

Patient Blood Management Guidelines: Module 3

Medical

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Patient Blood Management Guidelines: Module 3 – Medical

This module was developed through clinical input and expertise of representatives from the colleges and societies listed below, a patient blood management advocate, an independent gastroenterology expert and an independent nephrology expert (see [Appendix A](#)).

Australian and New Zealand Intensive Care Society

Australian and New Zealand Society of Blood Transfusion

Australian Red Cross Blood Service

College of Intensive Care Medicine of Australia and New Zealand

Haematology Society of Australia and New Zealand

Royal Australian College of General Practitioners

Royal Australasian College of Physicians

Royal College of Nursing Australia

Royal College of Pathologists of Australasia

Abbreviations and acronyms

ACS	acute coronary syndrome
AHCDO	Australian Haemophilia Centre Directors' Organisation
AHMAC	Australian Health Ministers' Advisory Council
AIDS	acquired immunodeficiency syndrome
ANZSBT	Australian & New Zealand Society of Blood Transfusion
APTT	activated partial thromboplastin time
ASBT	Australasian Society of Blood Transfusion
CARI	Caring for Australians with Renal Impairment
CHF	chronic heart failure
CKD	chronic kidney disease
COI	conflict of interest
CRG	Clinical/Consumer Reference Group
CTEPC	Clinical, Technical and Ethical Principal Committee
DIC	disseminated intravascular coagulation
DNA	deoxyribonucleic acid
ES	evidence statement
ESA	erythropoiesis-stimulating agent
EWG	Expert Working Group
FACT	Functional Assessment of Cancer Therapy
FFP	fresh frozen plasma
FID	functional iron deficiency
Hb	haemoglobin
HIF	hypoxia-inducible factor
HIT	heparin-induced thrombocytopenia
HIV	human immunodeficiency virus
HSCT	haematopoietic stem cell transplantation
IBD	inflammatory bowel disease
IV	intravenous
INR	international normalised ratio
JBC	Jurisdictional Blood Committee
MDS	myelodysplastic syndrome
MI	myocardial infarction
NBA	National Blood Authority
NHMRC	National Health and Medical Research Council

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Executive summary

This document, *Patient Blood Management Guidelines: Module 3 – Medical*, is the third in a series of six modules that focus on evidence-based patient blood management. The other five modules are critical bleeding/massive transfusion, perioperative, critical care, obstetrics and paediatrics (including neonates). Together, Module 2 (Perioperative) and Module 3 (Medical) cover all the patient groups addressed by the 2001 document *Clinical Practice Guidelines on the Use of Blood Components*¹ (National Health and Medical Research Council/Australasian Society of Blood Transfusion, NHMRC/ASBT). Thus, the 2001 guidelines have now been replaced.

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.

Details of the systematic reviews used in the development of this module are given in the two-volume technical report that accompanies this document.

Materials relevant to consumers and to clinicians managing medical patients 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 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, set by the NHMRC:

	Body of evidence can be trusted to guide practice
	Body of evidence can be trusted to guide practice in most situations
	Body of evidence provides some support for recommendation(s), but care should be taken in its application
	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.

[Appendix F](#) gives the recommendations and practice points by clinical condition.

Recommendations

CONDITIONS

IDENTIFIER AND GRADE	GUIDANCE	RELEVANT SECTION OF DOCUMENT	General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia
G ADEC	In ACS patients with a Hb concentration >100 g/L, RBC transfusion is not advisable because of an association with increased mortality.	3.2.2	✓									
G ADEA	In cancer patients with anaemia, the routine use of ESAs is not recommended because of the increased risks of mortality and thromboembolic events.	3.3.1			✓							
G ADE ¹	In patients with CHF, identification and treatment of iron deficiency (absolute and functional) is recommended to improve functional or performance status. This is consistent with the 2011 update to the <i>Guidelines for the Prevention, Detection and Management of Chronic Heart Failure in Australia, 2006</i> . ² Note: The studies reviewed only included patients treated with IV iron, and of NYHA functional classes II or III.	3.3.2			✓							
G ADE ¹	In anaemic patients with CKD, ESA therapy to a low to intermediate Hb target may be used to avoid RBC transfusion, after consideration of risks and benefits for the individual patient (Grade B). Note: The CARI guidelines recommend a Hb target between 100-115 g/L ⁵	3.3.3						✓				






Practice points

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	CONDITIONS
	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.	3.2.1	General medical Cardiac – acute coronary syndrome Heart failure Cancer Gastrointestinal Chronic kidney disease Chemotherapy and haematopoietic stem cell transplantation Thalassaemia and myelodysplasia
	Where indicated, transfusion of a single unit of RBC, -aCflowed		Coagulopathy Thrombocytopenia

CONDITIONS

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia
	<p>Direct evidence is not available in general medical patients.^a Evidence from other patient groups and CRC consensus suggests that, with a:</p> <ul style="list-style-type: none"> • • b on\ r t a on , RBC transfusion may be associated with reduced mortality and is likely to be appropriate. 											

CONDITIONS

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia
	In patients with iron deficiency anaemia, iron therapy is required to replenish iron stores regardless of whether a transfusion is indicated.	3.2.1	✓	✓	✓	✓	✓	✓	✓			
	In patients with ACS and a Hb concentration <80 g/L, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. (See PP1 and PP2).	3.2.2		✓								
	In patients with ACS and a Hb concentration of 80 – 100 g/L, the effect of RBC transfusion on mortality is uncertain and may be associated with an increased risk of recurrence of MI. Any decision to transfuse should be made with caution and based on careful consideration of the risks and benefits. (See PP1 and PP2).	3.2.2		✓								
	In all patients with heart failure, there is an increased risk of transfusion-associated circulatory overload. This needs to be considered in all transfusion decisions. Where indicated, transfusion should be of a single unit of RBC followed by reassessment of clinical efficacy and fluid status. For further guidance on how to manage patients with heart failure, refer to general medical or ACS sections, as appropriate (R1, R3, PP3–PP6).	3.2.3			✓							
	In patients with cancer, the aetiology of anaemia is often multifactorial; where appropriate, reversible causes should be identified and treated.	3.2.4 3.3.1				✓						



CONDITIONS

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT
		General medical
		Cardiac – acute coronary syndrome
		Heart failure
		Cancer
		Gastrointestinal
		Chronic kidney disease
		Chemotherapy and haematopoietic stem cell transplantation
		Thalassaemia and





CONDITIONS

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia
	In patients with thalassaemia, the evidence does not support any change to the current practice of maintaining a pretransfusion Hb concentration of 90 – 100 g/L, with transfusions at about monthly intervals.	3.6.1								✓		
	In patients with myelodysplasia who are regularly and chronically transfused, there is no evidence to guide particular Hb thresholds. Decisions around appropriate triggers and frequency of transfusion need to be individualised, taking into account anaemia-related symptoms, functional or performance status, and the patient's response to previous transfusions.	3.6.2								✓		

ACS, acute coronary syndrome; AHCD0, Australian Haemophilia Centre Directors' Organisation; CARI, Caring for Australasians with Renal Impairment; CHF, chronic heart failure; CKD, chronic kidney disease; CRG, Clinical/Consumer Reference Group; DIC, disseminated intravascular coagulation; ESA, erythropoiesis-stimulating agent; FFP, fresh frozen plasma; Hb, haemoglobin; HIT, heparin-induced thrombocytopenia; IBD, inflammatory bowel disease; IV, intravenous; MI, myocardial infarction; PP, practice point; R, recommendation; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura



1 Introduction

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

This document, *Patient Blood Management Guidelines: Module 3 – Medical*, is the third in a series of six modules that focus on evidence-based patient blood management. The other five modules are listed in [Table 1.1](#), below. Together, Module 2 (Perioperative) and Module 3 (Medical) cover all the patient groups addressed by the 2001 document *Clinical Practice Guidelines on the Use of Blood Components*¹ (National Health and Medical Research Council/Australasian Society of Blood Transfusion, NHMRC/ASBT). Thus, the 2001 guidelines have now been replaced.

This module is intended to assist and guide clinical decisions and coordination of health-care across the primary, secondary and tertiary care settings for patients with acute or chronic medical conditions requiring haematological intervention. Transfusion decisions for patients should also take into account each individual's clinical circumstances and physiological status, and their treatment preferences and choices.

Revision of the 2001 guidelines¹ was needed because of the:

- 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 guidelines, indicated by a high degree of variation in transfusion practices
- failure of the 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.

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)² agreed to develop a series of six patient-focused, evidence-based modules that together 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	1 – Critical Bleeding/Massive Transfusion 2 – Perioperative
II	3 – Medical 4 – Critical Care
III	5 – Obstetrics 6 – Paediatrics/Neonates

^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
- an independent systematic review expert, to provide advice and mentoring to the systematic reviewers, technical writer, EWG and CRGs; and to ensure that the development process and the revised guidelines 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.⁹ [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

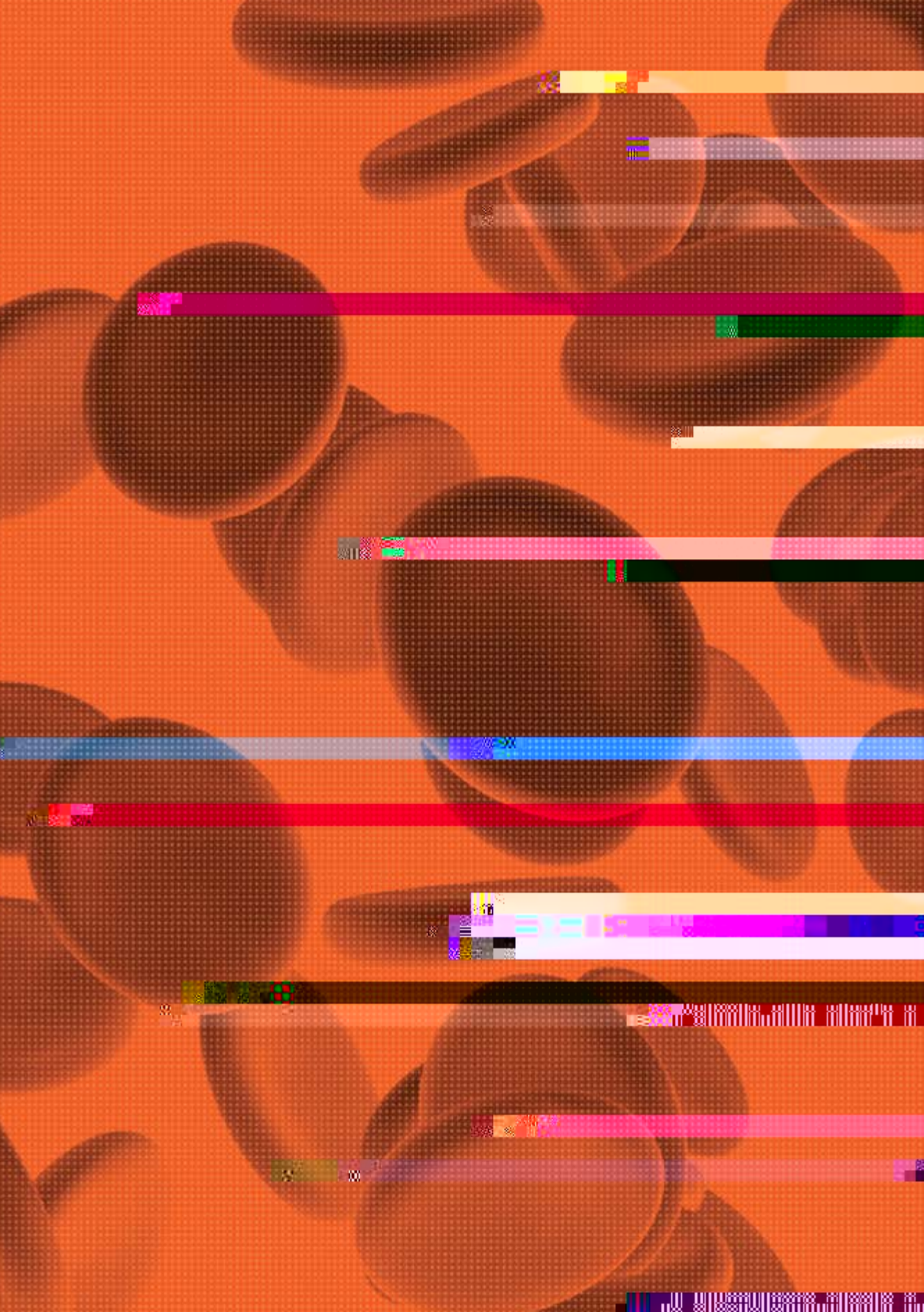
This module includes:

- *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 where it was considered that clinicians require guidance to ensure good clinical practice.

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2 Methods

The development of evidence-based clinical practice guidelines that meet

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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 independent systematic review expert 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 independent systematic review expert. Details of research question criteria are presented in Volume 1 of the technical report.¹⁰

2.2 Review and research

2.2.1 Systematic review process

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

Box 2.1 Systematic review questions

Questions 1 – 5 are relevant to all six modules of these guidelines; Question 6 is specific to medical transfusion (i.e. to this module).

- **Question 1** – In medical patients, is anaemia an independent risk factor for adverse outcomes? (Aetiological question)
- **Question 2** – In medical patients, what is the effect of RBC transfusion on patient outcomes? (Interventional question)
- **Question 3** – In medical patients, what is the effect of non-transfusion interventions to increase Hb concentration on morbidity, mortality and need for RBC blood transfusion? (Interventional question)
- **Question 4** – In medical patients, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes? (Interventional question)
- **Question 5** – In medical patients, at what INR (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? (Interventional and Prognostic question)
- **Question 6** – In specific regularly and chronically transfused patients, at what Hb threshold should patients be transfused to avoid adverse outcomes? (Interventional question)

APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; Hb, haemoglobin; INR, international normalised ratio; PT, prothrombin time; RBC, red blood cell

2.2.2 Background material

Material relevant to background questions 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 questions researched are listed in Box 2.2.

Box 2.2 Background research questions

- **Background question 1** – In patients with malignancies (solid tumours) undergoing radiotherapy, do interventions (transfusion or ESAs) aimed at raising the Hb concentration during radiotherapy affect patient outcomes (e.g. response rate, tumour recurrence or tumour-free survival)?
- **Background question 2** – When should a patient be retested after a transfusion to assess the response, guide if further transfusions are required and avoid over-transfusion?

ESA, erythropoiesis-stimulating agent; Hb, haemoglobin

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 2.1](#) (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 of evidence (i.e. Levels III or IV). 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 2.2](#), 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



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 six 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.

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. The experience of many clinicians working with Aboriginal and Torres Strait Islander communities suggests a high rate of anaemia. This has particularly influenced their care of children and pregnant women. As has been noted in the past, there is a paucity of population evidence regarding the prevalence and aetiology of anaemia in Aboriginal and Torres Strait Islander populations. Given the burden of disease carried by these populations, research in this area is overdue and Aboriginal communities may wish to initiate research that could help ensure that the urgent need to provide high quality, targeted care is better informed.

3.1 Effect of anaemia on outcomes

Question 1 (Aetiological question)

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

Anaemia as defined by the World Health Organization (WHO) is a haemoglobin (Hb) level of ≤ 130 g/L in males and ≤ 120 g/L in females. It has been assumed that patients with coronary, cerebrovascular or respiratory diseases, or even the elderly, tolerate anaemia poorly, and therefore suffer from increased morbidity and perhaps mortality. This has led to higher Hb levels being used for transfusion in these patient populations. The 2001 NHMRC/ASBT guidelines identified gaps in knowledge about anaemia in such patient populations.¹ The aim of this question was to establish whether anaemia is an independent risk factor for adverse outcomes.

The population groups prespecified as essential for the review were acute coronary syndrome (ACS) and the elderly. Heart failure, cancer and renal patients were also included because systematic reviews of these populations had already been published.

The findings of the review indicate whether anaemia is an independent risk factor for adverse outcomes. However, they do not prove that anaemia causes these outcomes or that correction of the anaemia will reverse the outcomes.

3.1.1 Acute coronary syndrome

EVIDENCE STATEMENTS –

Twelve prospective cohort studies (Level II) were included for the ACS population; 10 provided evidence for mortality,¹⁵⁻²⁴ and 4 for composite or cardiovascular outcomes.^{21,22,25,26}

A fair-quality study showed that anaemia, as defined by WHO, was an independent risk factor for all-cause mortality and death due to progressive heart failure in patients diagnosed with acute myocardial infarction (MI), but was not an independent risk factor for sudden cardiac death.¹⁵ In a study by Valeur et al, WHO-defined anaemia was an independent risk factor for mortality in patients with ACS with heart failure only.¹⁶ This study also showed that a one standard deviation increase in Hb resulted in a significantly decreased risk of all-cause mortality (12% reduction) and death due to progressive heart failure (20% reduction). Most of the analyses showed that Hb concentrations below 150 – 160 g/L were a significant independent risk factor for 30-day mortality.¹⁶ In addition, a 10 g/L decrease in Hb significantly increased the risk of mortality.

In summary, the results were generally consistent across all included studies, with most suggesting that anaemia is an independent risk factor for mortality and adverse cardiovascular outcomes. Evidence from one large good-quality study suggests that any decrease in baseline Hb concentration is associated with an increased risk of mortality.¹⁹

3.1.2 Heart failure

EVIDENCE STATEMENTS – heart failure		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES1.4	In patients with heart failure, anaemia is independently associated with mortality.	✓✓✓	✓✓	✓✓	✓✓✓	✓✓✓
ES1.5	In patients with heart failure, anaemia may be independently associated with reduced functional or performance status and quality of life.	✓✓	⚡ ^A		✓✓	✓✓

ES, evidence statement

✓✓✓=A; ✓✓=B; =D; ⚡, A, not applicable (see Table 2.1)

The literature search identified three systematic reviews (which did not strictly meet the requirements for Level I evidence, and were therefore not formally included in the review) and 15 prospective cohort studies (Level II evidence). Fourteen studies provided evidence for mortality^{15,27-39} and one study provided evidence for functional or performance status or quality of life.⁴⁰

All included studies showed that anaemia (as defined by WHO) was associated with an increased risk of all-cause mortality. The association was particularly strong for studies with more than 1 year of follow-up, with four fair to good-quality studies showing increased risks of mortality of 21 – 47%.^{15,27,35,36} Analyses of different Hb concentrations consistently showed that lower Hb concentrations were significantly associated with increased risk of mortality. It was not obvious whether the increased mortality was due to specific cardiovascular events.

One good-quality study assessed the association between various Hb concentrations and functional or performance status using the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the Minnesota Living with Heart Failure Questionnaire (MLHFQ).⁴⁰ The study found that low Hb is an independent risk factor for reduced quality of life.

3.1.3 Community-dwelling elderly

EVIDENCE STATEMENTS – community-dwelling elderly		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES1.6	In a community-dwelling elderly population, anaemia is independently associated with mortality.	✓✓✓	✓✓	✓✓	✓✓✓	✓✓
ES1.7	In a community-dwelling elderly population, anaemia may be independently associated with reduced functional or performance status and quality of life.	✓✓	✓✓		✓✓	✓✓

ES, evidence statement

✓✓✓=A; ✓✓=B; =D; A, not applicable (see Table 2.1)

For the purposes of the systematic review, the population ‘community-dwelling elderly’ was defined as those aged >65 years who were community dwelling and had no significant morbidity. The review identified no Level I evidence and 12 prospective cohort studies (Level II) for this population.⁴¹⁻⁵¹

Four fair-quality studies of subjects aged ≥ 65 years found that anaemia was independently associated with mortality.^{42,45,49,51} One of these studies also found that, although anaemia was independently associated with all-cause and non-cardiovascular mortality, it was not an independent predictor of cardiovascular mortality.⁵¹ Additional studies assessing different Hb concentrations consistently showed that low Hb was associated with increased mortality.^{41-43,46,48}

The findings suggest that anaemia is an independent risk factor for mortality in the elderly community-

The review identified four systematic reviews that did not strictly meet the criteria for Level I evidence and were therefore not formally included in the review. Thirteen prospective cohort studies (Level II) were identified, conducted in subjects with a range of different types of cancer including prostate cancer, breast cancer, lung cancer, colorectal cancer, renal cancer and multiple myeloma.⁵³⁻⁶⁵

One good-quality study found a significant association between anaemia (as defined by WHO) and post-progression survival in 640 men with metastatic prostate cancer.⁵³

Ten studies of poor to fair quality examined the relationship between different Hb concentrations and mortality. Seven of these studies showed a significant relationship between low Hb and an increase in mortality or a reduction in survival.^{54-57,59,60,62} Overall, the results of these studies suggest that anaemia or low Hb is associated with decreased survival.

Two poor-quality studies examined the relationship between lower Hb and quality of life using two quality-of-life instruments: the Short Form-36 (SF-36) and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (QLQ-C30).^{51,65} The results suggest an association between low Hb and quality of life; however, due to the poor quality of these studies, this relationship remains uncertain.

3.1.5 Renal

EVIDENCE STATEMENTS – chronic kidney disease		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES1.10	In patients with CKD (including dialysis patients), anaemia is independently associated with all-cause or cardiovascular mortality.	✓✓	✓✓	✓✓	✓✓✓	✓✓✓
ES1.11	In adults with CKD, anaemia is independently associated with stroke.	✓	⚡ ^A	✓✓	✓✓	✓✓
ES1.12	In patients with CKD (including dialysis patients), Hb concentration is associated with reduced quality of life.	✓	✓✓	✓	✓✓✓	✓✓

CKD, chronic kidney disease; ES, evidence statement; Hb, haemoglobin

✓✓✓=A; ✓✓=B; ✓=C; ⚡^A, not applicable (see Table 2.1)

One systematic review⁶⁶ was identified that did not strictly meet the definition of a Level I study because it included both prospective and retrospective cohort studies. The review concluded that studies consistently show an association between reduced Hb and increased mortality. The review also identified 15 prospective cohort studies (Level II), mainly of fair quality, that included patients predialysis and on dialysis.⁶⁷⁻⁸¹ Eight fair to good-quality prospective cohort studies showed the relationship between different Hb concentrations and mortality.^{68,69,71,72,74,75,77,79} These studies consistently showed that anaemia is independently associated with all-cause or cardiovascular mortality, with lower Hb concentrations increasing the risk of mortality up to two-fold. There was also evidence from one fair-quality prospective cohort study that anaemia was an independent risk factor for stroke.⁶⁷

Six fair to poor-quality prospective cohort studies assessed quality of life using the SF-36.^{70,73,76,78,80,81} These studies concluded that higher Hb concentrations are independently associated with improved quality of life in both predialysis and dialysis patients.

3.2 Effect of red blood cell transfusion on outcomes

Question 2 (Interventional question)

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

RBC, red blood cell

Patients are transfused to treat symptoms, reduce morbidity and mortality, and improve their quality of life. The literature review aimed to establish whether receiving a transfusion affects patient outcomes. The review examined the effect of red blood cell (RBC) transfusions in a general population of medical patients, and in subsets of patients in whom a different management strategy might be appropriate. These subsets included patients with ACS, heart failure, cancer or upper gastrointestinal blood loss.

The evidence included some studies comparing restrictive and liberal transfusion strategies, and some observational studies comparing outcomes in patients receiving transfusion to patients who were not transfused. The review included only those studies that had at least 500 subjects, and that adjusted for potential confounding variables using multivariate analysis.




3.2.1 Medical population

EVIDENCE STATEMENTS – medical population		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.1	In medical patients, the effect of a restrictive versus liberal RBC transfusion strategy on mortality is uncertain.	✓	✓✓		✓	✓✓

ES, evidence statement; RBC, red blood cell

✓✓=B; ✓=C; =D; (see [Table 2.1](#))

PRACTICE POINTS – medical population

	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.
	Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.
	

specific medical populations – for example, ACS, heart failure, cancer and acute upper gastrointestinal blood loss – are presented in the following sections. In addition, advice relating to the management of chronically transfused patients (including patients with thalassaemia and myelodysplasia) is presented under Question 6.

3.2.2 Acute coronary syndrome

In patients with ACS, four retrospective cohort studies (Level III-2) assessed the relationship between mortality and transfusion at varying Hb concentrations.^{21,84-86} Although the included studies analysed the data using a range of haematocrit or Hb categories, the results have been consolidated into specific Hb ranges to best inform clinical practice. The results of these studies consistently indicate that in ACS patients with a Hb concentration >100 g/L, RBC transfusion may be associated with a higher risk of mortality, proportional to Hb concentration. In ACS patients with a Hb concentration of 80–100 g/L, RBC transfusion is not associated with an altered mortality risk, and may be associated with an increased risk of recurrence of MI.

In patients with a Hb concentration of <80 g/L, the association between RBC transfusion and mortality is less clear. The results of Wu⁸⁶ and Sabatine²¹ showed reduced mortality in patients receiving transfusions at lower *admission* Hb concentrations; however, the studies by Rao⁸⁷ and Alexander⁸⁴ found that transfusion at lower *nadir* Hb concentrations was not associated with reduced mortality. The CRG considered that *nadir* Hb may be more relevant than admission Hb for clinical decision making.

An additional study by Shishehbor⁸⁸ reported that, in patients with ACS, RBC transfusion may be


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3.2.5 Acute upper gastrointestinal blood loss

EVIDENCE STATEMENTS – acute upper gastrointestinal blood loss		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.10	In patients with acute upper gastrointestinal blood loss, the effect of a restrictive versus liberal RBC transfusion strategy on mortality is uncertain.		↙ ^A	↙ ^A	✓✓✓	
ES2.11	In patients with acute upper gastrointestinal blood loss, the effect of RBC transfusion on mortality is uncertain.	✓	↙ ^A	↙ ^A	✓✓✓	✓

ES, evidence statement; RBC, red blood cell

✓✓✓=A; ✓=C; =D; ↙^A, not applicable (see Table 2.1)

PRACTICE POINTS – acute upper gastrointestinal blood loss	
	In well-compensated patients with acute upper gastrointestinal blood loss that is non-critical, there is no evidence to favour a liberal transfusion policy. ^{692 Tm (In 3o7cGore, tris)e}

3.3 Effect of erythropoiesis - stimulating agents and iron

Question 3 (Interventional question)

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

EVIDENCE STATEMENTS – cancer (iron therapy)

		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.7	In anaemic adults with cancer receiving ESAs, the effect of IV iron versus oral or no iron on short-term mortality is uncertain.	✓✓	✓✓	↙ ^A	✓✓	✓✓
ES3.8	In adults with cancer-related anaemia receiving ESAs, IV iron may reduce the incidence of RBC transfusion.	✓✓	✓✓	✓	✓✓	✓
ES3.9	In anaemic patients with gynaecological cancer receiving chemotherapy, IV iron may reduce the incidence and volume of RBC transfusion.	✓	↙ ^A	✓✓	✓✓✓	✓
ES3.10	In adults with chemotherapy-induced anaemia receiving ESAs, the effect of IV iron versus oral or no iron on the incidence of thromboembolic events is uncertain.	✓✓	✓✓	↙ ^A	✓✓	✓
ES3.11	In adults with non-myeloid malignancies and chemotherapy-induced anaemia receiving ESAs, IV iron versus oral or no iron appears to have no effect on functional or performance status.	✓	↙ ^A	↙ ^A	✓✓	✓
ES3.12	In anaemic patients with gynaecological cancer receiving chemotherapy, the effect of IV iron versus oral iron on functional or performance status is uncertain.	✓	↙ ^A	↙ ^A	✓✓✓	✓

ES, evidence statement; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; IV, intravenous; RBC, red blood cell

✓✓✓=A; ✓✓=B; ✓=C; =D; ↙^A, not applicable (see Table 2.1)

RECOMMENDATION – cancer

G ADE A

In cancer patients with anaemia, the *routine* use of ESAs is not recommended because of the increased risks of mortality and thromboembolic events.

PRACTICE POINTS – cancer

a

In patients with cancer, the aetiology of anaemia is often multifactorial; where appropriate, reversible causes should be identified and treated.

a

In anaemic patients with cancer receiving ESAs, evaluate iron status to guide adjuvant iron therapy.

^a Repeated from Section 3.2.4, above

ESA, erythropoiesis-stimulating agent; PP, practice point; R, recommendation

3.3.2 Chronic heart failure

**EVIDENCE STATEMENTS –
chronic heart failure
(erythropoiesis-stimulating agents)**

		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.13	In anaemic patients with CHF, the effect of ESAs on mortality is uncertain.	✓✓✓			✓✓	✓✓✓
ES3.14	In anaemic patients with CHF, the effect of ESAs on transfusion requirements					

—

RECOMMENDATION – chronic heart failure

G AD¹

In patients with CHF, identification and treatment of iron deficiency (absolute and functional) is recommended to improve functional or performance status.

This is consistent with the 2011 update to the *Guidelines for the Prevention, Detection and Management of Chronic Heart Failure in Australia, 2006*.²

Note: The studies reviewed only included patients treated with IV iron, and of NYHA functional classes II or III.

CHF, chronic heart failure; IV, intravenous; NYHA, New York Heart Association; R, recommendation

Erythropoiesis-stimulating agents – chronic heart failure

One systematic review (Level I), which included a large subset of patients with diabetes and congestive cardiac failure, found that ESA therapy was associated with reduced mortality.¹⁰³ In a separate systematic review, the incidence of thromboembolic events, mortality and heart failure-related hospitalisations were not affected by ESAs,¹⁰⁴ but there was a significant improvement in exercise tolerance. ESAs are not currently listed on the PBS for reimbursement for patients with cardiac failure.

Intravenous iron – chronic heart failure

Iron deficiency is common in patients with CHF, and is usually associated with anaemia.

Two RCTs (Level II), one of good quality¹⁵ and one of poor quality,¹⁰⁵ evaluated the use of IV iron therapy in patients with CHF (New York Heart Association (NYHA) class II or III). Both studies included anaemic and nonanaemic patients who were likely to have either absolute iron deficiency (ferritin <100 mcg/L) or FID (ferritin 100 – 300 mcg/L with a transferrin saturation of 20%).

There was no significant difference in mortality between patients treated with IV iron and patients who did not receive IV iron, including after meta-analysis; however, the studies were underpowered. Neither study reported the incidence or volume of blood transfusion. Both studies showed a significant improvement in NYHA classification with IV iron.

The good-quality, multicentre RCT by Anker et al included CHF patients with absolute iron deficiency and FID, with Hb concentrations of 95 – 135 g/L.¹⁵ The study demonstrated reduced symptoms and improved submaximal exercise tolerance and quality of life with use of IV ferric carboxymaltose compared to a placebo. Improvements were independent of Hb concentrations. There was no significant difference between IV iron and the placebo in the rates of hospitalisation for any cardiovascular cause or for vascular disorders.

It is important to look for and treat iron deficiency in patients with CHF to reduce symptoms and improve exercise tolerance and quality of life. This advice has been incorporated as a Grade B recommendation in the 2011 update to the *Guidelines for the Prevention, Detection and Management of Chronic Heart Failure in Australia*, from the National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand.²

3.3.3 Chronic kidney disease



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None of the included studies reported the incidence of thromboembolic events.

Two of the included RCTs^{119,121} reported on functional or performance status. One of these studies¹²¹ showed an improvement. Patients treated with IV iron experienced significantly greater improvements in two measures of quality of life (Symptoms and Effects of CKD on Kidney Disease Quality of Life Questionnaire: KDQoL) than patients treated with oral iron.

3.3.4 Elderly patients

EVIDENCE STATEMENTS – community-dwelling elderly		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.30	In community-dwelling elderly patients with anaemia who are ambulatory, the effect of ESAs on mortality is uncertain.	✓	↙ ^A	↙ ^A	✓	✓✓
ES3.31	In community-dwelling elderly patients with anaemia who are ambulatory, the effect of ESAs on thromboembolic events is uncertain.	✓	↙ ^A	↙ ^A	✓	✓✓
ES3.32	In community-dwelling elderly patients with anaemia who are ambulatory, the effect of ESAs on functional or performance status is uncertain.	✓	↙ ^A		✓	✓✓

ES, evidence statement; ESA, erythropoiesis-stimulating agent

✓✓✓=A; ✓✓=B; ✓=C; =D; ↙^A, not applicable (see Table 2.1)

Erythropoiesis-stimulating agents – elderly patients

A single fair-quality RCT (Level II) of anaemic elderly patients receiving ESAs did not identify an effect on mortality or the incidence of thromboembolic complications.¹²² ESA treatment was associated with functional improvement.

3.3.6 Myelodysplastic syndrome

EVIDENCE STATEMENTS – myelodysplastic syndrome		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.35	In anaemic patients with MDS, the effect of ESAs on mortality is uncertain.		✓✓		✓✓	✓
ES3.36	In anaemic patients with MDS receiving GM-					

3.4 Effect of blood components on outcomes

Question 4 (Interventional)

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

FFP, fresh frozen plasma

There is controversy over the benefit of using fresh frozen plasma (FFP), cryoprecipitate and platelet concentrates to improve haemostasis in both procedural and non-procedural settings. The aim of this question was to determine the effect of using such products on mortality, bleeding events and transfusion-related adverse events.

3.4.1 Fresh frozen plasma

EVIDENCE STATEMENTS – fresh frozen plasma		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES4.1	In patients with acute pancreatitis, the effect of FFP on mortality is uncertain.		✓	↙ ^A		
ES4.2	In patients with acute pancreatitis, the effect of FFP on bleeding events is uncertain.		✓	↙ ^A		
ES4.3	In patients with liver disease, the effect of FFP on mortality is uncertain.		↙ ^A	↙ ^A	✓	✓
ES4.4	In patients with liver disease, the effect of FFP on bleeding events is uncertain.		↙ ^A	↙ ^A		✓

ES, evidence statement; FFP, fresh frozen plasma

✓=C; =D; ↙^A, not applicable (see Table 2.1)

PRACTICE POINTS – fresh frozen plasma



The *routine* use of FFP in medical patients with coagulopathy (including those with liver impairment) is not supported. Tests for coagulation correlate poorly with bleeding risk in liver impairment.

The underlying causes of coagulopathy should be assessed. Where FFP transfusion is considered necessary, the risks and benefits should be considered for each patient, and expert guidance sought.



For guidance on the use of FFP in specific patient groups, refer to:

- *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion (2011)*⁴
- *Patient Blood Management Guidelines: Module 2 – Perioperative (2012)*⁶
- *Warfarin Reversal: Consensus Guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis (2004)*⁷
- AHCDO guidelines for patients with specific factor deficiencies (www.ahcdo.org.au)
- TTP: *Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant (2004)*.⁸

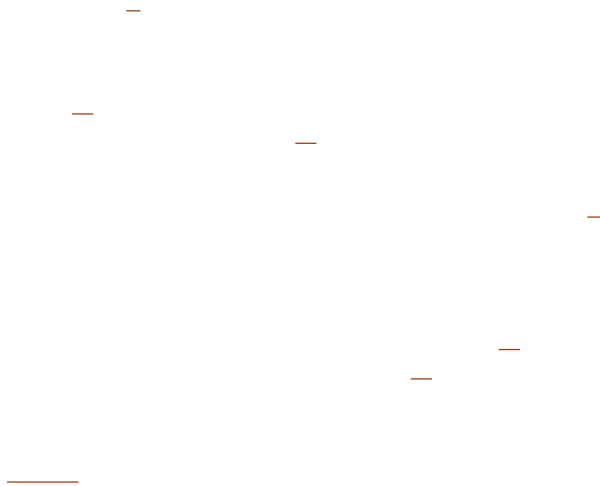
AHCDO, Australian Haemophilia Centre Directors' Organisation; FFP, fresh frozen plasma; PP, practice point; TTP, thrombotic thrombocytopenic purpura

FFP contains all the coagulation factors and proteins present in normal plasma. FFP is transfused in a range of clinical settings, including critical bleeding/massive transfusion, perioperative, warfarin reversal, liver disease, coagulation factor deficiencies and thrombotic thrombocytopenic purpura (TTP). The literature search identified Level II evidence relating to the use of FFP in two medical populations:

3.4.2 Fibrinogen and cryoprecipitate

EVIDENCE STATEMENTS –

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Platelet transfusion doses

Five RCTs (Level II) assessed platelet dose in patients with haematological malignancies receiving chemotherapy.¹³⁷⁻¹⁴¹ The definitions of thrombocytopenia and the assessed dose ranges varied widely between the studies. Mortality was reported in only one study;¹³⁷ this study found no significant difference between any of the assessed platelet doses, but was underpowered.

Four studies reported the incidence of bleeding events. Slichter et al¹³⁷ and Heddle et al¹³⁸ found no significant difference between study arms in any of the dose comparisons presented. Tinmouth et al found a higher risk of experiencing a minor bleed in patients receiving three platelet units than five platelet units, but no significant difference between different platelet doses for the incidence of major bleeds.¹³⁹ The study by Sensebé et al was underpowered to detect an effect of platelet dose on the incidence of haemorrhage.¹⁴¹

There was no significant difference between study arms in the two studies that reported the incidence of transfusion-related serious adverse events.^{132,137} However, the overall rate of serious adverse events was relatively high in both studies.

3.5 Blood component transfusion

Question 5 (Interventional/Prognostic)

In medical patients, 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

There is controversy over the benefit of using FFP, cryoprecipitate and platelet concentrates to improve haemostasis in both procedural and non-procedural settings. In the absence of high-quality evidence, clinicians have traditionally relied on laboratory indexes for making decisions about transfusion of these products. The systematic review considered purported 'transfusion-trigger' levels of these various indexes, excluding studies of patients with massive bleeding or requiring warfarin reversal.

Question 5 was originally defined as a prognostic question. It was expected that the best evidence relating to this question would come from large cohort studies that stratified results according to baseline international normalised ratio (INR)/fibrinogen/platelet count. However, the literature search for this module identified a number of highly relevant RCTs that compared different transfusion triggers. Therefore, the CRG decided that this question would be approached initially as an interventional question, and then as a prognostic question if relevant evidence from RCTs was not found. High-quality evidence from RCTs was found for platelet transfusion; hence, this part of the question was treated as an interventional question. In contrast, studies relevant to use of cryoprecipitate and FFP were primarily cohort studies in which patients were stratified by INR, prothrombin time/activated partial thromboplastin time (PT/APTT) or fibrinogen at baseline. Hence, these parts of the question were treated as prognostic questions.

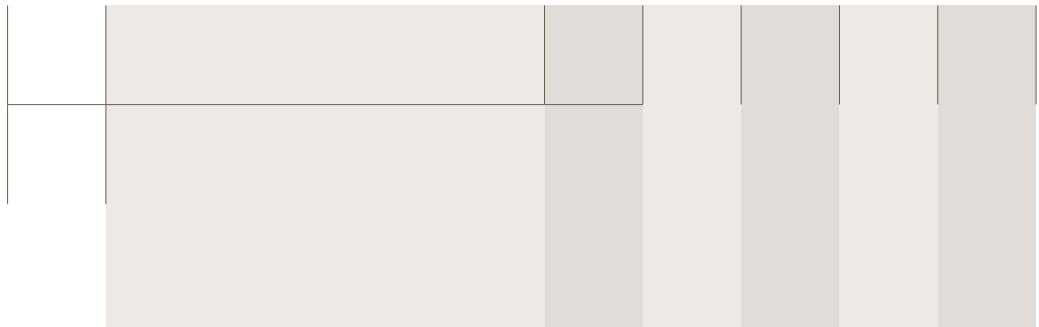
3.5.1 Coagulation parameters and fresh frozen plasma transfusion

EVIDENCE STATEMENTS – coagulation parameters and transfusion		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES5.1	In patients with liver disease, an elevated INR/PT/APTT level is independently associated with an increased risk of mortality.	✓	✓✓	✓✓	✓✓	✓✓
ES5.2	In patients with acute leukaemia, INR/PT/APTT levels may be independently associated with mortality.	✓	← ^A	✓	✓✓	✓✓
ES5.3	In patients with acute promyelocytic leukaemia, the independent association between INR/PT/APTT levels and bleeding events is uncertain.	✓	← ^A		✓✓✓	✓✓
ES5.4	In heparinised patients with ACS receiving					

procoagulant factors. Thus, the balance of pro and anticoagulants may be normal, even in the presence of prolongation of PT and APTT.

Only one retrospective cohort study in patients with acute leukaemia reported an association between coagulation parameters and mortality.¹⁴⁴ This study demonstrated that an INR ≥ 1.5 was an independent risk factor for fatal intracranial haemorrhage, but APTT was not. Only one study considered bleeding risk in acute promyelocytic leukaemia (APML) in relation to coagulation indexes.¹⁴⁵ This study found that neither PT nor APTT were independent risks factors for mortality.

3.5.2 Fibrinogen level and use of cryoprecipitate or fibrinogen concentrate



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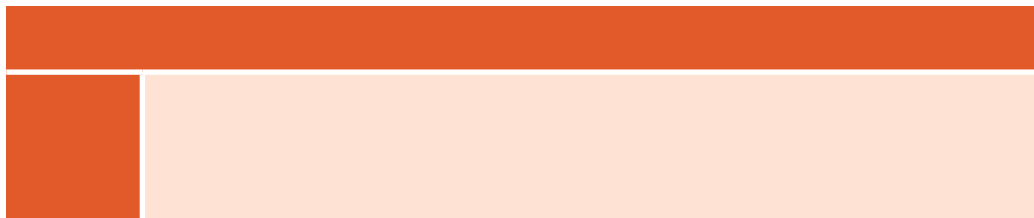
Two relevant retrospective cohort studies (Level III) in patients with acute leukaemia were found. One poor-quality study looked at patients receiving induction chemotherapy for acute promyelocytic leukaemia.¹⁴⁵ Fibrinogen level was not an independent risk factor for bleeding in this setting. The other study examined the risk of fatal intracranial haemorrhage in acute leukaemia patients, but found no significant association between fibrinogen level and fatal intracranial haemorrhage.¹⁴⁶ No studies of acute leukaemia patients were found that reported on an association between fibrinogen level and risk of transfusion.

3.5.3 Platelet count and prophylactic platelet transfusion in patients undergoing chemotherapy and haematopoietic stem cell transplantation

EVIDENCE STATEMENTS – chemotherapy and haematopoietic stem cell transplantation		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES5.9	In patients undergoing chemotherapy and haematopoietic stem cell transplantation – in relation to the effect on mortality – the difference between a prophylactic platelet transfusion trigger of $<10 \times 10^9/L$ without risk factors or $<20 \times 10^9/L$ plus risk factors versus a higher trigger is uncertain. The effect at lower values is unknown.	✓✓	✓✓		✓✓	✓✓
ES5.10	In patients undergoing chemotherapy and haematopoietic stem cell transplantation – in relation to major bleeding events – there is no difference between a prophylactic platelet transfusion trigger of $<10 \times 10^9/L$ without risk factors or $<20 \times 10^9/L$ plus risk factors and a higher trigger. The effect at lower values is unknown.	✓✓	✓✓✓		✓✓	✓✓
ES5.11	In patients undergoing chemotherapy and haematopoietic stem cell transplantation – in relation to RBC transfusion – there is no difference between a prophylactic platelet transfusion trigger of $<10 \times 10^9/L$ without risk factors or $<20 \times 10^9/L$ plus risk factors and a higher trigger. The effect at lower values is unknown.	✓✓	✓✓✓		✓✓	✓✓

ES, evidence statement

✓✓✓=A; ✓✓=B; =D; (see Table 2.1)



PRACTICE POINT – chemotherapy and haematopoietic stem cell transplantation



In patients undergoing chemotherapy and haematopoietic stem cell transplantation, there is no evidence to support:

- a lower trigger for prophylactic platelet transfusion for patients with risk factors (e.g. fever, minor bleeding)
- a strategy of therapeutic-only platelet transfusions (i.e. for treatment of clinically significant bleeding).

Further research to determine the safety and efficacy of a lower platelet transfusion trigger is underway.

PP, practice point; R, recommendation

The use of prophylactic platelet transfusions in patients receiving myelosuppressive chemotherapy or undergoing allogeneic haematopoietic stem cell transplantation (HSCT) is significant. It currently accounts for most of the platelet concentrate usage in Australia. In this clinical setting – in the absence of acute bleeding or the need for an invasive procedure – prophylactic platelet transfusion is usually guided by platelet counts.

The review examined studies concerning platelet count and bleeding risk, together with the intervention of platelet transfusion, but excluded studies in perioperative or acute bleeding settings.

The review identified four RCTs (Level II) comparing different platelet transfusion triggers. Three studies¹⁴⁷⁻¹⁴⁹ compared a platelet transfusion trigger of $10 \times 10^9/L$ with one of $20 \times 10^9/L$. Another study used $30 \times 10^9/L$ as the higher trigger.¹⁵⁰ Of these studies, three^{147,149,150} did not demonstrate a significant difference in mortality between the two study arms. These three studies reported bleeding events, but none observed a significant difference in bleeding rates between the two study arms, nor in bleeding rates in relation to a more restrictive platelet transfusion trigger. RBC transfusion rates were reported in all four studies. None of the studies demonstrated significant differences in number of RBC units transfused, or in the number of transfusions, between study arms.

Based on these results, in patients undergoing myelosuppressive chemotherapy or HSCT, the recommended strategy for prophylactic platelet transfusion is at a platelet count of $<10 \times 10^9/L$ in the absence of risk factors, and at $<20 \times 10^9/L$ in the presence of risk factors (see recommendation R8 above).

There is no evidence at this time to support a lower threshold for prophylaxis, or for the absence of prophylaxis. However, these questions are the current focus of two major international RCTs.

3.6 Red blood cell transfusion in chronically transfused patients

Question 6 (Interventional)

In specific regularly and chronically transfused patients, at what Hb threshold should patients be transfused to avoid adverse outcomes?

Hb, haemoglobin

Patients requiring chronic RBC transfusions account for a significant proportion of blood usage. This includes patients with thalassaemia major, sickle cell disease and myelodysplasia. Hence, appropriate use of red blood cells in these patients is of great importance, both for patient welfare and for the appropriate use of a scarce and valuable resource.

Chronic hypoproduction of RBCs means that regular transfusions are generally required to maintain the Hb at a particular level. The 2001 *Clinical Practice Guidelines on the Use of Blood Components*³ indicated that maintaining Hb at >80 g/L was likely to be appropriate on the basis of physiological principles. These patients are usually managed as outpatients. Hence, for practical reasons, they are often prescribed a predetermined number of RBC units (intended to achieve a defined Hb concentration), rather than having their response assessed after each unit. In addition, these patients may be deliberately transfused to a higher level of Hb than is physiologically necessary, in an attempt to maximise the interval between transfusions. This decision making appears to be based on historical practice; the triggers for initiating transfusion in such patients are different to the triggers for patients with anaemia who do not have bone marrow dysfunction.

Due to the chronic nature of the disorder, patients with chronic anaemia may receive multiple transfusions over a long period. Therefore, in addition to the usual risks associated with transfusion, patients are at risk of complications such as human leukocyte antigen (HLA) and red cell alloimmunisation, and iron overload. For the latter, use of chelation therapy should be considered.

3.6.1 Thalassaemia

EVIDENCE STATEMENTS – thalassaemia		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES6.1	In patients with thalassaemia, the effect of the pretransfusion Hb threshold on mortality is uncertain.		⚡ ^A	✓	✓✓✓	
ES6.2	In patients with thalassaemia, a pretransfusion Hb concentration of 90 – 100 g/L may reduce transfusion volume, compared with 100 – 120 g/L.	✓	✓	✓	✓✓	✓

PRACTICE POINT – thalassaemia

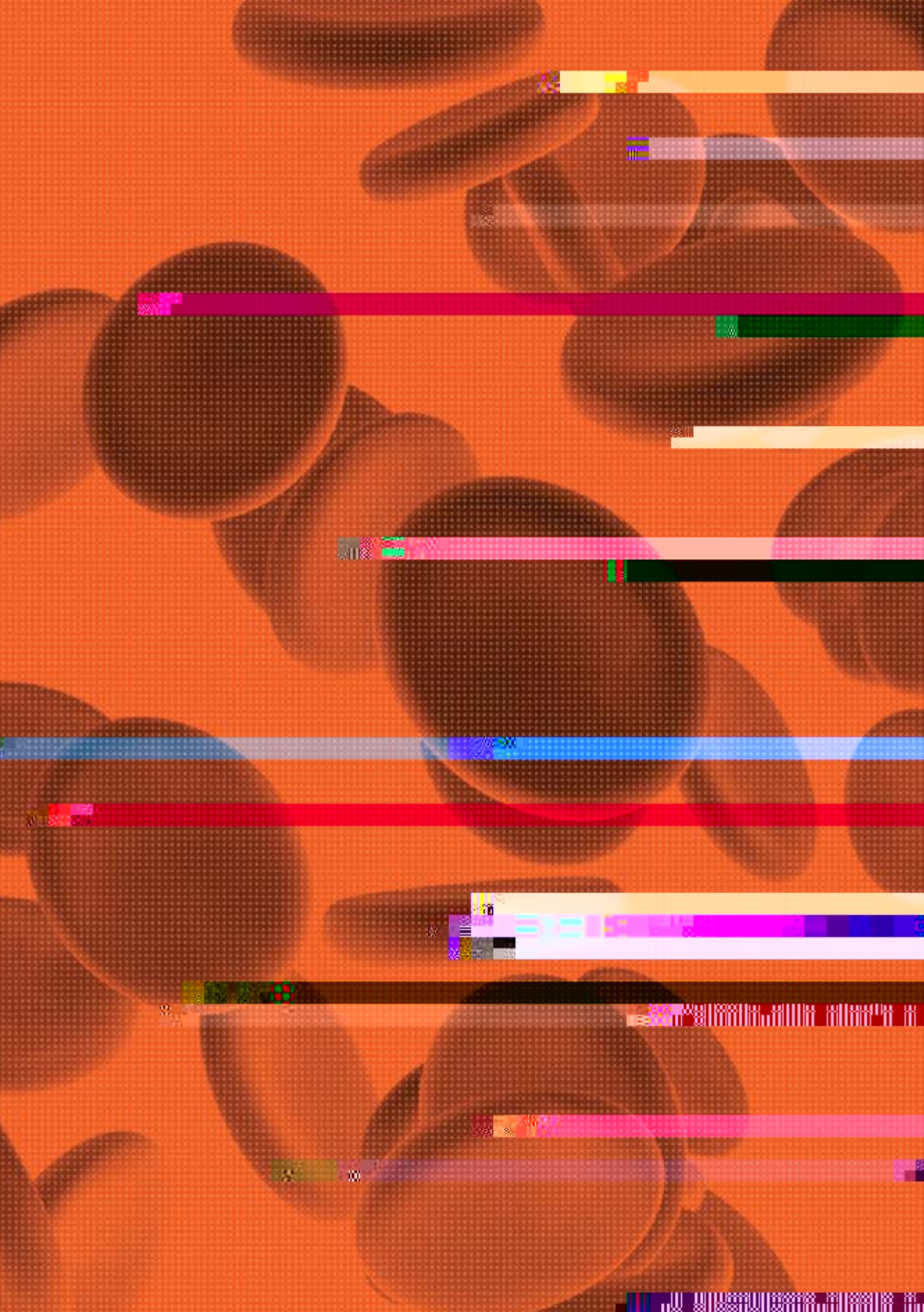


In patients with thalassaemia, the evidence does not support any change to the current practice of maintaining a pretransfusion Hb concentration of 90 – 100 g/L, with transfusions at about monthly intervals.

Hb, haemoglobin; PP, practice point

The use of chronic RBC transfusions intensified in 1978, when iron chelation therapy using subcutaneous desferrioxamine infusions was introduced to improve the management of iron overload in

3.6.2 Myelodysplasia



4 Background questions

4.1 Interventions to raise haemoglobin levels in patients with malignancies

Background question 1

In patients with malignancies (solid tumours) undergoing radiotherapy, do interventions (transfusion or ESAs) aimed at raising the Hb concentration during radiotherapy affect patient outcomes (e.g. response rate, tumour recurrence or tumour-free survival)?

ESA, erythropoiesis-stimulating agent; Hb, haemoglobin

4.1.1 Tumour hypoxia: pathophysiology and effects

Heterogeneously distributed hypoxic areas ($pO_2 < 2.5$ mm Hg) are seen in up to 60% of locally advanced solid tumours, such as breast, uterine, cervix, head, neck and rectal cancers, soft tissue sarcomas and malignant melanomas.¹⁵⁶ A high incidence of hypoxic areas has been correlated with aggressive tumour behaviour and a propensity for metastasis.

Hypoxia affects signalling pathways involved in angiogenesis, glucose transport, pH regulation and erythropoiesis.¹⁵⁷ Hence, tumours become hypoxic because of the development of abnormal vasculature. The hypoxia-inducible factor (HIF) family of transcription factors is important in the cellular response to oxygen homeostasis; overexpression of HIF-1 in human cancers correlates with poor prognosis and increased tumour aggression.¹⁵⁸ Sustained tumour hypoxia alters the response to radiation and to many chemotherapeutic agents in cell lines, but this effect also depends on microenvironmental pH and glucose depletion.

Anaemia is common in patients with solid tumours, and is related to the tumour's malignancy and treatment. An association between low haemoglobin levels and poor outcome of both radiotherapy and chemotherapy has been observed in various solid tumours.^{159,160} Reduced blood oxygen carrying capacity in anaemia may be a major contributor to tissue hypoxia, because the abnormal tumour vasculature is less able to compensate for anaemia by increasing tissue perfusion.

4.1.2 Tumour hypoxia and radiotherapy resistance

High-energy photons used in radiotherapy induce deoxyribonucleic acid (DNA) damage. The photons can either directly cause electrons to ionize DNA helix atoms, or can produce highly reactive free radical species, which then interact with and damage DNA. Unrepaired DNA damage inhibits cell proliferation and leads to cell death. The presence of oxygen contributes to the indirect process by prolonging the life span of the free radicals. Oxygen also decreases the ability of cells to repair DNA damage, so that well-oxygenated cells are more radiosensitive than hypoxic cells.

Hypoxia may also contribute to tumour radiation resistance. This can be caused by altered cell proliferation kinetics, reduction of apoptosis and differentiation, and reduced cell growth associated with slowed protein synthesis. Hypoxia may also increase malignant progression and aggressiveness through clonal selection and genome changes, with an adverse effect on patient outcomes.

4.1.3 Impact of correction of anaemia on radiotherapy outcome



4.2 Assessment of patients after red blood cell transfusion

Background question 2

When should a patient be retested after a transfusion to assess the response, guide whether further transfusions are required and avoid over transfusion?



5 Future directions

The systematic review for this module found adequate evidence to confirm that anaemia is an independent predictor of poorer patient outcomes. However, the findings did not prove that anaemia causes these outcomes, or that correction of the anaemia will reverse the outcomes. Since aetiological questions cannot give rise to recommendations, further investment in systematic reviews in this area is unwarranted.

There was surprisingly little evidence for the benefit of RBC transfusions to correct anaemia in both general and specific medical populations. Thus, it has been difficult to provide guidance on RBC transfusion thresholds while ensuring a patient focus. Any future studies should focus on a formal evaluation of effects on well-being, because this is one of the most common justifications for transfusion. In addition, although there is some evidence of short-term harm associated with transfusion, there is uncertainty about the long-term consequences.

5.1 Evidence gaps and areas of future research

In this review, there were a number of areas where evidence was not sufficient to generate recommendations. Further research in the following areas may be profitable:

- evaluating the incidence, prevalence and management of anaemia (including identification and treatment of underlying causes) in Aboriginal and Torres Strait Islander populations
- identifying the clinical factors, including Hb concentration, that should guide RBC transfusion in medical patients
- evaluating the role and timing of RBC transfusion in patients with acute upper gastrointestinal blood loss, focusing on the effect on rebleeding
- investigating the management of bleeding patients administered antifibrinolytics, and newer anticoagulant and antiplatelet agents
- identifying subsets of patients with cancer in whom ESAs can safely be used
- identifying medical populations who may benefit from the use of FFP
- evaluating the use of fibrinogen concentrate as an alternative to cryoprecipitate
- determining the appropriate trigger for RBC transfusion in patients with thalassaemia and patients with bone marrow failure
- validating the signs and symptoms that indicate a need for RBC transfusion, and evaluating changes in post-transfusion clinical and laboratory indexes over time, to guide management.

5.2 Topics for future consideration

The following topics were not included in the systematic review, but may be considered in revisions of this module:

- the effect of the age of blood on patient outcomes
- the appropriate use of blood products in patients with DIC.



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 module as necessary to reduce variation in-25(00873)JJ 13 TL T

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. The recommendations are likely to reduce product associated expenditure. All recommendations (R1–R8) within this Module either constrain the use of more expensive products (such as blood and blood products and erythropoietin stimulating agents) or replace them with less expensive products (such as iron therapy).

Patient blood management however, requires effective coordination of care. The cost of introducing a coordinated patient blood management approach is anticipated to be offset by savings in reduced product consumption. The NBA, together with the Jurisdictional Blood Committee (JBC) and key stakeholders, is developing a program to facilitate uptake of the PBM guidelines.

The program will include the development of a comprehensive toolkit to support the introduction of patient blood management practices in the clinical setting. The toolkit is being developed with the help of a network of patient blood management practitioners, who will facilitate uptake of the guidelines. The NBA has also funded the development of an online iron deficiency anaemia course within the BloodSafe eLearning Program. Funding has been provided for this course to be marketed to health-care practitioners in the primary and secondary care setting. In addition, the NBA is working with the Australian Commission on Safety and Quality in Healthcare (ACSQHC) to develop a hospital guide to support the implementation of the *National Safety and Quality Health Service Standards*.¹⁷⁶ The guide will provide links to the patient blood management guidelines and toolkit, and the BloodSafe eLearning course. These resources provide explicit tools to support uptake of the recommendations in this module.

This module will be reviewed and amended in 2017, unless an issue arises (e.g. new clinical evidence relevant to practice) that triggers a need for an earlier review.

The PBM Guidelines Project Manager at the NBA will convene the group of experts to undertake the review, and will be the person to contact about 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



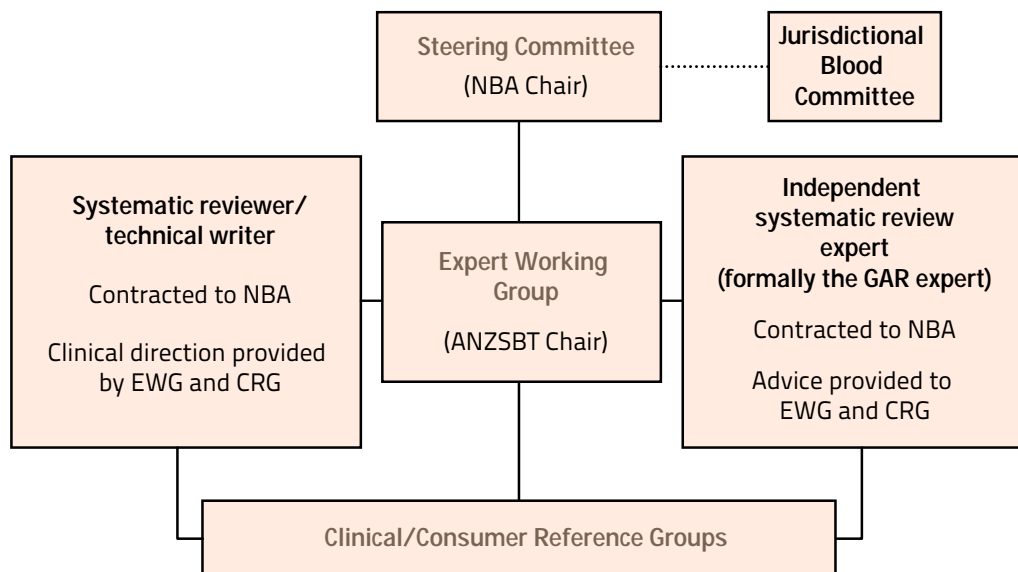
Appendix A

Governance

A1 Management framework for guideline development

Figure A1 illustrates the framework used to manage the development of the six modules of the guidelines, described in [Section 1.2](#) of [Chapter 1](#).

Figure A1 Management framework for development of the guidelines



ANZSBT, Australian & New Zealand Society of Blood Transfusion; CRG, Clinical/Consumer Reference Group; EWG, Expert Working Group; GAR, NHMRC Guidelines Assessment Register; NBA, National Blood Authority

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 Jurisdictional Blood Committee and a clinical representative from the Australian Government Department of Health and Ageing. The role of the Steering Committee was to:

- provide information on the project through the NBA to the JBC
- 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.

A3 Membership of bodies involved in governance of the guidelines

Steering Committee

Ms Stephanie Gunn (Chair)	National Blood Authority
Mr Ken Davis	Australian & New Zealand Society of Blood Transfusion
Prof Henry Ekert	Australian Government Department of Health and 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	Patient Blood Management 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 Michael Permezel	Royal Australian & New Zealand College of Obstetricians and Gynaecologists
Dr Kathryn Robinson	Australian Red Cross Blood Service
Dr Richard Seigne	Australian & New Zealand Society of Blood Transfusion
Dr Philip Truskett	Royal Australasian College of Surgeons
Dr John Vinen	Australasian College for Emergency Medicine

Clinical/Consumer Reference Group – Medical Module

A/Prof Mark Dean (Chair)	Haematologist	Royal College of Physicians & Haematology Society of Australia & New Zealand
Dr Lilon Bandler	General practitioner and Indigenous health representative	Royal Australian College of General Practitioners
A/Prof Donald Bowden	Haematologist	Thalassemia Australia
Prof John Duggan*	Gastroenterologist	Independent expert – gastroenterology
Mr Shannon Farmer	Researcher	Patient Blood Management Advocate
Dr Craig French	Intensive care physician	College of Intensive Care Medicine of Australia and New Zealand, and Australian & New Zealand Intensive Care Society
Dr Chris Hogan	Haematologist	National Blood Authority
Dr Robert Lindeman	Haematologist	Royal College of Pathologists Australia
Prof Lawrence McMahon*	Nephrologist	Independent expert – renal medicine
Ms Penny O'Beid	Clinical Nurse Consultant, Transfusion Medicine	Royal College of Nursing Australia
Dr Kathryn Robinson	Haematologist	Australian Red Cross Blood Service
Dr Amanda Thomson	Haematologist	Australian & New Zealand Society of Blood Transfusion

* Two members joined the CRG for the final four of 12 meetings after the review of the evidence and formulation of recommendations. This additional membership was sought to provide specialist input for specific populations (i.e. renal medicine and gastroenterology) and to ensure that the guidance developed by the CRG accorded, in so far as the evidence allowed, with other guidelines for these specific populations

Background research

Dr Nina Dhondy	Haematology Registrar	Royal North Shore Hospital, Sydney
Dr Chris Hogan	Haematologist	National Blood Authority
Dr Robert Lindeman	Haematologist	Royal College of Pathologists Australia
Dr Amanda Thomson	Haematologist	Australian & New Zealand Society of Blood Transfusion

Acknowledgements – additional clinical input

A/Prof Jane Andrews	Gastroenterologist	Royal Adelaide Hospital
Dr Jeffrey Roland	Geriatrician	The Prince Charles Hospital
Dr Jenny Shannon	Oncologist	Nepean Cancer Care Centre

Independent systematic review expert

Ms Tracy Merlin	Adelaide Health Technology Assessment (AHTA), University of Adelaide
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Project Management and Committee Secretariat – provided by the NBA

Ms Leia Earnshaw	A/g Assistant Director, Blood Sector Clinical Development
Dr Paul Hyland	Assistant Director, Blood Sector Clinical Development
Ms Jennifer Roberts	Director, Blood Sector Clinical Development

Systematic review team

Ms Nimita Arora	OptumInsight (Senior Project Leader)
Dr Kristina Coleman	OptumInsight (Principal Analyst)
Dr Briony Jack	OptumInsight (Research Analyst)
Mr Gregory Merlo	OptumInsight (Senior Analyst)

Medical writing and technical editing – OptumInsight

Dr Hilary Cadman	Cadman Editing Services (independent contractor to OptumInsight)
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A4 Conflict of interest

All members of the Steering Committee, CRG, EWG and systematic review team declared any interests before starting work on the guidelines. Interests were also reviewed at intervals, and were required to be declared at the start of each meeting. The NBA keeps a register of all declared interests. If an interest is declared, the CRG decide by consensus if it affects the proceedings. If the interest is considered to be competing or in conflict, the Chair can prevent the member from participating in discussions and decisions pertaining to the declared interest. Three members declared interests during the guideline development process. Mr Shannon Farmer declared the following patient advocacy roles: the Society for the Advancement of Blood Management, the Medical Society for Blood Management and the Network for Advancement of Transfusion Alternatives. Professor Lawrence McMahon declared that he was a prescriber of erythropoiesis stimulating agents. He declared travel grants to attend the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Annual Scientific Meeting in 2010 from Roche and in 2012 from Amgen. He received a research grant from Amgen in 2009 and an unrestricted educational grant for research from Roche in 2011. He was on the Roche Advisory Board for Mircera (continuous erythropoietin receptor activator) in 2008. Dr Kathryn Robinson declared an interstate airfare and accommodation for one night paid directly by Aspen Pharmacare for presenting at an educational iron forum organised by Aspen in February 2008; information from her presentation was used for an Aspen educational newsletter but no payment was received.

The chair considered these declarations and determined that they did not constitute a sufficient conflict to require members to leave the room or excuse themselves from discussion at any time during the guideline development process. No other members declared any interests.



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 serious non-viral adverse events, such as transfusion-associated circulatory overload (TACO) or transfusion-related acute lung injury (TRALI), are more common than previously thought, and that more recently identified conditions (e.g. transfusion-related immunomodulation) may cause patients harm.

The risk of transmission of infectious diseases through blood transfusions has reduced significantly in recent years, through improved manufacturing and laboratory processes. However, there is 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.

If the patient requires therapy for anaemia, thrombocytopenia or coagulopathy, transfusion should not be a default decision. Instead, the decision on whether to transfuse should be carefully considered, and should:

- take into account the full range of available therapies
- balance the evidence for efficacy and improved clinical outcome against the risks
- take into account patient values and choices.

In the process of obtaining informed 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.

All elements of the consent process should reflect local state, territory or national requirements.

[Table B.1](#) summarises transfusion risks, and [Table B.2](#) presents the Calman Chart, which may be useful to clinicians for explaining risks to patients.¹⁷⁷

Table B.1 Transfusion risks

TRANSFUSION RISK	ESTIMATED RATE ^a (HIGHEST TO LOWEST RISK)	CALMAN RATING ^b
Transfusion-associated circulatory overload (iatrogenic)	Up to 1 in 100 transfusions	High
Transfusion-related acute lung injury	1 in 1200 – 190,000	Low to minimal
Haemolytic reactions	Delayed: 1 in 2500 – 11,000 Acute: 1 in 76,000 Fatal: Less than 1 in 1 million	Low to very low Very low Negligible
Anaphylactoid reactions or anaphylaxis (usually due to IgA deficiency)	1 in 20,000 – 50,000	Very low
Bacterial sepsis: platelets	1 in 75,000	Very low
Bacterial sepsis: red blood cells	1 in 500,000	Minimal
Hepatitis B	Less than 1 in 1 million	Negligible
Hepatitis C	Less than 1 in 1 million	Negligible
Human immunodeficiency virus	Less than 1 in 1 million	Negligible
Human T-lymphotropic virus (types 1 and 2)	Less than 1 in 1 million	Negligible

TRANSFUSION RISK	ESTIMATED RATE ^a (HIGHEST TO LOWEST RISK)	CALMAN RATING ^b
Malaria	Less than 1 in 1 million	Negligible
Variant Creutzfeldt-Jakob disease (not tested)	Never reported in Australia	Negligible
Transfusion-associated graft-versus-host disease	Rare	Negligible
Transfusion-related immunomodulation	Not quantified	Unknown

^a Risk per unit transfused unless otherwise specified

^b See Calman 1996¹⁷⁷

Source: Australian Red Cross Blood Service website (www.transfusion.com.au)

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.2 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 1996¹⁷⁷



Appendix C

Blood sectors

C1 Australian blood sector

Standing Committee on Health and Australian Health Ministers' Advisory Council

The Standing Committee on Health (SCoH) is responsible for the oversight and management of the Australian blood sector. The committee'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. SCoH 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 SCoH 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 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 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 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 Australian Red Cross Blood Service 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 Australian Red Cross Blood Service 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 blood centres in accordance with good manufacturing practice
- issuing product recalls
- approving changes to the NZBS Collection and Manufacturing Standards.

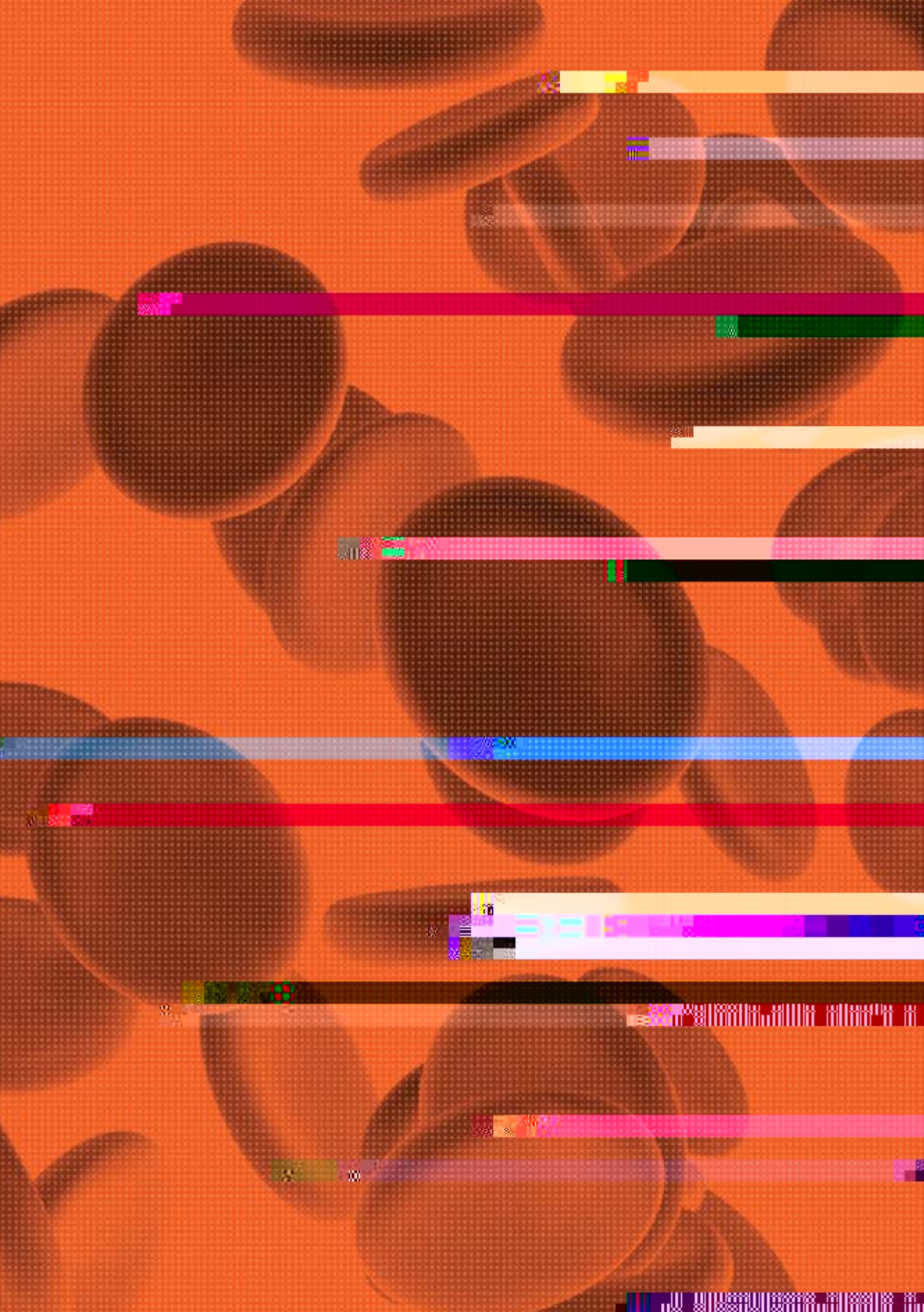
New Zealand Blood Service

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 third. 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 a patient blood management advocate and representation from relevant colleges and societies, was established to develop the medical module. The CRG received assistance from systematic reviewers and a technical writer, and advice and mentoring from a systematic review expert. 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 reviewers, CRG, NBA and the systematic review expert.

D3 Methodology

Methods are outlined in [Chapter 2](#), with greater detail given in the technical reports. Briefly, the clinical research questions for systematic review were structured according to three criteria: 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. 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

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D4 Public consultation

Public consultation was conducted from 23 January to 16 March 2012, 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.

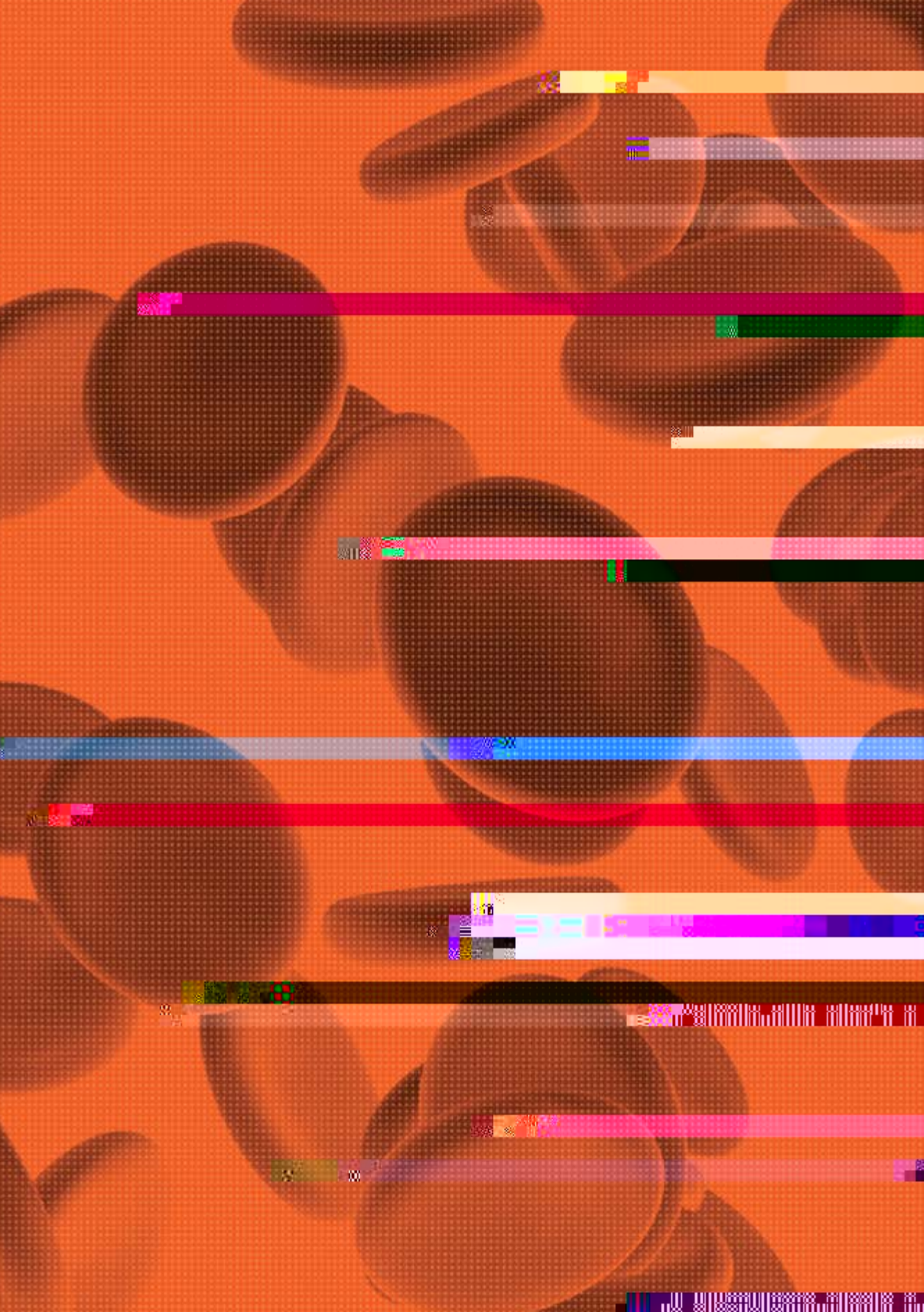
Eleven submissions were received. The CRG met in April 2012 to consider all the public consultation submissions and, where necessary, revise this module in accordance with the submissions. Changes were made to the module to address comments and concerns raised in submissions, and to improve clarity.

D5 Finalising the guidelines

The final drafts of the module and technical reports were reviewed by a guidelines development expert (formerly a Guidelines Assessment Register 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 20 April 2012.

Approval from the NHMRC was received on 18 July 2012.

^d <http://www.nba.gov.au/>



Appendix E

Product information

For information on blood products available in Australia, see the website of the Australian Red Cross Blood Service (www.transfusion.com.au).

For information on blood products available in New Zealand, see the website of the New Zealand Blood Service (www.nzblood.co.nz).



Appendix F

Summary of recommendations and practice points by clinical condition

F1 General medical

Identifier	Guidance – recommendations and practice points	Relevant section of document
RED CELLS		



F2 Cardiac – acute coronary syndrome

Identifier and grade ^e	Guidance – recommendations and practice points	Relevant section of document
RED CELLS		
G ADEC	In ACS patients with a Hb concentration >100 g/L, RBC transfusion is not advisable because of an association with increased mortality.	3.2.2
PP	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.	3.2.1
PP	Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.	3.2.1
PP	In patients with iron deficiency anaemia, iron therapy is required to replenish iron stores regardless of whether a transfusion is indicated.	3.2.1
PP	In patients with ACS and a Hb concentration <80 g/L, RBC transfusion may be associated with reduced mortality and is likely to be appropriate.	3.2.2
PP	In patients with ACS and a Hb concentration of 80 – 100 g/L, the effect of RBC transfusion on mortality is uncertain and may be associated with an increased risk of recurrence of MI. Any decision to transfuse should be made with caution and based on careful consideration of the risks and benefits.	3.2.2

ACS, acute coronary syndrome; Hb, haemoglobin; MI, myocardial infarction; PP, practice point; R, recommendation; RBC, red blood cell

^e As noted above, recommendations are graded and practice points are not.

F3 Heart failure


Identifier and grade ^e	Guidance – recommendations and practice points	Relevant section of document
IRON AND ERYTHROPOIESIS-STIMULATING AGENTS		
R3	<p>In patients with CHF, identification and treatment of iron deficiency (absolute and functional) is recommended to improve functional or performance status.</p> <p>This is consistent with the 2011 update to the <i>Guidelines for the Prevention, Detection and Management of Chronic Heart Failure in Australia, 2006</i>.²</p> <p>Note: The studies reviewed only included patients treated with IV iron, and of NYHA functional classes II or III.</p>	<u>3.3.2</u>
RED CELLS		
	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.	<u>3.2.1</u>
		

Identifier and grade^e




Guidance – recommendations and practice points




Relevant section of document



RED CELLS

	<p>Direct evidence is not available in general medical patients.^a Evidence from other patient groups and CRG consensus suggests that, with a:</p> <ul style="list-style-type: none">• Low risk of bleeding, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available.• Low risk of bleeding, RBC transfusion is not associated with reduced mortality. The decision to transfuse patients (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. No evidence was found to warrant a different approach for patients who are elderly or who have respiratory or cerebrovascular disease.• High risk of bleeding, RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with ACS. <p>^a Recommendations and practice points for medical patients in a critical care setting will be found in the <i>Patient Blood Management Guidelines: Module 4 – Critical Care</i>.³</p>	

F4 Cancer


Identifier and grade ^e	Guidance – recommendations and practice points	Relevant section of document
RED CELLS		
	<p>RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.</p>	<p>3.2.1</p>
	<p>Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.</p>	<p>3.2.1</p>
	<p>Direct evidence is not available in general medical patients.^a Evidence from other patient groups and CRG consensus suggests that, with a:</p> <ul style="list-style-type: none"> • b on t t on 	

Identifier and grade ^e	Guidance – recommendations and practice points	Relevant section of document
	There is a lack of specific evidence relating to the effects of RBC transfusion in patients with cancer. Any decision to transfuse should be based on the need to relieve clinical signs and symptoms of anaemia. When treating patients with cancer, refer also to the general medical population PP1–PP4.	3.2.4
IRON AND ERYTHROPOIESIS-STIMULATING AGENTS		
	In cancer patients with anaemia, the <i>routine</i> use of ESAs is not recommended because of the increased risks of mortality and thromboembolic events.	3.3.1
	In anaemic patients with cancer receiving ESAs, evaluate iron status to guide adjuvant iron therapy.	3.3.1





Identifier	Guidance – recommendations and practice points	Relevant section of document
	<p>Direct evidence is not available in general medical patients.^a Evidence from other patient groups and CRG consensus suggests that, with a:</p> <ul style="list-style-type: none"> • Strong recommendation, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available. • Strong recommendation, RBC transfusion is not associated with reduced mortality. The decision to transfuse patients (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. No evidence was found to warrant a different approach for patients who are elderly or who have respiratory or cerebrovascular disease. • Strong recommendation, RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with ACS. <p>^a Recommendations and practice points for medical patients in a critical care setting will be found in the <i>Patient Blood Management Guidelines: Module 4 – Critical Care</i>.³ Recommendations and practice points for specific medical subgroups (ACS, CHF, cancer, acute upper gastrointestinal bleeding and chronically transfused) appear elsewhere in this module.</p>	<p><u>3.2.1</u></p>
		

F6 Chronic kidney disease

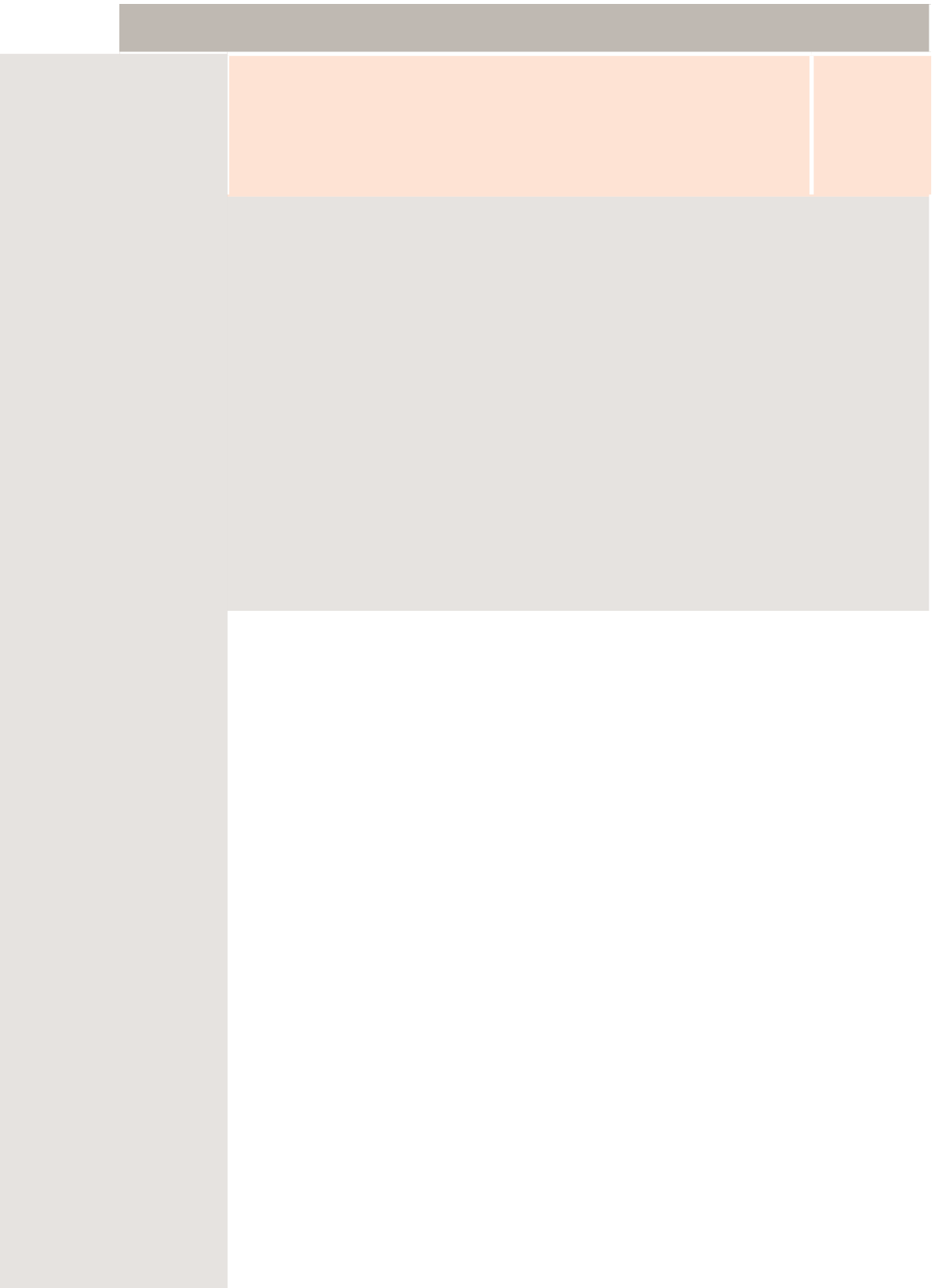
Identifier and grade ^e	Guidance – recommendations and practice points	Relevant section of document
IRON AND ERYTHROPOIESIS-STIMULATING AGENTS		
	<p>In anaemic patients with CKD, ESA therapy to a low to intermediate Hb target may be used to avoid RBC transfusion, after consideration of risks and benefits for the individual patient. (Grade B)</p> <p>Note: The CARI guidelines recommend a Hb target between 100-115 g/L⁵</p>	<u>3.3.3</u>
R5	<p>In anaemic patients with CKD, ESA therapy to a low to intermediate Hb target may be used to relieve fatigue, after consideration of risks and benefits for the individual patient. (Grade C)</p> <p>Note: The CARI guidelines recommend a Hb target between 100-115 g/L⁵</p>	<u>3.3.3</u>
R6	<p>In anaemic patients with CKD, ESA therapy to a Hb target of over 130 g/L is not recommended because of increased morbidity.</p>	<u>3.3.3</u>
R7	<p>In anaemic patients with non dialysis-dependent CKD, type 2 diabetes and a history of malignancy, the <i>routine</i> use of ESAs is not recommended because of the increased risk of cancer-related mortality.</p>	<u>3.3.3</u>

Identifier and grade ^e	Guidance – recommendations and practice points	Relevant section of document
	<p>Direct evidence is not available in general medical patients.^a Evidence from other patient groups and CRG consensus suggests that, with a:</p> <ul style="list-style-type: none"> • Strong recommendation, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available. • Strong recommendation, RBC transfusion is not associated with reduced mortality. The decision to transfuse patients (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. No evidence was found to warrant a different approach for patients who are elderly or who have respiratory or cerebrovascular disease. • Strong recommendation, RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with ACS. 	




F7 Chemotherapy and haematopoietic stem cell transplantation

Identifier and grade ^e	Guidance – recommendations and practice points	Relevant section of document
RED CELLS		
	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.	3.2.1
	Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.	3.2.1
	<p>Direct evidence is not available in general medical patients.^a Evidence from other patient groups and CRG consensus suggests that, with a:</p> <ul style="list-style-type: none"> • Recommendation: In general medical patients, RBC transfusion may be associated with reduced mortality and is likely to be appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available. • Recommendation: In patients with acute coronary syndrome (ACS), RBC transfusion is not associated with reduced mortality. The decision to transfuse patients (with a single unit followed by reassessment) should be based on the need to relieve clinical signs and symptoms of anaemia, and the patient's response to previous transfusions. No evidence was found to warrant a different approach for patients who are elderly or who have respiratory or cerebrovascular disease. • Recommendation: In patients with acute coronary syndrome (ACS), RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with ACS. <p>^a Recommendations and practice points for medical patients in a critical care setting will be found in the <i>Patient Blood Management Guidelines: Module 4 – Critical Care</i>.³ Recommendations and practice points for specific medical subgroups (ACS, CHF, cancer, acute upper gastrointestinal bleeding and chronically transfused) appear elsewhere in this module.</p>	3.2.1
	In patients with iron deficiency anaemia, iron therapy is required to replenish iron stores regardless of whether a transfusion is indicated.	3.2.1





^e As noted above, recommendations are graded and practice points are not.



F8 Thalassaemia and myelodysplasia

Identifier	Guidance – recommendations and practice points	Relevant section of document
RED CELLS		
	<p>RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.</p>	<p>3.2.1</p>
	<p>Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.</p>	<p>3.2.1</p>
	<p>In patients with thalassaemia, the evidence does not support any change to the current practice of maintaining a pretransfusion</p>	

F9 Coagulopathy

Identifier	Guidance – recommendations and practice points	Relevant section of document
FRESH FROZEN PLASMA		
	<p>The <i>routine</i> use of FFP in medical patients with coagulopathy (including those with liver impairment) is not supported. Tests for coagulation correlate poorly with bleeding risk in liver impairment.</p> <p>The underlying causes of coagulopathy should be assessed. Where FFP transfusion is considered necessary, the risks and benefits should be considered for each patient, and expert guidance sought.</p>	3.4.1
	<p>For guidance on the use of FFP in specific patient groups, refer to:</p> <ul style="list-style-type: none"> • <i>Patient Blood Management Guidelines: Module 1 – Critical Bleeding/ Massive Transfusion</i> (2011)⁴ • <i>Patient Blood Management Guidelines: Module 2 – Perioperative</i> (2012)⁶ • <i>Warfarin Reversal: Consensus Guidelines, on behalf of the Australasian Society of Thrombosis and Haemostasis</i> (2004)⁷ • AHCDO guidelines for patients with specific factor deficiencies (http://www.ahcdo.org.au) • TTP: <i>Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant</i> (2004).⁸ 	3.4.1
CRYOPRECIPITATE OR FIBRINOGEN CONCENTRATE		
	<p>The routine use of cryoprecipitate or fibrinogen concentrate in medical patients with coagulopathy is not advised. The underlying causes of coagulopathy should be identified; where transfusion is considered necessary, the risks and benefits should be considered for each patient. Specialist opinion is advised for the management of DIC.</p>	3.4.2
	<p>For guidance on the use of cryoprecipitate or fibrinogen concentrate in specific patient groups, refer to:</p> <ul style="list-style-type: none"> • <i>Patient Blood Management Guidelines: Module 1 – Critical Bleeding/ Massive Transfusion</i> (2011)⁴ • AHCDO guidelines for patients with specific factor deficiencies (www.ahcdo.org.au) • TTP: <i>Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant</i> (2004).⁸ 	3.4.2

AHCDO, Australian Haemophilia Centre Directors' Organisation; DIC, disseminated intravascular coagulation; FFP, fresh frozen plasma; PP, practice point

F10 Thrombocytopenia

Identifier Guidance –
recommendations and practice points

Guidance – recommendations and practice points		



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