Patient Blood Management Guidelines: Module 2

Perioperative

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Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the circumstances, clinician's judgement and patient's preferences in each individual case. It is designed to provide information to assist decision making. Recommendations contained herein are based on the best available evidence published up to the dates shown in Appendix D. The relevance and appropriateness of the information and recommendations in this document depend on the individual circumstances. Moreover, the recommendations and guidelines are subject to change over time.

Each of the parties involved in developing this document expressly disclaims and accepts no responsibility for any undesirable consequences arising from relying on the information or recommendations contained herein.

Publication approval

Australian Government
National Health and Medical Research Council

These guidelines were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 15 November 2011, under Section 14A of the *National Health and Medical Research Council Act 1992*. In approving these guidelines the NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of five years.

NHMRC is satisfied that they are based on the systematic identification and synthesis of the best available scientific evidence and make clear recommendations for health professionals practising in an Australian health care setting. The NHMRC expects that all guidelines will be reviewed no less than once every five years.

This publication reflects the views of the authors and not necessarily the views of the Australian Government.

Patient Blood Management Guidelines: Module 2 - Perioperative

Development of this module was achieved through clinical input and expertise of representatives from the Colleges and Societies listed below and an independent consumer advocate (see Appendix A).

Australasian College for Emergency Medicine

Australian and New Zealand College of Anaesthetists

Australian and New Zealand Intensive Care Society

Australian and New Zealand Society of Blood Transfusion

Australian Orthopaedic Association

Australian Red Cross Blood Service

College of Intensive Care Medicine of Australia and New Zealand

Haematology Society of Australia and New Zealand

Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Royal Australasian College of Physicians

Royal Australasian College of Surgeons

Royal College of Nursing Australia

Royal College of Pathologists of Australasia

Thalassaemia Australia

The National Blood Authority gratefully acknowledges these contributions. College and Society endorsement of this Module can be found at http://www.nba.gov.au

National Blood Authority Australia

Funding, Secretariat and Project Management was provided by the National Blood Authority Australia. The systematic review methods, writing of the document or development of the final recommendations and practice points have not been influenced by the views or interests of the funding body.

Abbreviations and acronyms

AHMAC	Australian Health Ministers' Advisory Council
AHMC	Australian Health Ministers' Conference
ANH	acute normovolemic haemodilution
ANZSBT	Australian & New Zealand Society of Blood Transfusion
APTT	activated partial thromboplastin time
ARCBS	Australian Red Cross Blood Service
ASBT	Australasian Society of Blood Transfusion
CABG	coronary artery bypass surgery
CPB	cardiopulmonary bypass surgery
CRG	Clinical/Consumer Reference Group
CTEPC	Clinical, Technical and Ethical Principal Committee
ESA	erythropoiesis-stimulating agent
EWG	Expert Working Group
FFP	fresh frozen plasma
GAR	Guidelines Assessment Register
ICU	intensive care unit
INR	international normalised ratio
JBC	Jurisdictional Blood Committee
MAP	mean arterial blood pressure
MI	myocardial infarction
NBA	National Blood Authority
NHMRC	National Health and Medical Research Council
NSAID	nonsteroidal anti-inflammatory drug
OPCAB	off-pump coronary artery bypass
PAD	preoperative autologous donation
PICO	population, intervention, comparator and outcome
PP	practice point
PPO	population, predictor and outcome
PT	prothrombin time
R	recommendation
RBC	red blood cell
RCT	randomised controlled trial
rFVIIa	recombinant activated factor VII
ROTEM	rotational thromboelastometry
TEG	thromboelastography
TGA	Therapeutic Goods Administration
THJR	total hip joint replacement
TIVA	total intravenous anaesthesia

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Executive summary

This document, *Patient Blood Management Guidelines: Module 2 – Perioperative*, is the second in a series of six modules that focus on evidence-based patient blood management. The other five modules are critical bleeding/massive transfusion, medical, critical care, obstetrics and paediatrics (including neonates). Together, the six modules supersede the 2001 National Health and Medical Research Council/Australasian Society of Blood Transfusion (NHMRC/ASBT) *Clinical Practice Guidelines on the Use of Blood Components*.[1]

This document was developed by a Clinical/Consumer Reference Group (CRG) representing specialist colleges, organisations and societies, with the active participation of the clinical community.

This Executive summary includes:

- a summary of the *recommendations* that were developed by the CRG, based on evidence from a systematic review
- a summary of the *practice points* that were developed by the CRG through consensus decision making
- a preoperative anaemia management algorithm template.

Details of the systematic reviews used in the development of this module, for which the search cut-off dates were in mid-2009, are given in the technical reports that accompany this document.[2–5]

Materials relevant to consumers and to clinicians undertaking surgery will be developed to accompany this module; these materials will be available online and in print.

Summary of recommendations and practice points

The CRG developed recommendations (given below) where sufficient evidence was available from the systematic review of the literature. The recommendations have been carefully worded to reflect the strength of the body of evidence. Each recommendation has been given a grade, using the following definitions, which were set by the NHMRC:

GRADE A	Body of evidence can be trusted to guide practice
GRADE B	Body of evidence can be trusted to guide practice in most situations
GRADE C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
GRADE D	Body of evidence is weak and recommendations must be applied with caution.

The CRG developed practice points where the systematic review found insufficient high-quality data to produce evidence-based recommendations, but the CRG felt that clinicians require guidance to ensure good clinical practice. These points are based on consensus among the members of the committee.

A full list of recommendations and practice points, in numerical order, is given in Appendix G. This section summarises the recommendations and practice points in a sequence that reflects clinical practice. The table below lists the elements of patient blood management; for each element, it shows the relevant recommendations, practice points and section of the document. It is followed by a series of tables giving the full recommendations and practice points for each component.

ELEMENT OF PATIENT BLOOD MANAGEMENT	RECOMMENDATION	PRACTICE POINT	RELEVANT SECTION OF DOCUMENT
Patient blood management program			
Establishment	R1		3.1
Implementation			3.3
Procedural guidelines		PP12–13	3.6.5, 3.6.6
Anaemia and haemostasis management			
Preoperative anaemia assessment	R2–3	PP1, PP4–5	3.3, 3.4
Iron and ESA therapy	R4–6	PP6–7	3.4
Haemostasis management	R7–10	PP8–10	3.5
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Preoperative			
Preoperative autologous donation	R11		3.6.1
Intraoperative			
Surgical haemostasis			3.6
Prevention of hypothermia	R12		3.6.2

ELEMENT OF PATIENT BLOOD MANAGEMENT	RECOMMENDATION	PRACTICE POINT	RELEVANT SECTION OF DOCUMENT
Appropriate patient positioning		PP11	3.6.3
Deliberate induced hypotension	R13		3.6.4
Acute normovolemic haemodilution	R14	PP12	3.6.5
Intraoperative cell salvage	R15	PP13	3.6.6
Haemostasis analysis	R16		3.6.8
Medications	R17–19	PP14–16	3.6.9
Postoperative			
Postoperative cell salvage	R20		3.6.10
Appropriate transfusion practices			
Triggers for component transfusion		PP2–3, 17–18	3.3, 3.7
Fresh frozen plasma	R21		3.8
Platelets		PP19	3.8
Recombinant activated factor VII	R22	PP20	3.9

Patient blood management program

RECOMMENDATION – establishment

R1

GRADE C

Health-care services should establish a multidisciplinary, multimodal perioperative patient blood management program (Grade C). This should include preoperative optimisation of red cell mass and coagulation status; minimisation of perioperative blood loss, including meticulous attention to surgical haemostasis; and tolerance of postoperative anaemia.

PRACTICE POINT – implementation

PP1

To implement the above recommendations, a multimodal, multidisciplinary patient blood management program is required. All surgical patients should be evaluated as early as possible to coordinate scheduling of surgery with optimisation of the patient's haemoglobin and iron stores.

PRACTICE POINTS – procedural guidelines

PP12

ANH requires a local procedural guideline that addresses patient selection, vascular access, volume of blood withdrawn, choice of replacement fluid, blood storage and handling, and timing of reinfusion.

PP13

Intraoperative cell salvage requires a local procedural guideline that should include patient selection, use of equipment and reinfusion. All staff operating cell salvage devices should receive appropriate training, to ensure knowledge of the technique and proficiency in using it.

ANH, acute normovolemic haemodilution

Anaemia and haemostasis management

RECOMMENDATIONS – preoperative anaemia assessment	
R2 GRADE C	In patients undergoing cardiac surgery, preoperative anaemia should be identified, evaluated and managed to minimise RBC transfusion, which may be associated with an increased risk of morbidity, mortality, ICU length of stay and hospital length of stay (Grade C).
R3 GRADE C	In patients undergoing noncardiac surgery, preoperative anaemia should be identified, evaluated and managed to minimise RBC transfusion, which may be associated with an increased risk of morbidity, mortality, ICU length of stay and hospital length of stay (Grade C).

PRACTICE POINTS – preoperative anaemia assessment	
PP1	To implement the above recommendations, a multimodal, multidisciplinary patient blood management program is required. All surgical patients should be evaluated as early as possible to coordinate scheduling of surgery with optimisation of the patient's haemoglobin and iron stores.
PP4	All surgical patients should be evaluated as early as possible to manage and optimise haemoglobin and iron stores
PP5	Elective surgery should be scheduled to allow optimisation of patients' haemoglobin and iron stores.

RECOMMENDATIONS – iron and erythropoiesis-stimulating agents	
R4 GRADE B	In surgical patients with, or at risk of, iron-deficiency anaemia, preoperative oral iron therapy is recommended (Grade B). Refer to the preoperative haemoglobin assessment and optimisation template [Appendix F] for further information on the optimal dosing strategy.
R5 GRADE A	In patients with preoperative anaemia, where an ESA is indicated, it must be combined with iron therapy (Grade A).
R6 GRADE B	In patients with postoperative anaemia, early oral iron therapy is not clinically effective; its routine use in this setting is not recommended (Grade B).

PRACTICE POINTS – iron and erythropoiesis-stimulating agents

PP6	Surgical patients with suboptimal iron stores (as defined by a ferritin level <100 µg/L) in whom substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, should be treated with preoperative iron therapy. Refer to the preoperative haemoglobin assessment and optimisation template [Appendix F] for further information on the evaluation and management of preoperative patients.
PP7	In patients with preoperative iron-deficiency anaemia or depleted iron stores, treatment should be with iron alone. In patients with anaemia of chronic disease (also known as anaemia of inflammation), ESAs may be indicated. Refer to the preoperative haemoglobin assessment and optimisation template [Appendix F] for further information on the evaluation and management of preoperative patients.

ESA, erythropoiesis-stimulating agent

RECOMMENDATIONS – haemostasis management

R7 **GRADE C**	In patients undergoing CABG either with or without CPB (OPCAB), clopidogrel therapy should be stopped, where possible, at least 5 days before surgery (Grade C).
R8 **GRADE C**	In patients undergoing noncardiac surgery, it is reasonable to continue low dose aspirin therapy. This may require specific evaluation in neurosurgery and intraocular surgery (Grade C).
R9 **GRADE C**	In patients undergoing elective orthopaedic surgery, NSAID therapy should be ceased preoperatively to reduce blood loss and transfusion (Grade C). The timing of the cessation should reflect the agent's pharmacology.
R10 **GRADE B**	In patients undergoing minor dental procedures, arthrocentesis, cataract surgery, upper gastrointestinal endoscopy without biopsy or colonoscopy without biopsy, warfarin may be continued (Grade B).

PRACTICE POINTS – haemostasis management

PP8	In patients undergoing cardiac surgery, aspirin may be continued until the time of surgery.
PP9	In patients receiving clopidogrel who are scheduled for elective noncardiac surgery or other invasive procedures, a multidisciplinary approach should be used to decide whether to cease therapy or defer surgery, balancing the risk of bleeding and thrombotic events. Specific evaluation is required for patients who had a recent stroke, or received a drug-eluting stent within the last 12 months or a bare metal stent within the last 6 weeks. If a decision is made to cease therapy preoperatively, this should occur 7–10 days before surgery.

PRACTICE POINTS – haemostasis management	
PP10	In patients receiving warfarin who are scheduled for elective noncardiac surgery or other invasive procedures (excluding minor procedures—see Recommendation 10); specific management according to current guidelines is required (e.g. guidelines from the American College of Chest Physicians[6] and the Australasian Society of Thrombosis and Haemostasis).[7]

CABG, coronary artery bypass surgery; CPB, cardiopulmonary bypass; NSAID, nonsteroidal anti-inflammatory drug; OPCAB, off-pump coronary artery bypass

Blood conservation strategies

Preoperative

RECOMMENDATION – preoperative autologous donation	
R11 **GRADE C**	The *routine* use of PAD is not recommended because, although it reduces the risk of allogeneic RBC transfusion, it increases the risk of receiving any RBC transfusion (allogeneic and autologous) (Grade C).

PAD, preoperative autologous donation; RBC, red blood cell

Intraoperative

RECOMMENDATION – prevention of hypothermia	
R12 **GRADE A**	In patients undergoing surgery, measures to prevent hypothermia should be used (Grade A).

PRACTICE POINT – appropriate patient positioning	
PP11	Excessive venous pressure at the site of surgery should be avoided by appropriate patient positioning, both during and after the procedure.

RECOMMENDATION – deliberate induced hypotension	
R13 **GRADE C**	In patients undergoing radical prostatectomy or major joint replacement, if substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, deliberate induced hypotension (MAP 50–60 mmHg) should be considered, balancing the risk of blood loss and the preservation of vital organ perfusion (Grade C).

MAP, mean arterial blood pressure

RECOMMENDATION – acute normovolemic haemodilution

R14

GRADE C

In adult patients undergoing surgery in which substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, the use of ANH should be considered (Grade C).

PRACTICE POINT – acute normovolemic haemodilution

PP12

ANH requires a local procedural guideline that addresses patient selection, vascular access, volume of blood withdrawn, choice of replacement fluid, blood storage and handling, and timing of reinfusion.

ANH, acute normovolemic haemodilution

RECOMMENDATION – intraoperative cell salvage

R15

GRADE C

In adult patients undergoing surgery in which substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, intraoperative cell salvage is recommended (Grade C).

PRACTICE POINT – intraoperative cell salvage

PP13

Intraoperative cell salvage requires a local procedural guideline that should include patient selection, use of equipment and reinfusion. All staff operating cell salvage devices should receive appropriate training, to ensure knowledge of the technique and proficiency in using it.

RECOMMENDATION – haemostasis analysis

R16

GRADE C

In adult patients undergoing cardiac surgery, the use of TEG should be considered (Grade C).

TEG, thromboelastography

PRACTICE POINT – medications (aprotinin)

PP14

There is evidence for the beneficial effect of intravenous aprotinin on incidence and volume of transfusion, blood loss, and the risk of reoperation for bleeding. However, the drug has been withdrawn due to concerns that it is less safe than alternative therapies.[a]

[a] Websites of the Therapeutic Goods Administration (www.tga.gov.au), MedSafe (www.medsafe.govt.nz) and United States Food and Drug Administration (www.fda.gov)

RECOMMENDATIONS – medications (tranexamic acid)	
R17 GRADE A	In adult patients undergoing cardiac surgery, the use of intravenous tranexamic acid is recommended (Grade A).
R18 GRADE B	In adult patients undergoing noncardiac surgery, if substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, the use of intravenous tranexamic acid is recommended (Grade B).

RECOMMENDATION – medications (ε-aminocaproic acid)	
R19 GRADE C	In adult patients undergoing cardiac surgery, the use of intravenous ε-aminocaproic acid is recommended (Grade C).

PRACTICE POINT – medications (ε-aminocaproic acid)	
PP15	There is evidence for the beneficial effect of intravenous ε-aminocaproic acid on reduction of perioperative blood loss and volume of transfusion (Grade C). However, the drug is not marketed in Australia and New Zealand.

PRACTICE POINT – medications (desmopressin)	
PP16	In adult patients undergoing surgery in which substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, the *routine* use of desmopressin is not supported, due to uncertainty about the risk of stroke and mortality.

Postoperative

RECOMMENDATION – postoperative cell salvage	
R20 GRADE C	In adult patients undergoing cardiac surgery or total knee arthroplasty, in whom significant postoperative blood loss is anticipated, postoperative cell salvage should be considered (Grade C).

Appropriate transfusion practices

PRACTICE POINTS – triggers for blood component transfusion	
PP2	RBC transfusion should not be dictated by a haemoglobin 'trigger' alone, but should be based on assessment of the patient's clinical status. In the absence of acute myocardial or cerebrovascular ischaemia, postoperative transfusion may be inappropriate for patients with a haemoglobin level of >80 g/L.
PP3	Patients should not receive a transfusion when the haemoglobin level is ≥100 g/L. In postoperative patients with acute myocardial or cerebrovascular ischaemia and a haemoglobin level of 70–100 g/L, transfusion of a single unit of RBC, followed by reassessment of clinical efficacy, is appropriate.
PP17	In general, patients with a platelet count ≥50 $\times 10^9$/L *or* an INR ≤2 can undergo invasive procedures without any serious bleeding; however, lower platelet counts and higher INRs may be tolerated.
PP18	Specialist guidelines or haematology advice should be sought for at-risk patients undergoing intracranial, intraocular and neuraxial procedures, and for patients with severe thrombocytopenia or coagulopathy.

INR, international normalised ratio; RBC, red blood cell

RECOMMENDATION – fresh frozen plasma	
R21 **GRADE B**	The prophylactic use of FFP in cardiac surgery is not recommended (Grade B).

FFP, fresh frozen plasma

PRACTICE POINT– platelets	
PP19	The prophylactic use of platelets after cardiac surgery is not supported.

RECOMMENDATION – recombinant activated factor VII	
R22 **GRADE C**	The prophylactic or routine therapeutic use of rFVIIa is not recommended because concerns remain about its safety profile, particularly in relation to thrombotic adverse events (Grade C).

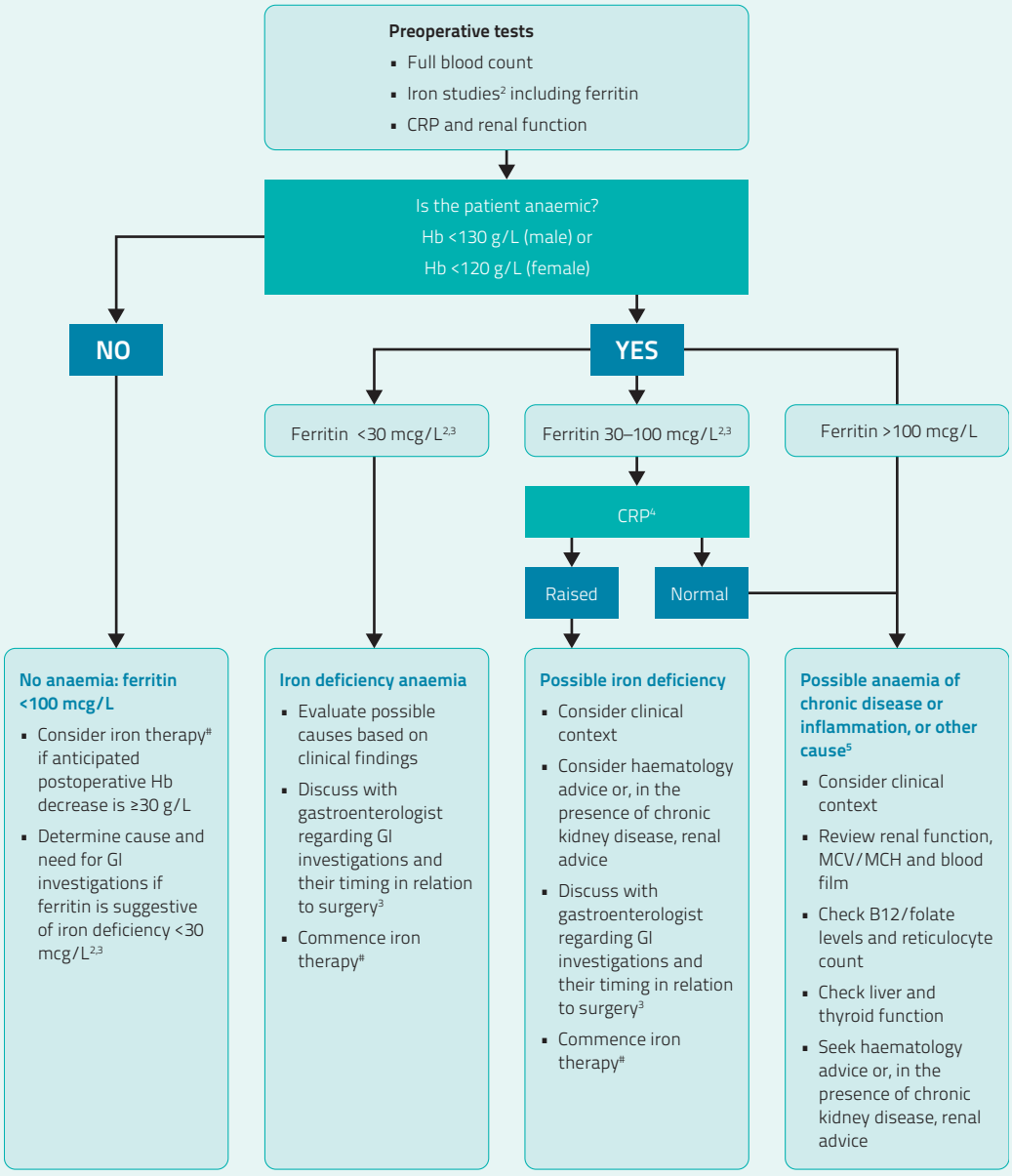
PRACTICE POINT – recombinant activated factor VII	
PP20	The administration of rFVIIa may be considered in the perioperative patient with life-threatening haemorrhage after conventional measures, including surgical haemostasis, use of antifibrinolytics and appropriate blood component therapy have failed.

rFVIIa, recombinant activated factor VII

Preoperative haemoglobin assessment and optimisation template

This template[1] is for patients undergoing procedures in which substantial blood loss is anticipated such as cardiac surgery, major orthopaedic, vascular and general surgery. Specific details, including reference ranges and therapies, may need adaptation for local needs, expertise or patient groups.

An editable electronic copy of this template is available on the National Blood Authority's website (www.nba.gov.au).



[#] Iron therapy

Oral iron in divided daily doses. Evaluate response after 1 month. Provide patient information material.

IV iron if oral iron contraindicated, is not tolerated or effective; and consider if rapid iron repletion is clinically important (e.g. <2 months to non deferrable surgery).

NOTE: 1 mcg/L of ferritin is equivalent to 8–10 mg of storage iron. It will take approximately 165 mg of storage iron to reconstitute 10 g/L of Hb in a 70 kg adult. If preoperative ferritin is <100 mcg/L, blood loss resulting in a postoperative Hb drop of ≥30 g/L would deplete iron stores.

In patients not receiving preoperative iron therapy, if unanticipated blood loss is encountered, 150 mg IV iron per 10g/L Hb drop may be given to compensate for bleeding related iron loss (1 ml blood contains ~0.5 mg elemental iron)

Abbreviations

CRP = C-reactive protein

GI = gastrointestinal

Hb = haemoglobin

IV = intravenous

MCV = mean cell/corpuscular volume (fL)

MCH = mean cell/corpuscular haemoglobin (pg)

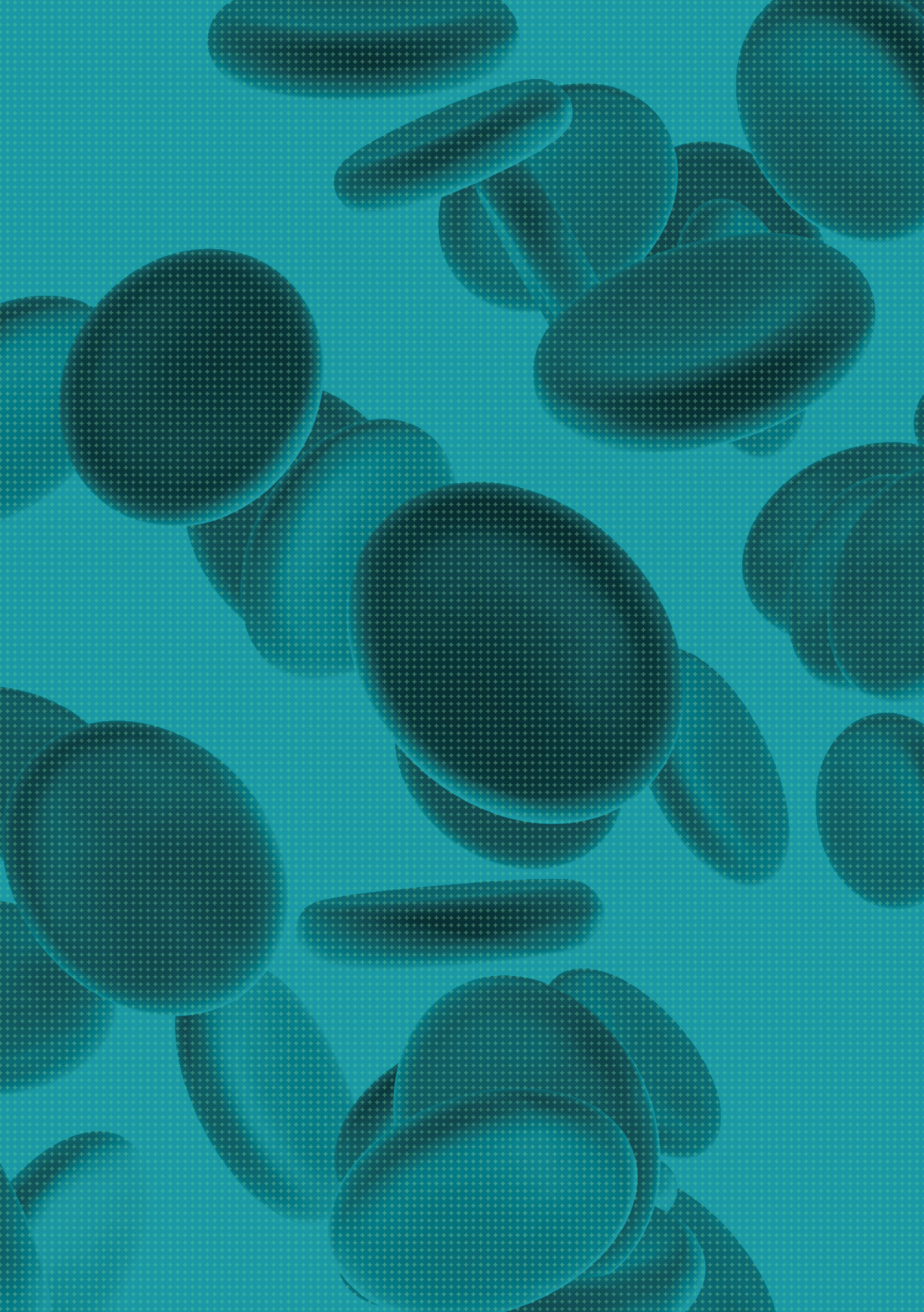
Footnotes

1. Anaemia may be multifactorial, especially in the elderly or in those with chronic disease, renal impairment, nutritional deficiencies or malabsorption.
2. In an anaemic adult, a ferritin level <15 mcg/L is diagnostic of iron deficiency, and levels between 15–30 mcg/L are highly suggestive. However, ferritin is elevated in inflammation, infection, liver disease and malignancy. This can result in misleadingly elevated ferritin levels in iron-deficient patients with coexisting systemic illness. In the elderly or in patients with inflammation, iron deficiency may still be present with ferritin values up to 60–100 mcg/L.
3. Patients without a clear physiological explanation for iron deficiency (especially men and postmenopausal women) should be evaluated by gastroscopy/colonoscopy to exclude a source of GI bleeding, particularly a malignant lesion. Determine possible causes based on history and examination; initiate iron therapy; screen for coeliac disease; discuss timing of scopes with a gastroenterologist.
4. CRP may be normal in the presence of chronic disease and inflammation.
5. Consider thalassaemia if MCH or MCV is low and not explained by iron deficiency, or if long standing. Check B12/folate if macrocytic or if there are risk factors for deficiency (e.g. decreased intake or absorption), or if anaemia is unexplained. Consider blood loss or haemolysis if reticulocyte count is increased. Seek haematology advice or, in presence of chronic kidney disease, nephrology advice

For more information on the diagnosis, investigation and management of iron deficiency anaemia refer to Pasricha SR, Flecknoe-Brown SC, Allen KJ et al. Diagnosis and management of iron deficiency anaemia: a clinical update. Med J Aust, 2010, 193(9):525–532.

Disclaimer

The information above, developed by consensus, can be used as a guide. Any algorithm should always take into account the patient's history and clinical assessment, and the nature of the proposed surgical procedure.



1 Introduction

Patient blood management aims to improve clinical outcomes by avoiding unnecessary exposure to blood components. It includes the three pillars of:

- optimisation of blood volume and red cell mass
- minimisation of blood loss
- optimisation of the patient's tolerance of anaemia.

These principles apply in the management of any haematological disorder. Patient blood management optimises the use of donor blood and reduces transfusion-associated risk.

This document, *Patient Blood Management Guidelines: Module 2 –Perioperative* is the second in a series of six modules that focus on evidence-based patient blood management. This module aims to support the introduction of patient blood management practices in the perioperative setting. The other five modules are listed in , below. Together, the six modules will supersede the 2001 National Health and Medical Research Council/Australasian Society of Blood Transfusion (NHMRC/ASBT) *Clinical Practice Guidelines on the Use of Blood Components.*[1]

Revision of the 2001 guidelines[1] was needed because of:

- increasing evidence of transfusion-related adverse outcomes, leading to the emergence of new practices, including restrictive transfusion strategies and the increased use of alternatives to transfusion in the management of anaemia
- variable (and frequently poor) compliance with the recommendations of the 2001 guidelines, indicated by a high degree of variation in transfusion practices
- failure of the 2001 guidelines to address a range of clinical settings where blood management is commonly required, including critical bleeding and massive transfusion, chronic medical conditions, obstetrics and paediatrics.

This document is intended to inform health-care practitioners, health educators, and health service managers and policy makers about the pre, intra and postoperative care of patients undergoing surgery or invasive procedures, particularly those in which blood loss is anticipated. Transfusion decisions for patients should take into account each individual's clinical circumstances and physiological status, and their treatment preferences and choices.

If blood components are likely to be indicated, transfusion should not be a default decision. Instead, the decision on whether to transfuse should be carefully considered, taking into account the full range of available therapies, and balancing the evidence for efficacy and improved clinical outcome against the potential risks (Appendix B).

1.1 Development of the guidelines

In response to the situation outlined above, the NHMRC, the Australia & New Zealand Society of Blood Transfusion (ANZSBT) and the National Blood Authority (NBA)[a] agreed to develop a series of six patient-focused, evidence-based modules that together will comprise new patient blood management guidelines.

The six modules of the guidelines are being developed in three phases, as shown in Table 1.1.

Table 1.1 Phases of development of guideline modules

PHASE	MODULES
I	Critical bleeding/massive transfusion Perioperative
II	Medical Critical care
III	Obstetrics Paediatric/neonatal

[a] The structure of the Australian blood sector is outlined in Appendix C

1.2 Governance structure

A multilevel management framework was established by the NBA to coordinate the development of the new patient blood management guidelines. The management framework (illustrated in Appendix A) consists of:

- a Steering Committee, responsible for the overall development and governance of the entire project
- an Expert Working Group (EWG), responsible for clinical oversight and integration of the six modules
- Clinical/Consumer Reference Groups (CRGs – one for each of the six modules), with membership including representation from relevant colleges, societies and consumer groups, to provide expert knowledge and input
- systematic reviewers and a technical writer, contracted by the NBA to review the literature and develop a draft of each module
- Guidelines Assessment Register (GAR) consultants, to provide advice and mentoring to the systematic reviewers, technical writer, EWG and CRGs; and to ensure that the development process and the guidelines produced comply with NHMRC requirements.

The NBA provided the secretariat, project funding and project management. The NBA website includes a list of colleges and societies that have endorsed these guidelines.[b] Appendix A lists the membership of the bodies involved in governance of the guidelines. Details of how the guidelines will be implemented and updated are provided in Chapter 6.

1.3 Structure of the document and related materials

1.3.1 The document

This module includes:

- *recommendations* – based on evidence from the systematic review
- *practice points* – based on consensus decision making, where the systematic review found insufficient high-quality data to produce evidence-based recommendations, but clinicians require guidance to ensure good clinical practice
- *a template* – for developing a preoperative anaemia management algorithm.

The recommendations and practice points are summarised in the Executive summary.

The remainder of this document includes:

- an outline of the methods used to develop the clinical research questions, undertake a systematic review of the literature, and develop recommendations and practice points (Chapter 2)
- clinical practice guidance, setting out the main findings of the systematic review and other considerations documented by the CRG, and recommendations and practice points, as appropriate (Chapter 3)

[b] http://www.nba.gov.au/

- a discussion of anaesthesia and patient blood management (Chapter 4)
- recommendations for future directions (Chapter 5)
- information on implementing, evaluating and maintaining the guidelines (Chapter 6).

The document also includes appendixes that provide an overview of the blood sectors in Australia and New Zealand, membership of the governance bodies for guideline development, information on transfusion risks, a process report, evidence statements and information about blood components. Finally, the document contains a list of references.

1.3.2 Related materials

Materials relevant to clinicians will be developed to accompany this module; these materials will be available online and in print from the NBA.

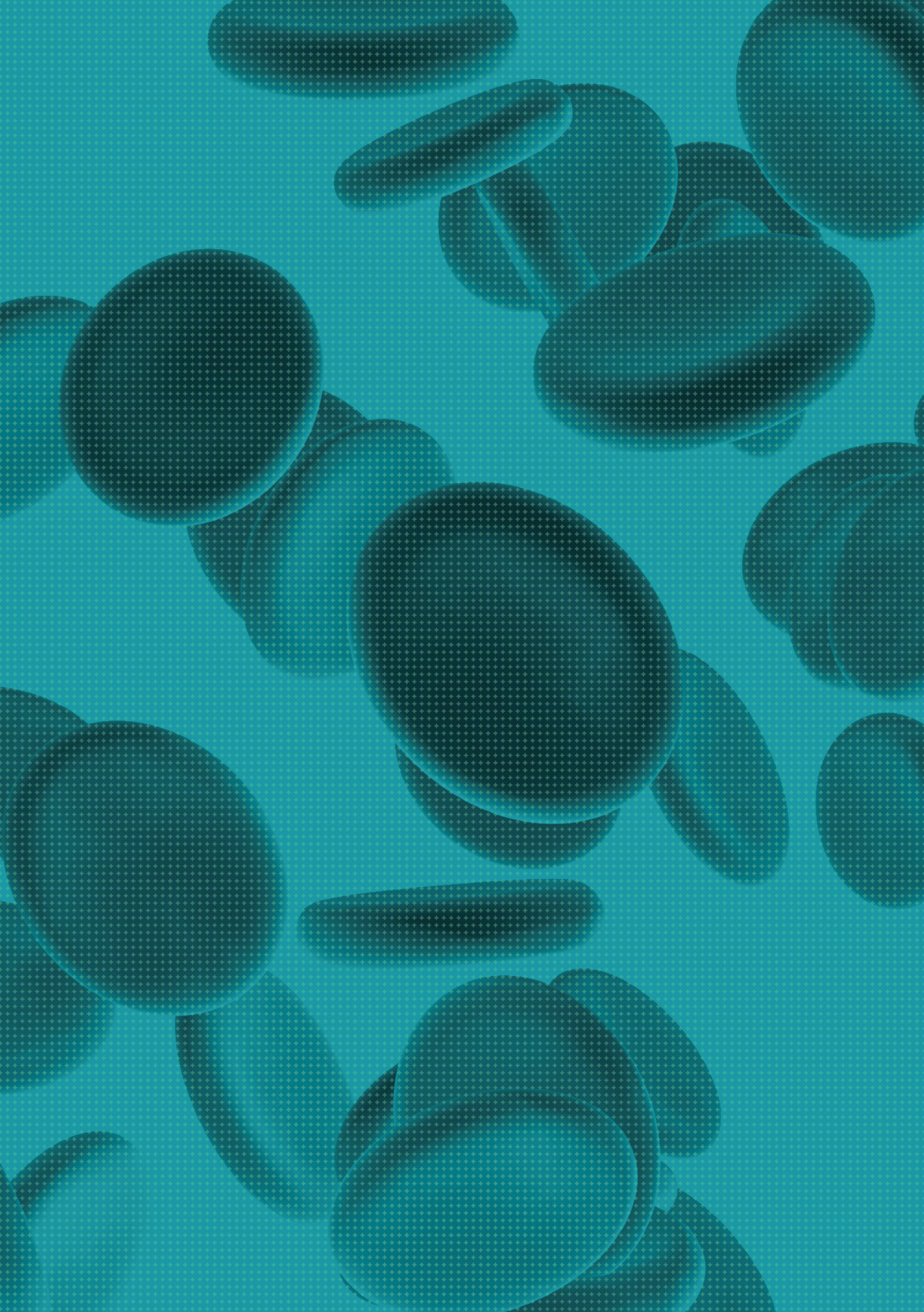
The technical reports that underpin this document are also available online, in four volumes:

- *Volumes 1a*[2] *and 1b*[4]

  These volumes include background information and the results of the systematic reviews pertaining to the clinical questions posed within this guideline

- *Volumes 2a*[3] *and 2b*[5]

  These volumes contain appendixes that document the literature searches, study quality appraisal, NHMRC evidence statement forms and evidence summaries for the individual studies.



2 Methods

The development of evidence-based clinical practice guidelines that meet NHMRC standards involves developing a set of clinical research questions, systematically reviewing the scientific literature for evidence related to those questions, and then developing and grading recommendations based on a structured assessment of the evidence.[8] The methods used in applying this process to the development of this module are outlined below, and are given in full in the accompanying technical reports. A summary of the overall process for development of this module is given in Appendix D.

2.1 Clinical research questions – development and details

Between April and June 2009, the relevant clinical research questions for this module were developed, prioritised, combined and refined by the EWG, the NHMRC GAR consultants and the CRG (Appendix A). The process resulted in two different types of questions – those that are specific to this module, and those that are generic (i.e. relevant to all six modules that make up the guidelines).

The specific and generic questions were crafted in such a way that they attempted to provide answers in clinically relevant areas of uncertainty. The questions were further refined through consultation among the systematic reviewer, CRG, NBA and NHMRC GAR consultants. Details of research question criteria are presented in Volumes 1a[2] and 1b[4] of the technical reports.

2.2 Review and research

2.2.1 Systematic review process

Systematic reviews were undertaken to attempt to answer the questions specific to perioperative transfusion, and the generic questions relevant to all six modules. The systematic review questions are listed in Box 2.1.

To answer these questions, comprehensive search strategies were designed, as detailed in Volumes 2a and 2b of the technical report. Searches were conducted in relevant electronic databases, bibliographies of studies identified as relevant, and literature recommended by expert members of the CRG.

The systematic review included only data from studies that met the relevant inclusion criteria, were of adequate quality and were published before July 2009 (for exact dates of searches, see Table D.1 in Appendix D). Identification of relevant evidence and assessment of evidence was conducted in accordance with NHMRC standards and procedures for externally developed guidelines.[9] Table D.2 in Appendix D gives specific patient populations and subgroups.

The search terms did not specifically search for or limit retrieval of articles to studies that addressed socioeconomic, Aboriginal or Torres Strait Islander subgroups. However, the reviewers were required to isolate any papers addressing these populations for specific consideration by the CRG. No papers were identified that addressed these populations specifically.

Box 2.1 Systematic review questions

Questions 1–3 are specific to perioperative transfusion (i.e. to this module); questions 4–9 are relevant to all six modules of these guidelines.

- **Question 1** – In patients undergoing surgery, what is the effect of a multidisciplinary, multimodal, programmatic approach to perioperative patient blood management on patient outcomes?

  (Interventional question, referred to as POQ1 in the technical report)

- **Question 2** – In patients undergoing surgery, what effect does the cessation and timing of cessation of medication that affects haemostasis have on morbidity, mortality and RBC transfusion?

  (Interventional question, referred to as POQ2 in the technical report)

- **Question 3** – In patients undergoing surgery, what is the effect of perioperative strategies that minimise blood loss on morbidity, mortality and blood transfusion?

  (Interventional question, referred to as POQ3 in the technical report)

- **Question 4** – In patients undergoing surgery, is anaemia an independent risk factor for adverse outcomes?

  (Aetiological question, referred to as GNQ1 in the technical report)

- **Question 5** – In patients undergoing surgery, what is the effect of RBC transfusion on patient outcomes?

  (Interventional question, referred to as GNQ2 in the technical report)

- **Question 6** – In patients undergoing surgery, what is the effect of non-transfusion interventions to increase haemoglobin concentration on morbidity, mortality and the need for RBC blood transfusion?

  (Interventional question, referred to as GNQ3 in the technical report)

- **Question 7** – In patients undergoing surgery, what is the effect of rFVIIa (prophylaxis or treatment) on morbidity, mortality and transfusion rate?

  (Interventional question, referred to as GNQ4 in the technical report)

- **Question 8** – In patients undergoing surgery, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes?

  (Interventional question, referred to as GNQ5 in the technical report)

- **Question 9** – In patients undergoing surgery, at what INR (PT/ APTT) for FFP, fibrinogen level for cryoprecipitate and platelet count for platelet concentrates should patients be transfused to avoid risks of significant adverse events?

  (Prognostic question, referred to as GNQ6 in the technical report)

APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalised ratio; PT, prothrombin time; RBC, red blood cell; rFVIIa, recombinant activated factor VII

2.2.2 Background material

Material relevant to the background question was gathered by fellows or registrars under the supervision of CRG members. Sources included medical textbooks, grey literature, published scientific and review articles, series yearbooks and other relevant medical literature; however, systematic review processes were not applied. The question researched is given in Box 2.2.

Box 2.2 Background research question

Background question 1 – Does choice of anaesthetic agent or technique reduce blood loss and transfusion?

2.3 Development of evidence statements, recommendations and practice points

For each research question addressed by the systematic review, the body of evidence was consolidated into evidence statements and rated according to the matrix shown in Table 2.2 (below), which considers five domains: evidence base, consistency, clinical impact, generalisability and applicability. For included studies, evidence base and consistency were derived directly from the literature identified for each research question, whereas clinical impact, generalisability and applicability were assessed with guidance from the CRG. To ensure that the best available evidence was used, studies of higher levels of evidence (i.e. Levels I or II) were included in preference to those presenting lower levels (i.e. Levels III or IV) of evidence. This minimised the potential for bias in the evidence base for each systematically reviewed question. However, lower level studies were reviewed where evidence was not available in higher level studies for any of the primary outcomes.

Evidence statements were only transformed into 'action-oriented' recommendations where:

- the body of evidence was sufficient – that is, wherever the evidence yielded support for recommendations of at least NHMRC grade C (see Table 2.3, below)
- the question type was interventional – that is, it evaluated the effectiveness of an intervention.

The recommendations were carefully worded to reflect the strength of the body of evidence.

Where there was insufficient quality or quantity of evidence, it was not possible to develop evidence-based recommendations. In this situation, the CRG developed practice points through a consensus-based process, to guide clinical practice.

For prognostic and aetiological questions, the evidence base provided only an indication of the risk associated with a particular factor; thus, it was not possible to make an evidence-based recommendation for a change in practice. Instead, the CRG's consensus-based process (used to develop practice points to guide practice) was informed by the prognostic and aetiologic review, and by clinical experience.

Table 2.2 Body of evidence matrix

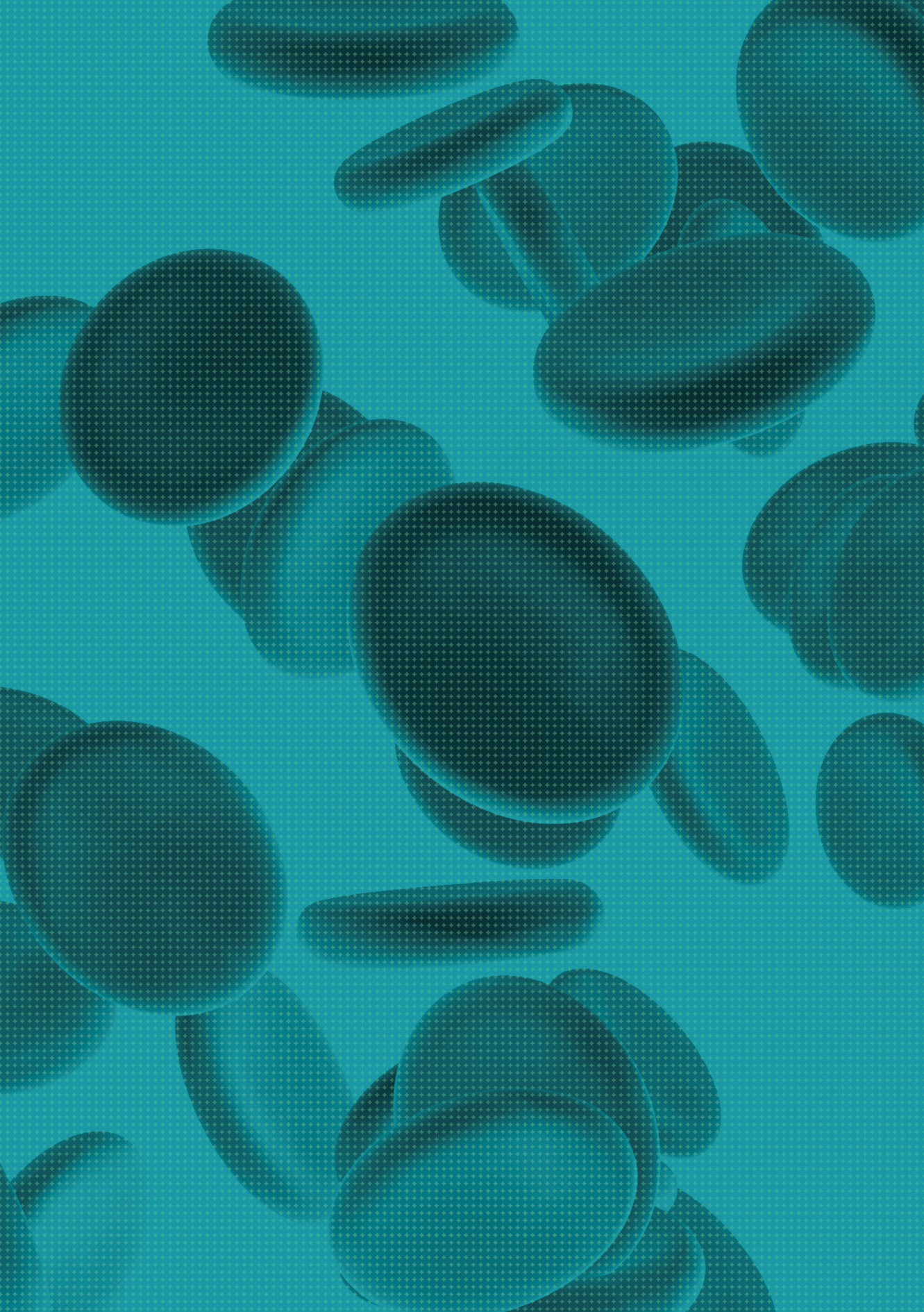
COMPONENT	A	B	C	D
	Excellent	Good	Satisfactory	Poor
Evidence base	Several Level I or II studies with low risk of bias	One or two Level II studies with low risk of bias or a systematic review, or multiple Level III studies with low risk of bias	Level III studies with low risk of bias, or Level I or II studies with moderate risk of bias	Level IV studies, or Level I–III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency can be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in the body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in the body of evidence are different to the target population, but it is clinically sensible to apply this evidence to the target population for the guideline	Population/s studied in the body of evidence are different to the target population and it is hard to judge whether it is sensible to generalise to the target population for the guideline
Applicability	Directly applicable to the Australian health-care context	Applicable to the Australian health-care context, with a few caveats	Probably applicable to the Australian health-care context, with some caveats	Not applicable to the Australian health-care context

Source: NHMRC 2009[10]

Table 2.3 Definitions of NHMRC grades for recommendations

Grade	Definition
GRADE A	Body of evidence can be trusted to guide practice
GRADE B	Body of evidence can be trusted to guide practice in most situations
GRADE C	Body of evidence provides some support for recommendation(s) but care should be taken in its application
GRADE D	Body of evidence is weak and recommendations must be applied with caution

Source: NHMRC 2009[10]



3 Clinical guidance

This chapter provides clinical guidance in the form of recommendations (based on evidence) and practice points (based on CRG consensus). The guidance is organised around the nine questions that formed the basis of the systematic review. Full details of the findings of the systematic review are given in the accompanying technical report.

This chapter also outlines the need for an algorithm to assess and optimise perioperative haemoglobin (Appendix F), which can be used as a guide to suit the local patient population and health-care resources.

3.1 Effect of a perioperative patient blood management program

Question 1 (Interventional question) (POQ1)

In patients undergoing surgery, what is the effect of a multidisciplinary, multimodal, programmatic approach to perioperative patient blood management on patient outcomes?

The aim of this question was to establish the effect of a coordinated, multidisciplinary patient blood management program on clinical outcomes and blood component use in surgical patients.

The evidence for this question was obtained from one Level I study,[11] five Level III studies[12–16] and one Level IV study.[17] All of these studies were assessed as being of poor quality. They employed a variety of elements within a patient blood management program; however, all used an approach that was coordinated by either an individual or a group.

In all patients undergoing surgery, the primary objectives should be preoperative optimisation of red cell mass and coagulation status; minimisation of perioperative blood loss, including meticulous attention to surgical haemostasis; and tolerance of postoperative anaemia.

EVIDENCE STATEMENT – for perioperative patient blood management program	Evidence	Consistency	Clinical impact	Generalisability	Applicability
A multidisciplinary, multimodal programmatic approach to perioperative blood management is associated with a reduction in transfusion requirements during cardiac or noncardiac surgery. The effect of such programs on morbidity and mortality is uncertain.	X	✓✓	✓✓	✓✓	✓

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2)

RECOMMENDATION for perioperative patient blood management program

R1

GRADE C

Health-care services should establish a multidisciplinary, multimodal perioperative patient blood management program (Grade C). This should include preoperative optimisation of red cell mass and coagulation status; minimisation of perioperative blood loss, including meticulous attention to surgical haemostasis; and tolerance of postoperative anaemia.

3.2 Effect of anaemia on outcomes

Question 4 (Aetiological question) (GNQ1)

In patients undergoing surgery, is anaemia an independent risk factor for adverse outcomes?

Anaemia has been defined by the World Health Organization (WHO) as a haemoglobin level <130 g/L in males and <120 g/L in females.

No Level I evidence was identified for cardiac surgery. One fair-quality systematic review was identified for noncardiac surgery. Of the Level II studies identified that investigated the relationship of anaemia as an adverse outcome in patients undergoing surgery, 10 involved cardiac surgery,[18–27] and 8 involved noncardiac surgery.[19,28–34] A further 14 cardiac[35–48] and 11 noncardiac[49–59] Level III studies were identified.

Preoperative anaemia is independently associated with an increased risk of morbidity and mortality.

Collectively, these studies provide a good evidence base – in cardiac and noncardiac surgical patients – for an independent relationship between preoperative anaemia and an increased risk of postoperative morbidity and mortality.

As would be expected, preoperative anaemia is associated with an increased likelihood of red blood cell (RBC) transfusion.

EVIDENCE STATEMENTS – anaemia	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In patients undergoing cardiac surgery, preoperative anaemia is associated with an increased risk of morbidity and mortality.	✓✓	✓✓	✓	✓✓	✓
In patients undergoing cardiac surgery, preoperative anaemia is associated with an increased likelihood of transfusion.	✓✓	✓✓✓	✓✓	✓✓	✓
In patients undergoing cardiac surgery, preoperative and intraoperative anaemia are associated with increased hospital length of stay.	**X**	✓	**X**	✓	✓
In patients undergoing cardiac surgery, an intraoperative/operative haematocrit level below 20% is associated with an increased risk of morbidity and mortality.	✓	✓✓	✓	✓✓	✓
In patients undergoing noncardiac surgery, preoperative anaemia is associated with an increased risk of postoperative morbidity and mortality.	✓✓	✓✓	✓	✓✓	✓
In patients undergoing noncardiac surgery, preoperative anaemia is associated with an increased likelihood of transfusion and increased hospital length of stay.	✓	✓✓✓	✓✓	**X**	✓
In patients undergoing noncardiac surgery, postoperative anaemia is associated with an increased risk of morbidity and mortality.	✓✓	✓✓	✓	**X**	✓
In patients undergoing noncardiac surgery, postoperative anaemia is associated with an increased likelihood of transfusion.	✓	**NA**	✓	✓	✓

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

3.3 Effect of red blood cell transfusion on outcomes

Question 5 (Interventional question) (GNQ2)

In patients undergoing surgery, what is the effect of RBC transfusion on patient outcomes?

RBC, red blood cell

Thirty-seven studies were identified that assessed the effect of transfusions on outcomes; of these, 21 involved cardiac surgery and 16 noncardiac surgery. These studies were all Level III (of poor to fair quality) and did not control who did or did not receive the intervention (RBC transfusion). Many studies demonstrated a dose-dependent relationship between RBC transfusion and morbidity or mortality. However, the design of the studies was such that it was not possible to prove a causal relationship between the intervention and the *observed* outcomes.

The CRG has made no assumption of causality; however, an association between red cell transfusion and adverse patient outcome has been reported. Therefore, the CRG advocates a precautionary approach to blood transfusion, balancing the potential harms of blood transfusion and anaemia.

The paucity of evidence in this area to guide clinical practice has been highlighted by the recent publication from the International Consensus Conference on Transfusion Outcomes (ICCTO) group.[60]

3.3.1 Effect of red blood cell transfusion

Mortality

In patients undergoing cardiac surgery, seven studies found that RBC transfusion was a significant predictor of short-term mortality.[61–67] The odds of death increased with increasing units of blood transfused;[62,66] however, a study of patients undergoing thoracic aortic surgery found no relationship.[68] Three studies investigated longer term mortality[63,69,70] and demonstrated that RBC transfusion was a significant predictor of 6-month,[70] 1-year[63] and 5-year mortality.[69]

In patients undergoing noncardiac surgery, studies were less consistent. Five studies found that RBC transfusion was significantly associated with a higher risk of mortality;[71–75] this association was dose dependent in two studies.[71, 75] In contrast, three other studies found that RBC transfusion was not a significant predictor of mortality.[76–78]

Morbidity

In patients undergoing cardiac surgery, infection was the most common morbid outcome observed; it included wound infection, sepsis and pneumonia.[61,64–66,79–84] All 10 studies found that RBC transfusion was a significant predictor of infection, and the odds of infection increased with increasing numbers of units of blood transfused. RBC transfusion was a significant predictor, in dose-dependent fashion, of cardiac,[61,65,66,85,86] renal,[61,66] respiratory[61] and neurologic morbidities.[61]

In patients undergoing noncardiac surgery, the most common morbidity outcome investigated was also infection. Five studies found that RBC transfusion was a significant predictor for development of infection, including wound infections, sepsis and pneumonia.[71,73,76,87,88] In patients undergoing major vascular surgery, RBC transfusion predicted development of venous thromboembolism.[56] No studies reported cardiac, renal or neurological morbidity.

Hospital and ICU length of stay

RBC transfusion is associated with significantly longer stays in hospital and ICU in patients undergoing cardiac and noncardiac surgery.[64,65,67,73,78,88,89] In patients undergoing surgery for hip fracture, RBC transfusion is associated with an increase in hospital readmission.[77]

3.3.2 Effect of liberal versus restrictive red blood cell transfusion protocols

Five randomised controlled trials (RCTs) investigated the effect of a restrictive transfusion strategy (in which transfusion was not undertaken until the haemoglobin reached a defined threshold, unless symptoms of oxygen transport deficit were present) on patient outcomes in a perioperative population (one cardiac[90] and four noncardiac[91–94]), as described below.

Cardiac

The one study in cardiac patients[90] was of poor quality; thus, the effect of a restrictive transfusion strategy is unclear.

Noncardiac studies

The four studies in noncardiac patients[91–94] were small, underpowered RCTs of fair to good quality; thus, the effect of a restrictive transfusion strategy on morbidity and mortality is unclear.

EVIDENCE STATEMENTS – red blood cell transfusion and restrictive transfusion strategy	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In patients undergoing cardiac surgery, RBC transfusion is independently associated with increased morbidity. This relationship is dose dependent.	✓	✓✓✓	✓✓	✓✓	✓
In patients undergoing cardiac surgery, RBC transfusion is independently associated with increased mortality. This relationship is dose dependent.	✓	✓✓	✓	✓✓	✓✓
In patients undergoing cardiac surgery, RBC transfusion is independently associated with increased ICU and hospital length of stay.	✓	✓✓✓	✓	✓✓✓	✓
In patients undergoing cardiac surgery, there is insufficient evidence to determine the effect of RBC transfusion on quality of life.	X	NA	✓	✓	✓
In patients undergoing noncardiac surgery, RBC transfusion is independently associated with increased morbidity. This relationship is dose dependent.	✓	✓✓	✓✓	✓✓	✓
In patients undergoing noncardiac surgery, RBC transfusion is independently associated with increased mortality. This relationship is dose dependent.	✓	✓	✓	✓✓	✓

EVIDENCE STATEMENTS – red blood cell transfusion and restrictive transfusion strategy	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In patients undergoing noncardiac surgery, RBC transfusion is independently associated with increased ICU length of stay and hospital length of stay.	✓	✓✓✓	✓	✓✓	✓
In patients undergoing cardiac surgery, use of a restrictive transfusion strategy is not associated with increased mortality, morbidity or hospital length of stay.	✓	**NA**	✓	✓✓✓	✓
In patients undergoing noncardiac surgery, the effect of a restrictive transfusion strategy on mortality and morbidity is uncertain.	✓✓	✓	✓	**X**	✓
In patients undergoing orthopaedic or vascular surgery, the use of a restrictive transfusion strategy is not associated with increased hospital length of stay.	✓✓	✓✓✓	✓	✓	✓

ICU, intensive care unit; RBC, red blood cell

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

RECOMMENDATIONS – red blood cell transfusion

R2
GRADE C

In patients undergoing cardiac surgery, preoperative anaemia should be identified, evaluated and managed to minimise RBC transfusion, which may be associated with an increased risk of morbidity, mortality, ICU length of stay and hospital length of stay (Grade C).

R3
GRADE C

In patients undergoing noncardiac surgery, preoperative anaemia should be identified, evaluated and managed to minimise RBC transfusion, which may be associated with an increased risk of morbidity, mortality, ICU length of stay and hospital length of stay (Grade C).

PRACTICE POINTS – red blood cell transfusion

PP1

To implement the above recommendations, a multimodal, multidisciplinary patient blood management program is required. All surgical patients should be evaluated as early as possible to coordinate scheduling of surgery with optimisation of the patient's haemoglobin and iron stores.

PP2

RBC transfusion should not be dictated by a haemoglobin 'trigger' alone, but should be based on assessment of the patient's clinical status. In the absence of acute myocardial or cerebrovascular ischaemia, postoperative transfusion may be inappropriate for patients with a haemoglobin level of >80 g/L.

PRACTICE POINTS – red blood cell transfusion	
PP3	Patients should not receive a transfusion when the haemoglobin level is ≥100 g/L. In postoperative patients with acute myocardial or cerebrovascular ischaemia and a haemoglobin level of 70–100 g/L, transfusion of a single unit of RBC, followed by reassessment of clinical efficacy, is appropriate.

ICU, intensive care unit; RBC, red blood cell

3.4 Effect of non-transfusion interventions to increase haemoglobin concentration

Question 6 (Interventional question) (GNQ3)

In patients undergoing surgery, what is the effect of non-transfusion interventions to increase haemoglobin concentration on morbidity, mortality and need for RBC blood transfusion?

RBC, red blood cell

Iron is one of the main regulators of erythropoiesis: iron supply may be a limiting factor in erythropoiesis following surgery. It is essential that preoperative iron stores are adequate, so that patients can respond to the increase in erythropoiesis stimulated by blood loss.

Where preoperative anaemia is identified, it is important to determine its aetiology, so that appropriate therapy can be given. For example, in iron deficiency anaemia, iron therapy will correct anaemia, whereas, in anaemia of chronic disease (also known as anaemia of inflammation) and anaemia of renal impairment, the addition of erythropoiesis-stimulating agents (ESAs) may be required.

3.4.1 Effect of iron therapy

A total of 13 studies of cardiac and noncardiac populations investigated the effects of iron therapy – either oral (8 studies), intravenous (3 studies) or oral versus intravenous (2 studies) – on morbidity, mortality or the need for blood transfusion. Of these, 8 were Level II (of which 2 were of good quality) and 5 were Level III (all of fair quality).

Interpretation of the evidence base was difficult because of variable definitions of anaemia, lack of categorisation of the cause of anaemia, and differences in treatment doses and schedules.

Preoperative oral iron therapy given to noncardiac surgery patients who were anaemic preoperatively was associated with an increase in haemoglobin,[95,96] and a reduction in transfusion requirements.[95–97] There were no studies of preoperative iron therapy in an anaemic cardiac surgical population; however, it is reasonable to expect that the findings would be similar.

The effect of postoperative oral iron was investigated in patients found to be anaemic postcardiac[98–100] and noncardiac surgery.[101,102] The effect on haemoglobin concentration was minimal. This finding is not unexpected, because the acute inflammatory response after surgery is associated with reduced iron absorption.

The only study of postoperative intravenous (IV) iron administration in a noncardiac surgery population showed a significant reduction in the number of units of blood transfused postoperatively per patient.[103]

Patients who are at risk of significant blood loss or preoperative anaemia should have their haemoglobin and iron stores assessed. In patients with iron deficiency anaemia or suboptimal iron stores (defined by a ferritin level of <100 µg/L), preoperative iron therapy is suggested. Preoperative assessment should be performed as early as possible, to allow an adequate course of treatment. The choice of iron therapy will depend on individual clinical assessment, taking into account the haemoglobin level, the nature and urgency of surgery, and the patient's ability to tolerate and comply with therapy. See the preoperative haemoglobin assessment and optimisation template (Appendix F) for guidance. The template was developed by consensus; use of an algorithm should always take into account the patient's history and clinical assessment, and the nature of the proposed surgical procedure.

3.4.2 Effect of erythropoiesis-stimulating agents

Thirty-two studies investigated the effect of ESAs on morbidity, mortality and need for RBC transfusion in a perioperative population. All 32 studies combined ESAs with oral or intravenous iron therapy. Of these, 14 were Level II studies (some of which were included in 2 Level I studies); these formed the evidence base.

Of the 14 RCTs investigating the efficacy of erythropoietin in an anaemic perioperative patient population, 2 were in cardiac surgery, as postoperative therapy.[104,105] The remaining 12 studies were in noncardiac surgery,[106–116] with only 1 as postoperative therapy.[117] These studies used a variety of ESA treatment doses and regimens, and were of fair to good quality.

Morbidity and mortality

The studies were too small to detect any effect of perioperative ESA therapy on mortality.

No difference was observed in the incidence of morbidity outcomes between ESA-treated and control patients, including the incidence of thrombotic vascular events,[106,108] or the incidence of infections.[113] However, the studies investigating thrombotic vascular events were underpowered to detect a difference in this outcome. Therefore, no conclusion could be drawn regarding the safety of perioperative use of ESAs.

Haemoglobin concentration and incidence of transfusion

The results of ESA treatment on haemoglobin concentration and transfusion use varied between surgical populations.

In noncardiac surgery patients, preoperative erythropoietin treatment resulted in higher haemoglobin levels preoperatively[110,113,116,118] and postoperatively.[112–116] The effect on transfusion requirements in oncology surgery patients remains uncertain;[107,110–112,114] however, in patients who underwent orthopaedic surgery, treatment with preoperative ESA reduced both the use[106,108,115] and rate[108] of blood transfusion.

Postoperative treatment with ESA plus intravenous iron in patients who were anaemic following cardiac surgery was compared to intravenous iron alone or standard care.[104,105] Treatment with ESA did not affect postoperative haemoglobin levels or decrease the incidence of transfusion or number of units transfused per patient.

A small, single study in orthopaedic surgery found a modest increase in haemoglobin concentration in patients treated postoperatively with ESA and oral iron.[117]

EVIDENCE STATEMENTS – iron and erythropoiesis-stimulating agents	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In paediatric and adult cardiac surgery patients with postoperative anaemia, postoperative oral iron had no effect on haemoglobin.	✓	✓✓✓	X	✓	✓
In patients with preoperative anaemia undergoing noncardiac surgery, preoperative oral iron increases haemoglobin levels.	✓✓	✓✓	✓	✓✓	✓✓
In patients with preoperative anaemia undergoing noncardiac surgery, preoperative oral iron reduces the incidence of transfusion requirements.	✓✓	✓✓✓	✓✓	✓✓	✓
In noncardiac surgery patients without preoperative anaemia, there is insufficient evidence to determine whether oral iron treatment before surgery affects the incidence of transfusion.	✓	NA	✓	✓	✓
In noncardiac surgery patients with postoperative anaemia, postoperative oral iron is not clinically effective.	✓✓	✓✓	X	✓	✓✓
In noncardiac surgery patients, preoperative and postoperative intravenous iron may reduce mortality and hospital length of stay, risk of infection and incidence of transfusion.	X	✓	X	✓	✓
In cardiac and orthopaedic surgery patients, the effectiveness of postoperative intravenous iron plus oral iron compared with postoperative oral iron alone on the incidence of transfusion and postoperative haemoglobin levels and ferritin levels is uncertain.	✓	NA	X	✓	✓✓
In gynaecological surgical patients with iron deficiency anaemia, preoperative intravenous iron is more effective than preoperative oral iron at increasing postoperative haemoglobin and ferritin levels.	X	NA	X	✓	✓
In noncardiac surgery patients, there is insufficient evidence to determine the effect on morbidity of preoperative treatment with an ESA in combination with oral iron.	✓✓✓	✓	✓	✓✓	✓✓
In orthopaedic surgery patients, preoperative treatment of anaemia with an ESA in combination with oral iron reduces the incidence of transfusion.	✓✓✓	✓✓✓	✓✓	✓✓✓	✓✓
In colorectal surgery patients, preoperative treatment of anaemia with an ESA in combination with oral iron starting less than 10 days before surgery has an inconsistent effect on incidence of transfusion.	✓✓	✓	✓	✓✓✓	✓

EVIDENCE STATEMENTS – iron and erythropoiesis-stimulating agents	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In noncardiac surgery patients, preoperative treatment of anaemia with an ESA in combination with iron increases preoperative haemoglobin levels.	✓✓✓	✓✓✓	✓✓	✓✓	✓✓
In noncardiac surgery patients, preoperative treatment of anaemia with an ESA in combination with oral iron does not affect hospital length of stay.	✓✓	✓✓	✓	✓✓	✓✓
In orthopaedic surgery patients with anaemia, preoperative administration of an ESA (epoetin alfa) weekly is no different to daily administration in combination with oral iron at increasing preoperative haemoglobin levels.	✓	**NA**	✓	✓✓	✓
In cardiac and orthopaedic surgery patients, treatment of postoperative anaemia with an ESA in combination with intravenous iron may not decrease the incidence of transfusion compared with intravenous iron plus oral iron, or oral iron alone.	✓	**NA**	**X**	✓✓	✓✓
In orthopaedic surgery patients with postoperative anaemia, treatment with an ESA in combination with oral iron increases haemoglobin levels.	✓✓	**NA**	**X**	✓	✓

ESA, erythropoiesis-stimulating agent

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

RECOMMENDATION – iron and erythropoiesis-stimulating agents

R4 **GRADE B**

In surgical patients with, or at risk of, iron-deficiency anaemia, preoperative oral iron therapy is recommended (Grade B).

Refer to the preoperative haemoglobin assessment and optimisation template [Appendix F] for further information on the optimal dosing strategy.

R5 **GRADE A**

In patients with preoperative anaemia, where an ESA is indicated, it must be combined with iron therapy (Grade A).

R6 **GRADE B**

In patients with postoperative anaemia, early oral iron therapy is not clinically effective; its routine use in this setting is not recommended (Grade B).

PRACTICE POINTS – iron and erythropoiesis-stimulating agents	
PP4	All surgical patients should be evaluated as early as possible to manage and optimise haemoglobin and iron stores.
PP5	Elective surgery should be scheduled to allow optimisation of patients' haemoglobin and iron stores.
PP6	Surgical patients with suboptimal iron stores (as defined by a ferritin level <100 µg/L) in whom substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, should be treated with preoperative iron therapy. Refer to the preoperative haemoglobin assessment and optimisation template [Appendix F] for further information on the evaluation and management of preoperative patients.
PP7	In patients with preoperative iron-deficiency anaemia or depleted iron stores, treatment should be with iron alone. In patients with anaemia of chronic disease (also known as anaemia of inflammation), ESAs may be indicated. Refer to the preoperative haemoglobin assessment and optimisation template [Appendix F] for further information on the evaluation and management of preoperative patients.

ESA, erythropoiesis-stimulating agent

3.5 Cessation of medications that affect haemostasis

Question 2 (Interventional) POQ2

In patients undergoing surgery or invasive procedures, what effect does the cessation and timing of cessation of medications that affect haemostasis have on morbidity, mortality and RBC transfusion?

3.5.1 Cardiac surgery

The systematic review process identified 13 studies that investigated the effect of cessation and the timing of cessation of antiplatelet medication on patient outcomes in cardiac surgery, specifically coronary artery bypass graft surgery (CABG).[119–131] One study was Level II[123] and 12 were Level III studies.[119–122,124–131] They included studies of aspirin alone,[122–125,131] clopidogrel alone,[119–121] and dual antiplatelet therapy (aspirin and clopidogrel).[126–130] The study populations included patients having either CABG with cardiopulmonary bypass (CPB) or off-pump coronary artery bypass surgery (OPCAB).

For the purpose of this research question, patients were classified as having received the intervention (i.e. cessation of antiplatelet therapy, including conversion to substitution therapy) where antiplatelet therapy was stopped before surgery for a longer period than an alternative perioperative antiplatelet management strategy. Patients were classified as having received the comparator (i.e. no cessation of antiplatelet therapy) where antiplatelet therapy was stopped before surgery for a shorter period than an alternative strategy, including continuation until surgery, or was not stopped before surgery.

Aspirin monotherapy

Overall, results from the studies that investigated the timing of aspirin cessation indicate that the effect on patient outcomes remains uncertain.[122–124,131] Mortality, morbidity (myocardial infarction [MI] and pericardial effusion), hospital length of stay and ICU length of stay were similar, regardless of the timing of aspirin cessation; however, the studies were not powered to detect a difference. Blood loss (postoperative) and transfusion requirements (intraoperative and postoperative) were also similar, despite analyses that claimed statistical significance.

Clopidogrel monotherapy

Only three studies investigated the timing of cessation of clopidogrel monotherapy on patient outcomes in CABG surgery.[119–121] Administration of clopidogrel within 5 days of surgery may be associated with an increase in transfusion, blood loss, risk of reoperation for bleeding and hospital length of stay.[120,121] The effect on mortality is uncertain.[119–121]

Combination antiplatelet therapy

Five Level III studies reported on the perioperative management of patients who received combination antiplatelet medication.[126–130] Patients underwent OPCAB[127,129,130] and CABG with CPB.[126,128] There was considerable variability and inconsistency of documentation regarding the timing of cessation of clopidogrel or aspirin (or both) in these studies.

In the highest quality study,[127] the continuation of clopidogrel up to the time of surgery increased the need for RBC transfusion and the likelihood of reoperation.

Other anticoagulant therapy

No relevant evidence was identified on the perioperative management of cardiac surgery patients who had been receiving warfarin, nonsteroidal anti-inflammatory drugs (NSAIDs), statins, complementary medicines, vitamins or any other medications affecting haemostasis.

3.5.2 Noncardiac surgery or other invasive procedures

Aspirin therapy

One systematic review[132] and one prospective cohort study published since the publication of that review[133] compared outcomes among patients whose aspirin therapy was stopped before noncardiac surgery or invasive procedure with patients whose aspirin therapy was continued. The systematic review identified Level II and III studies of aspirin cessation versus aspirin continuation in a number of different surgeries and procedures, including spinal and epidural anaesthesia, oral surgery, biopsy, ophthalmology, orthopaedic surgery, urology and vascular surgery.

Overall, the authors of the systematic review concluded that aspirin should only be ceased before noncardiac surgery or invasive procedures if the bleeding risks associated with its continuation outweigh the cardiovascular risks of its withdrawal.

Clopidogrel therapy

Only one study was identified investigating the cessation of clopidogrel in patients undergoing noncardiac surgery or invasive procedures.[134] The study was of poor quality and the results could not be relied on.

NSAID therapy

The evidence base for NSAID therapy comprised one RCT,[135] one prospective cohort study,[136] and one retrospective cohort study.[137] All three studies were in patients undergoing hip arthroplasty. The studies demonstrated that blood loss during and after surgery was greater in patients not ceasing NSAID therapy before surgery, compared with patients either not receiving NSAID therapy or ceasing therapy at least 2 weeks before surgery. NSAID therapy did not affect haemoglobin levels,[136,137] but appeared to affect transfusion requirements, with more blood being transfused in patients on NSAID therapy compared with patients who did not receive NSAID therapy.[136]

Warfarin

The review identified eight studies comparing the discontinuation of warfarin therapy before surgery or procedure with continuing warfarin therapy until surgery or procedure, or receiving bridging therapy until surgery or procedure.[133,134,138–143] The evidence base included two systematic reviews,[140,144] three RCTs,[138,139,141] one prospective cohort study[143] and one retrospective cohort study[142] that were not included in the published reviews.

One systematic review found that arterial thromboembolism and stroke rates for patients undergoing all types of surgery and invasive procedures were not higher for patients discontinuing warfarin without bridging therapy compared with patients continuing warfarin therapy or receiving heparin bridging therapy.[140] The review also found that major bleeding was rare in patients undergoing dental procedures, arthrocentesis, cataract surgery and upper endoscopy or colonoscopy, with or without biopsy. The authors concluded that warfarin therapy does not need to be withheld for patients undergoing these procedures. These findings were supported by the second systematic review,[144] and by two RCTs in dental surgery;[138,139] all of which found no difference in bleeding between patients ceasing warfarin therapy before the procedure or continuing therapy until surgery. The remaining RCT also found no increase in haematoma formation with continuing warfarin therapy in patients undergoing transfemoral coronary angiography, compared with patients who had their warfarin therapy withheld.[141]

The analysis by Dunn and Turpie (2003) concluded that for other invasive and surgical procedures, warfarin needs to be withheld.[140] The decision on whether to administer perioperative intravenous heparin or subcutaneous low-molecular-weight heparin should be individualised, based on an estimation of the patient's risks of thromboembolism and bleeding, and reference to relevant guidelines (e.g. those from the American College of Chest Physicians[6] and the Australasian Society of Thrombosis and Haemostasis[7]).

EVIDENCE STATEMENTS – cessation of medications	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In patients undergoing coronary artery bypass surgery, the effect of continuing aspirin monotherapy until the day of surgery on mortality, morbidity (myocardial infarction and pericardial effusion), ICU length of stay, hospital length of stay, perioperative blood loss and transfusion requirement is uncertain.	✓✓	✓	x	✓✓✓	✓
In patients undergoing coronary artery bypass surgery, there may be an increased risk of bleeding, transfusion requirement and reoperation for bleeding if clopidogrel is not ceased at least 5 days before surgery. The impact on morbidity and mortality is uncertain.	x	✓	✓✓	✓✓✓	✓✓
In patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass who are receiving combination antiplatelet medication, the continuation of clopidogrel until the time of surgery may be associated with an increase in volume of transfusion; however, the available evidence is poor.	x	✓	✓	✓✓✓	✓

EVIDENCE STATEMENTS – cessation of medications	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In patients undergoing off-pump coronary artery bypass graft surgery who are receiving combination antiplatelet therapy, continuing clopidogrel within the 7-day period before surgery may be associated with an increased likelihood of red blood cell transfusion and reoperation for bleeding. The effect on mortality, ICU length of stay or hospital length of stay is uncertain.	X	✓	✓✓	✓✓✓	✓
In patients undergoing noncardiac surgery or invasive procedures, the effect of continuing aspirin therapy on morbidity, mortality and transfusion is uncertain, given the heterogeneity of the populations studied.	✓	✓✓	✓	✓✓	✓✓
In patients undergoing orthopaedic surgery receiving NSAID therapy, blood loss and transfusion requirements are increased when NSAID therapy is continued until the day of surgery. There was insufficient evidence to determine the effect of the timing of cessation of NSAID therapy.	✓✓	✓✓	✓	✓✓	✓✓
In patients undergoing noncardiac surgery, the effect of continuing clopidogrel on morbidity, mortality and transfusion is uncertain.	X	NA	X	✓✓	✓
In patients undergoing minor dental procedures, arthrocentesis, cataract surgery, upper gastrointestinal endoscopy or colonoscopy with or without biopsy, morbidity and mortality are unaffected when warfarin is continued. In patients undergoing more complex procedures, the effect on mortality and morbidity is unclear when warfarin is continued or when bridging therapy is administered.	✓✓✓	✓✓	✓✓	✓✓✓	✓✓

ICU, intensive care unit; NSAID, nonsteroidal anti-inflammatory drug

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

RECOMMENDATIONS – cessation of medication

R7
GRADE C

In patients undergoing CABG either with or without CPB (OPCAB), clopidogrel therapy should be stopped, where possible, at least 5 days before surgery (Grade C).

R8
GRADE C

In patients undergoing noncardiac surgery, it is reasonable to continue low dose aspirin therapy. This may require specific evaluation in neurosurgery and intraocular surgery (Grade C).

RECOMMENDATIONS – cessation of medication	
R9 GRADE C	In patients undergoing elective orthopaedic surgery, NSAID therapy should be ceased preoperatively to reduce blood loss and transfusion (Grade C). The timing of the cessation should reflect the agent's pharmacology.
R10 GRADE B	In patients undergoing minor dental procedures, arthrocentesis, cataract surgery, upper gastrointestinal endoscopy without biopsy or colonoscopy without biopsy, warfarin may be continued (Grade B).

PRACTICE POINTS – cessation of medication	
PP8	In patients undergoing cardiac surgery, aspirin may be continued until the time of surgery.
PP9	In patients receiving clopidogrel who are scheduled for elective noncardiac surgery or other invasive procedures, a multidisciplinary approach should be used to decide whether to cease therapy or defer surgery, balancing the risk of bleeding and thrombotic events. Specific evaluation is required for patients who had a recent stroke, or received a drug-eluting stent within the last 12 months or a bare metal stent within the last 6 weeks. If a decision is made to cease therapy preoperatively, this should occur 7–10 days before surgery.
PP10	In patients receiving warfarin who are scheduled for elective noncardiac surgery or other invasive procedures (excluding minor procedures—see Recommendation 10); specific management according to current guidelines is required (e.g. guidelines from the American College of Chest Physicians[6] and the Australasian Society of Thrombosis and Haemostasis).[7]

CABG, coronary artery bypass surgery; CPB, cardiopulmonary bypass; NSAID, nonsteroidal anti-inflammatory drug; OPCAB, off-pump coronary artery bypass

3.6 Effect of perioperative strategies that minimise blood loss

Question 3 (Interventional) POQ3

In patients undergoing surgery, what is the effect of perioperative strategies that minimise blood loss on morbidity, mortality and blood transfusion?

Meticulous surgical technique is the cornerstone of intraoperative blood conservation. Additional measures contributing to surgical haemostasis are summarised in Box 3.1.

Box 3.1 Surgical haemostasis options

- Careful planning of actual surgical procedure, taking account of blood conservation
- Vascular conserving anatomical operative approaches
- Minimally invasive surgery
- Positioning of patient to reduce venous and arterial pressure in the surgical field
- Limb exsanguination before the application of a tourniquet
- Use of a surgical tourniquet at correct limb occlusion pressure to enable surgeons to work in a bloodless operative field
- Perioperative use of vasoconstrictors such as ropivacaine or dilute adrenaline (+/– local anaesthetics)
- Electrosurgical diathermy and harmonic scalpel techniques (e.g. argon beam, cavitational ultrasonic surgical aspirator [CUSA])
- Controlled intraoperative hypotension
- Use of topical agents (e.g. thrombin, collagen, fibrin glue, tranexamic acid)[145]
- Systemic antifibrinolytics (e.g. tranexamic acid)
- Consideration of the use of reduced prime volume and smaller circuits in patients undergoing cardiopulmonary bypass (retrograde autologous priming)[146]

3.6.1 Preoperative autologous donation

The detailed findings of the systematic review for this intervention can be found in Section 3.10.1 of Volume 1b of the technical report.[4] The systematic review process identified nine Level I studies and two RCTs that assessed the effect of preoperative autologous donation (PAD) in patients undergoing surgery. There was substantial overlap between many of the systematic reviews. Therefore, two Cochrane reviews, both of good quality, were chosen as the basis of the evidence review.[146,147]

Transfusion requirements

In adult patients undergoing surgery in which substantial blood loss is anticipated, although PAD decreases the incidence of allogeneic RBC transfusion, it increases the *overall* incidence of RBC transfusion.[147] The authors concluded that, 'although the use of PAD provides the patient with a sense of wellbeing, knowing they will receive their own blood if needed, the process is not without its own risks'.

Haemoglobin concentration

Henry et al (2001) found that patients who underwent PAD had significantly lower preoperative haemoglobin concentration than patients who did not pre-donate blood.[147] However, Bouchard et al (2008) found no significant difference in haemoglobin concentration between PAD patients and control, preoperatively or 5 days after surgery.[148]

EVIDENCE STATEMENTS – preoperative autologous donation	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing surgery in which substantial blood loss is anticipated, PAD reduces the incidence of allogeneic blood transfusion.	✓	✓✓	✓✓✓	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, PAD increases the overall incidence of blood transfusion.	✓	✓	✓✓	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, PAD may reduce the volume of allogeneic blood transfusion.	✓	**NA**	✓✓	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, PAD does not appear to have an effect on the overall volume of blood transfusion.	✓	**NA**	✓✓	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of PAD on blood loss is uncertain.	✓	✓	**X**	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of PAD on mortality is uncertain.	**X**	**NA**	**X**	✓	✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of PAD on morbidity is uncertain.	✓	✓	**X**	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of PAD on quality of life is unknown.	**NA**	**NA**	**NA**	**NA**	**NA**
In adult patients undergoing surgery in which substantial blood loss is anticipated, PAD reduces preoperative haemoglobin concentration.	✓	✓✓	✓	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, PAD does not appear to have an effect on prothrombin time.	✓	✓✓✓	**X**	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of PAD on length of hospital stay is uncertain.	✓	✓✓✓	**X**	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of PAD on length of ICU stay is uncertain.	✓	**NA**	**X**	✓	✓✓

ICU, intensive care unit; PAD, preoperative autologous donation; RBC, red blood cell

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

RECOMMENDATION – preoperative autologous donation

R11
GRADE C

The *routine* use of PAD is not recommended because, although it reduces the risk of allogeneic RBC transfusion, it increases the risk of receiving any RBC transfusion (allogeneic and autologous) (Grade C).

PAD, preoperative autologous donation; RBC, red blood cell

3.6.2 Prevention of hypothermia

The detailed findings of the systematic review for this intervention can be found in Section 3.6.1 of Volume 1b of the technical report.[4] The literature search identified three Level I systematic reviews[149–151] and five Level II studies[152–156] – of varying quality – examining the effect of hypothermia prevention strategies during surgery.

Transfusion requirements and blood loss

Meta-analyses of the treatment effect reported in Level I and II studies indicated that use of hypothermia prevention strategies resulted in significant reductions in transfusion incidence (22%) and blood loss (14%).

Morbidity

One RCT found that hypothermia prevention during surgery significantly reduced the risk of morbid cardiac events and wound infection.[151] Another RCT found that the rate of wound infection was significantly lower in patients who were warmed preoperatively.[154]

EVIDENCE STATEMENTS – prevention of hypothermia	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing surgery in which substantial blood loss is anticipated, the prevention of hypothermia reduces the incidence of transfusion.	✓✓✓	✓✓	✓✓	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the prevention of hypothermia may reduce the volume of transfusion.	✓	✓	X	✓	✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the prevention of hypothermia reduces blood loss.	✓✓✓	✓	✓✓	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of the prevention of hypothermia on mortality is uncertain.	✓	NA	X	✓✓	✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the prevention of hypothermia reduces the incidence of wound infection.	✓✓	✓✓	✓	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of the prevention of hypothermia on quality of life is unknown.	NA	NA	NA	NA	NA

EVIDENCE STATEMENTS – prevention of hypothermia	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of the prevention of hypothermia on haemoglobin concentration is uncertain.	✓	✓✓✓	X	✓	X
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of the prevention of hypothermia on length of hospital stay is uncertain.	✓	✓	NA	X	✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of the prevention of hypothermia on length of intensive care unit stay is uncertain.	✓	✓	NA	X	✓

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

RECOMMENDATION – prevention of hypothermia

R12

GRADE A

In patients undergoing surgery, measures to prevent hypothermia should be used (Grade A).

3.6.3 Appropriate patient positioning

The detailed findings of the systematic review for this intervention can be found in Section 3.9.1 of Volume 1b of the technical report.[4] The systematic review process identified six RCTs of fair to good quality examining the effect of appropriate patient positioning during surgery.[157–162] Four studies examined the effect of patient posture on blood loss; of these, three demonstrated that lateral, reverse Trendelenburg or appropriate prone positioning reduced blood loss.[158,161,162]

EVIDENCE STATEMENTS – appropriate patient positioning	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing orthopaedic surgery, the effect of patient positioning on the incidence of allogeneic blood transfusion is uncertain.	✓✓	✓✓	X	✓✓	✓✓
In adult patients undergoing orthopaedic surgery, the effect of patient positioning on the volume of allogeneic blood transfusion is uncertain.	✓✓	✓✓✓	X	✓✓	✓
In adult patients undergoing certain types of surgery, the head-up and lateral patient positions are associated with reduced blood loss.	✓	✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of patient positioning on mortality is unknown.	**NA**	**NA**	**NA**	**NA**	**NA**
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of patient positioning on morbidity is uncertain.	✓	✓✓✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of patient positioning on quality of life is unknown.	**NA**	**NA**	**NA**	**NA**	**NA**

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

PRACTICE POINT – appropriate patient positioning

PP11	**Excessive venous pressure at the site of surgery should be avoided by appropriate patient positioning, both during and after the procedure.**

3.6.4 Deliberate induced hypotension

The detailed findings of the systematic review for this intervention can be found in Section 3.5.1 of Volume 1b of the technical report.[4] The systematic review process identified one Level I study that assessed the effect of deliberate induced hypotension on blood loss and transfusion volume in patients undergoing orthopaedic surgery.[163] The systematic review also identified 10 Level II studies (RCTs) of fair to good quality, in patients undergoing a variety of surgical procedures.[164–172]

The Level I study included 17 RCTs, which covered six different methods of deliberate hypotension: sodium nitroprusside, volatile anaesthetic, prostaglandin E, epidural blockade, reminfentanil and propranolol. In 16 of the 17 RCTs, the measured mean arterial blood pressure ranged from about 50–80 mmHg.

In patients undergoing radical prostatectomy or major joint replacement, deliberate induced hypotension was associated with a significant reduction in operative blood loss. Induced hypotension also significantly reduced the volume of blood transfusion – the incidence of receiving a blood transfusion in the hypotensive groups was 55.8%, compared to 78.7% in the control groups.[163]

EVIDENCE STATEMENTS for deliberate induced hypotension	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing radical prostatectomy, deliberate induced hypotension (MAP 50–60 mmHg) reduces the incidence of allogeneic blood transfusion.	✓✓	✓✓	✓✓✓	✓	✓
In adult patients undergoing radical prostatectomy or major joint replacement, deliberate induced hypotension (MAP 50–60 mmHg) reduces the volume of allogeneic blood transfusion.	✓✓✓	✓✓✓	✓✓	✓✓	✓✓
In adult patients undergoing radical prostatectomy, major joint replacement or breast reduction surgery, deliberate induced hypotension (MAP 50–60 mmHg) reduces the volume of blood loss.	✓✓✓	✓✓✓	✓✓	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of deliberate induced hypotension (MAP 50–60 mmHg) on mortality is uncertain.	✓✓	**NA**	**X**	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of deliberate induced hypotension (MAP 50–60 mmHg) on morbidity is uncertain.	✓✓	✓✓	**X**	✓	✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of deliberate induced hypotension (MAP 50–60 mmHg) on quality of life is unknown.	**NA**	**NA**	**NA**	**NA**	**NA**
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of deliberate induced hypotension (MAP 50–60 mmHg) on haemoglobin concentration is uncertain.	✓	**X**	**X**	✓	✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of deliberate induced hypotension (MAP 50–60 mmHg) on coagulation status is uncertain.	✓✓	**NA**	**X**	✓	✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of deliberate induced hypotension (MAP 50–60 mmHg) on length of hospital stay is uncertain.	✓✓	**NA**	**X**	✓	✓✓

MAP, mean arterial pressure

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

RECOMMENDATION – deliberate induced hypotension	
R13 **GRADE C**	In patients undergoing radical prostatectomy or major joint replacement, if substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, deliberate induced hypotension (MAP 50–60 mmHg) should be considered, balancing the risk of blood loss and the preservation of vital organ perfusion (Grade C).

MAP, mean arterial blood pressure

3.6.5 Acute normovolemic haemodilution

The detailed findings of the systematic review for this intervention can be found in Section 3.1.1 of Volume 1b of the technical report.[4] The systematic review process identified 5 Level I studies[146,173–176] and 14 Level II studies[177–190] (RCTs) of variable quality that assessed the effect of acute normovolemic haemodilution (ANH) in patients undergoing surgery.

Transfusion requirements

A meta-analysis demonstrated that, overall, the incidence and volume of allogeneic blood transfusion were significantly lower for patients who received ANH. However, methods of ANH differed between studies, and the results were not consistent for all types of surgery studied.

EVIDENCE STATEMENTS – acute normovolemic haemodilution	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing surgery in which substantial blood loss is anticipated, ANH reduces the incidence of allogeneic blood transfusion.	✓	✓	✓✓	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, ANH may reduce the volume of allogeneic blood transfusion.	✓	✓	✓	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on blood loss is uncertain.	✓	✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on mortality is uncertain.	✓	✓✓✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on morbidity is uncertain.	✓	✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on quality of life is unknown.	NA	NA	NA	NA	NA

EVIDENCE STATEMENTS – acute normovolemic haemodilution	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on postoperative haemoglobin concentration is uncertain.	✓	✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on risk of reoperation for bleeding is uncertain.	✓	✓✓✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on coagulation parameters is uncertain.	✓	**NA**	X	✓	✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on length of hospital stay is uncertain.	✓	✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of ANH on length of ICU stay is uncertain.	✓	✓✓✓	X	✓✓	✓✓

ANH, acute normovolemic haemodilution; ICU, intensive care unit

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

RECOMMENDATION – acute normovolemic haemodilution

R14

GRADE C

In adult patients undergoing surgery in which substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, the use of ANH should be considered (Grade C).

PRACTICE POINT – acute normovolemic haemodilution

PP12

ANH requires a local procedural guideline that addresses patient selection, vascular access, volume of blood withdrawn, choice of replacement fluid, blood storage and handling, and timing of reinfusion.

ANH, acute normovolemic haemodilution

3.6.6 Intraoperative cell salvage

The detailed findings of the systematic review for this intervention can be found in Section 3.2.1 of Volume 1b of the technical report.[4] The systematic review process identified five Level I studies[174,191–194] and nine Level II studies[195–203] (RCTs), of fair to good quality.

Transfusion requirements

Meta-analyses found that, overall, the incidence and volume of allogeneic blood transfused were significantly lower for the individuals who received intraoperative cell salvage.

EVIDENCE STATEMENTS – for intraoperative cell salvage	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing surgery in which substantial blood loss is anticipated, intraoperative cell salvage reduces the incidence of allogeneic blood transfusion.	✓✓	✓	✓✓	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, intraoperative cell salvage may reduce the volume of allogeneic blood transfused.	✓✓	✓	✓	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intraoperative cell salvage on operative blood loss is uncertain.	✓✓✓	✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intraoperative cell salvage on mortality is uncertain.	✓✓	✓✓✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intraoperative cell salvage on morbidity is uncertain.	✓✓	✓✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intraoperative cell salvage on quality of life is unknown.	**NA**	**NA**	**NA**	**NA**	**NA**
In adult patients undergoing off-pump coronary artery surgery, intraoperative cell salvage may increase postoperative haemoglobin concentration and haematocrit.	✓✓	✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intraoperative cell salvage on risk of reoperation for bleeding is uncertain.	✓	✓✓✓	X	✓✓	✓✓
In adult patients undergoing off-pump coronary artery surgery, the effect of intraoperative cell salvage on coagulation status is uncertain.	✓	✓✓✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intraoperative cell salvage on length of hospital stay is uncertain.	✓✓✓	✓✓✓	X	✓✓	✓✓
In adult patients undergoing cardiac surgery, the effect of intraoperative cell salvage on intensive care unit admission and length of stay is uncertain.	✓✓	✓✓✓	X	✓✓	✓✓

RBC, red blood cell

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

RECOMMENDATION – intraoperative cell salvage	
R15 **GRADE C**	In adult patients undergoing surgery in which substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, intraoperative cell salvage is recommended (Grade C).

PRACTICE POINT – intraoperative cell salvage	
PP13	Intraoperative cell salvage requires a local procedural guideline that should include patient selection, use of equipment and reinfusion. All staff operating cell salvage devices should receive appropriate training, to ensure knowledge of the technique and proficiency in using it.

3.6.7 Perioperative acute normovolemic haemodilution combined with intraoperative cell salvage

The detailed findings of the systematic review for this intervention can be found in Section 3.3.1 of Volume 1b of the technical report.[4] The systematic review identified two fair-quality Level II studies (RCTs) examining the effect of combined perioperative ANH and intraoperative cell salvage.[204,205]

Transfusion requirements

One study observed a significant reduction in both the incidence and volume of allogeneic blood transfusion.[204] The other study found a significant reduction in volume of allogeneic blood transfused compared with the control, but no effect on incidence.[205] However, neither study demonstrated an additive effect of the combined interventions.

EVIDENCE STATEMENTS – perioperative acute normovolemic haemodilution combined with intraoperative cell salvage	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing surgery in which substantial blood loss is anticipated, a combination of ANH and intraoperative cell salvage may reduce the incidence of allogeneic blood transfusion.	✓	✓✓	✓✓	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, a combination of ANH and intraoperative cell salvage may reduce the volume of allogeneic blood transfusion.	✓	✓✓✓	✓	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of a combination of ANH and intraoperative cell salvage on blood loss is uncertain.	✓	NA	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of a combination of perioperative ANH and intraoperative cell salvage on mortality is uncertain.	✓	NA	X	✓	✓✓

EVIDENCE STATEMENTS – perioperative acute normovolemic haemodilution combined with intraoperative cell salvage	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of a combination of perioperative ANH and intraoperative cell salvage on morbidity is uncertain.	✓	✓✓✓	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of a combination of ANH and intraoperative cell salvage on quality of life is unknown.	**NA**	**NA**	**NA**	**NA**	**NA**
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of a combination of ANH and intraoperative cell salvage on postoperative haemoglobin concentration is uncertain.	✓	**NA**	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of a combination of ANH and intraoperative cell salvage on risk of reoperation for bleeding is uncertain.	✓	**NA**	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of a combination of ANH and intraoperative cell salvage on hospital length of stay is uncertain.	✓	✓✓✓	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of a combination of ANH and intraoperative cell salvage on ICU length of stay is uncertain.	✓	✓✓✓	X	✓	✓✓

ANH, acute normovolemic haemodilution

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

3.6.8 Point-of-care testing

The detailed findings of the systematic review for this intervention can be found in Section 3.7.1 of Volume 1b of the technical report.[4] A preliminary literature search found limited evidence for the effect of point-of-care testing other than thromboelastography (TEG). The CRG decided to limit the scope of this intervention to comparative studies of TEG and TEG-based point-of-care tests, which are predominantly used intraoperatively. Five Level II studies and two Level III studies were identified, of poor to fair quality.[205–210]

Transfusion requirements

A meta-analysis found that the use of a TEG-based transfusion algorithm resulted in a significant reduction in the incidence of transfusion with fresh frozen plasma (FFP) and platelets, and may have reduced the incidence of RBC transfusion, compared with the use of a transfusion protocol that was not TEG based.

EVIDENCE STATEMENTS – point-of-care testing	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing cardiac surgery, the use of thromboelastography may reduce the incidence of FFP transfusion.	✓	✓	✓✓	✓✓	✓✓
In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on the incidence of RBC transfusion is uncertain.	✓	✓	X	✓✓	✓✓
In adult patients undergoing cardiac surgery, the use of thromboelastography may reduce the incidence of platelet transfusion.	✓	✓	✓✓	✓✓	✓✓
In adult patients undergoing cardiac surgery, the use of thromboelastography may reduce the volume of FFP transfused.	✓	✓✓	✓	✓✓	✓✓
In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on volume of RBC transfusion is uncertain.	✓	✓✓✓	X	✓✓	✓✓
In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on volume of platelet transfusion is uncertain.	✓	✓	✓	✓✓	✓✓
In adult patients undergoing cardiac surgery, the use of thromboelastography does not appear to have an effect on blood loss.	✓	✓✓	X	✓✓	✓✓
In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on mortality is uncertain.	✓	✓✓✓	X	✓✓	✓
In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on morbidity is uncertain.	✓	NA	X	✓✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of the use of thromboelastography on quality of life is unknown.	NA	NA	NA	NA	NA
In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on haemoglobin concentration is uncertain.	✓	✓✓✓	X	✓✓	✓✓
In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on the risk of reoperation for bleeding is uncertain.	✓	✓✓✓	X	✓✓	✓✓
In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on coagulation status is uncertain.	✓	NA	X	✓✓✓	✓✓

EVIDENCE STATEMENTS – point-of-care testing	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on length of hospital stay is uncertain.	✓	**NA**	**X**	✓✓✓	✓✓✓
In adult patients undergoing cardiac surgery, the effect of the use of thromboelastography on length of ICU stay is uncertain.	✓	**NA**	**X**	✓✓✓	✓✓✓

FFP, fresh frozen plasma; ICU, intensive care unit; RBC, red blood cell

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

RECOMMENDATION – point-of-care testing

R16

GRADE C

In adult patients undergoing cardiac surgery, the use of TEG should be considered (Grade C).

TEG, thromboelastography

3.6.9 Administration of antifibrinolytics and desmopressin

The detailed findings of the systematic review for these interventions can be found in Section 3.8.1 of Volume 1b of the technical report.[4] Only intravenous administration of these agents was considered in this guideline. Some evidence was identified for other types of administration; this is presented in Section 3.8.1 of Volume 1b of the technical report.[4]

Aprotinin

The results of a head-to-head RCT comparing aprotinin with the lysine analogues tranexamic acid and ε-aminocaproic acid in patients undergoing high-risk cardiac surgery were published in 2008.[211] Due to the higher death rate associated with aprotinin compared with the lysine analogues, this study was terminated early, and a worldwide suspension of the supply of aprotinin injection was announced.

Due to these safety concerns, and the restricted availability of aprotinin, these guidelines make no recommendations on the use of aprotinin. However, the available evidence regarding aprotinin is included here.

The systematic literature search for evidence of the effectiveness and safety of aprotinin was limited to the comparison between aprotinin therapy and no therapy (i.e. no treatment or placebo). The systematic review identified 19 Level I studies, of which a good-quality Cochrane review was chosen to provide the pivotal evidence for intravenous aprotinin in an adult perioperative population,[212] and five reviews of fair to good quality to provide supportive evidence.[213–217] An additional six recent Level II studies (RCTs) of fair to good quality were identified that compared intravenous aprotinin therapy with no therapy.[218–223]

Transfusion requirements

Published meta-analyses demonstrated that aprotinin therapy compared with no therapy was highly effective at reducing the incidence and volume of allogeneic blood transfusion, and the volume of total blood loss.[212] These findings were consistent across most surgery types and, in particular, the most commonly studied surgery types: cardiac and orthopaedic surgery.

Reoperation for bleeding

Meta-analyses demonstrated that aprotinin therapy, compared with no therapy, significantly reduced the rate of reoperation for bleeding.[212]

Mortality and morbidity

Overall, the effect of aprotinin on mortality and morbidity is uncertain due to underpowering in the trials comparing aprotinin therapy with no therapy.

EVIDENCE STATEMENTS – aprotinin	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous aprotinin therapy reduces the incidence of allogeneic blood transfusion compared with no therapy.	✓✓✓	✓✓	✓✓	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous aprotinin therapy reduces the volume of allogeneic blood transfusion compared with no therapy.	✓✓✓	✓✓	✓✓	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous aprotinin therapy reduces blood loss compared with no therapy.	✓✓✓	✓✓	✓	✓✓	✓✓
In adult patients undergoing cardiac surgery, the effect of intravenous aprotinin therapy on mortality, compared with no therapy, is uncertain.	✓✓✓	✓	x	✓✓	✓✓
In adult patients undergoing coronary artery bypass surgery, the effect of intravenous aprotinin therapy on coronary artery graft occlusion, compared with no therapy, is uncertain.	✓✓✓	✓	x	✓✓✓	✓
In adult patients undergoing cardiac surgery, intravenous aprotinin therapy does not appear to have an effect on the risk of myocardial infarction compared with no therapy.	✓✓✓	✓✓	x	✓✓	✓✓
In adult patients undergoing hip replacement surgery, the effect of intravenous aprotinin therapy on the risk of myocardial infarction, compared with no therapy, is uncertain.	✓✓✓	✓✓	x	✓✓	✓✓

EVIDENCE STATEMENTS – aprotinin	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous aprotinin therapy does not appear to affect the risk of postoperative renal failure.	✓✓✓	✓	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous aprotinin therapy may impair postoperative renal function compared with no therapy.	✓✓✓	✓	✓	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous aprotinin therapy on the risk of stroke, compared with no therapy, is uncertain.	✓✓✓	✓✓✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous aprotinin therapy on the risk of venous thromboembolism, compared with no therapy, is uncertain.	✓✓✓	✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous aprotinin therapy on quality of life, compared with no therapy, is unknown.	**NA**	**NA**	**NA**	**NA**	**NA**
In adult patients undergoing cardiac surgery, intravenous aprotinin therapy reduces the risk of reoperation for bleeding compared with no therapy.	✓✓✓	✓✓	✓✓	✓✓	✓✓
In adult patients undergoing noncardiac surgery, the effect of intravenous aprotinin therapy on reoperation for bleeding, compared with no therapy, is uncertain.	✓✓✓	✓✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous aprotinin therapy has no effect on hospital length of stay compared with no therapy.	✓✓✓	✓✓	X	✓✓	✓✓

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

PRACTICE POINT – aprotinin

PP14 There is evidence for the beneficial effect of intravenous aprotinin on incidence and volume of transfusion, blood loss, and the risk of reoperation for bleeding. However, the drug has been withdrawn due to concerns that it is less safe than alternative therapies.[a]

[a] Websites of the Therapeutic Goods Administration (www.tga.gov.au), MedSafe (www.medsafe.govt.nz) and United States Food and Drug Administration (www.fda.gov)

Tranexamic acid

The systematic literature search for evidence of the effectiveness and safety of tranexamic acid was limited to the comparison between tranexamic acid therapy and no therapy (i.e. no treatment or placebo). Thus, a formal systematic review comparing tranexamic acid with other agents (e.g. aprotinin, ε-aminocaproic acid and desmopressin) was not conducted. The systematic review identified 19 Level I studies, of which one good-quality Cochrane review provided the pivotal evidence for intravenous tranexamic acid in an adult perioperative population,[212] and five reviews of fair to good quality provided supportive evidence.[213,215–217,224] An additional 13 recent Level II studies (RCTs) of variable quality were identified that compared intravenous tranexamic acid therapy with no therapy.[221,225–236]

In the pivotal evidence review, the authors note that the dose regimens for tranexamic acid varied significantly between trials. In the cardiac trials, the loading or bolus dose ranged from 2.5 mg/kg to 100 mg/kg, while the maintenance dose ranged from 0.25 mg/kg/hour to 4.0 mg/kg/hour delivered over 1–12 hours.[212] Similar dosing variations were observed in trials assessing other surgery types. As such, the CRG was unable to recommend an evidence-based dosing regimen. Clinicians are referred to the manufacturer's product information to determine dosing for the clinical setting.

Transfusion requirements

Meta-analyses conducted in the Henry et al (2007) review showed that tranexamic acid therapy significantly reduces the incidence of allogeneic transfusion in patients undergoing cardiac surgery (by 31%) and major orthopaedic surgery (by 56%).[212] In the subgroup of RCTs in which a transfusion protocol was used, tranexamic acid therapy resulted in a significant decrease in the incidence of transfusion compared to no therapy; however, there was no significant difference in studies where no transfusion protocol was used.

Of trials that reported units of allogeneic blood transfused in the overall study population, meta-analysis indicated that tranexamic acid therapy significantly reduced (by an average of 1.12 units) the volume of allogeneic transfusion compared with no therapy.[212]

Blood loss

Meta-analysis showed that tranexamic acid therapy significantly reduced the total volume of blood loss compared with no therapy.[212] For patients undergoing cardiac surgery or orthopaedic surgery, the reduction in total blood loss was approximately 440 mL.

Mortality and morbidity

Overall, the effect of tranexamic acid on mortality and morbidity is uncertain due to underpowering in the trials comparing tranexamic therapy with no therapy. Meta-analyses indicated that treatment with tranexamic acid therapy was not associated with increased mortality or morbidity.[212]

EVIDENCE STATEMENTS – tranexamic acid	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing cardiac surgery and major orthopaedic surgery, intravenous tranexamic acid therapy reduces the incidence of allogeneic blood transfusion compared with no therapy.	✓✓✓	✓✓	✓✓	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous tranexamic acid therapy may reduce the volume of allogeneic blood transfusion compared with no therapy.	✓✓✓	✓✓	✓	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous tranexamic acid therapy reduces blood loss compared with no therapy.	✓✓✓	✓✓	✓✓	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous tranexamic acid therapy on mortality, compared with no therapy, is uncertain.	✓✓✓	✓✓✓	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous tranexamic acid therapy does not appear to have an effect on risk of myocardial infarction compared with no therapy.	✓✓✓	✓✓✓	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous tranexamic acid therapy on risk of stroke, compared with no therapy, is uncertain.	✓✓✓	✓✓✓	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous tranexamic acid therapy on risk of thrombosis, compared with no therapy, is uncertain.	✓✓✓	✓✓✓	X	✓	✓✓
In adult patients undergoing cardiac surgery, the effect of intravenous tranexamic acid therapy on risk of renal failure or dysfunction, compared with no therapy, is uncertain.	✓✓✓	X	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous tranexamic acid therapy on quality of life, compared with no therapy, is unknown.	NA	NA	NA	NA	NA

EVIDENCE STATEMENTS – tranexamic acid	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing cardiac surgery, the effect of intravenous tranexamic acid therapy on risk of reoperation for bleeding, compared with no therapy, is uncertain.	✓✓✓	✓✓✓	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous tranexamic acid therapy does not appear to affect hospital length of stay compared with no therapy.	✓✓✓	X	X	✓	✓✓

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

RECOMMENDATIONS – tranexamic acid

R17
GRADE A

In adult patients undergoing cardiac surgery, the use of intravenous tranexamic acid is recommended (Grade A).

R18
GRADE B

In adult patients undergoing noncardiac surgery, if substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, the use of intravenous tranexamic acid is recommended (Grade B).

Epsilon-aminocaproic acid

The following text should be read while keeping in mind that ε-aminocaproic acid injection is not currently registered in Australia.

The systematic literature search for evidence of the effectiveness and safety of ε-aminocaproic acid was limited to the comparison between ε-aminocaproic acid therapy and no therapy (i.e. no treatment or placebo). Thus, a formal systematic review comparing ε-aminocaproic acid with other agents (e.g. aprotinin, tranexamic acid and desmopressin) was not conducted. The systematic review identified 13 Level I studies, of which a good-quality Cochrane review provided the pivotal evidence for intravenous ε-aminocaproic acid in an adult perioperative population,[212] and four reviews of fair to good quality provided supportive evidence.[213,215–217] An additional two recent Level II studies (RCTs) of good and fair quality were identified that compared intravenous ε-aminocaproic acid therapy with no therapy.[237,238]

In the pivotal evidence review, the authors noted that the dose regimens for ε-aminocaproic acid varied significantly between trials.[212] The loading dose ranged from 80 mg to 15 g (75–150 mg/kg); and the maintenance dose ranged from 1 g/hour to 2 g/hour (12.5–30 mg/kg/hour), infused over varying time periods.

Transfusion requirements

Meta-analyses conducted in the Henry et al (2007) review showed that intravenous ε-aminocaproic acid significantly reduced the incidence of allogeneic transfusion in patients undergoing cardiac surgery (by 35%) but not orthopaedic surgery or liver surgery; however, this may be due to the smaller amount of evidence available for noncardiac surgery.[212] In the subgroup of RCTs in which a transfusion protocol was used, ε-aminocaproic acid therapy resulted in a significant decrease in the incidence of transfusion compared with no therapy; there was no significant difference in the one study where no transfusion protocol was used.

Of trials that reported units of allogeneic blood transfused in the overall study population, meta-analysis indicated that ε-aminocaproic acid therapy significantly reduced (by an average of 1.77 units) the volume of allogeneic transfusion compared with no therapy.[212] However, there was no significant difference in trials that reported units of allogeneic blood transfused in those patients that received transfusion.

Blood loss

Meta-analysis showed that ε-aminocaproic acid therapy reduced postoperative blood loss compared with no therapy.[212] For patients undergoing cardiac surgery or orthopaedic surgery, the reduction in postoperative blood loss was approximately 196 mL and 276 mL, respectively. In the six trials that reported intraoperative blood loss, there was a reduction in blood loss in favour of ε-aminocaproic acid in patients undergoing cardiac surgery but not orthopaedic surgery.[212,237,238]

Mortality and morbidity

Overall, the effect of ε-aminocaproic acid on mortality and morbidity is uncertain due to a lack of power in the studies reviewed.

EVIDENCE STATEMENTS – ε-aminocaproic acid	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing cardiac surgery, intravenous ε-aminocaproic acid therapy reduces the incidence of allogeneic blood transfusion compared with no therapy.	✓✓✓	✓✓	✓✓	✓✓✓	✓✓
In adult patients undergoing noncardiac surgery in which substantial blood loss is anticipated, the effect of intravenous ε-aminocaproic acid therapy on the incidence of allogeneic blood transfusion, compared with no therapy, is uncertain.	✓✓✓	✓✓	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous ε-aminocaproic acid therapy on volume of allogeneic blood transfusion, compared with no therapy, is uncertain.	✓✓✓	✓	X	✓	✓
In adult patients undergoing cardiac surgery, intravenous ε-aminocaproic acid therapy reduces blood loss compared with no therapy.	✓✓✓	✓✓	✓✓	✓✓✓	✓✓
In adult patients undergoing major orthopaedic surgery, intravenous ε-aminocaproic acid therapy may reduce blood loss compared with no therapy.	✓✓✓	✓	✓	✓✓	✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous ε-aminocaproic acid therapy on mortality, compared with no therapy, is uncertain.	✓✓✓	✓✓✓	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous ε-aminocaproic acid therapy on risk of myocardial infarction, compared with no therapy, is uncertain.	✓✓✓	✓✓	X	✓	✓✓

EVIDENCE STATEMENTS – ε-aminocaproic acid	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous ε-aminocaproic acid therapy on risk of stroke, compared with no therapy, is uncertain.	✓✓✓	✓✓✓	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous ε-aminocaproic acid therapy on risk of venous thromboembolism, compared with no therapy, is uncertain.	✓✓	✓✓✓	X	✓	✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous ε-aminocaproic acid therapy on quality of life, compared with no therapy, is unknown.	**NA**	**NA**	**NA**	**NA**	**NA**
In adult patients undergoing cardiac surgery, the effect of intravenous ε-aminocaproic acid therapy on risk of reoperation for bleeding, compared with no therapy, is uncertain.	✓✓✓	✓✓✓	✓✓	✓✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous ε-aminocaproic acid therapy on length of hospital stay, compared with no therapy, is uncertain.	✓✓	X	X	✓	✓

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

RECOMMENDATION – ε-aminocaproic acid

R19

GRADE C

In adult patients undergoing cardiac surgery, the use of intravenous ε-aminocaproic acid is recommended (Grade C).

PRACTICE POINT – ε-aminocaproic acid

PP15

There is evidence for the beneficial effect of intravenous ε-aminocaproic acid on reduction of perioperative blood loss and volume of transfusion (Grade C). However, the drug is not marketed in Australia and New Zealand.

Desmopressin

Desmopressin is registered in Australia for use as an antidiuretic; in diabetes insipidus, mild to moderate haemophilia A, von Willebrand disease (excluding type IIB) in pre-dental or minor surgery; and in cases of excessive bleeding associated with platelet disorders. In relation to minimisation of bleeding and transfusion, the product information for desmopressin states that it is indicated for:

> *… patients undergoing cardiac surgery with cardiopulmonary bypass for prosthetic valve replacement or aortocoronary bypass grafting, especially when it is complicated by platelet function defects sufficient to prolong bleeding time despite relatively normal platelet cover. Desmopressin acetate offers no benefit as routine therapy in patients having an uncomplicated (simple) cardiopulmonary bypass procedure.*

The systematic literature search for evidence of the effectiveness and safety of desmopressin was limited to the comparison between desmopressin therapy and no therapy (i.e. no treatment or placebo). Thus, a formal systematic review comparing desmopressin with other agents (e.g. aprotinin, tranexamic acid and ε-aminocaproic acid) was not conducted. The systematic review identified seven Level I studies, of which one fair-quality review provided the pivotal evidence for intravenous desmopressin in an adult perioperative population;[239] and two reviews of good quality provided supportive evidence.[214,240] A literature search was conducted to identify recent Level II evidence; no additional RCTs were identified.

In the pivotal evidence review, the authors noted that the dose of desmopressin varied slightly across the 42 included RCTs, being mostly a single 0.3 µg/kg dose administered over 15–30 minutes during surgical haemostasis.[239] In six studies the dose was repeated, and in eight studies it was administered immediately before surgery.

Transfusion requirements

Meta-analyses conducted in the Crescenzi et al (2008) review showed that desmopressin did not significantly reduce the incidence of transfusion of blood products (including red blood cells, FFP and platelets) for cardiac surgery or noncardiac surgery.[239] However, meta-analysis of the subgroup of RCTs that assessed desmopressin therapy in patients undergoing primary coronary artery bypass surgery showed a significant reduction in transfusion incidence (by 15%) compared with no therapy, which was not seen in the subgroup of RCTs that assessed desmopressin therapy in patients undergoing complex cardiac surgery.[240] Of the RCTs in patients undergoing cardiac surgery that reported the incidence of transfusion with platelets only, desmopressin therapy did not significantly reduce the incidence of transfusion compared with no therapy.[239]

Desmopressin therapy significantly reduces the volume of transfusion overall; however, in the subgroup of RCTs that assessed desmopressin in patients undergoing cardiac surgery, the effect was not statistically significant.

Blood loss

Meta-analyses of the volume of blood loss showed a statistically significant reduction overall in patients on desmopressin therapy compared with no therapy. This effect was significant in the subgroup of RCTs that assessed desmopressin in patients undergoing cardiac surgery, but not in patients undergoing noncardiac surgery.[239]

Mortality and morbidity

Overall, the effect of intravenous desmopressin on mortality and morbidity is uncertain due to underpowering of studies. However, desmopressin use resulted in a large and statistically significantly increased risk of post-administration transient hypotension.[239,240] The direction and magnitude of the risks of mortality and stroke suggest that desmopressin may be associated with an increased risk for these outcomes.[239,240] Although the results of the meta-analyses did not reach statistical significance, this may have been due to a lack of statistical power rather than a lack of risk associated with desmopressin therapy.

EVIDENCE STATEMENTS – desmopressin	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing primary coronary artery bypass surgery, intravenous desmopressin therapy reduces the incidence of allogeneic blood transfusion compared with no therapy.	✓✓✓	✓✓	X	✓✓✓	✓✓
In adult patients undergoing complex cardiac surgery, intravenous desmopressin therapy does not reduce the incidence of allogeneic blood transfusion compared with no therapy.	✓✓✓	✓✓	X	✓✓✓	✓✓
In adult patients undergoing cardiac surgery, intravenous desmopressin therapy may reduce the incidence of platelet transfusion compared with no therapy.	✓✓✓	✓✓	X	✓✓✓	✓✓
In adult patients undergoing noncardiac surgery in which substantial blood loss is anticipated, intravenous desmopressin therapy does not appear to reduce the incidence of allogeneic blood transfusion compared with no therapy.	✓✓✓	✓✓	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous desmopressin therapy may reduce the volume of transfusion compared with no therapy.	✓✓✓	✓	✓✓	✓	✓✓
In adult patients undergoing cardiac surgery, intravenous desmopressin therapy reduces blood loss compared with no therapy.	✓✓✓	✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous desmopressin therapy on mortality, compared with no therapy, is uncertain.	✓✓✓	✓✓✓	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous desmopressin therapy on risk of myocardial infarction, compared with no therapy, is uncertain.	✓✓✓	✓✓	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous desmopressin therapy on risk of stroke, compared with no therapy, is uncertain.	✓✓✓	✓✓✓	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous desmopressin therapy on risk of thrombosis, compared with no therapy, is uncertain.	✓✓✓	✓✓✓	X	✓	✓✓

EVIDENCE STATEMENTS – desmopressin	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing surgery in which substantial blood loss is anticipated, intravenous desmopressin therapy increases the risk of mild and transient hypotension compared with no therapy.	✓✓✓	✓✓✓	X	✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of intravenous desmopressin therapy on quality of life, compared with no therapy, is unknown.	**NA**	**NA**	**NA**	**NA**	**NA**
In adult patients undergoing cardiac surgery, the effect of intravenous desmopressin therapy on risk of reoperation for bleeding, compared with no therapy, is uncertain.	✓✓✓	✓✓✓	✓✓	✓✓✓	✓✓

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

PRACTICE POINT – desmopressin

PP16 In adult patients undergoing surgery in which substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, the *routine* use of desmopressin is not supported, due to uncertainty about the risk of stroke and mortality.

3.6.10 Postoperative cell salvage

The detailed findings of the systematic review for this intervention can be found in Section 3.9.2 of Volume 1b of the technical report.[4] The systematic review identified five Level I studies, of fair to good quality, and three Level II studies, of poor to fair quality relevant to postoperative cell salvage.

Transfusion requirements

A meta-analysis showed that the use of postoperative cell salvage resulted in a significant reduction in the incidence of transfusion in patients undergoing orthopaedic surgery, but not in patients undergoing cardiac surgery.[191]

In studies that used transfusion protocols, postoperative cell salvage resulted in a significant decrease in the incidence of transfusion compared to no cell salvage; however, there was no significant difference in studies where no transfusion protocol was used.

EVIDENCE STATEMENTS – postoperative cell salvage	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In adult patients undergoing total knee arthroplasty, postoperative cell salvage reduces the incidence of allogeneic blood transfusion.	✓	✓✓	✓✓✓	✓✓	✓✓
In adult patients undergoing cardiac surgery, postoperative cell salvage may reduce the incidence of allogeneic blood transfusion.	✓	✓	X	✓✓	✓✓
In adult patients undergoing cardiac surgery or total knee arthroplasty, postoperative cell salvage reduces the volume of allogeneic blood transfusion.	✓	✓✓	✓	✓✓	✓✓
In adult patients undergoing cardiac surgery or total knee arthroplasty, postoperative cell salvage does not appear to have an effect on total blood loss.	✓	✓✓✓	X	✓✓	✓✓
In adult patients undergoing cardiac surgery, the effect of postoperative cell salvage on mortality is uncertain.	✓	✓✓✓	X	✓✓	✓✓
In adult patients undergoing cardiac surgery or total knee arthroplasty, postoperative cell salvage does not appear to have an effect on morbidity, including infection.	✓	✓✓✓	X	✓✓	✓✓
In adult patients undergoing surgery in which substantial blood loss is anticipated, the effect of postoperative cell salvage on quality of life is unknown.	**NA**	**NA**	**NA**	**NA**	**NA**
In adult patients undergoing total knee arthroplasty, the effect of postoperative cell salvage on haemoglobin concentration is uncertain.	✓	✓✓✓	X	✓✓✓	✓✓
In adult patients undergoing cardiac surgery, the effect of postoperative cell salvage on risk of reoperation for bleeding is uncertain.	✓	✓✓✓	X	✓✓	✓✓
In adult patients undergoing cardiac surgery and total knee arthroplasty, postoperative cell salvage may reduce length of hospital stay.	✓	✓	✓	✓✓	✓✓

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

RECOMMENDATION – postoperative cell salvage

R20

GRADE C

In adult patients undergoing cardiac surgery or total knee arthroplasty, in whom significant postoperative blood loss is anticipated, postoperative cell salvage should be considered (Grade C).

3.7 Triggers for blood component transfusion

Question 9 (Prognostic) GNQ6

In patients undergoing surgery, at what INR (PT/APTT) for FFP, fibrinogen level for cryoprecipitate and platelet count for platelet concentrates should patients be transfused to avoid risks of significant adverse events?

APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalised ratio; PT, prothrombin time

The systematic review identified 16 relevant studies (6 Level II and 10 Level III, of fair to good quality) examining the effect of abnormal coagulation parameters on outcomes in patients undergoing surgery or invasive procedures.[241–255] These studies included a diverse range of invasive procedures, including biopsies (visceral, endoscopic and laparoscopic), central venous cannulation, lumbar puncture, nephrostomy and femoral arteriography. There was insufficient evidence to define a threshold platelet count, fibrinogen level or INR that is associated with significant adverse events.[241–255] Worsening thrombocytopenia may be associated with an increase in minor bleeding complications.[242,243,248,252,256] Appendix E provides blood component information and dosage, for use if a decision is made to transfuse blood components.

EVIDENCE STATEMENT – triggers for blood component transfusion	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In patients undergoing invasive procedures, including biopsies (visceral, endoscopic and laparoscopic), central venous cannulation, lumbar puncture, nephrostomy and femoral arteriography, there is insufficient evidence to define a threshold platelet count, fibrinogen level or INR that is associated with significant adverse events. Worsening thrombocytopenia may be associated with an increase in minor bleeding complications.	✓✓	✓✓✓	X	✓✓	✓✓

INR, international normalised ratio

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

PRACTICE POINTS – triggers for blood component transfusion	
PP17	In general, patients with a platelet count ≥50 × 10^9/L *or* an INR ≤2 can undergo invasive procedures without any serious bleeding; however, lower platelet counts and higher INRs may be tolerated.
PP18	Specialist guidelines or haematology advice should be sought for at-risk patients undergoing intracranial, intraocular and neuraxial procedures, and for patients with severe thrombocytopenia or coagulopathy.

INR, international normalised ratio

3.8 Effect of blood components on outcomes

Question 8 (Interventional) GNQ5

In patients undergoing surgery, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes?

FFP, fresh frozen plasma

3.8.1 Effect of fresh frozen plasma

One systematic review of the effect of FFP on patient outcomes in a perioperative population was identified. The study included six Level II studies (poor quality, due to small numbers and lack of allocation concealment).[257] Overall, there was no evidence that the prophylactic use of FFP affected perioperative blood loss in cardiac surgery. In critically ill surgical patients, the administration of FFP may be associated with an increased risk of infection.[258]

3.8.2 Effect of cryoprecipitate or fibrinogen concentrate

No studies were identified that investigated the effect of cryoprecipitate or fibrinogen concentrate on patient outcomes in a perioperative population.

3.8.3 Effect of platelet transfusion

Three fair-quality Level III studies that investigated the effect of platelet transfusion on patient outcomes in a perioperative population were identified.[259–261] All studies were in cardiac surgery patients. The largest and smallest of these studies demonstrated an association between the administration of platelets, and hospital mortality and morbidity.[260,261] The remaining study did not demonstrate this association.[259]

EVIDENCE STATEMENTS – effect of blood components	Evidence	Consistency	Clinical impact	Generalisability	Applicability
The prophylactic administration of FFP following cardiopulmonary bypass does not reduce perioperative blood loss.	✓✓	✓✓	X	✓✓	✓
Administration of FFP to a post-surgical population in intensive care is associated with an increase in the rate of infection.	✓	NA	✓	✓	✓
In patients undergoing cardiac surgery, platelet transfusion may be associated with an increase in mortality.	✓✓	✓	✓✓	✓✓	✓

FFP, fresh frozen plasma

✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

RECOMMENDATION – fresh frozen plasma

R21

GRADE B

The prophylactic use of FFP in cardiac surgery is not recommended (Grade B).

FFP, fresh frozen plasma

PRACTICE POINT – platelets

PP19

The prophylactic use of platelets after cardiac surgery is not supported.

3.9 Effect of recombinant activated factor VII on outcomes

Question 7 (Interventional) GNQ4

In patients undergoing surgery, what is the effect of rFVIIa (prophylaxis or treatment) on morbidity, mortality and transfusion rate?

rFVIIa, recombinant activated factor VII

Currently, recombinant activated factor VII (rFVIIa) is approved in Australia and New Zealand for the control of bleeding and prophylaxis for surgery in patients with inhibitors to coagulation factors FVIII or FIX, congenital factor VII deficiency and Glanzmann's thrombasthenia (with glycoprotein IIb-IIIa, and/or antibodies to human leukocyte antigen plus refractoriness to platelet infusion). Any use outside of these indications is considered 'off-licence'.

Three systematic reviews (one of which was Level I and of good quality) were identified that investigated the clinical effectiveness of rFVIIa as either prophylaxis or treatment to manage bleeding in the perioperative setting.[262-264] Two reviews presented evidence pertaining only to cardiac surgery,[263,064] and one presented evidence from studies on a range of surgery types,[262] including prostatectomy, liver transplantation, orthopaedic surgery and cardiac surgery.

Another seven Level II studies (of poor to fair quality) were identified, of which three presented evidence pertaining to cardiac surgery,[265–267] and four presented evidence on a range of surgical procedures.[249,268–270]

EVIDENCE STATEMENTS – effect of recombinant factor VIIa	Evidence	Consistency	Clinical impact	Generalisability	Applicability
In surgical patients, there is insufficient evidence to determine the effect of prophylactic or therapeutic use of rFVIIa on mortality.	✓✓	✓	X	✓✓✓	✓✓
In surgical patients, there is insufficient evidence to determine the effect of prophylactic or therapeutic use of rFVIIa on the risk of thrombotic adverse events.	✓✓	✓	X	✓✓✓	✓✓
In surgical patients, the prophylactic or therapeutic use of rFVIIa may reduce the incidence of transfusion.	✓✓	✓✓	✓	✓✓✓	✓
In cardiac surgery patients, the prophylactic or therapeutic use of rFVIIa may reduce the likelihood of re-operation.	✓	✓✓	✓	✓✓✓	✓
In surgical patients, the prophylactic or therapeutic use of rFVIIa reduces blood loss.	✓	✓✓	✓	✓✓✓	✓
In surgical patients, there is insufficient evidence to determine the impact of prophylactic or therapeutic use of rFVIIa on hospital or ICU length of stay.	✓	✓✓	X	✓✓✓	✓

ICU, intensive care unit; rFVIIa, recombinant activated factor VII
✓✓✓= A; ✓✓= B; ✓= C; **X** = D (See Table 2.2); **NA** = not applicable

RECOMMENDATION – use of recombinant factor VIIa

R22

GRADE C

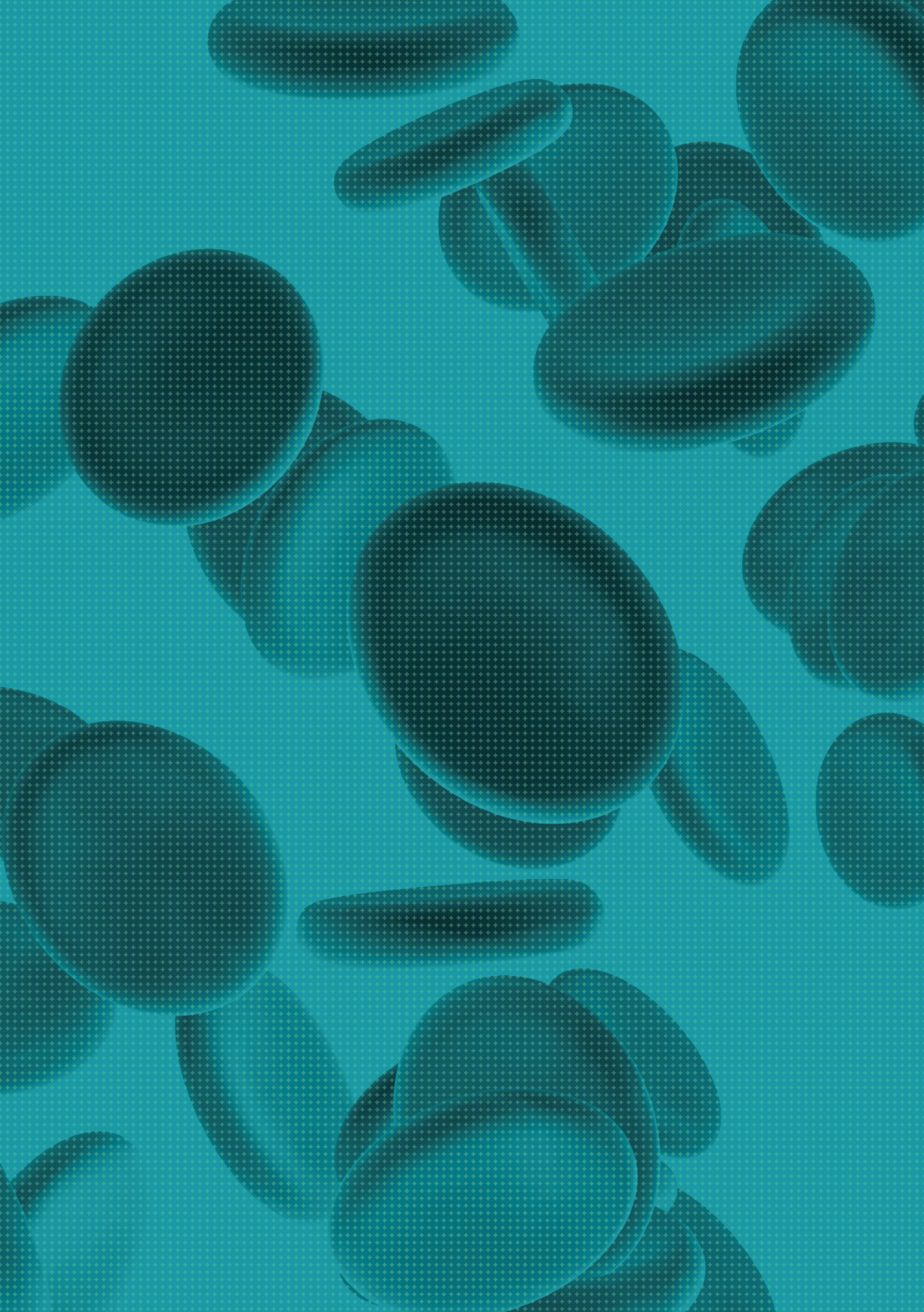
The prophylactic or routine therapeutic use of rFVIIa is not recommended because concerns remain about its safety profile, particularly in relation to thrombotic adverse events (Grade C).

PRACTICE POINT – use of recombinant factor VIIa

PP20

The administration of rFVIIa may be considered in the perioperative patient with life-threatening haemorrhage after conventional measures, including surgical haemostasis, use of antifibrinolytics and appropriate blood component therapy have failed.

rFVIIa, recombinant activated factor VII



4 Anaesthesia and patient blood management

The major role for the anaesthetist should be an active involvement in the multidisciplinary patient blood management program, including:

- preoperative optimisation of red cell mass and coagulation status
- meticulous attention to surgical haemostasis
- minimisation of perioperative blood loss (e.g. by optimising venous and arterial pressures at the site of surgery both during and after the procedure)
- appropriate management of postoperative anaemia.

This background section focuses on the influence of various anaesthetic agents and techniques on perioperative blood loss, including:

- volatile (inhalational) versus total intravenous anaesthesia (TIVA)
- regional (mainly neuraxial) versus general anaesthesia
- spontaneous versus controlled ventilation.

Increased emphasis on preservation of arterial blood pressure, particularly in the older patient with comorbidities, has meant that the practice of controlled intraoperative hypotension is being used less often (see also Section 3.6.4 in Chapter 3).

The impact that a particular anaesthetic technique can have on blood conservation depends not only on other blood conservation strategies employed, and the experience of the anaesthetist, but also the type of surgery and other factors that contribute to bleeding, such as anticoagulants and surgical technique.

Anaesthetists should be aware of the principles of perioperative patient blood management.

4.1 Volatile or total intravenous general anaesthesia?

Propofol-based TIVA has been associated with reduced blood loss in several settings, possibly due to the effects propofol has on haemodynamics and uterine tone.[271–273] Propofol, commonly combined with remifentanil, has been shown to result in less blood loss during endoscopic sinus surgery (median blood loss 19 mL vs 128 mL; p=0.004) and during tonsillectomy (1.2 mL/kg less; p=0.013)[274] when compared with volatile anaesthesia. Likewise, for first trimester pregnancy termination, propofol anaesthesia reduced blood loss (18.8 mL vs 40.4 mL; p=0.0011).[273] However, given the absolute reductions in blood loss found, the clinical impact of TIVA with regard to blood conservation must be minimal in these groups of patients.

Of potential benefit was reduction in blood loss observed during spinal surgery performed under propofol-based TIVA compared with sevoflurane (106 mL vs 315 mL; p=0.004), for the same blood pressure target.[272]

4.2 Neuraxial and other major regional techniques compared with general anaesthesia

A systematic review found that neuraxial block reduced requirement for transfusion of two or more units of RBCs by about 50% (p <0.001; OR=0.50, 95%CI: 0.39, 0.66), and that there was a similar reduction for postoperative bleeding that needed transfusion (OR=0.45; 95%CI: 0.29, 0.70).[275] Likewise, a meta-analysis found that neuraxial block reduced estimated blood loss by approximately 100–200 mL (p <0.001).[276]

Choice of anaesthesia technique for total hip arthroplasty should take account of the potential benefit of regional techniques with regard to blood conservation.

Reduced blood loss under neuraxial block is associated with lower arterial and central venous pressures, with spontaneous ventilation, and reduced wound venous pressures.[277–280]

Orthopaedics is the specialty in which there is the most reliable evidence for neuraxial block in reducing surgical bleeding. Blood loss for total hip joint replacement (THJR) can be reduced by an average of 275 mL[281] or 30–40%.[282] Neuraxial block also reduced blood loss during hip fracture repair by 85 mL (95% CI: –162, –9), although there was significant heterogeneity.[283] Similarly, neuraxial block with and without general anaesthesia for selected spinal column surgery has also been associated with reduced blood loss.[277,284] There is also evidence that lumbar plexus block reduces intraoperative (22%; 310 mL vs 617 mL) and total (45%; 712 mL vs 1074 mL) blood loss during THJR.[285,286]

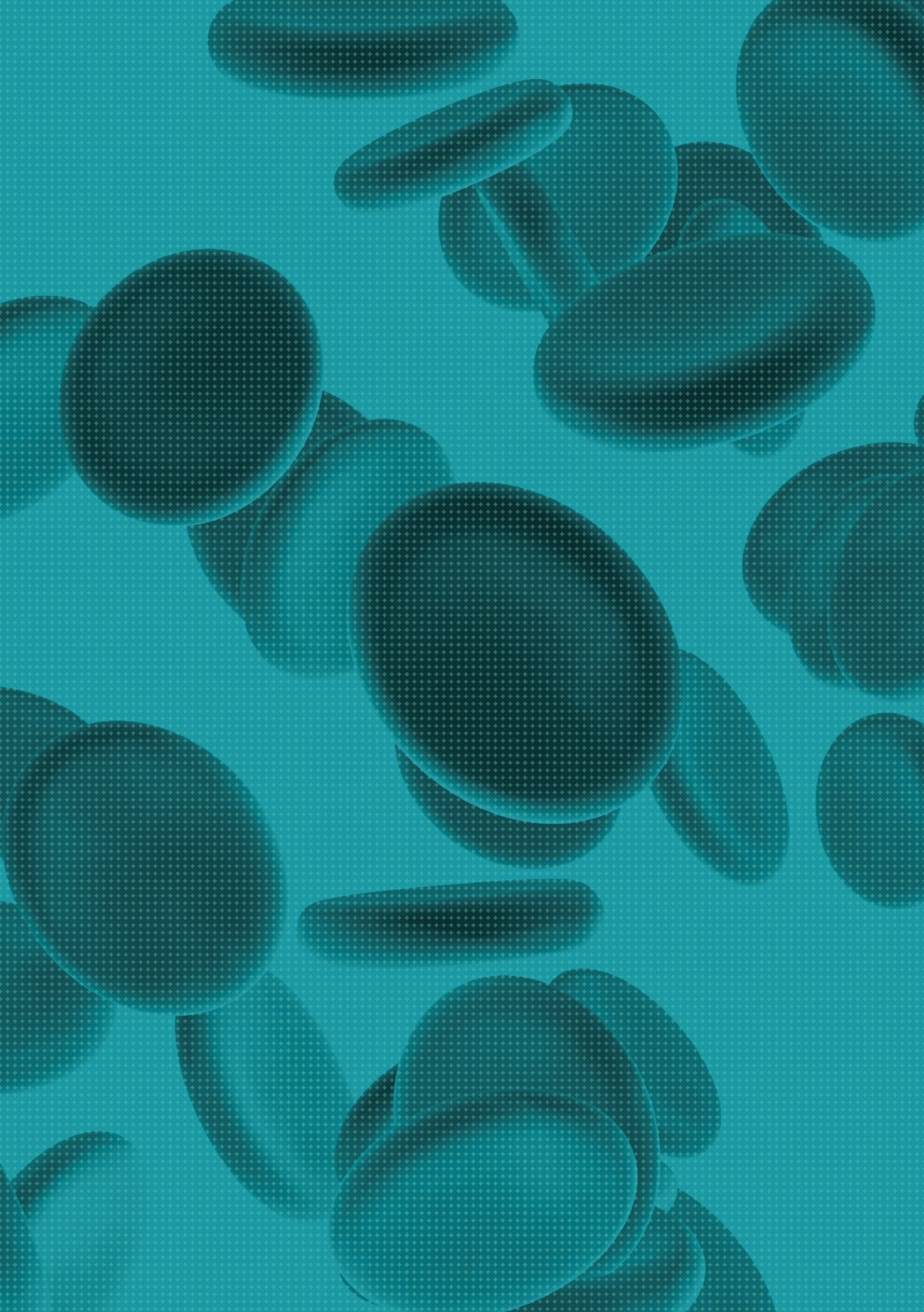
Although there is less evidence for the choice of anaesthesia having a significant effect on perioperative bleeding in other types of surgery, anaesthetists should be aware of the possible benefits of regional anaesthesia, TIVA and spontaneous ventilation in reducing blood loss.

Among others, several trials suggest that many previously identified benefits of neuraxial technique may be largely historical, with purported major benefits of neuraxial block having been eroded by progressive improvements in surgical, anaesthetic and perioperative care.[287–289] However, the previously identified intraoperative physiological effects of neuraxial techniques on blood loss might be expected to persist in at least some surgical populations. On the other hand, data heterogeneity was common in the meta-analyses,[287–289] and other practice changes, such as less tolerance of hypotension, may reverse some mechanisms, such as lowered central venous pressure, that are responsible for reducing blood loss.

The evidence for neuraxial anaesthesia reducing transfusion is also present, but should be considered in the context of current blood management. A meta-analysis reported a significant reduction for the surgical population as a whole (a heterogeneous group).[275] A study reporting total hip arthroplasty found that neuraxial anaesthesia reduced the transfusion rate to 12%, from 33% with general anaesthesia (OR 0.26, 95% CI: 0.06 to 1.05, p <0.001). Another study found that neuraxial anaesthesia was associated with an OR of 0.646 for needing transfusion.[290] However, the results of these studies should be interpreted with caution, given the more restrictive transfusion practices that have developed since much of the research was undertaken. Equally, the implementation of other blood conservation strategies may reduce or negate the illustrated benefits. Despite the limitations of these data, a reduction in surgical bleeding could be expected to reduce transfusion in at least a subgroup of patients.

4.3 Type of ventilation

Positive pressure ventilation has been associated with increased intraoperative blood loss compared with spontaneous ventilation during THJR under general anaesthesia.[279,282] This effect is possibly due to the impact that positive intrathoracic pressure has on decreasing venous return and increasing venous pressure at the operative site. Likewise, minimising expiratory resistance by manipulating ventilator parameters and optimising reactive airway disease should assist venous return and may reduce blood loss.[291] The impact that spontaneous ventilation has on reducing transfusion seems to be unclear.



5 Future directions

The systematic review for this module highlighted a lack of high-quality evidence. Further research is needed to provide a stronger evidence base. A number of the research gaps identified are currently being addressed; for example, through the FOCUS (Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair)[292] and TRIOS (Transfusion Requirements in Orthopaedic Patients Study)[293] trials.

This chapter:

- describes the evidence gaps identified for each review question and suggests areas of future research
- identifies topics that were not included in the systematic review, but may be considered in revisions of this module.

5.1 Evidence gaps and areas of future research

In this review, there are a number of evidence statements where the evidence is uncertain or unknown; these may present obvious avenues for further research.

The term 'perioperative', as used in this systematic review, did not necessarily capture the full range of emerging invasive procedures. Research specific to patient blood management in such procedures is an important area for investigation.

5.1.1 Effect of a multidisciplinary, multimodal, programmatic approach on outcomes

Question 1 (interventional)

In patients undergoing surgery, what is the effect of a multidisciplinary, multimodal, programmatic approach to perioperative patient blood management on patient outcomes?

Only a grade C recommendation could be made concerning the adoption of patient blood management programs. More evidence is required to support the use of such programs. An example is a recent study (published after the systematic review cut-off date) that demonstrated improved patient outcomes using a programmatic approach to patient blood management.[294]

5.1.2 Effect of haemostasis medication on outcomes

Question 2 (interventional)

In patients undergoing surgery, what effect does the cessation and timing of cessation of medication that affects haemostasis have on morbidity, mortality and RBC transfusion?

RBC, red blood cell

Further investigation is required regarding the perioperative management of surgical patients receiving antiplatelet agents, including aspirin or clopidogrel therapy.

5.1.3 Effect of minimisation of blood loss on outcomes

Question 3 (interventional)

In patients undergoing surgery, what is the effect of perioperative strategies that minimise blood loss on morbidity, mortality and blood transfusion?

Further studies are required on safety, efficacy and methodologies for ANH and perioperative cell salvage.

In the trials examined for this module, the role and methods of ANH and intraoperative cell salvage were biased, because the studies were not blinded and lacked sufficient power. The evidence for the use of washed rather than unwashed blood is unclear; further studies are needed to evaluate the safety of postoperative cell salvage using unwashed blood.

There is a need for further research in point-of-care testing including thromboelastographic techniques such as TEG and ROTEM (rotational thromboelastometry).

5.1.4 Effect of anaemia on outcomes

Question 4 (aetiological)

In patients undergoing surgery, is anaemia an independent risk factor for adverse outcomes?

There is a lack of studies assessing the effect of postoperative anaemia on patient outcomes. Such studies should address differing levels of anaemia and patient characteristics using outcomes such as functional recovery, morbidity and mortality.

5.1.5 Effect of red cell transfusion on outcomes

Question 5 (interventional)

In patients undergoing surgery, what is the effect of RBC transfusion on patient outcomes?

RBC, red blood cell

Studies evaluating mortality and morbidity were all Level III (i.e. of poor to fair quality) and did not control who received the intervention (i.e. RBC transfusion). Many studies demonstrated a dose-dependent relationship between RBC transfusion and increased risk of morbidity or mortality. However, the design of the studies was such that it was not possible to prove a causal relationship between the intervention and the observed outcomes.

The paucity of evidence in this area to guide clinical practice has been highlighted by the recent publication from the International Consensus Conference on Transfusion Outcomes (ICCTO) group.[60]

There is a need for well-designed studies on the effect of RBC transfusion on patient outcomes in a perioperative population.

5.1.6 Effect of non-transfusion interventions to increase haemoglobin concentration

Question 6 (interventional)

In patients undergoing surgery, what is the effect of non-transfusion interventions to increase haemoglobin concentration on morbidity, mortality and need for RBC blood transfusion?

RBC, red blood cell

Studies are needed in all preoperative anaemic patients, and in non-anaemic patients with depleted iron stores, to assess the efficacy and safety of non-transfusion interventions (including oral iron, IV iron or ESA therapy). Similar studies should be undertaken on postoperative patients.

5.1.7 Effect of recombinant activated factor VII on outcomes

Question 7 (interventional)

In patients undergoing surgery, what is the effect of rFVIIa (prophylaxis or treatment) on morbidity, mortality and transfusion rate?

rFVIIa, recombinant activated factor VII

Well-designed studies are needed to determine the impact of prophylactic or therapeutic use of rFVIIa on morbidity and mortality (including thrombosis) in surgical patients.

5.1.8 Effect of blood components on outcomes

Question 8 (interventional)

In patients undergoing surgery, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes?

FFP, fresh frozen plasma

There was no evidence to support the prophylactic use of FFP in patients undergoing cardiac surgery. Outside this context, the literature is insufficient to address the indications for, timing of and dose of blood component therapies. There remains a need for further studies to address these issues.

5.1.9 Triggers for blood component transfusion

Question 9 (prognostic)

In patients undergoing surgery, at what INR (or PT/APTT) for FFP, fibrinogen level for cryoprecipitate and platelet count for platelets concentrates should patients be transfused to avoid risks of significant adverse events?

APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalised ratio; PT, prothrombin time

There was insufficient evidence to define a threshold platelet count, fibrinogen level or INR (or PT/APTT) that is associated with significant adverse events in patients undergoing surgery. Well-designed studies are needed to address these evidence gaps.

5.2 Delivering patient blood management

The traditional laissez-faire attitude to blood administration results in risk to patients, expense to society and the waste of a gift given to save a life. Organisations should recognise and cherish the privilege of the responsibility of ensuring this gift is used in a way that exemplifies the best in health care. Patient blood management provides an opportunity to safely manage and moderate the use of products within Australia and New Zealand, while improving patient outcomes.

The CRG strongly advises that a nationally coordinated approach be developed for the implementation of perioperative patient blood management programs in Australia and New Zealand. This will require direct involvement by all levels of government. The CRG recognises there are significant challenges at national, jurisdictional and local levels that need to be addressed to facilitate the implementation of such an approach. The allocation of adequate resources is required. The recently established Western Australian Patient Blood Management Program provides a pilot model that is addressing many of these challenges.

A nationally coordinated approach to blood sector data management is needed, with close collaboration between clinical champions, academics, researchers and governments. Data linkage based on a standardised methodology, registry data, and standardised audits and surveys are all required to facilitate a better appreciation of where blood is being used and for what purpose.

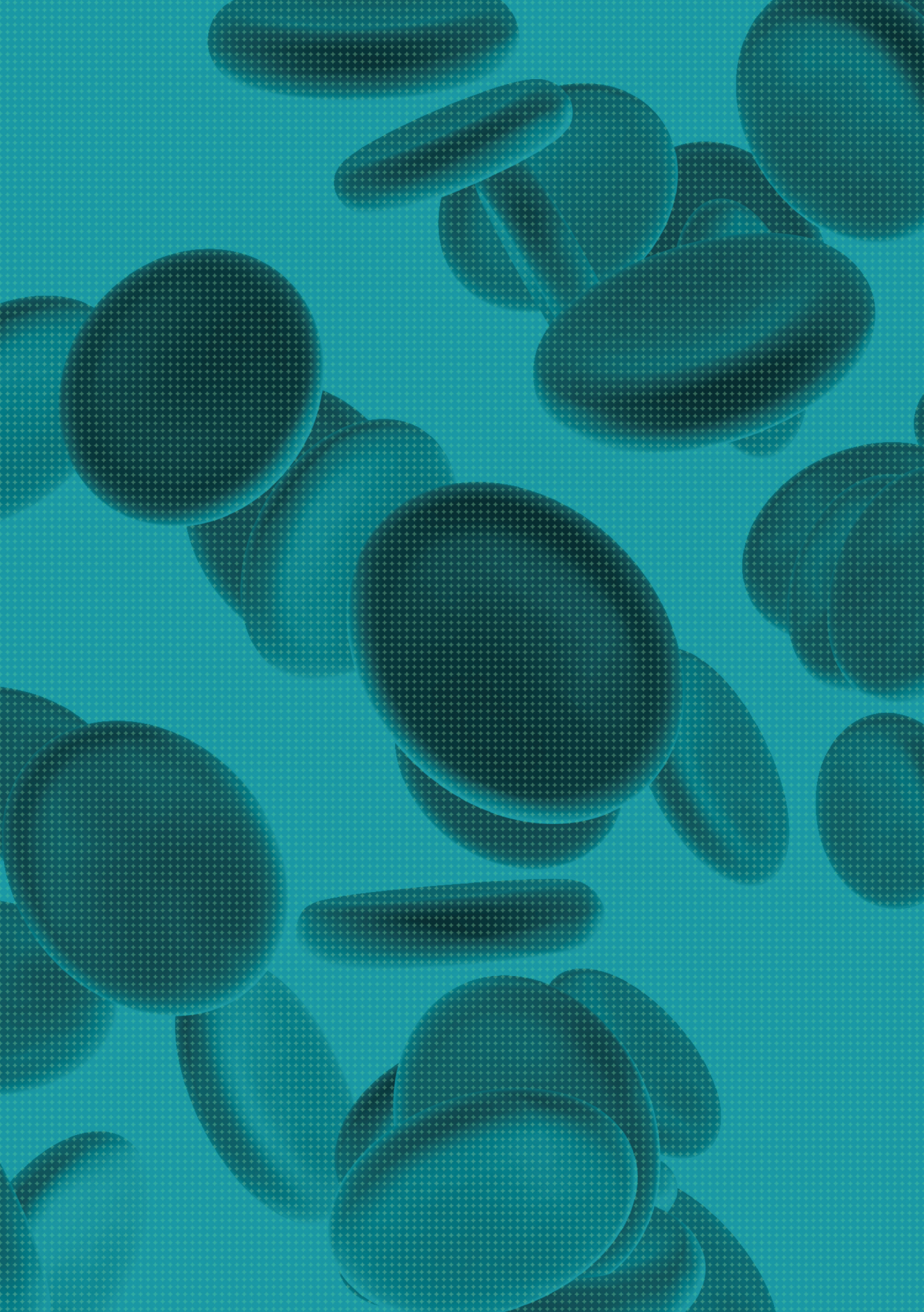
The establishment of coordinated patient blood management programs will help organisations to attain accreditation against national standards such as the new Blood and Blood Products Standard developed by the Australian Commission on Safety and Quality in Health Care. It will also help to meet the expectations expressed in the *Statement on National Stewardship Expectations in the Supply of Blood and Blood Products* endorsed by Australian health ministers. Similarly, in New Zealand, it will help hospitals and blood banks to comply with the standards used by Quality Health New Zealand and International Accreditation New Zealand, respectively.

Blood transfusion practice improvement programs have already been established in Australian jurisdictions. The CRG recommends that these programs be reviewed and adequately resourced to collaborate in the coordination and implementation of patient blood management.

Within this coordinated framework, each health service provider engaged in the delivery of major surgical services will need resources to systematically re-engineer the way perioperative care is delivered. This is crucial in order to initiate and sustain the key elements of a perioperative patient blood management program, including:

- preoperative identification and management of anaemia
- the use of a range of strategies for intraoperative blood conservation; importantly, the practice of safe meticulous surgery, preventing reckless loss of blood
- clinician re-education regarding patients' physiological tolerance of postoperative anaemia and awareness of the hazards of inappropriate use of RBC transfusion.

The widespread uptake and sustainability of coordinated multidisciplinary, multimodal patient blood management programs is important not only to provide improved clinical outcomes for individual patients, but also to preserve the national blood supply in the face of an ageing population, and the consequent increase in demand for blood component therapy. This also fulfils the ethical responsibility to all blood donors that their gift has improved the life of another.



6 Implementing, evaluating and maintaining the guidelines

The NBA, in collaboration with the Steering Committee and EWG members, developed a plan to guide appropriate communication on the implementation of this module. The plan identifies target audiences for the module, strategies and tools for effective implementation, communication channels and key messages.

Continued re-evaluation of the guidelines is necessary to reduce variation in practice patterns, support appropriate use of blood component therapy and reduce inappropriate exposure of patients to blood components.[295] A plan was designed to evaluate implementation of the six modules of the guidelines and to determine:

- the extent to which the guidelines influence changes in clinical practice and health outcomes
- what factors (if any) contribute to noncompliance with the guidelines.

The results of the evaluation will be used to inform future review of the guidelines. Economic issues were considered when formulating the evidence-based recommendations, and the recommendations will have cost implications. Savings are expected to be derived from reduced use of product and an associated reduction in hospital and laboratory costs. However, the CRG anticipates that additional costs will be incurred due to the system re-design and training associated with wider implementation of preoperative anaemia assessment and treatment, improved collection and use of data to inform practice, introduction of new surgical techniques and wider uptake of other technologies such as cell salvage. While economic models have indicated a net benefit from the implementation of patient blood management practices,[14,15] no economic model has been developed for the Australian setting. The NBA, together with the JBC and key stakeholders, is developing a program to facilitate uptake of the guidelines that take into account the challenges raised in Section 5.2. A number of initiatives have commenced, including initial investment in the development of a patient blood management toolkit that will help jurisdictions and individual hospitals to implement patient blood management practices. Patient blood management content has been included in nationally available education programs such as the BloodSafe eLearning Program and the Post Graduate Certificate in Transfusion Practice that is available through the University of Melbourne. Also under development is a national data dictionary that will facilitate data linkage and thus support jurisdictional evaluation of appropriate use of red cells.

This module will be reviewed and amended in 5 years unless an issue arises (e.g. new clinical evidence relevant to practice) that triggers a need for an earlier review.

The Principal Medical Officer of the NBA will convene the group of experts to undertake the review, and will be the person who can be contacted on major issues, events or practice changes.

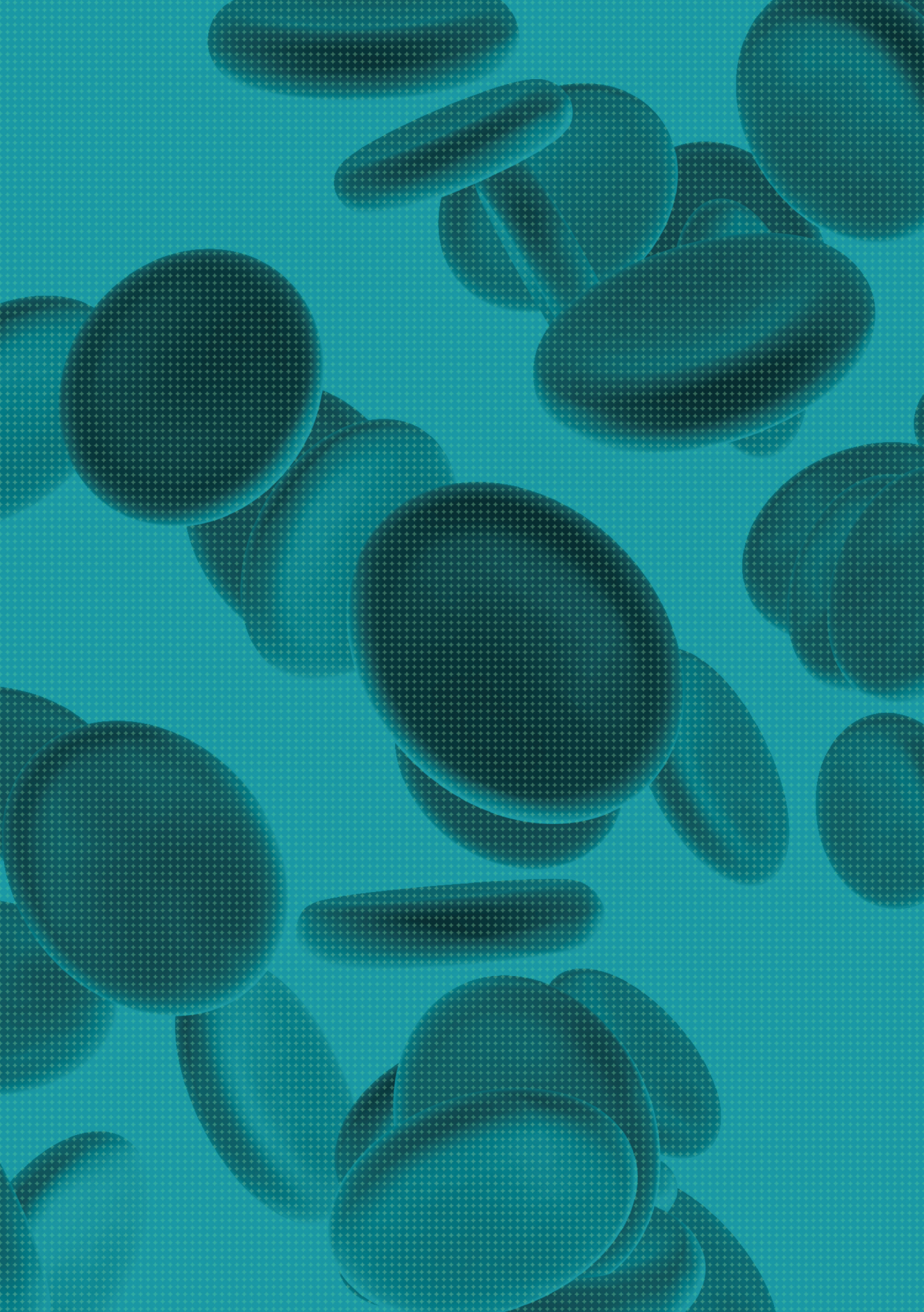
To provide feedback and inform future reviews of this module, please send any comments on its content or implementation, or on the accompanying materials, to:

- Email: guidelines@nba.gov.au
- Mail: Patient Blood Management Guidelines
  National Blood Authority
  Locked Bag 8430
  Canberra ACT 2601
- Fax: (02) 6211 8330

Any correspondence will be forwarded to the Principal Medical Officer for consideration in the next scheduled review.

A list of colleges and societies that have endorsed this module of the guidelines will be available on the NBA website.[c]

[c] http://www.nba.gov.au

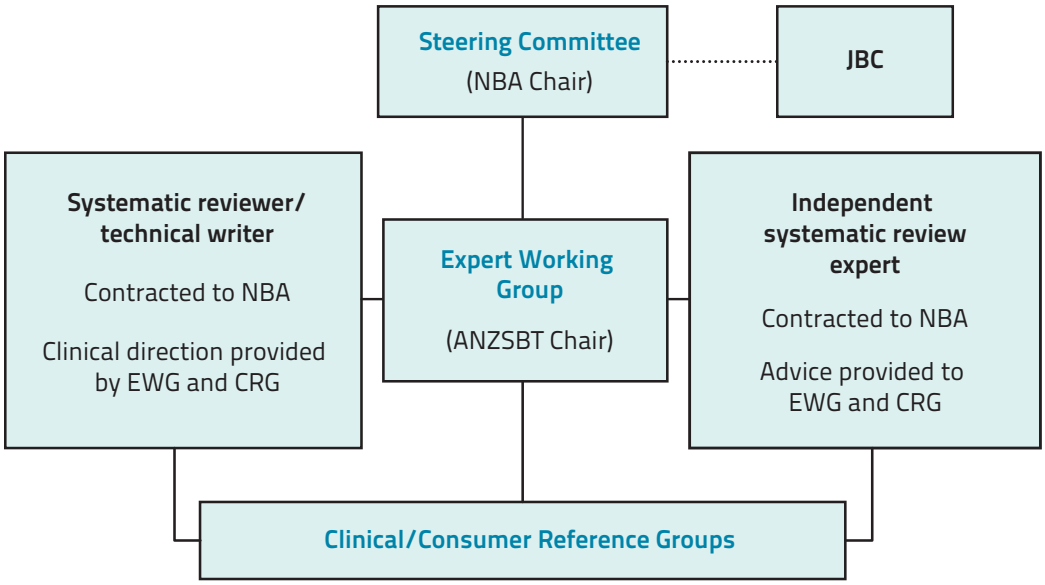


Appendix A
Governance

A1 Management framework for guideline development

Figure A.1 illustrates the management framework used to manage the development of the six modules of the guidelines, described in Section 1.2 of Chapter 1.

Figure A.1 Management framework for development of the guidelines



ANZSBT, Australian & New Zealand Society of Blood Transfusion; CRG, Clinical/Consumer Reference Group; EWG, Expert Working Group; JBC, Jurisdictional Blood Committee; NBA, National Blood Authority; NHMRC, National Health and Medical Research Council

A2 Terms of reference

Steering Committee

The overarching Steering Committee was established to provide coordination and direction for development of the guidelines. It was chaired by the NBA, with representation from the ANZSBT, the NHMRC (including a member from the National Institute of Clinical Studies), a state expert and an expert from the Australian Government Department of Health and Ageing. The role of the Steering Committee was to:

- develop and oversee the project plan for the revision of the guidelines
- recommend the membership of the EWG to the NBA Chief Executive Officer, who will appoint the recommended members
- endorse the scope of the project as proposed by the EWG, and the process by which it will be undertaken

- ensure that there is effective communication and consultation with all relevant stakeholders for the duration of the project, including the development of a communications and engagement strategy that meets NHMRC requirements
- provide information through the NBA to the JBC on the project
- review resources that are dedicated to the project, to ensure that they are sufficient for the project to meet its deadlines
- review and approve revisions to the project plan and terms of reference
- address other matters as raised by members of the Steering Committee or EWG.

Expert Working Group

The EWG was formed to advise the Steering Committee about the scope and structure of the guidelines, and to determine the focus of the systematic review of the evidence-based literature. The group's terms of reference were:

- to consider the scope of the project and proposed structure of the guidelines, as referred by the Steering Committee and, if necessary, to present recommendations for revisions to the Steering Committee
- under the guidance of the NHMRC GAR expert, to formulate the clinical questions to be answered by the literature review
- to provide clinical oversight for the development of the content of the guidelines, in particular, ensuring that:
  - the research undertaken is comprehensive
  - the quality of the revised guidelines will meet with clinical approval
- to provide recommendations on the terms of reference for the CRGs and oversee coordination of the activities of the CRGs
- to ensure appropriate engagement by consumers at all relevant points
- to assist in the development or review of tools and strategies to support the implementation and audit of the guidelines and review their uptake
- to facilitate consultation and the uptake of the guidelines
- to respond to any additional requirements to ensure compliance with the NHMRC guidelines development processes.

Systematic reviewers and technical writers

The NBA contracted systematic reviewers and technical writers to conduct systematic reviews of the scientific literature and provide technical writing services to produce each module and associated deliverables, including technical reports.

Clinical/Consumer Reference Groups

A CRG was formed to review each phase of the guidelines during development and, with the assistance of technical writers, to formulate recommendations aimed at optimising patient blood management based on systematic review findings, or, in the absence of evidence, to develop practice points through a consensus-based process. The CRG also provided advice to the EWG on guideline relevance and utility for targeted service providers and recipients who will use or benefit from the guidelines. Pertinent terms of reference for guidelines development included:

- the CRGs may review and offer advice on the set of questions to be put to the systematic review for the project
- the CRGs may review the draft guidelines and consumer materials, and offer advice on the way information is presented in terms of relevance and utility to the groups they represent
- the CRGs will not have authority or decision-making power over how that advice is used.

Guidelines Assessment Register expert

Two GAR experts were appointed by the NHMRC to provide advice and mentoring to the EWG and CRG, and to ensure that the new guidelines and the development process implemented by each reference group complied with NHMRC requirements.

A3 Membership of bodies involved in governance of the guidelines

Steering Committee

Dr Alison Turner (Chair)	National Blood Authority
Dr Heather Buchan	National Institute of Clinical Studies
Ms Cathy Clutton	National Health and Medical Research Council
Ms Vesna Cvjeticanin	National Health and Medical Research Council
Mr Ken Davis	Australian & New Zealand Society of Blood Transfusion
Prof Henry Ekert	Australian Government Department of Health & Ageing
Ms Sue Ireland	Jurisdictional Blood Committee
Dr Amanda Thomson	Australian & New Zealand Society of Blood Transfusion

Expert Working Group

Dr Craig French (Co-chair)	College of Intensive Care Medicine of Australia and New Zealand, and Australian & New Zealand Intensive Care Society
Dr Amanda Thomson (Co-chair)	Australian & New Zealand Society of Blood Transfusion
A/Prof Donald Bowden	Thalassaemia Australia

A/Prof Mark Dean	Haematology Society of Australia and New Zealand & Royal Australasian College of Physicians
Mr Shannon Farmer	Independent consumer advocate
Dr Chris Hogan	National Blood Authority
Ms Janine Learmont	Royal College of Nursing, Australia
Dr Helen Liley	Royal Australasian College of Physicians, Paediatric & Child Health Division
Dr Robert Lindeman	Royal College of Pathologists of Australasia
A/Prof Larry McNicol	Australian & New Zealand College of Anaesthetists
Prof John Olynyk	University of Western Australia Department of Medicine, Fremantle Hospital
Prof Michael Permezel	Royal Australian & New Zealand College of Obstetricians and Gynaecologists
Dr Kathryn Robinson	Australian Red Cross Blood Service
Dr Helen Savoia	Royal College of Pathologists of Australasia
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A4 Conflict of interest

All members of the Steering Committee, CRG and EWG declared any conflicts of interest before starting work on the guideline. Conflicts of interest were also reviewed at intervals, and were required to be declared at the start of each meeting. No conflicts of interest were declared, by any Steering Committee, CRG or EWG member, during the development of the *Patient Blood Management Guidelines: Module 2 Perioperative*.

A5 Acknowledgements

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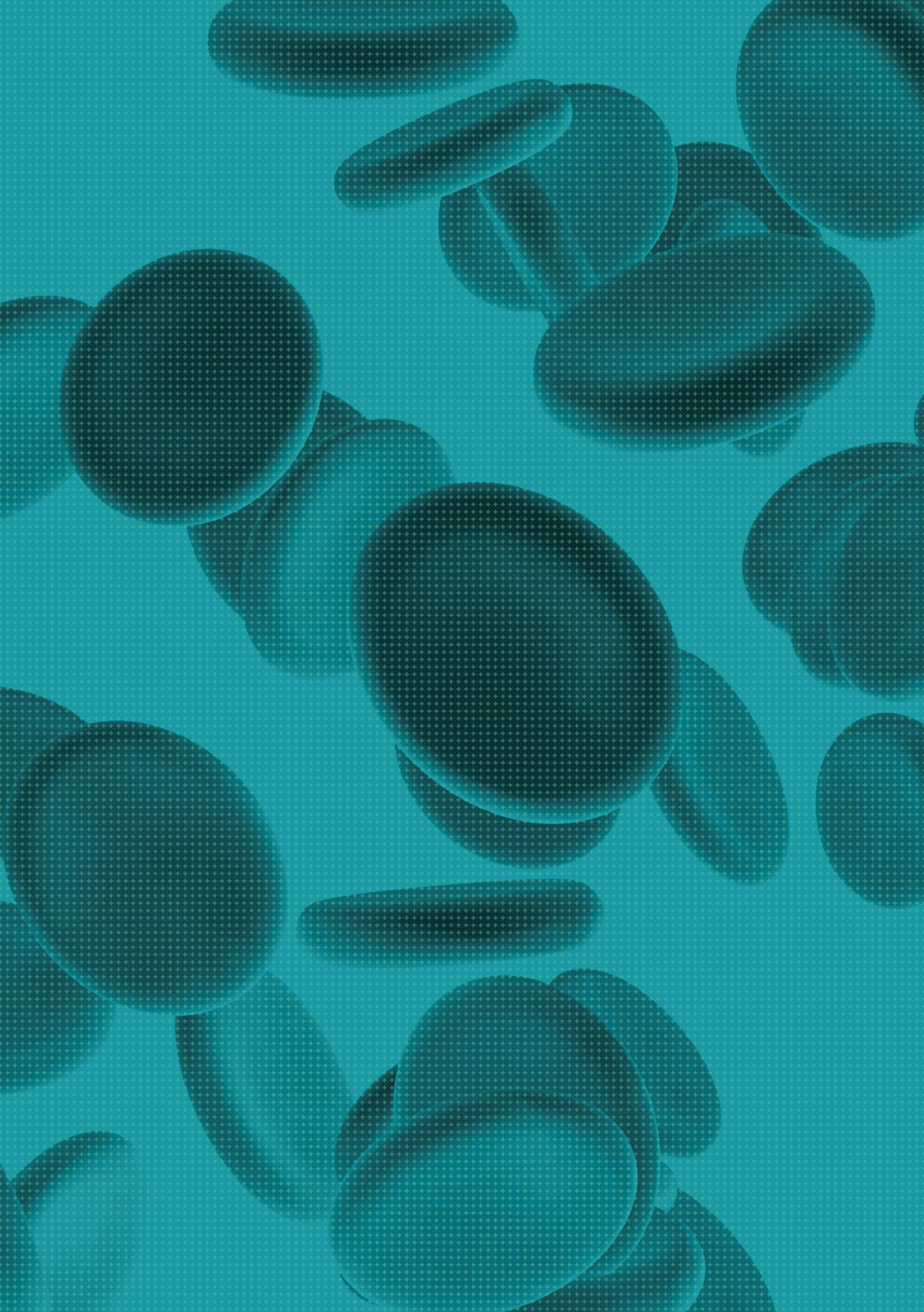
- the Western Australia Department of Health Patient Blood Management program
- the Medical Society for Blood Management
- the NBA Anaemia Management Working Group
- the Australian Iron Deficiency Expert Group.



Appendix B
Transfusion risks in the context of patient blood management

Traditionally, it has been assumed that blood transfusion benefits patients; however, a benefit has not been demonstrable in many clinical scenarios. In addition, evidence is accumulating that transfusion-related acute lung injury is more common than previously thought, and that more recently identified conditions – including transfusion-related immunomodulation – may cause patients harm.

The risk of transmission of infectious diseases has reduced significantly in recent years through improved manufacturing and laboratory processes. Nevertheless, there is still a small potential for transfusion of an unrecognised infectious agent.

Despite improvements in systems management, there remains a risk of transfusion-related harm due to administrative error. Such an error has the potential to result in acute haemolytic reaction from ABO incompatibility, which may be fatal.

Of the recognised adverse events associated with transfusion, the most common is transfusion-associated circulatory overload, which is reported in up to 1% of patients receiving transfusions.

The clinical decision to undertake transfusion therapy should only be made after full consideration of the risks and benefits. Table B.1 summarises the risks and benefits; Table B.2 puts the risks into perspective; and Table B.3 presents the Calman chart, which may be useful to clinicians for explaining risks to patients.[296]

Table B.1 Transfusion risks and benefits

THERAPY	RISKS	BENEFITS
Blood transfusion, including RBCs, platelets, FFP and cryoprecipitate	▪ Administrative error leading to transfusion of incorrect blood component, with potential for severe transfusion reaction (haemolytic) due to blood group (ABO) incompatibility ▪ Transfusion transmitted infections (extremely rare) ▪ Transfusion-related acute lung injury ▪ Other transfusion reactions (mild febrile to severe anaphylaxis) ▪ Bacterial infection from contaminated blood or platelets ▪ Transfusion-associated circulatory overload (usually iatrogenic) ▪ Transfusion-related immunomodulation	▪ RBC to prevent critical lack of oxygen to the body tissues ▪ Platelets to treat or prevent bleeding ▪ FFP to treat or prevent bleeding ▪ Cryoprecipitate to treat or prevent bleeding

FFP, fresh frozen plasma; RBC, red blood cell

Table B.2 Transfusion risks in perspective

TRANSFUSION RISK	ESTIMATED RATE [a] (HIGHEST TO LOWEST RISK)	CALMAN RATING [b]
Transfusion-associated circulatory overload (iatrogenic)	Up to 1 in 100 transfusions	High
Haemolytic reactions	Delayed: 1 in 4,000–9,000 Acute: 1 in 12,000–77,000	Low Very low
Anaphylaxis (IgA deficiency)	1 in 20,000–50,000	Very low
Bacterial sepsis: platelets	1 in 75,000	Very low
Bacterial sepsis: RBCs	1 in 500,000	Minimal
Transfusion-related acute lung injury	1 in 5,000–190,000	Low to minimal
Hepatitis B	1 in 739,000	Minimal
HIV	1 in 5.4 million	Negligible
Hepatitis C	1 in 2.7 million	Negligible
Malaria	1 in 4.9 million – 10.2 million	Negligible
Variant CJD (not tested)	Never reported in Australia	Negligible
Transfusion-associated graft-versus-host disease	Rare	Negligible
Transfusion-related immunomodulation	Not quantified	Unknown

CJD, Creutzfeldt-Jakob disease; IgA, immunoglobulin A; RBC, red blood cell

[a] Risk per unit transfused unless otherwise specified

[b] See Calman 1996[296]

Source: Australian Red Cross Blood Service website (www.transfusion.com.au), accessed 9 December, 2009

Note: The above estimates may change over time. Refer to the Australian Red Cross Blood Service website (www.transfusion.com.au) for the most recent risk estimates.

Table B.3 Calman chart [a] (United Kingdom risk per one year)

RATING	RATE	EXAMPLE
Negligible	<1 in 1,000,000	Death from lightning strike
Minimal	1 in 100,000–1,000,000	Death from train accident
Very low	1 in 10,000–100,000	Death from an accident at work
Low	1 in 1,000–10,000	Death from a road accident
High	>1 in 1,000	Transmission of chicken pox to susceptible household contacts

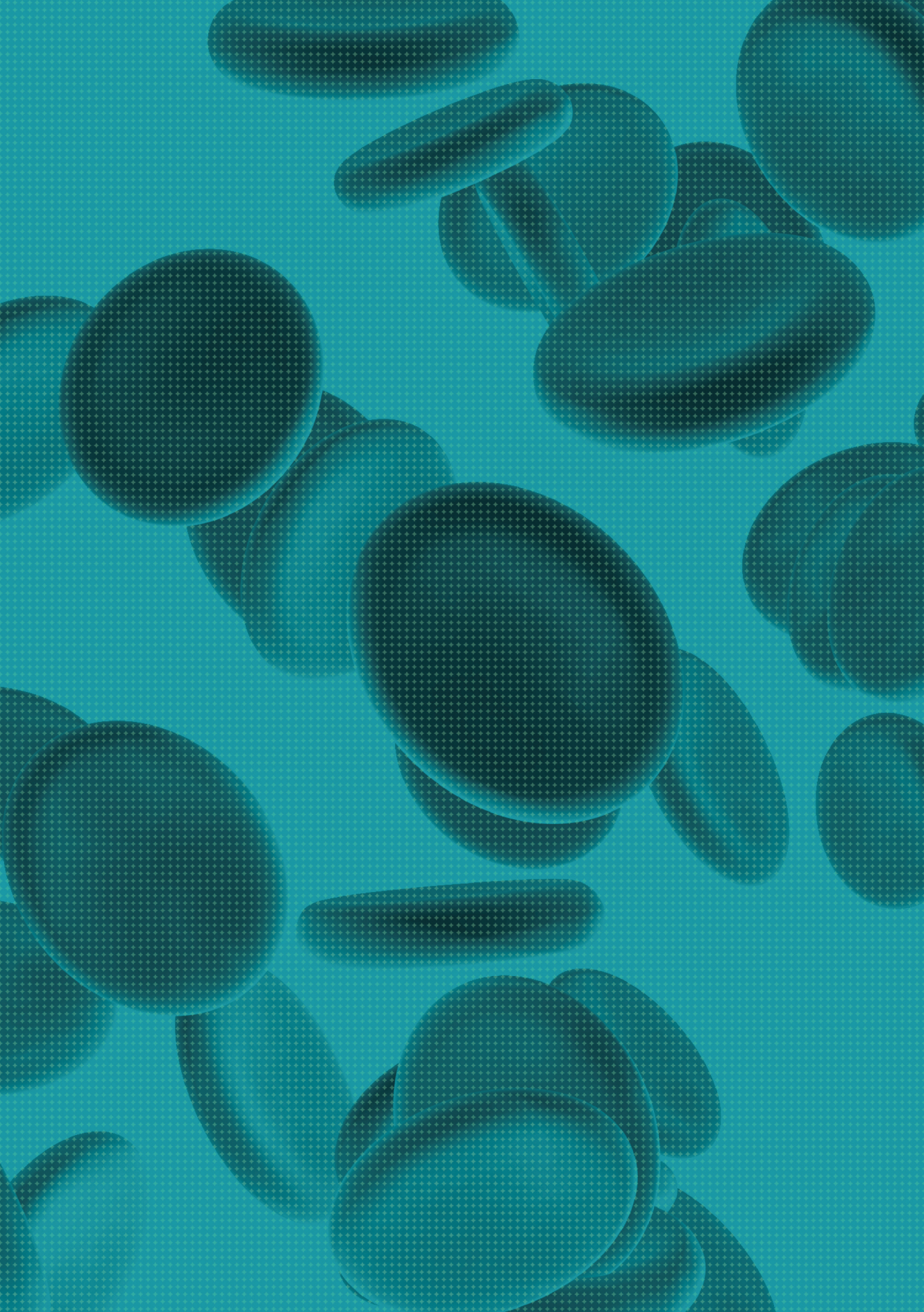
[a] See Calman 1996[296]

Patient blood management involves a precautionary approach to the administration of blood components, particularly red cells. Discussion of alternative strategies is relevant for all patients, not just those who choose not to accept a transfusion.

Patient blood management aims to improve clinical outcomes by avoiding unnecessary exposure to blood components. It includes the three pillars of:

- optimisation of blood volume and red cell mass
- minimisation of blood loss
- optimisation of the patient's tolerance of anaemia.

In the process of obtaining consent, a clinician should allow the patient sufficient time to ask questions, and should answer those questions. If the patient is unable to speak or understand English, the clinician may need to involve an interpreter. In certain contexts, a trained medical interpreter may be required (rather than a family member or a friend). Written information and diagrams may be appropriate in certain circumstances to aid understanding.



Appendix C
Blood sectors

C1 Australian blood sector

Australian Health Ministers' Conference and Australian Health Ministers' Advisory Council

The Australian Health Ministers' Conference (AHMC) is responsible for the oversight and management of the Australian blood sector. The conference's responsibilities include national policy and financial decisions in relation to the supply of blood and blood products, and the determination of which products and services can be bought with public funds. AHMC oversees the implementation of the National Blood Agreement (described below), and is supported in its roles by the Australian Health Ministers' Advisory Council (AHMAC).

Clinical, Technical and Ethical Principal Committee

The Clinical, Technical and Ethical Principal Committee (CTEPC) was established in 2006 to consider and provide advice to the AHMAC on a range of issues. Areas covered include:

- clinical, technical and medico-ethical developments that are likely to affect more than one jurisdiction
- options for ongoing coordination of the clinical and technical services that are managed on a national basis
- the appropriateness, effectiveness and safety of clinical and technical developments
- any policy implications arising from the issues considered by the committee
- the impact of clinical and technical developments on the delivery and management of health-care and other services
- the impact of clinical and technical developments outside the health-care sector.

Jurisdictional Blood Committee

All Australian governments are represented on the JBC, which was established by the National Blood Agreement in 2003. The committee:

- is the conduit between governments and the NBA
- represents the Australian state and territory governments' positions on:
  - blood policy, demand, supply planning and product distribution
  - funding
  - evidence-based approaches to emerging products, services and technologies
- oversees the NBA's role in blood supply contracting.

The committee is the primary body responsible for providing advice and support on these matters to the AHMC through the CTEPC (of which it has been a subcommittee since September 2006) and the AHMAC.

National Blood Authority

The NBA was established in 2003, as an Australian Government agency within the health and ageing portfolio. It is responsible for ensuring the adequate, safe, secure and affordable supply of blood and blood products. The role of the NBA is outlined in the *National Blood Authority Act 2003* and the National Blood Agreement.

Part 5 of the National Blood Agreement requires the development and implementation of specific safety and quality strategies, including development, implementation and review of evidence-based national clinical practice guidelines for blood, blood products and blood-related services. The aim is to encourage best practice in the management and use of such products and services.

Therapeutic Goods Administration

The Therapeutic Goods Administration (TGA) is the regulator for blood and blood products in Australia. The TGA is responsible for:

- regulating the sector in terms of the safety and quality of blood and blood products under the *Therapeutic Goods Act 1989*
- auditing of good manufacturing practice
- issuing product recalls
- modifying safety standards
- issuing directives such as donor deferral.

Australian Red Cross Blood Service

The Australian Red Cross Blood Service (ARCBS) was established as a national organisation in 1996. It is responsible for collecting, processing and distributing blood and blood components sourced from voluntary donors in Australia. The ARCBS works alongside Australian regulators, government departments, and commercial and professional organisations, and with international bodies, to constantly review and improve the safety and provision of blood and blood components in Australia. The ARCBS also has significant transfusion medicine expertise and clinical involvement.

C2 New Zealand blood sector

Ministry of Health

The New Zealand Minister of Health is the government owner of the New Zealand Blood Service (NZBS). The Minister appoints the NZBS Board and approves the Statement of Intent and Output Agreement.

The Ministry of Health monitors the performance of the NZBS, and works closely with the organisation in setting the overall strategic direction for the provision of blood and blood products in New Zealand.

Medsafe

Medsafe is the regulator for blood and blood products in New Zealand. Medsafe is responsible for:

- regulating the sector in terms of the safety and quality of blood and blood products under the *Medicines Act 1981* and *Medicines Regulations 1984*
- auditing and licensing of blood centres in accordance with good manufacturing practice
- issuing product recalls
- approving changes to the NZBS Collection and Manufacturing Standards.

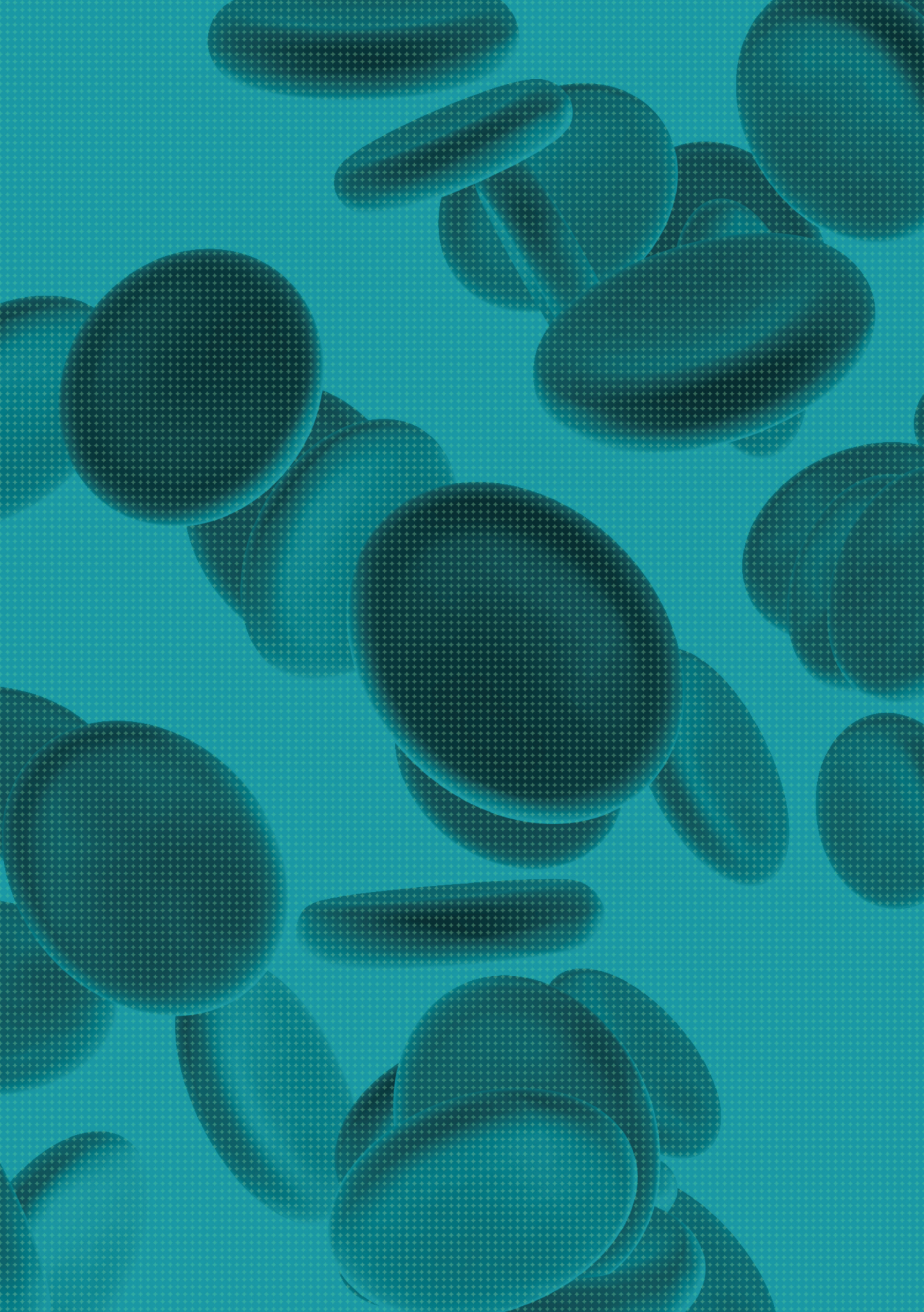
New Zealand Blood Service

The NZBS is a Crown Entity established under the *New Zealand Public Health and Disability Act 2000.* Its legislated purpose and core activity is the safe, timely, high-quality and efficient provision of blood and blood products to clinicians for the people of New Zealand. It also provides related services, including matching of patients and donors before organ or tissue transplantation, and provision of tissue banking (skin, bone and stem cell services).

The NZBS Board is appointed by, and responsible to, the Minister of Health, and performs strategic and governance functions in accordance with the Act.

The NZBS works closely with regulators, the Ministry of Health and international agencies to monitor international developments in the field of transfusion medicine, to develop national policies and to implement them as appropriate in the New Zealand setting.

In addition to its role in collecting, processing and distribution of blood and blood products, the NZBS is actively involved in the provision of blood banking and clinical services within New Zealand's major hospitals.



Appendix D
Process report

D1 Development process

A review by the NBA of the 2001 *Clinical Practice Guidelines on the Use of Blood Components*[1] led to a decision by the NHMRC, ANZSBT and NBA to develop a series of six guidelines on patient blood management, of which this document is the second. The guidelines development process was initiated by a Steering Committee chaired by the NBA. In 2008, an EWG was formed to oversee development of the series of guidelines.

A CRG, with membership including an independent consumer advocate and representation from relevant colleges and societies, was established to develop the perioperative module, with assistance from systematic reviewers and a technical writer, and advice and mentoring from GAR consultants initially contracted by the NHMRC. Further details of the governance framework are provided in Section 1.2 and Appendix A.

D2 Research phase

Relevant clinical research questions were developed, prioritised, combined and refined by the EWG and the CRG for this guideline, and further refined through consultation among the systematic reviewer, CRG, NBA and NHMRC GAR consultants.[2,4]

D3 Methodology

Methods are outlined in Chapter 2, with greater detail given in the technical reports.[2,4] Briefly, the clinical research questions for systematic review were structured according to PICO ('population, intervention, comparator and outcome' for intervention questions), PPO ('population, predictor and outcome' for prognostic questions) or PRO ('population, risk factor and outcome' for aetiology questions) criteria. Three main strategies were used to identify potentially relevant literature: electronic database searching, manual searching and use of literature recommended by expert members of the CRG.

The primary databases searched were EMBASE, Medline, the Cochrane Library Database and PreMedline. Additional searches were conducted of Cumulative Index to Nursing and Allied Health Literature and Australasian Medical Index. The electronic searches included articles published after 1966. Literature retrievals were limited by the holdings of the databases accessed. Publication cut-off points varied from 29 April 2009 to 30 June 2009, as shown in Table D.1, below. Any future searches undertaken to revise, reuse or update these searches should take 1 April 2009 as the start date, to ensure complete coverage of the date range.

Following a review of the search results by the CRG in November 2009, the terms for some searches (specific question 2 and generic question 6) were revised to ensure inclusion of patients undergoing invasive procedures and minimally invasive surgical procedures (see Table D.2, below, and Section 2.1.2 and Appendix 1 of Volume 1a of the technical report for specific patient populations and subgroups). Table D.1 shows the dates on which the revised searches were conducted. The cut-off date for these searches was 30 June 2009, to better align with previous cut-off dates.

Table D.1 Search dates and cut-off points

	CONDUCTED	WITH CUT-OFF	UPDATED	WITH CUT-OFF
Specific question 1				
EMBASE.com	4/06/2009	4/06/2009	–	–
Cochrane Library Database	12/06/2009	12/06/2009	–	–
PreMedline	15/06/2009	15/06/2009	–	–
CINAHL	11/06/2009	11/06/2009	–	–
AMI	11/06/2009	11/06/2009	–	–
BMJ Clinical Evidence	18/06/2009	18/06/2009	–	–
Specific question 2				
EMBASE.com	12/06/2009	12/06/2009	28/01/2010	30/06/2009
Cochrane Library Database	18/06/2009	18/06/2009	27/01/2010	30/06/2009
PreMedline	18/06/2009	18/06/2009	–	–
CINAHL	16/06/2009	16/06/2009	21/01/2010	30/06/2009
AMI	16/06/2009	16/06/2009	–	–
Specific question 3				
Searches by IMS Ltd.				
EMBASE.com	17/06/2009	17/06/2009	–	–
Cochrane Library Database	22/06/2009	22/06/2009	–	–
PreMedline	22/06/2009	22/06/2009	–	–
CINAHL	19/06/2009	19/06/2009	–	–
AMI	19/06/2009	19/06/2009	–	–
Searches by HTA Ltd.				
Intervention 1 (acute normovolemic haemodilution)				
Embase SR	21/12/2009	30/06/2009	–	–
Cochrane SR	22/12/2009	30/06/2009	–	–
Embase RCT	3/01/2010	30/06/2009	–	–
Cochrane RCT	3/01/2010	30/06/2009	–	–
Interventions 2–4 (cell salvage)				
EMBASE SR	22/12/2009	30/06/2009	–	–
Cochrane SR	22/12/2009	30/06/2009	–	–
Intervention 2 (intraoperative cell salvage)				
EMBASE RCT	3/01/2010	30/06/2009	–	–
Cochrane RCT	3/01/2010	30/06/2009	–	–

	CONDUCTED	WITH CUT-OFF	UPDATED	WITH CUT-OFF
Intervention 3 (ANH and intraoperative cell salvage)				
EMBASE RCT	3/01/2010	30/06/2009	–	–
Cochrane RCT	3/01/2010	30/06/2009	–	–
EMBASE lower level evidence	11/02/2010	30/06/2009	–	–
Intervention 4 (postoperative cell salvage)				
EMBASE RCT	3/01/2010	30/06/2009	–	–
Cochrane RCT	3/01/2010	30/06/2009	–	–
Intervention 5 (induced hypotension)				
EMBASE SR	21/12/2009	30/06/2009	–	–
Cochrane SR	22/12/2009	30/06/2009	–	–
EMBASE RCT	4/01/2010	30/06/2009	–	–
Cochrane RCT	4/01/2010	30/06/2009	–	–
Intervention 6 (prevention of hypothermia)				
EMBASE SR	21/12/2009	30/06/2009	–	–
Cochrane SR	22/10/2009	30/06/2009	–	–
EMBASE RCT	5/01/2010	30/06/2009	–	–
Cochrane RCT	5/01/2010	30/06/2009	–	–
Intervention 7 (point-of-care testing)				
EMBASE SR	21/12/2009	30/06/2009	–	–
Cochrane SR	22/12/2009	30/06/2009	–	–
EMBASE RCT	2/02/2010	30/06/2009	–	–
Cochrane RCT	2/02/2010	30/06/2009	–	–
EMBASE lower level evidence	8/04/2010	30/06/2009	–	–
Intervention 8 (antifibrinolytics)				
EMBASE SR	21/12/2009	30/06/2009	–	–
Cochrane SR	22/12/2009	30/06/2009	–	–
EMBASE RCT (desmopressin)	16/02/2010	30/06/2009	–	–
Cochrane RCT	16/02/2010	30/06/2009	–	–
EMBASE RCT (aminocaproic and tranexamic acid)	24/02/2010	30/06/2009	–	–
Intervention 9 (patient positioning)				
EMBASE SR	21/12/2009	30/06/2009	–	–
Cochrane SR	22/12/2009	30/06/2009	–	–

	CONDUCTED	WITH CUT-OFF	UPDATED	WITH CUT-OFF
EMBASE RCT	3/01/2009	30/06/2009	–	–
Cochrane RCT	3/01/2009	30/06/2009	–	–
Intervention 10 (autologous transfusion)				
EMBASE SR	22/12/2009	30/06/2009	–	–
Cochrane SR	22/12/2009	30/06/2009	–	–
EMBASE RCT	3/01/2010	30/06/2009	–	–
Cochrane RCT	3/01/2010	30/06/2009	–	–
Quality of life search (all interventions)				
EMBASE lower level evidence	14/02/2010	30/06/2009	–	–
Generic question 1				
EMBASE.com	29/04/2009	29/04/2009	–	–
Cochrane Library Database	14/05/2009	14/05/2009	–	–
PreMedline	14/05/2009	14/05/2009	–	–
CINAHL	14/05/2009	14/05/2009	–	–
AMI	26/06/2009	26/06/2009	–	–
Generic question 2				
EMBASE.com	13/05/2009	13/05/2009	–	–
Cochrane Library Database	13/05/2009	13/05/2009	–	–
PreMedline	18/05/2009	18/05/2009	–	–
CINAHL	28/05/2009	28/05/2009	–	–
AMI	11/06/2009	11/06/2009	–	–
Generic question 3				
EMBASE.com	27/05/2009	27/05/2009	–	–
Cochrane Library Database	21/05/2009	21/05/2009	–	–
PreMedline	28/05/2009	28/05/2009	–	–
CINAHL	14/05/2009	14/05/2009	–	–
AMI	14/05/2009	14/05/2009	–	–
Generic question 4				
EMBASE.com	24/06/2009	24/06/2009	–	–
Cochrane Library Database	24/06/2009	24/06/2009	–	–
PreMedline	24/06/2009	24/06/2009	–	–
CINAHL	23/06/2009	23/06/2009	–	–

	CONDUCTED	WITH CUT-OFF	UPDATED	WITH CUT-OFF
Generic question 5				
EMBASE.com	25/06/2009	25/06/2009	–	–
Cochrane Library Database	25/06/2009	25/06/2009	–	–
PreMedline	25/06/2009	25/06/2009	–	–
CINAHL	26/06/2009	26/06/2009	–	–
AMI	30/06/2009	30/06/2009	–	–
Generic question 6				
EMBASE.com	28/06/2009	28/06/2009	4/01/2010	30/06/2009
Cochrane Library Database	28/06/2009	28/06/2009	4/01/2010	30/06/2009
PreMedline	28/06/2009	28/06/2009	–	–
CINAHL	30/06/2009	30/06/2009	6/01/2010	30/06/2009
AMI	30/06/2009	30/06/2009	6/01/2010	30/06/2009

AMI, Australasian Medical Index; CINAHL, Cumulative Index to Nursing and Allied Health Literature; EMBASE, Excerpta Medica Database; RCT, randomised controlled trial; SR, systematic review

Table D.2 Populations, subgroups and stratification criteria

QUESTION	POPULATION	SUBGROUPS	STRATIFIED BY
1	All patients scheduled for surgery – elective and emergency patients	▪ Anaemic vs. non-anaemic	
2	All surgical and invasive procedures	▪ Obstetrics patients ▪ Patients scheduled for neurosurgery and ophthalmic surgery ▪ According to indication for intervention (prosthetic valve, VTE, AF, coronary stent)	
3	All surgical patients (elective, emergency, obstetrics and paediatric/neonates)	▪ Stratified by surgical type (e.g. cardiothoracic, neurosurgery or trauma) ▪ Massive transfusion	
4	All patients	▪ Perioperative ▪ Trauma ▪ Shock ▪ Massive transfusion ▪ Cardiothoracic ▪ Surgical	▪ Aetiology of anaemia if present (iron deficiency vs. other) ▪ Demographics (age/sex)

QUESTION	POPULATION	SUBGROUPS	STRATIFIED BY
5	All patients, with or without defined anaemia (however defined)	▪ Perioperative ▪ Trauma ▪ Shock ▪ Massive transfusion ▪ Cardiothoracic ▪ Surgical	▪ Anaemia status according to Hb level
6	All patients with anaemia	▪ Perioperative ▪ Trauma ▪ Shock ▪ Massive transfusion ▪ Cardiothoracic ▪ Surgical	
7	All patients, with and without anaemia	▪ Perioperative ▪ Trauma ▪ Shock ▪ Massive transfusion ▪ Cardiothoracic ▪ Surgical	
8	All patients, with and without anaemia	▪ Perioperative ▪ Trauma ▪ Shock ▪ Massive transfusion ▪ Cardiothoracic ▪ Surgical	
9	All adult (medical, surgical or obstetric), neonatal and paediatric patients eligible for transfusion, with and without anaemia	▪ Perioperative ▪ Trauma ▪ Shock ▪ Massive transfusion ▪ Cardiothoracic ▪ Surgical ▪ Non-surgical invasive procedures and minimally invasive surgical procedures	

Inclusion criteria were determined from the PICO, PPO or PRO criteria that formed the basis of the systematically reviewed research questions. Non-English publications were excluded. Studies that were eligible for inclusion were evaluated according to NHMRC levels of evidence hierarchy, dimensions of evidence and quality assessment criteria.[297,298] An NHMRC evidence statement form was completed for each systematically reviewed research question. Where there was sufficient evidence to formulate a recommendation, NHMRC grading criteria were applied to indicate the strength of the body of evidence underpinning the recommendation.[297] Where it was not possible to develop evidence-based recommendations because no evidence was identified, or where additional information was required to supplement recommendations and guide clinical practice, the CRG developed practice points through a consensus-based process.

D4 Public consultation

Public consultation was conducted for eight weeks, from 7 February 2011, during which time the draft module was available on the NBA website.[d] Notification was posted in *The Australian* national newspaper, and the NBA invited a range of stakeholders, committees, working groups and interested people to provide submissions.

Twenty-five submissions were received. The CRG met on 9–10 May and 12–13 July to consider all responses to the public consultation submissions and, where necessary, revise this module in accordance with the submissions. Many changes were made to the module, to address comments and concerns raised in submissions, and to improve clarity.

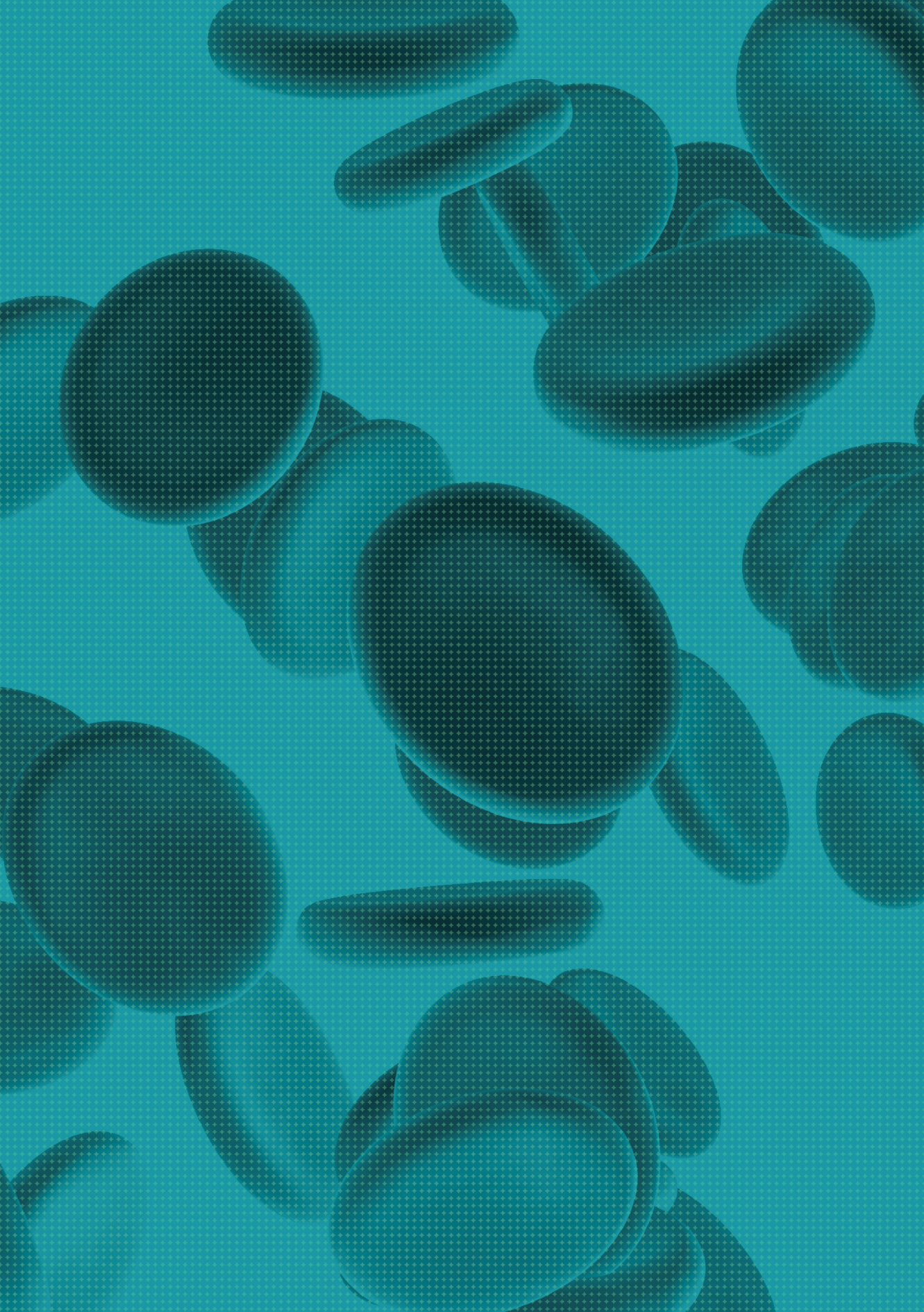
D5 Finalising the guidelines

The final drafts of the module and technical reports were reviewed by a guidelines development expert (formerly a GAR consultant) to assess compliance with NHMRC requirements for externally developed guidelines. The module was then reviewed by an AGREE II expert to assess it against international quality standards. The module and accompanying documents were then sent to the NHMRC for methodological and independent peer review on 4 August 2011.

The module was further refined in response to the reviewer's recommendations.

Approval from the NHMRC was received on 15 November 2011.

[d] http://www.nba.gov.au



Appendix E
Blood component product information

Table E.1 Blood component product information and dosage – Australia

COMPONENT	CONTENT AND CHARACTERISTICS	VOLUME PER BAG[a]	TYPICAL ADULT DOSE (~ 70 KG)	NUMBER OF BAGS TO PROVIDE TYPICAL DOSE
FFP	▪ Plasma recovered from a whole blood donation or apheresis collection ▪ Contains all coagulation factors	250–334 mL	10–15 mL/kg	3–4
Platelets: pooled	▪ A pool of platelets derived from the buffy coat of four whole blood donations ▪ Leucodepleted	>160 mL	1 bag	1
Platelets: apheresis	▪ A suspension of platelets prepared from a single apheresis donor ▪ Leucodepleted	100–400 mL	1 bag	1
Cryoprecipitate	▪ Prepared from a single donated whole blood unit ▪ Contains an average of >0.35 g/bag ▪ Contains high levels of fibrinogen, factor VIII, von Willebrand factor, factor XIII, fibronectin	30–40 mL	3–4 g fibrinogen	8–10
Cryoprecipitate: apheresis	▪ Prepared from FFP obtained from a plasmapheresis donor ▪ Contains an average of >0.8 g/bag	60 mL (± 10%)	3–4 g fibrinogen	4–5

FFP, fresh frozen plasma

[a] Actual volume indicated on label

Source: http://www.transfusion.com.au/sites/default/files/BCI%202009.pdf

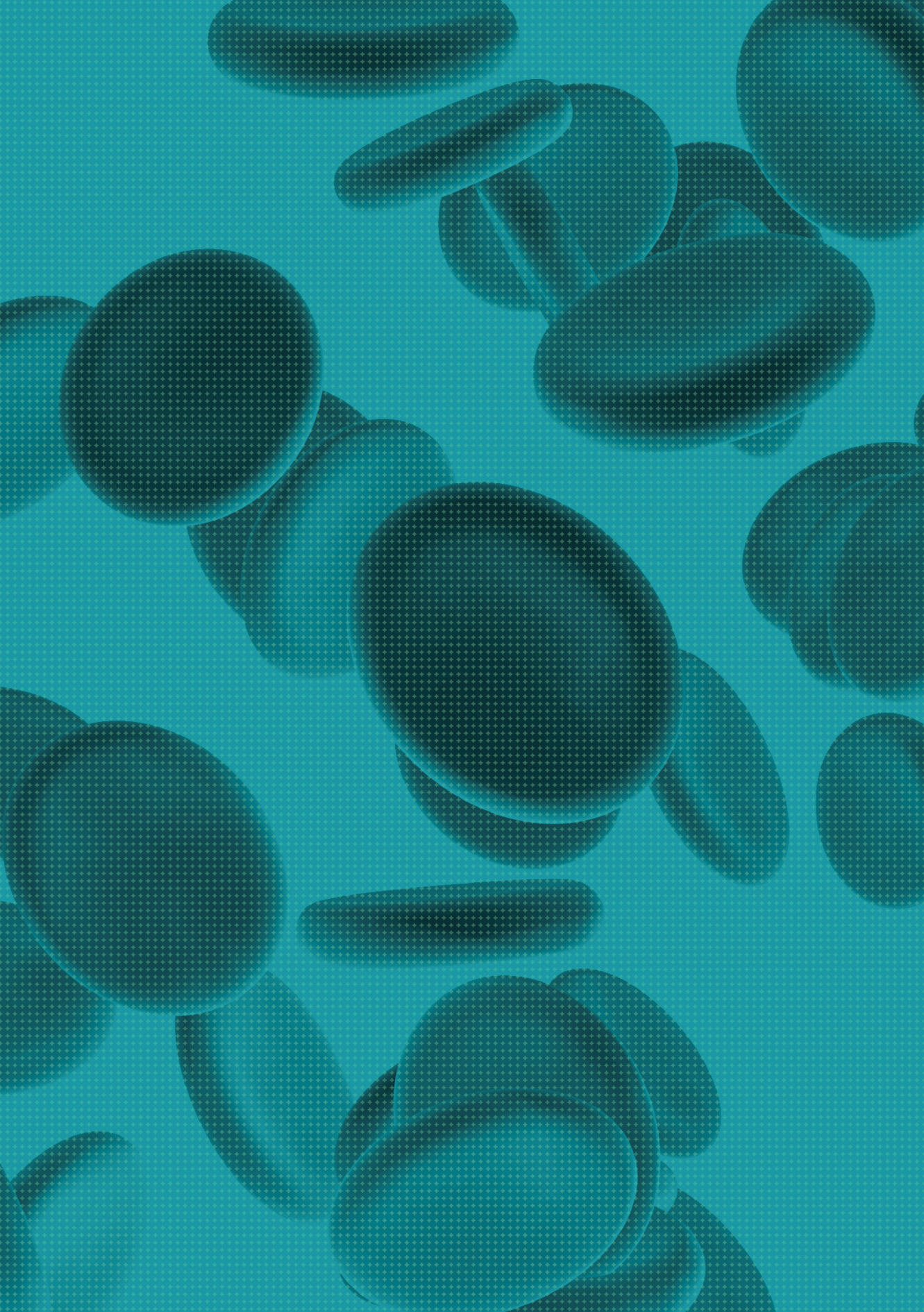
Table E.2 Blood component product information and dosage – New Zealand

COMPONENT	CONTENT AND CHARACTERISTICS	VOLUME PER BAG[a]	TYPICAL ADULT DOSE (~ 70 KG)	NUMBER OF BAGS TO PROVIDE TYPICAL DOSE
FFP	▪ Plasma recovered from a whole blood donation or apheresis collection ▪ Contains all coagulation factors ▪ Leucodepleted	180–300 mL	10–15 mL/kg	3–4
Platelets: pooled	▪ A pool of platelets derived from the buffy coat of four whole blood donations ▪ Leucodepleted	200–350 mL	NA	1
Platelets: apheresis	▪ A suspension of platelets prepared from a single apheresis donor ▪ Leucodepleted	180–400 mL	NA	1
Cryoprecipitate	▪ Prepared from FFP obtained from a plasmapheresis donor with a fibrinogen level >2.4 g/L ▪ Contains an average of 1.4 g/bag ▪ Contains high levels of factor VIII, von Willebrand factor, factor XIII, fibronectin ▪ Leucodepleted	80–120 mL	3–4 g	2–3

FFP, fresh frozen plasma; NA, not applicable

[a] Actual volume indicated on label

Source: http://www.nzblood.co.nz/Clinical-information/Transfusion-medicine/Clinical-compendium/NZBS-blood-component-datasheets

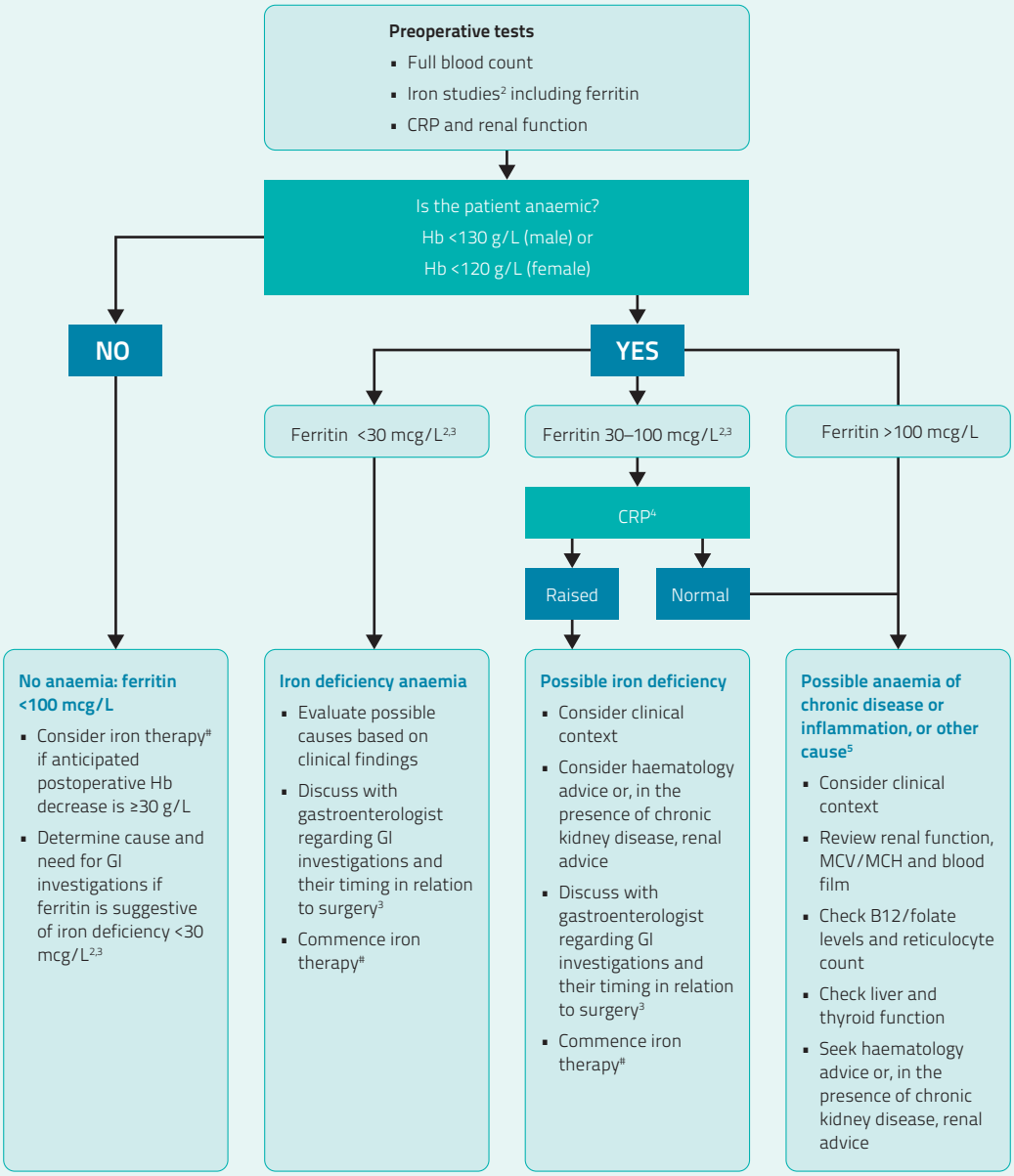


Appendix F
Preoperative haemoglobin assessment and optimisation template

Preoperative haemoglobin assessment and optimisation template

This template[1] is for patients undergoing procedures in which substantial blood loss is anticipated such as cardiac surgery, major orthopaedic, vascular and general surgery. Specific details, including reference ranges and therapies, may need adaptation for local needs, expertise or patient groups.

An editable electronic copy of this template is available on the National Blood Authority's website (www.nba.gov.au).



[#] Iron therapy

Oral iron in divided daily doses. Evaluate response after 1 month. Provide patient information material.

IV iron if oral iron contraindicated, is not tolerated or effective; and consider if rapid iron repletion is clinically important (e.g. <2 months to non deferrable surgery).

NOTE: 1 mcg/L of ferritin is equivalent to 8–10 mg of storage iron. It will take approximately 165 mg of storage iron to reconstitute 10 g/L of Hb in a 70 kg adult. If preoperative ferritin is <100 mcg/L, blood loss resulting in a postoperative Hb drop of ≥30 g/L would deplete iron stores.

In patients not receiving preoperative iron therapy, if unanticipated blood loss is encountered, 150 mg IV iron per 10g/L Hb drop may be given to compensate for bleeding related iron loss (1 ml blood contains ~0.5 mg elemental iron)

Abbreviations

CRP = C-reactive protein

GI = gastrointestinal

Hb = haemoglobin

IV = intravenous

MCV = mean cell/corpuscular volume (fL)

MCH = mean cell/corpuscular haemoglobin (pg)

Footnotes

1 Anaemia may be multifactorial, especially in the elderly or in those with chronic disease, renal impairment, nutritional deficiencies or malabsorption.

2 In an anaemic adult, a ferritin level <15 mcg/L is diagnostic of iron deficiency, and levels between 15–30 mcg/L are highly suggestive. However, ferritin is elevated in inflammation, infection, liver disease and malignancy. This can result in misleadingly elevated ferritin levels in iron-deficient patients with coexisting systemic illness. In the elderly or in patients with inflammation, iron deficiency may still be present with ferritin values up to 60–100 mcg/L.

3 Patients without a clear physiological explanation for iron deficiency (especially men and postmenopausal women) should be evaluated by gastroscopy/colonoscopy to exclude a source of GI bleeding, particularly a malignant lesion. Determine possible causes based on history and examination; initiate iron therapy; screen for coeliac disease; discuss timing of scopes with a gastroenterologist.

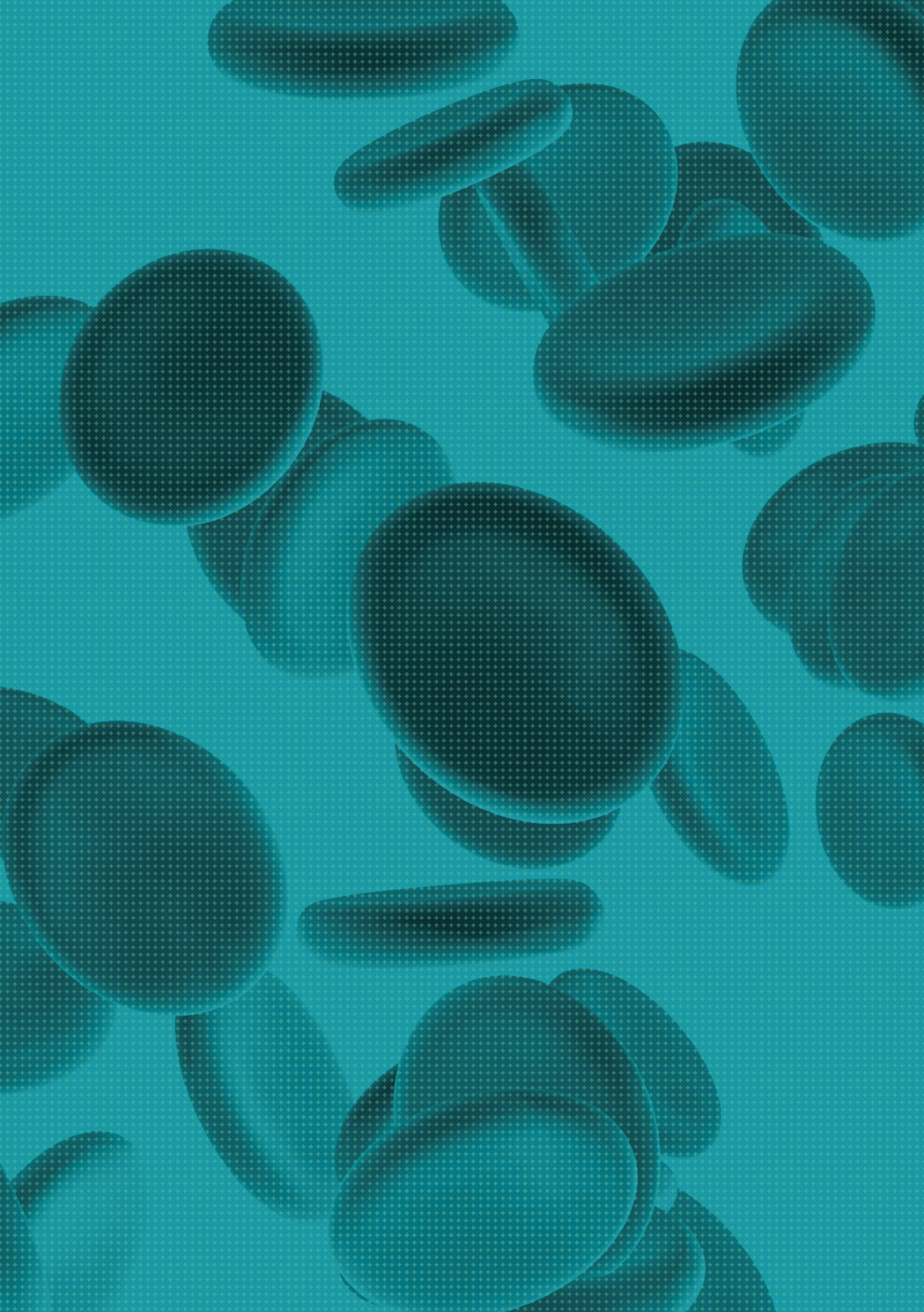
4 CRP may be normal in the presence of chronic disease and inflammation.

5 Consider thalassaemia if MCH or MCV is low and not explained by iron deficiency, or if long standing. Check B12/folate if macrocytic or if there are risk factors for deficiency (e.g. decreased intake or absorption), or if anaemia is unexplained. Consider blood loss or haemolysis if reticulocyte count is increased. Seek haematology advice or, in presence of chronic kidney disease, nephrology advice

For more information on the diagnosis, investigation and management of iron deficiency anaemia refer to Pasricha SR, Flecknoe-Brown SC, Allen KJ et al. Diagnosis and management of iron deficiency anaemia: a clinical update. Med J Aust, 2010, 193(9):525–532.

Disclaimer

The information above, developed by consensus, can be used as a guide. Any algorithm should always take into account the patient's history and clinical assessment, and the nature of the proposed surgical procedure.



Appendix G
List of recommendations and practice points

This appendix lists the recommendations and practice points in numerical order.

RECOMMENDATIONS		
No.	RECOMMENDATION	Relevant section of document
R1 **GRADE C**	Health-care services should establish a multidisciplinary, multimodal perioperative patient blood management program (Grade C). This should include preoperative optimisation of red cell mass and coagulation status; minimisation of perioperative blood loss, including meticulous attention to surgical haemostasis; and tolerance of postoperative anaemia.	3.1
R2 **GRADE C**	In patients undergoing cardiac surgery, preoperative anaemia should be identified, evaluated and managed to minimise RBC transfusion, which may be associated with an increased risk of morbidity, mortality, ICU length of stay and hospital length of stay (Grade C).	3.3
R3 **GRADE C**	In patients undergoing noncardiac surgery, preoperative anaemia should be identified, evaluated and managed to minimise RBC transfusion, which may be associated with an increased risk of morbidity, mortality, ICU length of stay and hospital length of stay (Grade C).	3.3
R4 **GRADE B**	In surgical patients with, or at risk of, iron deficiency anaemia, preoperative oral iron therapy is recommended (Grade B). *Refer to the preoperative haemoglobin assessment and optimisation template [Appendix F] for further information on the optimal dosing strategy.*	3.4
R5 **GRADE A**	In patients with preoperative anaemia, where an ESA is indicated, it must be combined with iron therapy (Grade A).	3.4
R6 **GRADE B**	In patients with postoperative anaemia, early oral iron therapy is not clinically effective; its routine use in this setting is not recommended (Grade B).	3.4
R7 **GRADE C**	In patients undergoing CABG either with or without CPB (OPCAB), clopidogrel therapy should be stopped, where possible, at least 5 days before surgery (Grade C).	3.5
R8 **GRADE C**	In patients undergoing noncardiac surgery, it is reasonable to continue low dose aspirin therapy. This may require specific evaluation in neurosurgery and intraocular surgery (Grade C).	3.5

RECOMMENDATIONS		
No.	RECOMMENDATION	Relevant section of document
R9 GRADE C	In patients undergoing elective orthopaedic surgery, NSAID therapy should be ceased preoperatively to reduce blood loss and transfusion (Grade C). The timing of the cessation should reflect the agent's pharmacology.	3.5
R10 GRADE B	In patients undergoing minor dental procedures, arthrocentesis, cataract surgery, upper gastrointestinal endoscopy without biopsy or colonoscopy without biopsy, warfarin may be continued (Grade B).	3.5
R11 GRADE C	The *routine* use of preoperative autologous donation is not recommended because, although it reduces the risk of allogeneic RBC transfusion, it increases the risk of receiving any RBC transfusion (allogeneic and autologous) (Grade C).	3.6
R12 GRADE A	In patients undergoing surgery, measures to prevent hypothermia should be used (Grade A).	3.6
R13 GRADE C	In patients undergoing radical prostatectomy or major joint replacement, if substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, deliberate induced hypotension (MAP 50–60 mmHg) should be considered, balancing the risk of blood loss and the preservation of vital organ perfusion (Grade C).	3.6
R14 GRADE C	In adult patients undergoing surgery in which substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, the use of ANH should be considered (Grade C).	3.6
R15 GRADE C	In adult patients undergoing surgery in which substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, intraoperative cell salvage is recommended (Grade C).	3.6
R16 GRADE C	In adult patients undergoing cardiac surgery, the use of TEG should be considered (Grade C).	3.6
R17 GRADE A	In adult patients undergoing cardiac surgery, the use of intravenous tranexamic acid is recommended (Grade A).	3.6

RECOMMENDATIONS		
No.	RECOMMENDATION	Relevant section of document
R18 GRADE B	In adult patients undergoing noncardiac surgery, if substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, the use of intravenous tranexamic acid is recommended (Grade B).	3.6
R19 GRADE C	In adult patients undergoing cardiac surgery, the use of intravenous ε-aminocaproic acid is recommended (Grade C).	3.6
R20 GRADE C	In adult patients undergoing cardiac surgery or total knee arthroplasty, in whom significant postoperative blood loss is anticipated, postoperative cell salvage should be considered (Grade C).	3.6
R21 GRADE B	The prophylactic use of FFP in cardiac surgery is not recommended (Grade B).	3.8
R22 GRADE C	The prophylactic or routine therapeutic use of rFVIIa is not recommended because concerns remain about its safety profile, particularly in relation to thrombotic adverse events (Grade C).	3.9

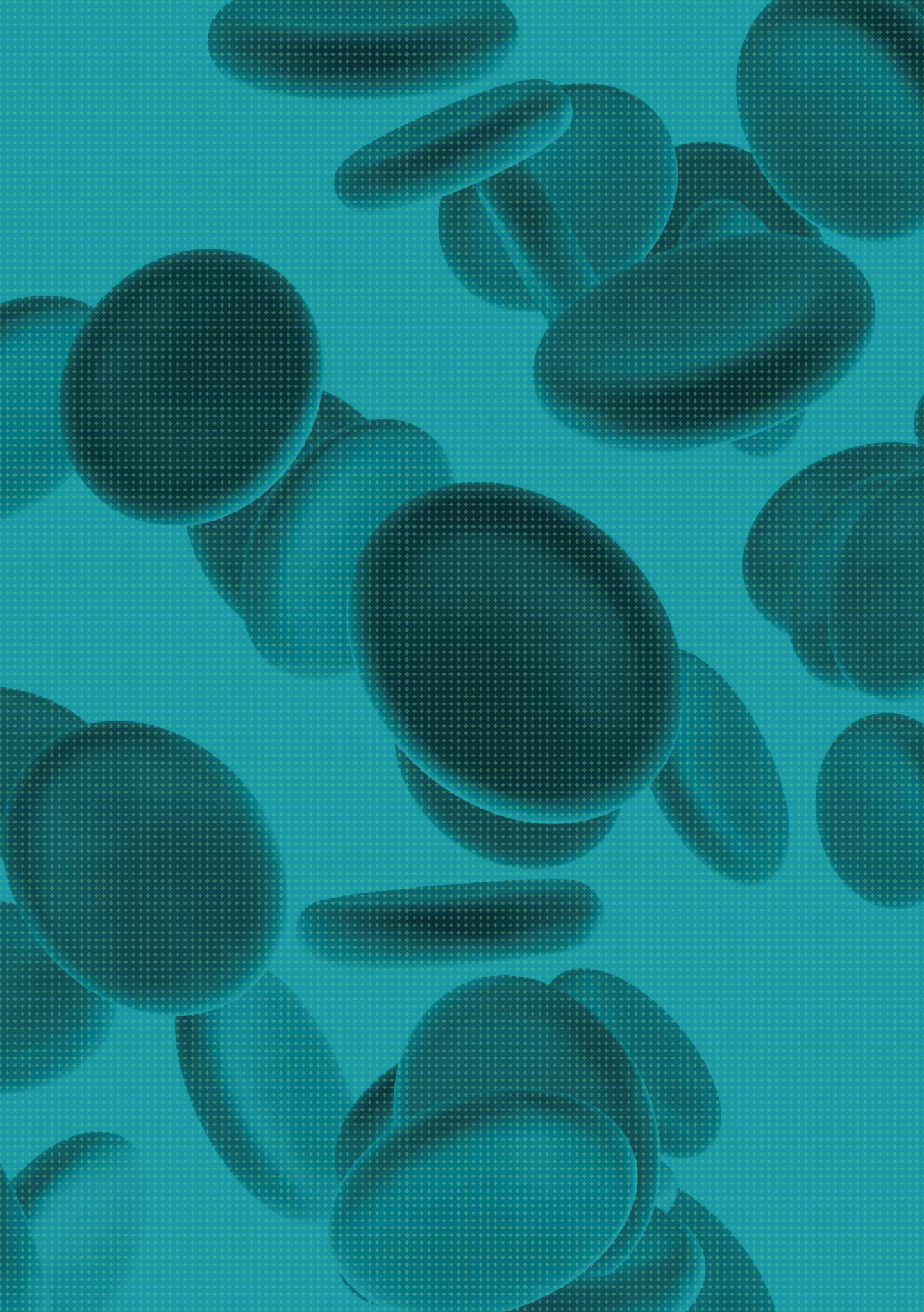
ANH, acute normovolemic haemodilution; CABG, coronary artery bypass surgery; CPB, cardiopulmonary bypass; ESA, erythropoiesis-stimulating agent; FFP, fresh frozen plasma; ICU, intensive care unit; NSAID, nonsteroidal anti-inflammatory drug; MAP, mean arterial blood pressure; OPCAB, off-pump coronary artery bypass; RBC, red blood cell; rFVIIa, recombinant activated factor VIIa; TEG, thromboelastography

Summary of practice points		
No.	PRACTICE POINT	Relevant Section of Document
PP1	To implement the above recommendations, a multimodal, multidisciplinary patient blood management program is required. All surgical patients should be evaluated as early as possible to coordinate scheduling of surgery with optimisation of the patient's haemoglobin and iron stores.	3.3
PP2	RBC transfusion should not be dictated by a haemoglobin 'trigger' alone, but should be based on assessment of the patient's clinical status. In the absence of acute myocardial or cerebrovascular ischaemia, postoperative transfusion may be inappropriate for patients with a haemoglobin level of >80 g/L.	3.3
PP3	Patients should not receive a transfusion when the haemoglobin level is ≥100 g/L. In postoperative patients with acute myocardial or cerebrovascular ischaemia and a haemoglobin level of 70–100 g/L, transfusion of a single unit of RBC, followed by reassessment of clinical efficacy, is appropriate.	3.3
PP4	All surgical patients should be evaluated as early as possible to manage and optimise haemoglobin and iron stores.	3.4
PP5	Elective surgery should be scheduled to allow optimisation of patients' haemoglobin and iron stores.	3.4
PP6	Surgical patients with suboptimal iron stores (as defined by a ferritin level <100 µg/L) in whom substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, should be treated with preoperative iron therapy. *Refer to the preoperative haemoglobin assessment and optimisation template [Appendix F] for further information on the evaluation and management of preoperative patients.*	3.4
PP7	In patients with preoperative iron deficiency anaemia or depleted iron stores, treatment should be with iron alone. In patients with anaemia of chronic disease (also known as anaemia of inflammation), ESAs may be indicated. *Refer to the preoperative haemoglobin assessment and optimisation template [Appendix F] for further information on the evaluation and management of preoperative patients.*	3.4
PP8	In patients undergoing cardiac surgery, aspirin may be continued until the time of surgery.	3.5

Summary of practice points		
No.	PRACTICE POINT	Relevant Section of Document
PP9	In patients receiving clopidogrel who are scheduled for elective noncardiac surgery or other invasive procedures, a multidisciplinary approach should be used to decide whether to cease therapy or defer surgery, balancing the risk of bleeding and thrombotic events. Specific evaluation is required for patients who had a recent stroke, or received a drug-eluting stent within the last 12 months or a bare metal stent within the last 6 weeks. If a decision is made to cease therapy preoperatively, this should occur 7–10 days before surgery.	3.5
PP10	In patients receiving warfarin who are scheduled for elective noncardiac surgery or other invasive procedures (excluding minor procedures—see Recommendation 10), specific management according to current guidelines is required (e.g. guidelines from the American College of Chest Physicians[6] and the Australasian Society of Thrombosis and Haemostasis)[7].	3.5
PP11	Excessive venous pressure at the site of surgery should be avoided by appropriate patient positioning, both during and after the procedure.	3.6
PP12	ANH requires a local procedural guideline that addresses patient selection, vascular access, volume of blood withdrawn, choice of replacement fluid, blood storage and handling, and timing of reinfusion.	3.6
PP13	Intraoperative cell salvage requires a local procedural guideline that should include patient selection, use of equipment and reinfusion. All staff operating cell salvage devices should receive appropriate training, to ensure knowledge of the technique and proficiency in using it.	3.6
PP14	There is evidence for the beneficial effect of intravenous aprotinin on incidence and volume of transfusion, blood loss, and the risk of re-operation for bleeding. However, the drug has been withdrawn due to concerns that it is less safe than alternative therapies.[a] [a] *Websites of the Therapeutic Goods Administration (www.tga.gov.au), MedSafe (www.medsafe.govt.nz) and United States Food and Drug Administration (www.fda.gov)*	3.6
PP15	There is evidence for the beneficial effect of intravenous ε-aminocaproic acid on reduction of perioperative blood loss and volume of transfusion (Grade C). However, the drug is not marketed in Australia and New Zealand.	3.6

Summary of practice points		
No.	PRACTICE POINT	Relevant Section of Document
PP16	In adult patients undergoing surgery in which substantial blood loss (blood loss of a volume great enough to induce anaemia that would require therapy) is anticipated, the routine use of desmopressin is not supported, due to uncertainty about the risk of stroke and mortality.	3.6
PP17	In general, patients with a platelet count ≥50 $\times 10^9$/L or an INR ≤2 can undergo invasive procedures without any serious bleeding; however, lower platelet counts and higher INRs may be tolerated.	3.7
PP18	Specialist guidelines or haematology advice should be sought for at-risk patients undergoing intracranial, intraocular and neuraxial procedures, and for patients with severe thrombocytopenia or coagulopathy.	3.7
PP19	The prophylactic use of platelets post cardiac surgery is not supported.	3.8
PP20	The administration of rFVIIa may be considered in the perioperative patient with life-threatening haemorrhage after conventional measures, including surgical haemostasis, use of anti-fibrinolytics, and appropriate blood component therapy have failed.	3.9

ANH, acute normovolemic haemodilution; ESA, erythropoiesis-stimulating agent; INR, international normalised ratio; RBC, red blood cell; rFVIIa, recombinant activated factor VIIa



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