfusion, and give further doses if needed.

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

Thresholds and targets

One Cochrane review (107) (3 completed trials; n=180 adults with thrombocytopenia) of prophylactic platelet transfusions prior to minor surgery for people with a low platelet count found no evidence of a significant effect on all-cause mortality at 30-days, major bleeding, or minor bleeding, compared with no platelet transfusion or an alternative to platelet transfusion. There was no evidence of a significant difference in adverse effects. The review authors concluded that further evidence is needed.

One Cochrane review (108) (3 trials; n=499 participants) of different platelet count thresholds to guide administration of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation was identified. The review found that a standard trigger level (10 x 10^9/L) was not associated with a significant increase in the risk of bleeding compared to a higher trigger level (20 x 10^9/L or 30 x 10^9/L). However, a standard trigger level was associated with a significantly reduced number of transfusion episodes compared to a higher trigger level. The review authors deemed that, in the absence of other risk factors for

bleeding, it was reasonable to continue with the current practice of using the standard trigger level (10 x 10^9/L) for prophylactic platelet transfusions.

One Cochrane review (109) (6 completed trials; n=1,195 participants) of a therapeutic-only versus prophylactic platelet transfusion strategy for preventing bleeding in patients with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation was found. The review found that a therapeutic-only platelet transfusion policy was associated with a significantly increased risk of bleeding, but a significant reduction in the number of platelet components administered, when compared with a prophylactic platelet transfusion policy. There was insufficient evidence to determine a difference in mortality rates and no significant difference in adverse events.

One Cochrane review (110) (2 cohorts; n=150 participants) of platelet transfusions prior to lumbar punctures or epidural anaesthesia for the prevention of complications in people with thrombocytopenia found no RCTs. Evidence from 2 cohort studies found no difference in the risk of minor bleeding for platelet transfusions before lumbar puncture compared with no platelet transfusion beforehand. The review authors recommended further research.

One Cochrane review (111)(0 completed trials) of different platelet transfusion thresholds prior to insertion of central lines in patients with thrombocytopenia found no completed RCTs. An ongoing RCT was identified but the authors deemed the study too small to be able to address the research question and suggested that further research is needed.

One Cochrane review (112) of different prophylactic plasma transfusion regimens prior to insertion of a lumbar puncture needle or epidural catheter in people with abnormal coagulation found no evidence (0 completed trials). The authors noted that a large study with around 50,000 people would be needed to address the research question.

One Cochrane review (113) (1 RCT; n=9 adults) found no evidence to determine the safety and efficacy of prophylactic platelet transfusion versus therapeutic platelet transfusion in myelodysplastic syndrome.

One RCT (114) (n=190 patients) of platelet transfusion with standard care, compared with standard care alone, after intracerebral haemorrhage associated with antiplatelet therapy was identified. The trial found that patients having a platelet transfusion had significantly increased odds of death or dependence at 3 months, compared with standard care alone.

Doses

One Cochrane review (115) (7 trials; n=1,814 participants) of different doses of prophylactic platelet transfusion for preventing bleeding in people with haematological disorders after myelosuppressive chemotherapy or stem cell transplantation was identified. The review found no evidence of a significant difference in risk of bleeding or 30-day mortality between low dose, standard-dose and high dose platelet transfusion policies. However, a low dose transfusion policy might be associated with an increase in number of transfusions, and a high dose policy may increase adverse events.

One RCT (116) (n=5,034 patients) of low dose, medium dose, or high dose platelet transfusion prophylaxis in haematology-oncology patients found that high dose transfusions were significantly more likely experience any transfusion related adverse event than medium or low dose transfusions. The most common adverse events were fever, allergic or hypersensitivity reactions, and sinus tachycardia.

Alternatives to platelet transfusion

One Cochrane review (117) (7 completed RCTs; n=472 participants) of alternative agents to prophylactic platelet transfusion for preventing bleeding in people with thrombocytopenia due to chronic bone marrow failure was identified. The review found insufficient evidence for thrombopoietin mimetics for the prevention of bleeding for people with thrombocytopenia due to chronic bone marrow failure. There was no RCT evidence available for artificial platelet substitutes, platelet-poor plasma, fibrinogen concentrate, recombinant activated factor VII, desmopressin, recombinant factor XIII, or recombinant interleukin.

One Cochrane review (118) (10 completed RCTs; n=554 participants) of alternatives, and adjuncts, to prophylactic platelet transfusion for people with haematological malignancies undergoing intensive chemotherapy or stem cell transplantation found unclear evidence for thrombopoietin mimetics or platelet-poor plasma.

Intelligence gathering

A topic expert thought that the paediatric population may be better served with a specific section within this guideline, but acknowledged that there is little evidence to support practice. The expert also stated that from his experience the following thresholds were clinical practice in the paediatric population: a threshold of 10 if no bleeding, 50 if bleeding and /or 'minor' surgery, and 100 if 'major' surgery in high risk areas.

Another topic expert felt that guidance on the use of platelets in haemorrhage was weak. The expert went on to say that the early use of fresh frozen plasma and platelets has been accepted by the clinical community but there is inconsistency in the response from transfusion laboratories in hospitals, which has been mentioned in previous national audits/studies.

Impact statements

Thresholds and targets

Seven Cochrane reviews and 1 RCT found evidence for platelet transfusions lacking in certain populations and clinical scenarios. Where evidence was available, the evidence showed a mixed picture with plasma transfusions potentially reducing bleeding but having no effect on mortality or for intracranial haemorrhage a possible increase in mortality. One Cochrane review indicated that it was reasonable to continue with the current practice of using the standard trigger level (10 x 10^9/L) for prophylactic platelet transfusions without other risk factors for bleeding. This is in line with the current guideline recommendation 1.3.3 and in

concordance with the evidence base which underpins this recommendation. As such, no update to this section of the guideline will be made.

A topic expert believed that the paediatric population may be better served with a specific section within this guideline, but acknowledged that there is little evidence to support practice. Another expert felt that the guidance on use of platelets in haemorrhage was weak but there was no new evidence that would address these issues and as such the guideline will not be updated.

New evidence is unlikely to change guideline recommendations.

Doses

One Cochrane review and 1 large RCT found that high dose prophylactic platelet transfusions increased transfusion related adverse events, and low dose transfusions may be associated with an increase in number of transfusions in people with haematological disorders after myelosuppressive chemotherapy. Currently the guideline suggests using a single dose of platelets unless severe thrombocytopenia or bleeding in a critical site. At the time of guideline development, the guideline committee noted that in England and North Wales one dose was roughly equivalent to a low to medium dose in the literature as low dose varied across studies. The lack of evidence for medium and higher doses was noted, as well as the potential harm and increased costs with higher doses. This new evidence broadly supports the guideline recommendations of not routinely using more than one dose of platelets. As such this section of the guideline will not be updated.

A topic expert believed that the paediatric population may be better served with a specific section within this guideline, but acknowledged there is little evidence to support practice. Another expert felt that the guidance on use of platelets in haemorrhage was weak but there was no new evidence that would address these issues and as such the guideline will not be updated.

New evidence is unlikely to change guideline recommendations.

Alternatives to platelet transfusion

Evidence from 2 Cochrane reviews on alternatives to prophylactic platelet transfusions for people with haematological malignancies undergoing intensive chemotherapy or stem cell transplantation and people with thrombocytopenia due to chronic bone marrow failure found insufficient evidence. The review authors identified a research gap for a number of agents, including artificial platelets, fibrinogen concentrate and desmopressin. Until the evidence base matures on alternatives to platelet transfusions it is not warranted to update this section of the guideline.

New evidence is unlikely to change guideline recommendations.

1.4 Fresh frozen plasma

Recommendations in this section of the guideline

Thresholds and targets

1.4.1 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).

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

- are not bleeding (unless they are having invasive procedures or surgery with a risk of clinically significant bleeding)
- need reversal of a vitamin K antagonist.

1.4.3 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.

Doses

1.4.4 Reassess the patient's clinical condition and repeat the coagulation tests after fresh frozen plasma transfusion to ensure that they are getting an adequate dose, and give further doses if needed.

Surveillance proposal

This section of the guideline should not be updated.

Fresh frozen plasma

2019 surveillance summary

One Cochrane review (119) (15 completed RCTs; n=755 participants) of fresh frozen plasma for cardiovascular surgery (14 trials prophylactic use) found no significant difference in mortality, risk of returning to theatre for re-operation, or blood loss in the first 24 hours, compared with no plasma. However, patients receiving fresh frozen plasma were significantly more likely to receive red blood cell transfusions compared with no plasma.

One Cochrane review (112) (0 completed or ongoing trials) of prophylactic plasma transfusions prior to lumbar punctures and epidural catheters for patients with abnormal coagulation found no evidence. The review authors noted that as the risk of bleeding after

epidural or lumbar puncture is low a very large sample size of 50,000 patients would be needed to address the research question.

One Cochrane review (120) (1 completed trial; n=81 participants) of plasma transfusions before central line insertion for people with abnormal coagulation found no clear effect on major or minor procedure-related bleeding within 24 hours. The trial authors noted that ongoing research will not answer the research question as a sample size of over 4,000 patients will be required.

Intelligence gathering

A topic expert thought that the paediatric population may be better served with a specific section within this guideline, but acknowledged that there is little evidence to support practice. The expert also stated that from his experience the following thresholds were clinical practice in the paediatric population: only give if coagulopathy (international normalised ratio>1.5 x normal) and bleeding, and usually aliquot 15-20mls/kg over 1 hour

Another topic expert felt that guidance on the use of fresh frozen plasma in haemorrhage was weak. The expert went on to say that the early use of fresh frozen plasma and platelets has been accepted by the clinical community but there is inconsistency in the response from transfusion laboratories in hospitals, which has been mentioned in previous national audits/studies.

Impact statement

Evidence from 3 Cochrane reviews was identified for plasma use during cardiovascular surgery, lumbar punctures and central line insertions. The evidence base for lumbar punctures and central line insertions was limited and no conclusions could be drawn. The evidence base in cardiovascular surgery indicated that prophylactic transfusions may not impact on mortality or blood loss, but may be associated with a significantly increased need for red blood cell transfusions, however the authors deemed that further research is needed.

At the time of guideline development, the evidence base for fresh frozen plasma was weak and the guideline committee used their knowledge and experience alongside the evidence to make recommendations. This new evidence identified through the surveillance review does not provide a clearer picture of the benefits of fresh frozen plasma in clinical practice, and as such no update to the guideline recommendations will be made.

A topic expert believed that the paediatric population may be better served with a specific section within this guideline, but acknowledged that there is little evidence to support practice. There was no new evidence that would address this issue and as such the guideline will not be updated.

New evidence is unlikely to change guideline recommendations.

1.5 Cryoprecipitate

Recommendations in this section of the guideline

Thresholds and targets

1.5.1 Consider cryoprecipitate transfusions for patients without major haemorrhage who have:

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

1.5.2 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.

1.5.3 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.

Doses

1.5.4 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).

1.5.5 Reassess the patient's clinical condition, repeat the fibrinogen level measurement and give further doses if needed.

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

One Systematic review (121) (1 RCT and 3 observational studies; n=284) comparing fibrinogen concentrate with cryoprecipitate in bleeding patients found no significant differences in fibrinogen level, bleeding, thromboembolic complications, or red blood cell transfusions. The review authors suggested that further research is needed.

Intelligence gathering

A topic expert thought that the paediatric population may be better served with a specific section within this guideline, but acknowledged that there is little evidence to support practice. However, the expert did indicate that for the paediatric population the current recommendations on cryoprecipitate are appropriate.

Another topic expert felt that the fibrinogen level below 1.5 g/litre, especially by the Clauss method, is inferior to point of care testing, but did not provide any evidence to support this view. Furthermore, point of care testing / near patient testing is out of scope.

Impact statement

Evidence from 1 systematic review found no benefit of cryoprecipitate in bleeding patients, however the authors deemed that further research is needed. At the time of guideline development, the evidence base for cryoprecipitate was weak and the guideline committee used their knowledge and experience alongside the evidence to make recommendations on cryoprecipitate, including when to consider cryoprecipitate use and when it should not be used. This new evidence does not provide a clearer picture of the benefits of cryoprecipitate in clinical practice, and as such no update to the guideline recommendations on cryoprecipitate appears warranted.

A topic expert believed that the paediatric population may be better served with a specific section within this guideline, but acknowledged that the current recommendations on cryoprecipitate may be appropriate as written. As such, the guideline will not be updated.

New evidence is unlikely to change guideline recommendations.

1.6 Prothrombin complex concentrate

Recommendations in this section of the guideline

Thresholds and targets

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

- severe bleeding **or**
- head injury with suspected intracerebral haemorrhage.

1.6.2 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.

1.6.3 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.

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

Surveillance proposal

This section of the guideline should not be updated.

2019 surveillance summary

One Cochrane review (122) (4 RCTs; n=453 participants) of prothrombin complex concentrate for reversal of vitamin K antagonist treatment in bleeding and non-bleeding scoliosis patients found no significant effect on overall mortality, complications or volume of fresh frozen plasma transfused. The review authors deemed that the included studies showed the potential for prothrombin complex to reverse vitamin K-induced coagulopathy without the need for transfusion of fresh frozen plasma, but that further research is needed.

Intelligence gathering

There was no intelligence relevant to this section of the guideline.

Impact statement

Evidence from 1 Cochrane review found no benefit of prothrombin complex concentrate for reversal of vitamin K antagonists in scoliosis patients, although the review authors deemed that further research was warranted. At the time of guideline development, the evidence base for prothrombin complex concentrate was weak and the guideline committee used their knowledge and experience alongside the evidence to make recommendations on the role of prothrombin complex concentrate, including offering immediate prothrombin complex concentrate transfusions for the emergency reversal of warfarin anticoagulation in patients

with either severe bleeding or head injury with suspected intracerebral haemorrhage. This new evidence does not provide a clearer picture of the benefits of prothrombin complex concentrate in clinical practice, and as such no update to the guideline recommendations will be made.

New evidence is unlikely to change guideline recommendations.

1.7 Patient safety

Recommendations in this section of the guideline

Monitoring for acute blood transfusion reactions

1.7.1 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.

1.7.2 Observe patients who are having or have had a blood transfusion in a suitable environment with staff who are able to monitor and manage acute reactions.

Electronic patient identification systems

1.7.3 Consider using a system that electronically identifies patients to improve the safety and efficiency of the blood transfusion process.

Surveillance proposal

No new information was identified at this surveillance review.

This section of the guideline should not be updated.

1.8 Patient information

Recommendations in this section of the guideline

1.8.1 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
- that they are no longer eligible to donate blood
- that they are encouraged to ask questions.

1.8.2 Document discussions in the patient's notes.

1.8.3 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
- that they are no longer eligible to donate blood.

1.8.4 For guidance on communication and patient-centred care for adults, see the NICE guideline on patient experience in adult NHS services.

Surveillance proposal

No new information was identified at this surveillance review.

This section of the guideline should not be updated.

1.9 Blood transfusions for patients with acute upper gastrointestinal bleeding

Recommendations in this section of the guideline

1.9.1 For guidance on blood transfusions for people with acute upper gastrointestinal bleeding, see section 1.2 in the NICE guideline on acute upper gastrointestinal bleeding.

Surveillance proposal

No new information was identified at this surveillance review.

This section of the guideline should not be updated.

Areas not currently covered in the guideline

In surveillance, evidence was identified for areas not covered by the guideline. This new evidence has been considered for possible addition as a new section of the guideline.

Combination iron, erythropoietin, B12 and folic acid therapy

Surveillance proposal

This new area should not be added.

2019 surveillance summary

One RCT (123) (n=1,006 patients) of combination therapy of a slow infusion of ferric carboxymaltose, subcutaneous erythropoietin alpha, subcutaneous vitamin B12, and oral folic acid or placebo on the day before surgery in patients undergoing elective cardiac surgery was identified. The trial found that compared with placebo, the combination therapy significantly reduced red blood cells transfused and total allogeneic blood product transfusions at 7 days. Rates of serious adverse events were similar.

Intelligence gathering

There was no intelligence relevant to this section of the guideline.

Impact statement

Evidence from 1 RCT indicates that a combination of ferric carboxymaltose, erythropoietin alpha, vitamin B12, and folic acid may be superior to placebo in patients undergoing elective cardiac surgery. This combination intervention is not specifically mentioned in the guideline, and whilst this intervention shows benefits for cardiac surgery patients, the comparator was placebo rather than interventions currently recommended in the guideline. As such the evidence is not deemed sufficient to warrant an update to the guideline.

New evidence is unlikely to impact on the guideline.

Desmopressin

Surveillance proposal

This new area should not be added.

2019 surveillance summary

One Cochrane review (124) (65 completed trials; n=3,874) of desmopressin versus placebo or an active comparator for minimising perioperative blood loss and red blood cell transfusion in people who do not have inherited bleeding disorder was found. The review found no clear evidence of an effect in non-cardiac surgery or children, but the evidence was deemed low quality for the majority of comparisons by review authors. There was a small significant decrease in total volume of red cells transfused in adult cardiac surgery patients and people with platelet dysfunction with desmopressin compared with placebo. Desmopressin was significantly less effective in reducing the volume of blood transfused and total blood loss compared with TXA, and significantly increased the number of people who received a blood transfusion compared with aprotinin, although the authors felt these results were uncertain due to there being few trials available. The authors deemed that differences in outcomes were unlikely to be clinically significant and suggested that further research is warranted.

One RCT (125) of intravenous desmopressin versus saline control for patients undergoing cardiopulmonary surgery (n=102 patients) found significantly reduced post-operative blood loss in the first 6 hours, and reduced incidence of fresh frozen plasma post-operatively with desmopressin. There was no significant difference in red blood cell transfusions and blood loss after 24 hours between groups.

One RCT (126) of intravenous desmopressin versus saline placebo in patients undergoing cardiac surgery who had been pre-treated with TXA (n=135 patients) was stopped early due to futility as there was no significant difference in red blood cell transfusions, blood loss, intensive care stay, or mortality between groups.

Intelligence gathering

Expert feedback indicates that there is a lack of guidance on desmopressin for thrombocytopaenia.

Impact statement

Evidence from 1 Cochrane review and 2 RCTs indicates that desmopressin may have some benefits in cardiac surgery patients compared with placebo, but not when compared with TXA. As such the evidence is not deemed sufficient to warrant an update to the guideline. Expert feedback indicates that there is a lack of guidance on desmopressin in thrombocytopenia; however currently the evidence base does not provide a clear picture of its benefits and further research appears warranted before considering for inclusion in the guideline.

New evidence is unlikely to impact on the guideline.

Red blood cell transfusion guided by near-infrared spectroscopy

Surveillance proposal

This new area should not be added.

2019 surveillance summary

One RCT (127) of a transcranial oxygen saturation threshold measured by near-infrared spectroscopy, compared with haemoglobin threshold measurement alone for guiding the need for red blood cell transfusions in neurocritically ill patients was identified (n=102 patients). The trial found significantly fewer red blood cell units with near-infrared spectroscopy. There were no significant differences in the percentage of transfused patients, neurocritical care unit stay, unfavourable Glasgow Outcome Scale scores on hospital discharge, in-hospital mortality, or 1 year mortality. The authors deemed that further research is warranted.

Intelligence gathering

There was no intelligence relevant to this section of the guideline.

Impact statement

One RCT indicated that transcranial oxygen saturation threshold measured by near-infrared spectroscopy may not provide a clear advantage in neurocritically ill patients compared with haemoglobin threshold. This intervention is not included within the guideline and it does not appear warranted to update the guideline based on these results.

New evidence is unlikely to impact on the guideline.

Choice of antifibrinolytic agents in children undergoing scoliosis surgery

Surveillance proposal

This new area should not be added.

2019 surveillance summary

One Cochrane review (128) (9 RCTs; n=656 participants) of antifibrinolytic agents for reducing blood loss in scoliosis surgery in children was identified. The review found that compared with placebo, antifibrinolytics significantly decreased perioperative blood loss, number of participants needing autologous or allogenic transfusions, and volume of blood transfused. The safety of the intervention was unclear. The authors noted that TXA (4 trials) may be preferred due to its widespread availability but there was insufficient data to determine differences between drugs.

Intelligence gathering

There was no intelligence relevant to this section of the guideline.

Impact statement

One Cochrane review found that antifibrinolytics significantly decreased blood loss, transfusions, and volume of blood transfused in scoliosis patients. The authors noted that it was not possible to determine a difference between antifibrinolytic drugs although suggested that TXA may be a preferred option due to its availability. TXA is already included in the guideline (see **Error! Reference source not found.** above) and this new evidence supports its use and is in line with current recommendations.

New evidence is unlikely to impact on the guideline.

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?

Summary of findings

No evidence was found for post-operative cell salvage in cardiac patients.

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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?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

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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?

Summary of findings

An NIHR signal highlighted a systematic review (91) in patients with cardiovascular disease not undergoing cardiac surgery that found that a restrictive strategy did not affect 30 day mortality or may significantly increase the risk of acute coronary syndromes. However, there was uncertainty as to the clinical utility and cost effectiveness of using a liberal threshold for all chronic cardiovascular patients (see section 1.2 Red blood cells above for a summary of evidence). As such it does not appear warranted to update the guideline recommendations until further research confirms the benefits of a liberal threshold in chronic cardiovascular patients.

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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?

Summary of findings

No new evidence relevant to the research recommendation was found and no ongoing studies were identified.

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