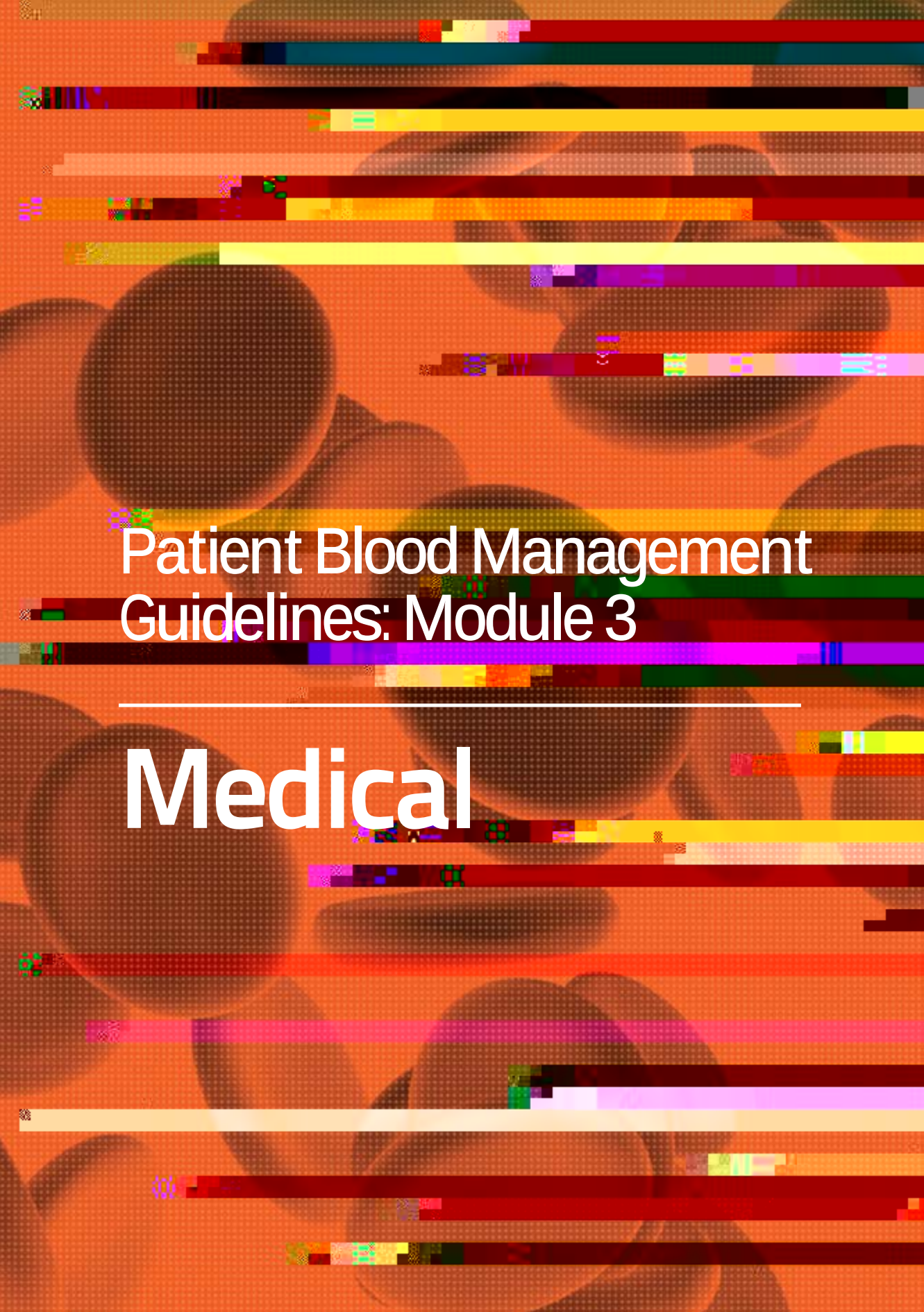


Patient Blood Management Guidelines: Module 3

Medical

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

Thalassaemia Australia

The National Blood Authority gratefully acknowledges these contributions. College and society endorsement of this module can be found at www.nba.gov.au.

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 thrombocytopaenia
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

NYHA	New York Heart Association
NZBS	New Zealand Blood Service
PBS	Pharmaceutical Benefits Scheme
PICO	population, intervention, comparator and outcome
PP	practice point
PPO	population, predictor and outcome
PRO	population, risk factor and outcome
PT	prothrombin time
R	recommendation
RBC	red blood cell
RCT	randomised controlled trial
SCoH	Standing Committee on Health
SF-36	Short Form-36
TGA	Therapeutic Goods Administration
TTP	thrombotic thrombocytopenic purpura
WHO	World Health Organization

Contents

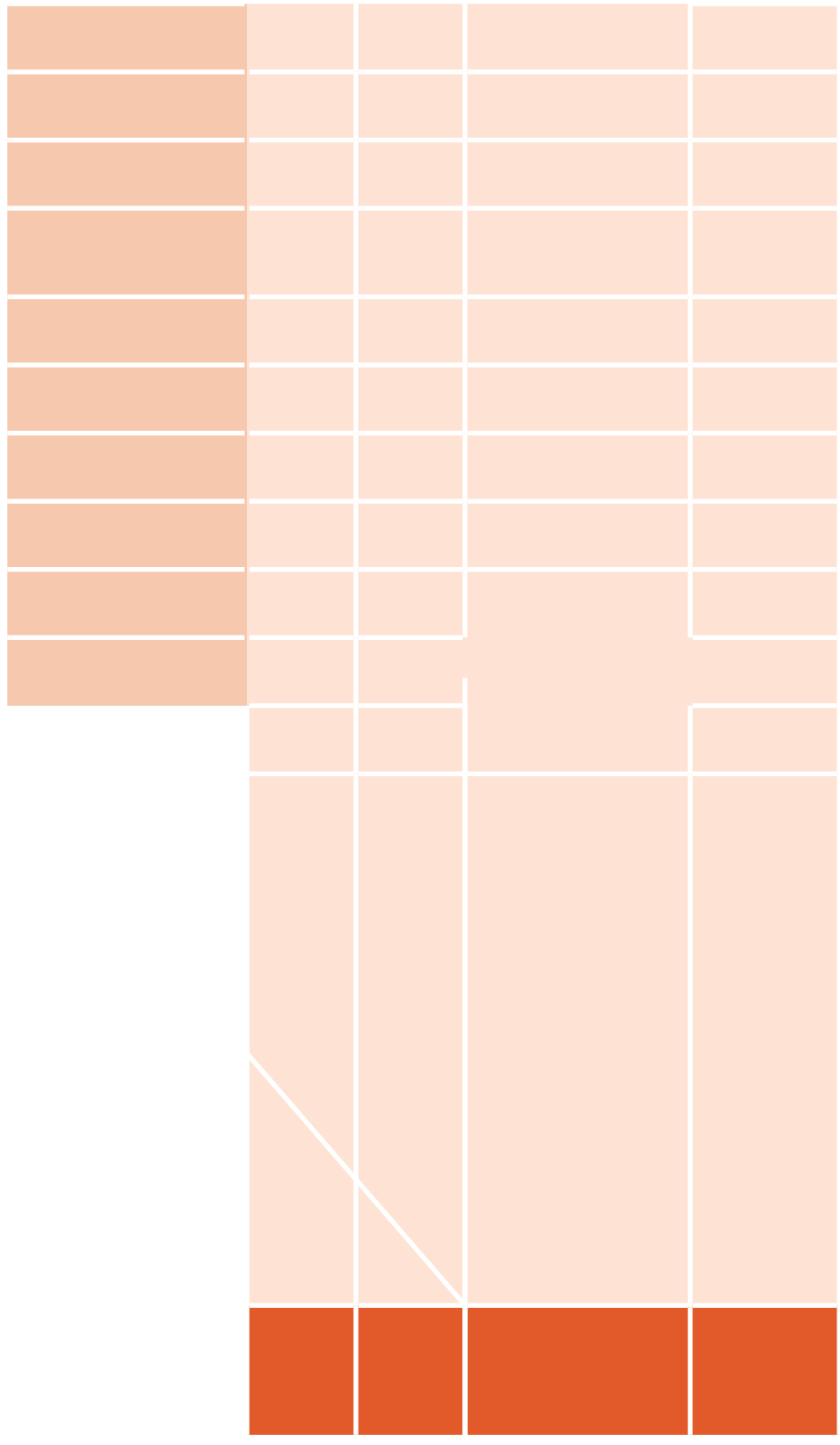
Executive summary

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

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



Practice points

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

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	CONDITIONS									
			General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia
	Direct evidence is not available in general medical patients.[a] Evidence from other patient groups and CRG consensus suggests that, with a: • , b on\ ‡ ‡ a on , , RBC transfusion may be associated with reduced mortality and is likely to be appropriate. hasion ma882 Tc -67.1591788283 (OF DOCUMENT)Tj 0 1 1788283 nd is l(002ents.)Tj .BC tra221 Tm (-0 g/L)Tj-14.25y as l(Hb concentration <70 g/L)Tj /R170 8 Tf 83.5423 0 Tof sfu–3649										

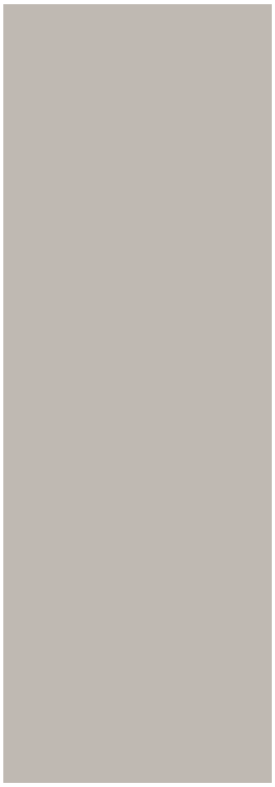
IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	CONDITIONS									
			General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia
	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 myelodysplasia	Coagulopathy	Thrombocytopenia
	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				✓						
	In well-compensated patients with acute upper gastrointestinal blood loss that is non-critical, there is no evidence to favour a liberal transfusion policy. Therefore, a more restrictive approach											

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	CONDITIONS										
			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 IBD, determine the cause of anaemia and treat reversible causes. IV iron may be required in patients who are intolerant of oral iron, or to avoid aggravation of intestinal inflammation.	3.3.5					✓					
	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.	3.4.1									✓	

Practice points

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	CONDITIONS									
			General medical	Cardiac – acute coronary syndrome	Heart failure	Cancer	Gastrointestinal	Chronic kidney disease	Chemotherapy and haematopoietic stem cell transplantation	Thalassaemia and myelodysplasia	Coagulopathy	Thrombocytopenia
	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]	3.4.1								✓	
	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.	3.4.2									✓	

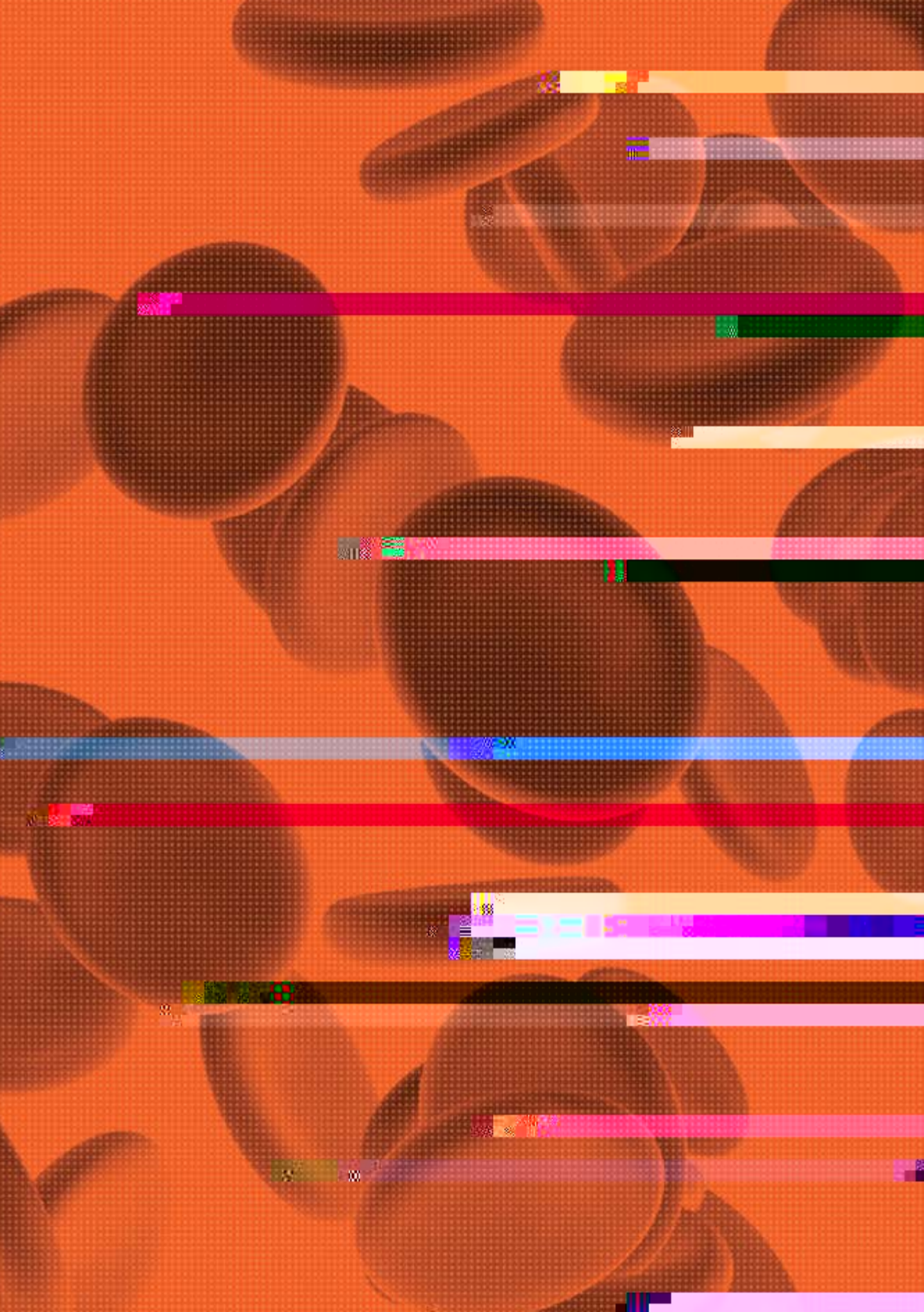


a strategy of therapeutic only platelet transfusions (i.e. for platelet transfusion triggers underway. 3) Further research to determine the safety and efficacy of a lower

a lower trigger for prophylactic platelet transfusion for patients with risk factors (e.g. fever, minor bleeding)

IDENTIFIER	GUIDANCE	RELEVANT SECTION OF DOCUMENT	CONDITIONS									
			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; AHCDO, 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 thrombocytopaenia; 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:

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

Patient blood management optimises the use of donor blood and reduces transfusion-associated risk.

If the patient requires therapy for anaemia, thrombocytopaenia or coagulopathy, transfusion should not be a default decision. Instead, the decision on whether to transfuse should be carefully considered, taking into account the full range of available therapies, and balancing the evidence for efficacy and improved clinical outcome against the potential risks (Appendix B). In the process of obtaining informed consent, a clinician should allow the patient sufficient time to ask questions, and should answer those questions.

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 addrestienbyhird 20 39nt,

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

- background material on clinical issues not covered by the systematic review (Chapter 4)
- recommendations for future directions (Chapter 5)
- information on implementing, evaluating and maintaining the guidelines (Chapter 6).

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

1.3.2 Related materials

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

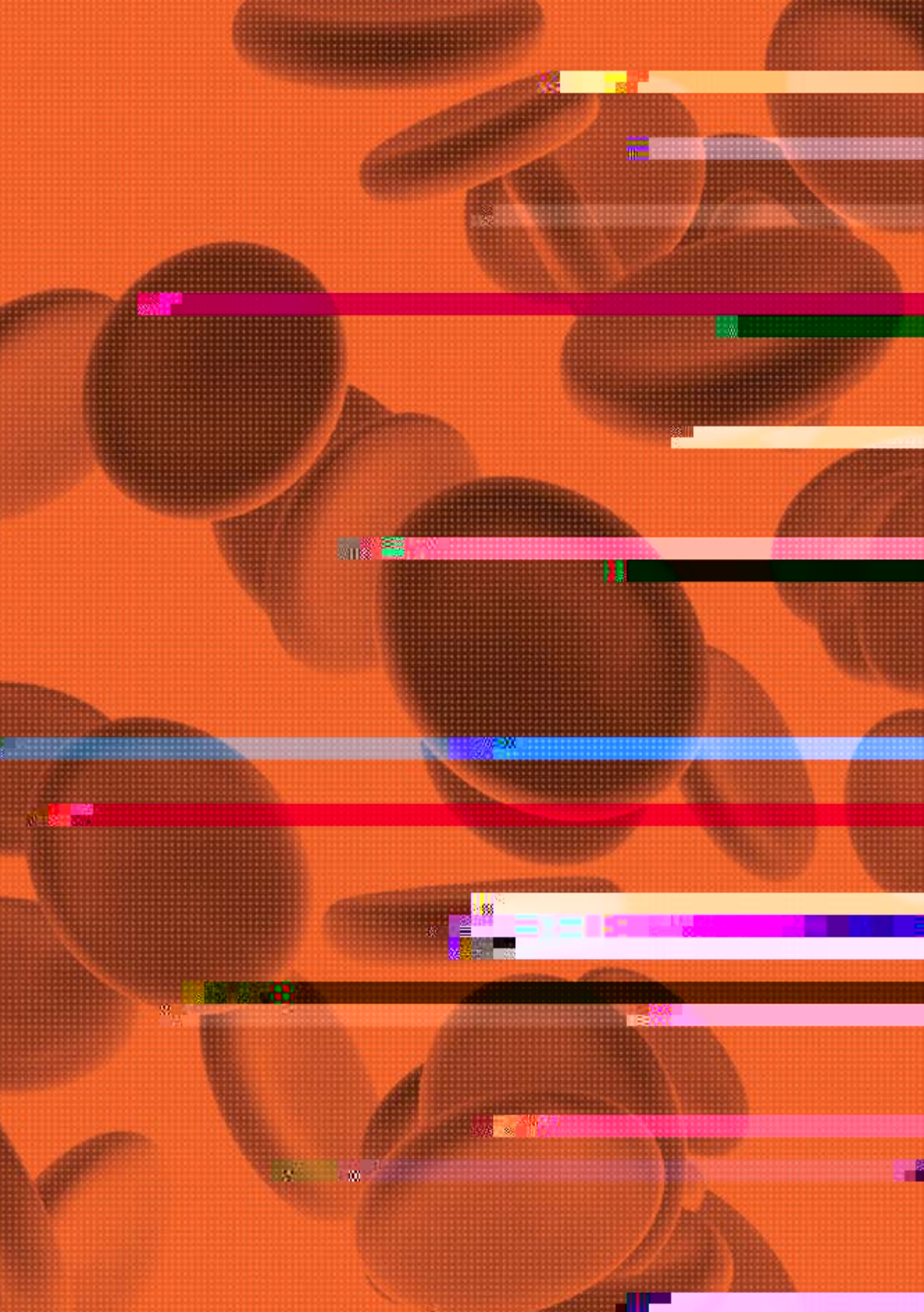
The technical report that underpins this document is available online, in two volumes:

- *Volume 1*

  This volume contains background information and the results of the systematic reviews pertaining to the clinical questions posed within this guideline.[10]

- *Volume 2*

  This volume contains appendixes that document the literature searches, study quality appraisal, NHMRC evidence statement forms and evidence summaries for the individual studies.[11]



2 Methods

The development of evidence-based clinical practice guidelines that meet NHMRC standards involves developing a set of clinical research questions, systematically reviewing the scientific literature for evidence related to those questions, and then developing and grading recommendations based on a structured assessment of the evidence.[12] The methods used in applying this process to the development of this module are outlined below, and are given in

2.1 Clinical research questions – development and details

Between April and June 2009, the relevant clinical research questions for this module were developed,

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:

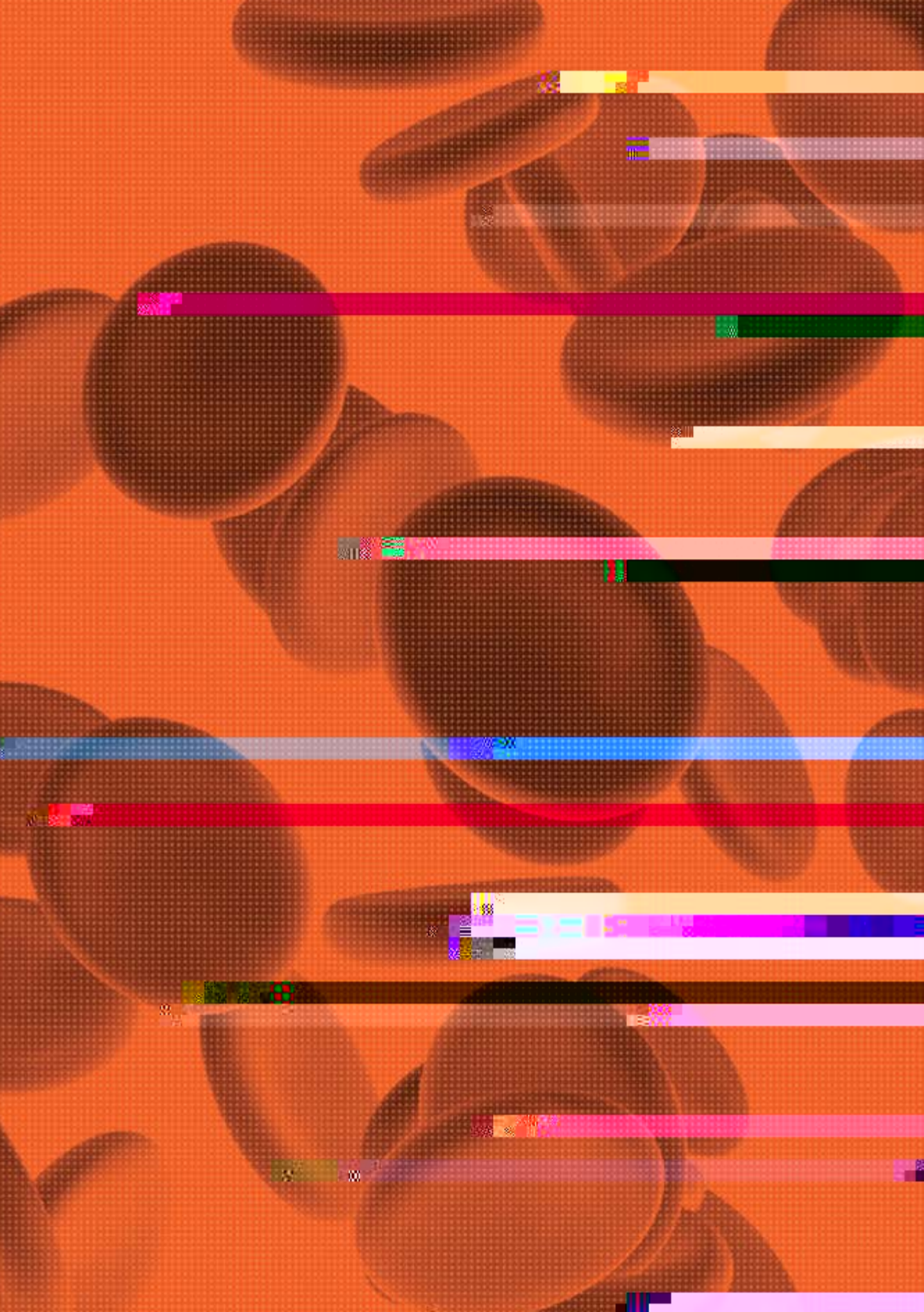
- the body of evidence was sufficient – that is, wherever the evidence yielded support for recommendations of at least NHMRC Grade C (see Table 2.2, below)
- the question type was interventional – that is, it evaluated the effectiveness of an intervention.

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

Table 2.1 Body of evidence matrix



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 – acute coronary syndrome		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES1.1	In patients with ACS, anaemia is independently associated with all-cause mortality.	✓✓✓	✓✓	✓✓	✓✓✓	✓✓✓
ES1.2	In patients with ACS, the effect of anaemia on cardiovascular mortality is uncertain.	✓✓✓	✓✓	✓✓	✓✓✓	✓✓✓
ES1.3	In patients with NSTE-ACS, anaemia is independently associated with MI and recurrent ischaemia.	✓✓	A	✓✓	✓✓✓	✓✓

ACS, acute coronary syndrome; ES, evidence statement; MI, myocardial infarction; NSTE-ACS, non-ST segment elevation acute coronary syndrome

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

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

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).[61,65] 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 review was identified that did not strictly meet the definition of a Level I study because it included both prospective and retrospective cohort studies.[66] 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	
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.
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.
PP	Direct evidence is not available in general medical patients.[a] Evidence from other patient groups and CRG consensus suggests that, with a: • b on\ ‡ on , 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. • b on\ ‡ on o , 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. • b on\ ‡ on , RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with ACS. [a] Recommendations and practice points for medical patients in a critical care setting will be found in the *Patient Blood Management Guidelines: Module 4 – Critical Care*.[3] Recommendations and practice points for specific medical subgroups (ACS, CHF, cancer, acute upper gastrointestinal bleeding and chronically transfused) appear elsewhere in this module.
PP	In patients with iron deficiency anaemia, iron therapy is required to replenish iron stores regardless of whether a transfusion is indicated.

ACS, acute coronary syndrome; CHF, chronic heart failure; CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; PP, practice point; RBC, red blood cell

For the comparison of restrictive and liberal transfusion strategies in general medical patients, a Cochrane review by Carless et al (Level I) was identified.[82] The review assessed data from 17 randomised controlled trials (RCTs) including mainly surgical, critical care and paediatric patients. Studies varied in their definition of restrictive and liberal policies. No difference in mortality or rate of stroke or thromboembolism was identified, but there was a reduction in in-hospital mortality, infection and cardiac events among patients transfused using a restrictive policy. As these findings were largely based on surgical patients, their generalisability to the medical population is limited.

In the absence of direct evidence to support recommendations for the general medical population, evidence from other patient groups was applied to derive a series of practice points. Decisions on whether to transfuse should take into account the absence of proven benefit, and should follow a precautionary principle. In medical patients, the aetiology of anaemia is often multifactorial; where appropriate, reversible causes should be identified and treated.

The Caring for Australasians with Renal Impairment (CARI) guidelines provide recommendations for the management of anaemia in patients with chronic kidney disease (CKD),[83] while the *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion* are appropriate for patients with decompensated upper gastrointestinal bleeding.[4] Practice points and recommendations for other

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

EVIDENCE STATEMENTS – acute coronary syndrome		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.2	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.	✓	✓✓	✓✓	✓✓✓	✓✓✓
ES2.3	In ACS patients with an *admission* Hb concentration <100 g/L, RBC transfusion may be associated with a lower risk of mortality.		✓✓	✓	✓✓✓	✓
ES2.4	In ACS patients with a *nadir* Hb concentration <80 g/L, RBC transfusion may be associated with a lower risk of mortality.	✓	✓✓		✓✓✓	✓✓✓
ES2.5	In ACS patients with a *nadir* Hb concentration of 80 – 100 g/L, RBC transfusion is not associated with an altered mortality risk.	✓	✓✓	A	✓✓✓	✓✓✓
ES2.6	In patients with ACS, RBC transfusion may be associated with an increased risk of recurrence (up to 6 months) of MI.	✓	A	✓✓	✓✓	✓✓✓

ACS, acute coronary syndrome; ES, evidence statement; Hb, haemoglobin; MI, myocardial infarction; RBC, red blood cell

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

RECOMMENDATION – acute coronary syndrome

GRADE C

In ACS patients with a Hb concentration >100 g/L, RBC transfusion is not advisable because of an association with increased mortality.

PRACTICE POINTS – acute coronary syndrome

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).

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).

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

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 Wu[86] and Sabatine[21] showed reduced mortality in patients receiving transfusions at lower *admission* Hb concentrations; however, the studies by Rao[87] and Alexander[84] 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 Shishehbor[88] reported that, in patients with ACS, RBC transfusion may be associated with an increased risk of recurrence of MI.

3.2.3 Heart failure

EVIDENCE STATEMENTS – heart failure		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.7	In patients with heart failure, the effect of RBC transfusion on the risk of mortality is uncertain.	✓	A	A	✓✓	✓✓

ES, evidence statement; RBC, red blood cell

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

PRACTICE POINT – heart failure

In all patients with heart failure, there is an increased risk of transfusion-associated of recurrthat in d, on on the rishould1898usia nge J 0uncatefsfusifollced mby sk oe re, re031( )[of recurrdec
In pants with heart failure, the effect off WuLevylll-2) assessed.613281 0.268066 0.13501 scn q 10 0 0 10 0

3.2.5 Acute upper gastrointestinal blood loss

3.3 Effect of erythropoiesis - stimulating agents and iron

3.3.1 Cancer

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 is uncertain.		A			✓✓
ES3.15	In anaemic patients with CHF, the effect of ESAs on the incidence of thromboembolic events is uncertain.	✓✓✓	✓✓	A	✓	✓✓
ES3.16	In anaemic patients with CHF, ESAs may improve functional or performance status compared with no ESAs.	✓✓✓	✓	✓	✓	✓✓

EVIDENCE STATEMENTS – chronic heart failure (iron therapy)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.17	In CHF patients with iron deficiency, the effect of IV iron on mortality is uncertain.	✓✓	✓✓	A	✓✓	✓✓
ES3.18	In CHF patients (NYHA functional classes II or III) with iron deficiency (absolute and functional), IV iron improves functional or performance status, independent of Hb concentration.	✓✓	✓✓	✓✓	✓✓	✓✓

CHF, chronic heart failure; ES, evidence statement; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; IV, intravenous; NYHA, New York Heart Association

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

RECOMMENDATION – chronic heart failure

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.

3.3.3 Chronic kidney disease

EVIDENCE STATEMENTS – chronic kidney disease (iron therapy)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.26	In anaemic patients with CKD receiving ESAs, the effect of IV iron on mortality is uncertain.	✓	✓✓	A	✓✓	✓✓
ES3.27	In anaemic patients with CKD on dialysis and receiving ESAs, IV iron may reduce the need for an anaemia intervention.[a]		A	✓	✓✓✓	✓✓
ES3.28	In anaemic patients with non dialysis-dependent CKD, the effect of IV iron on RBC transfusion requirement is uncertain.		A		✓✓	✓✓
ES3.29	In anaemic patients with non dialysis-dependent CKD, IV iron therapy may improve functional or performance status compared to oral iron therapy.	✓✓	✓✓		✓✓	✓✓

CKD, chronic kidney disease; ES, evidence statement; ESA, erythropoiesis-stimulating agent; Hb, haemoglobin; IV, intravenous; MI, myocardial infarction; RBC, red blood cell

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

[a] Anaemia intervention was defined as either an increase in ESA dose, non-protocol IV iron or RBC transfusion, resulting in non-completion of study.

RECOMMENDATIONS – chronic kidney disease	
GRADE B	**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]**
GRADE C	**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).** **Note: The CARI guidelines recommend a Hb target between 100-115 g/L[5]**
GRADE B	**In anaemic patients with CKD, ESA therapy to a Hb target of over 130 g/L is not recommended because of increased morbidity.**
GRADE B	**In anaemic patients with non dialysis-dependent CKD, type 2 diabetes and a history of malignancy, the *routine* use of ESAs is not recommended because of the increased risk of cancer-related mortality.**

3.3.5 Inflammatory bowel disease

EVIDENCE STATEMENTS – inflammatory bowel disease		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.33	In IBD patients with iron deficiency anaemia, the effect of IV iron versus oral iron on mortality is uncertain.	✓	A	A	✓✓	✓✓
ES3.34	In IBD patients with iron deficiency anaemia, it is uncertain whether there is any difference between the effects of IV iron and oral iron on functional or performance status.	✓	A		✓✓	✓✓

ES, evidence statement; IBD, inflammatory bowel disease; IV, intravenous

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

PRACTICE POINT – inflammatory bowel disease

In patients with IBD, determine the cause of anaemia and treat reversible causes. IV iron may be required in patients who are intolerant of oral iron, or to avoid aggravation of intestinal inflammation.

IBD, inflammatory bowel disease; IV, intravenous; PP, practice point

Intravenous iron – inflammatory bowel disease

Although anaemia in inflammatory bowel disease (IBD) is multifactorial, iron deficiency and anaemia of chronic disease are common aetiological factors. IV iron therapy is frequently used in IBD patients because oral iron has drawbacks (e.g. intolerance, lack of compliance, poor absorption and worsening of inflammation).

The review identified two RCTs (Level II) that evaluated the use of iron therapy in patients with IBD with iron deficiency anaemia.[123,124]

Kulnigg et al found no significant difference in mortality between IV and oral iron, but the study was underpowered.[123] Neither study reported on the incidence or volume of blood transfusion or thromboembolic events.

In Kulnigg et al, patients treated with IV iron had a greater improvement in SF-36 from baseline at follow-up than patients treated with oral iron.[123] In Schroder et al, there were similar improvements from baseline at follow-up for IV iron compared with oral iron for Crohn's Disease Activity Index, Colitis Activity Index (CAI) and SF-36.[124] These two studies provided insufficient detail to determine whether the treatment effect on this outcome was statistically significant.

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-CSF, ESAs may reduce transfusion incidence compared with no ESAs.		A	✓	✓✓	✓✓
ES3.37	In anaemic patients with MDS, the effect of ESAs on thromboembolic events is uncertain.		✓✓✓	A	✓✓	✓
ES3.38	In anaemic patients with MDS, the effect of ESAs on functional or performance status is uncertain.		A	A	✓✓	✓

ES, evidence statement; ESA, erythropoiesis-stimulating agent; GM-CSF, granulocyte/macrophage colony-stimulating factor; MDS, myelodysplastic syndrome

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

3.4 Effect of blood components on outcomes

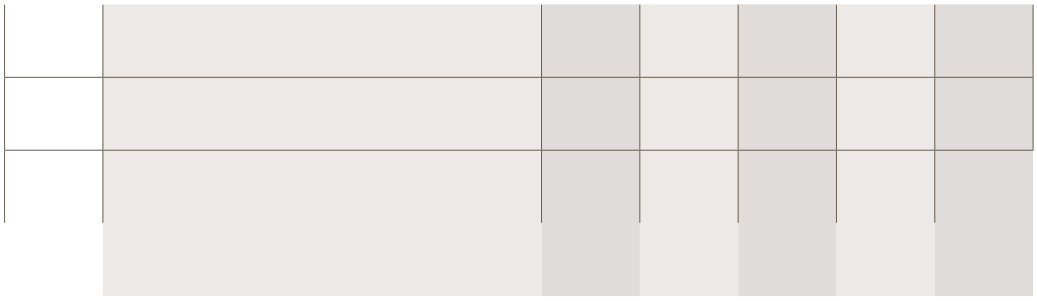
Question 4 (Interventional)

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



PRACTICE POINTS – fresh frozen plasma	
	The

3.4.2 Fibrinogen and cryoprecipitate

EVIDENCE STATEMENTS – fibrinogen and cryoprecipitate		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES4.5	In medical patients, no relevant studies were found reporting the effect of fibrinogen replacement, using cryoprecipitate or fibrinogen concentrate on mortality, bleeding events and transfusion-related serious adverse events.	A	A	A	A	A

ES, evidence statement; **A**, not applicable (see Table 2.1)

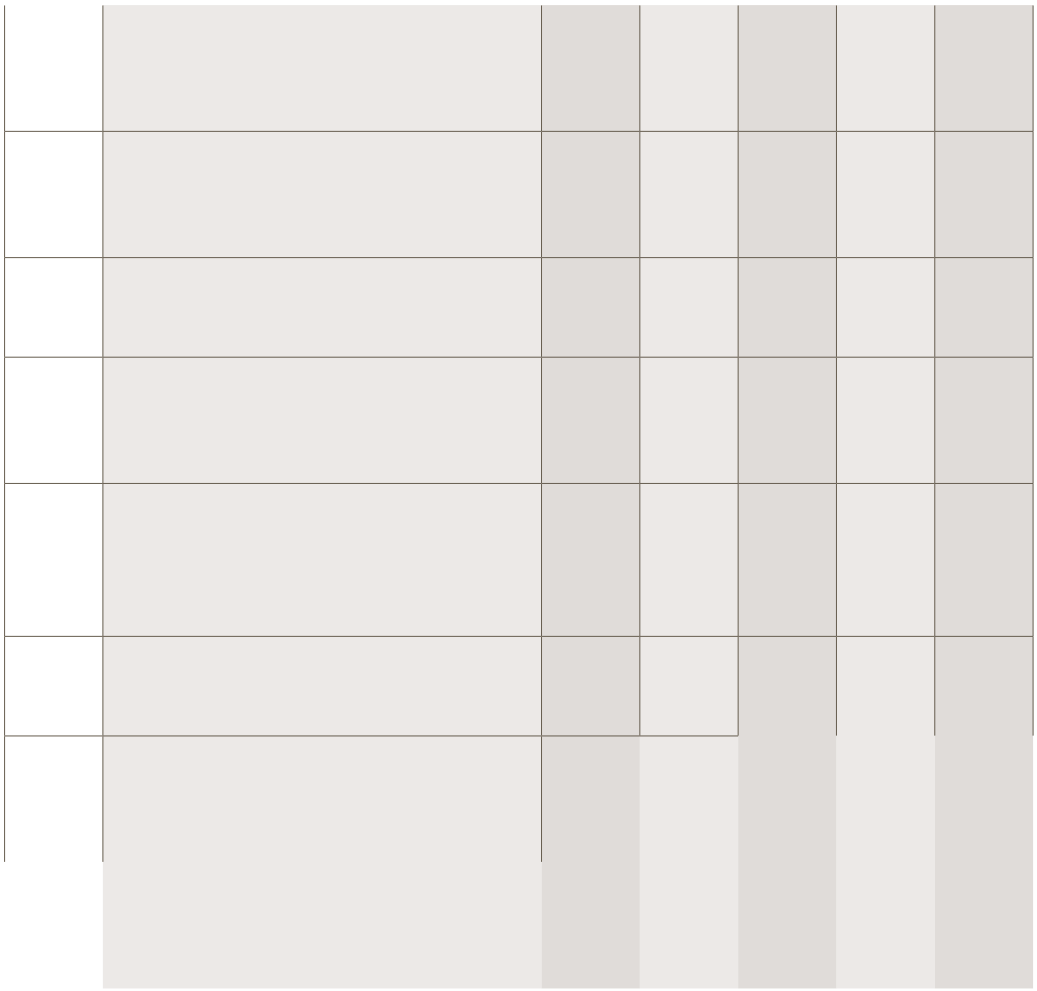
PRACTICE POINTS – fibrinogen and cryoprecipitate

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.

For guidance on the use of cryoprecipitate or fibrinogen concentrate in specific patient groups, refer to:

- *Patient Blood Management Guidelines: Module 1 – Critical Bleeding / Massive Transfusion* (2011)[4]
- 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]

3.4.3 Platelet transfusion



PRACTICE POINTS – platelet concentrates	
	

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 al[137] and Heddle et al[138] 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]

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 standard-dose reteplase or half-dose reteplase and full-dose abciximab, subtherapeutic peak APTT levels may be associated with an increased risk of mortality.	✓✓	A	✓	✓✓	✓✓
ES5.5	In heparinised patients with ACS receiving standard-dose reteplase or half-dose reteplase and full-dose abciximab, supratherapeutic peak APTT levels may be associated with an increased risk of moderate-to-severe bleeding.	✓✓	A	✓	✓✓	✓✓

ACS, acute coronary syndrome; APTT, activated partial thromboplastin time; ES, evidence statement; INR, international normalised ratio; PT, prothrombin time

✓

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.[144] 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 × 10^9/L without risk factors or <20 × 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 × 10^9/L without risk factors or <20 × 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 × 10^9/L without risk factors or <20 × 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)

RECOMMENDATION – chemotherapy and haematopoietic stem cell transplantation

GRADE

In patients undergoing chemotherapy and haematopoietic stem cell transplantation, the recommended strategy for prophylactic use of platelets is transfusion at a platelet count of <10 × 10^9/L in the absence of risk factors, and at <20 × 10^9/L in the presence of risk factors (e.g. fever, minor bleeding).

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 studies[147–149] compared a platelet transfusion trigger of 10×10^9/L with one of 20×10^9/L. Another study used 30×10^9/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.

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 **β** 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*[1] 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 900 0l4ppNr395usio thalass 1 -Bration of 90y10 s1N -0.2 Tc shuce986(Red bloodvolumg pts aarual risks					

PRACTICE POINT – thalassaemia

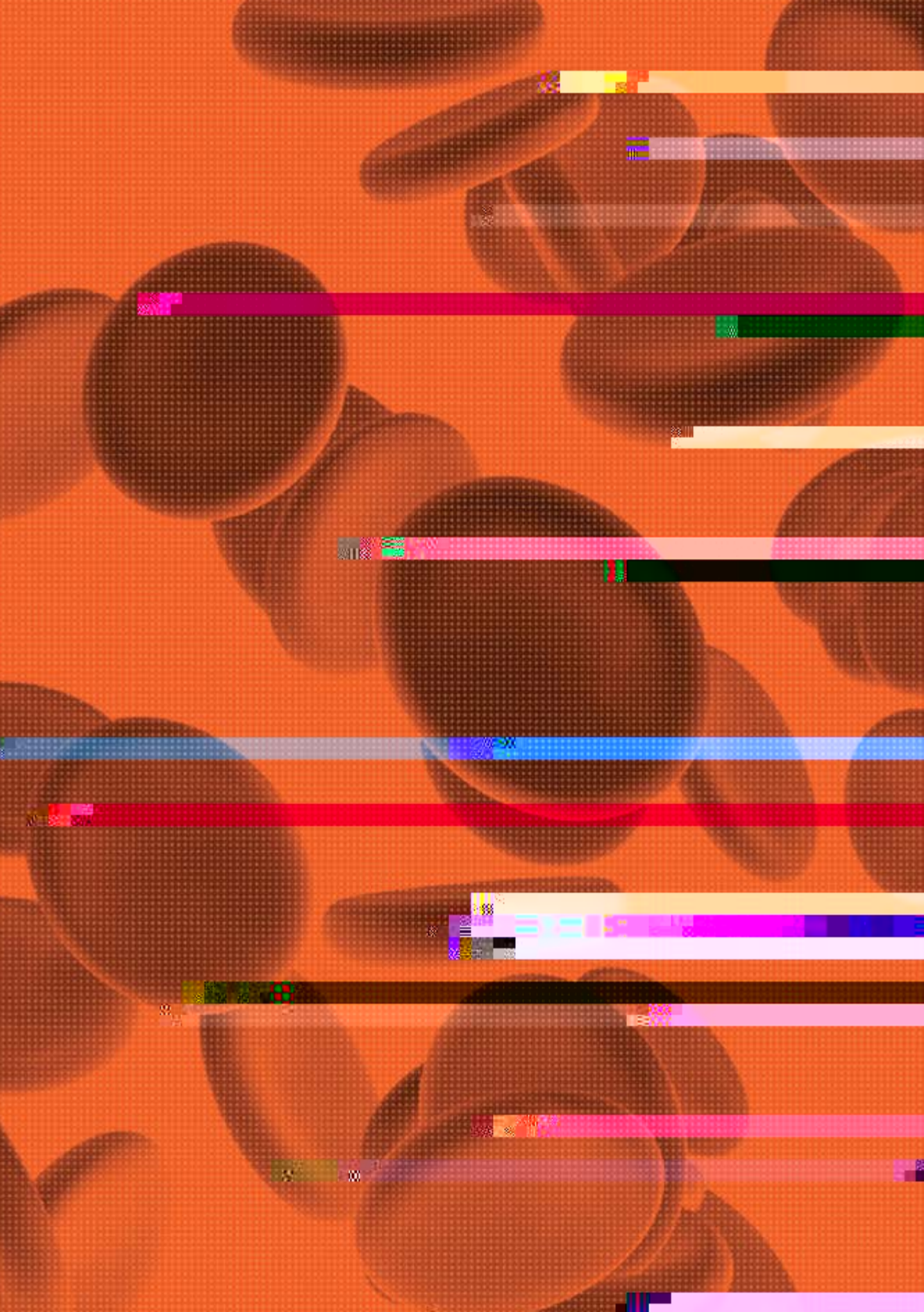
In patients with thalassaemia, the evidence does not support any change to the current practice of maintaining a pretransfusion Hb concentration of 90 – 100 g/L, with transfusions at about monthly intervals.

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 **β** thalassaemia major. The aim of the transfusions was to prevent severe anaemia and early mortality and to promote growth, development, well-being and quality of life. They were also intended to minimise or prevent the

3.6.2 Myelodysplasia

	EVIDENCE STATEMENTS – fibrinogen and cryoprecipitate	Evidence	Consistency			



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

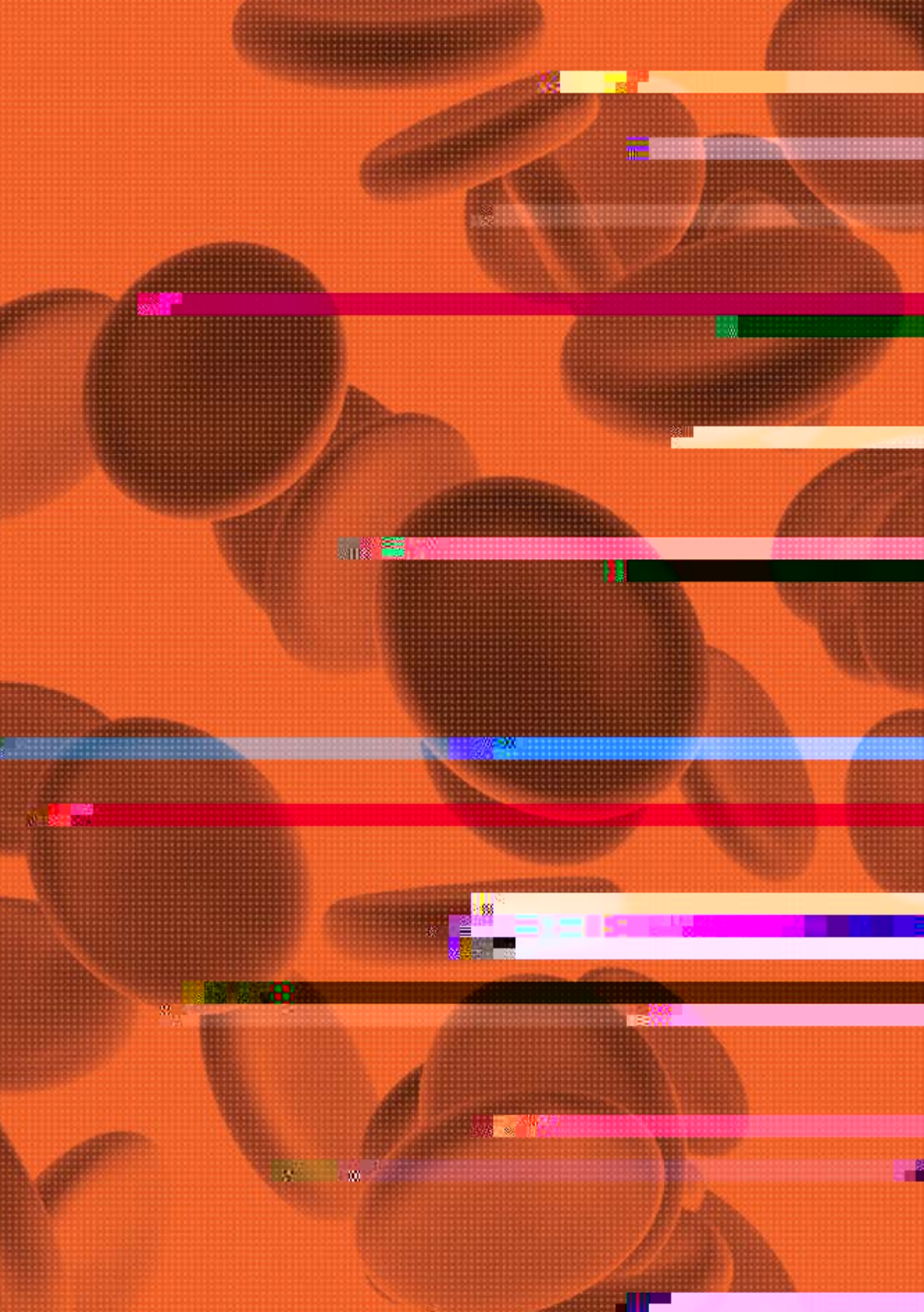
High-energy photons used in radiotherapy induce deoxyribonucleic acid (DNA) damage. The photons can either directly cause electrons to ionize DNA helix atoms, or can produce highly reactive free radical species, which then interact with and damage DNA. Unrepaired DNA damage inhibits cell proliferation 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

4.1.3 Impact of correction of anaemia on radiotherapy outcome

4.2 Assessment of patients after red blood cell transfusion

Background question 2



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

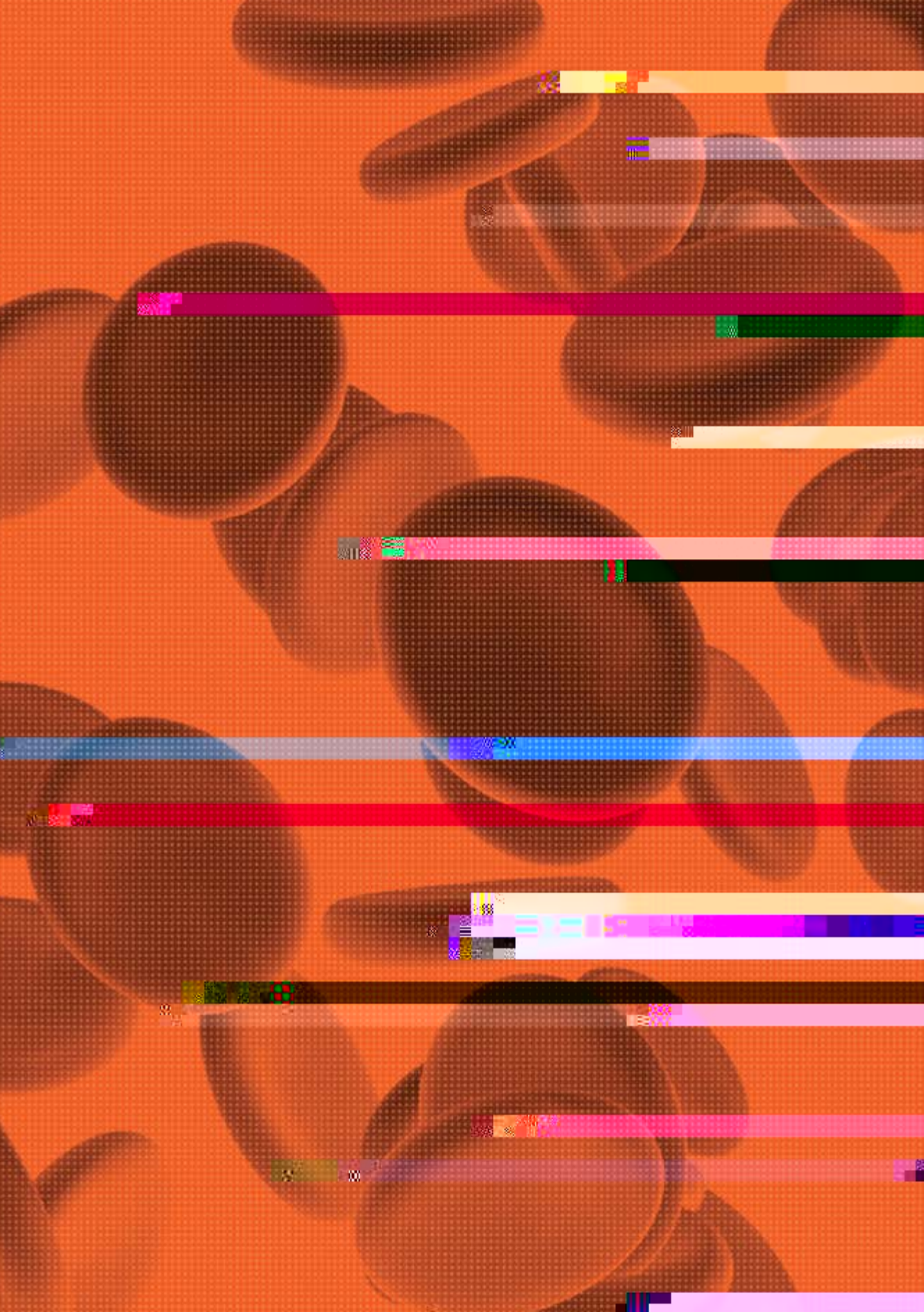
In this review, there were a number of areas where evidence was not sufficient to generate recommendations. Further research in the following areas may be profitable:

- 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

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.

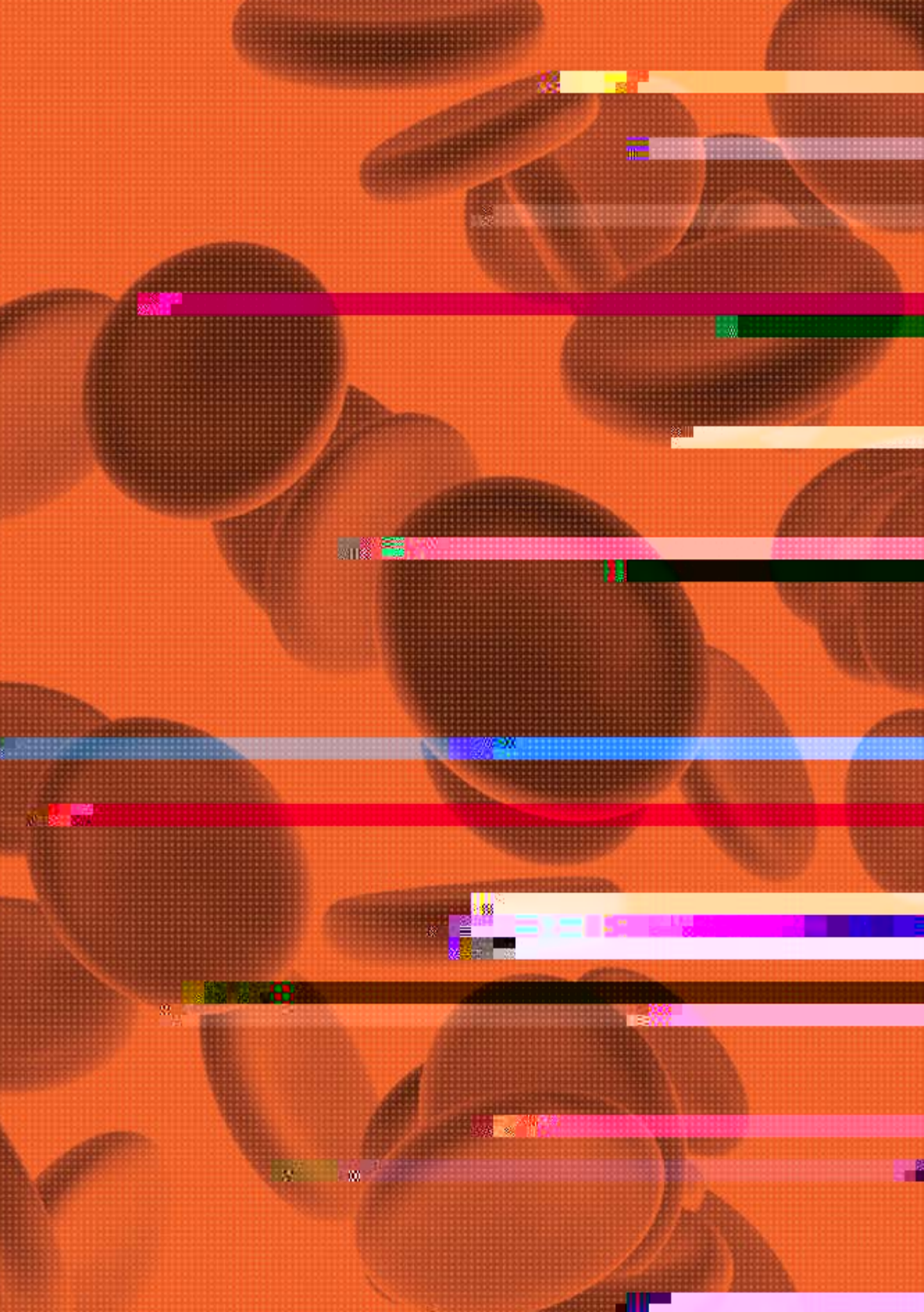
To provide feedback and inform future reviews of this module, please send any comments on its content or implementation, or on the accompanying materials, to:

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

Any correspondence will be forwarded to the PBM Guidelines Project Manager for consideration in the next scheduled review.

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

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



Appendix A
Governance

- 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

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)

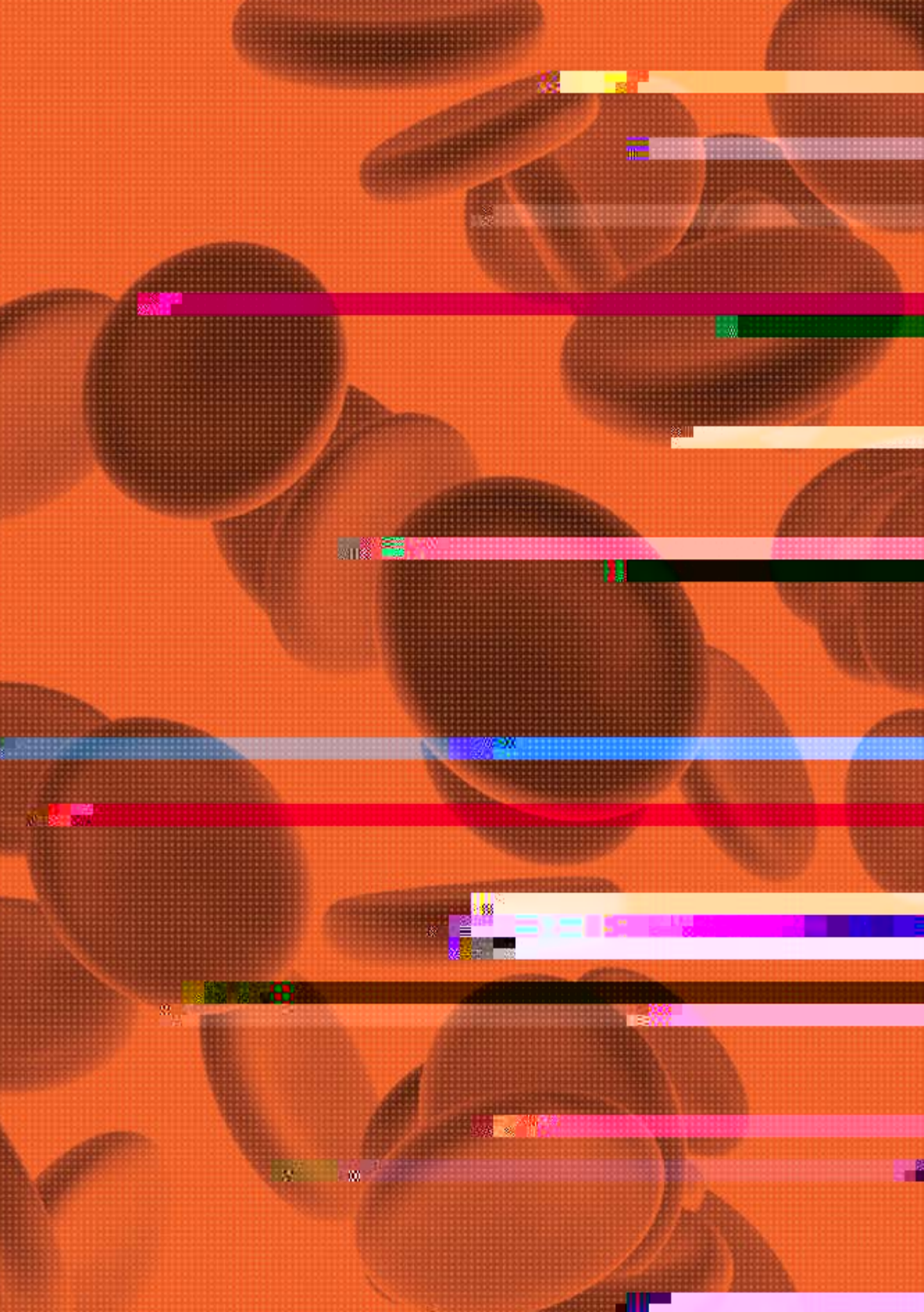
Medical writing and technical editing – OptumInsight

Dr Hilary Cadman	Cadman Editing Services (independent contractor to OptumInsight)

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.



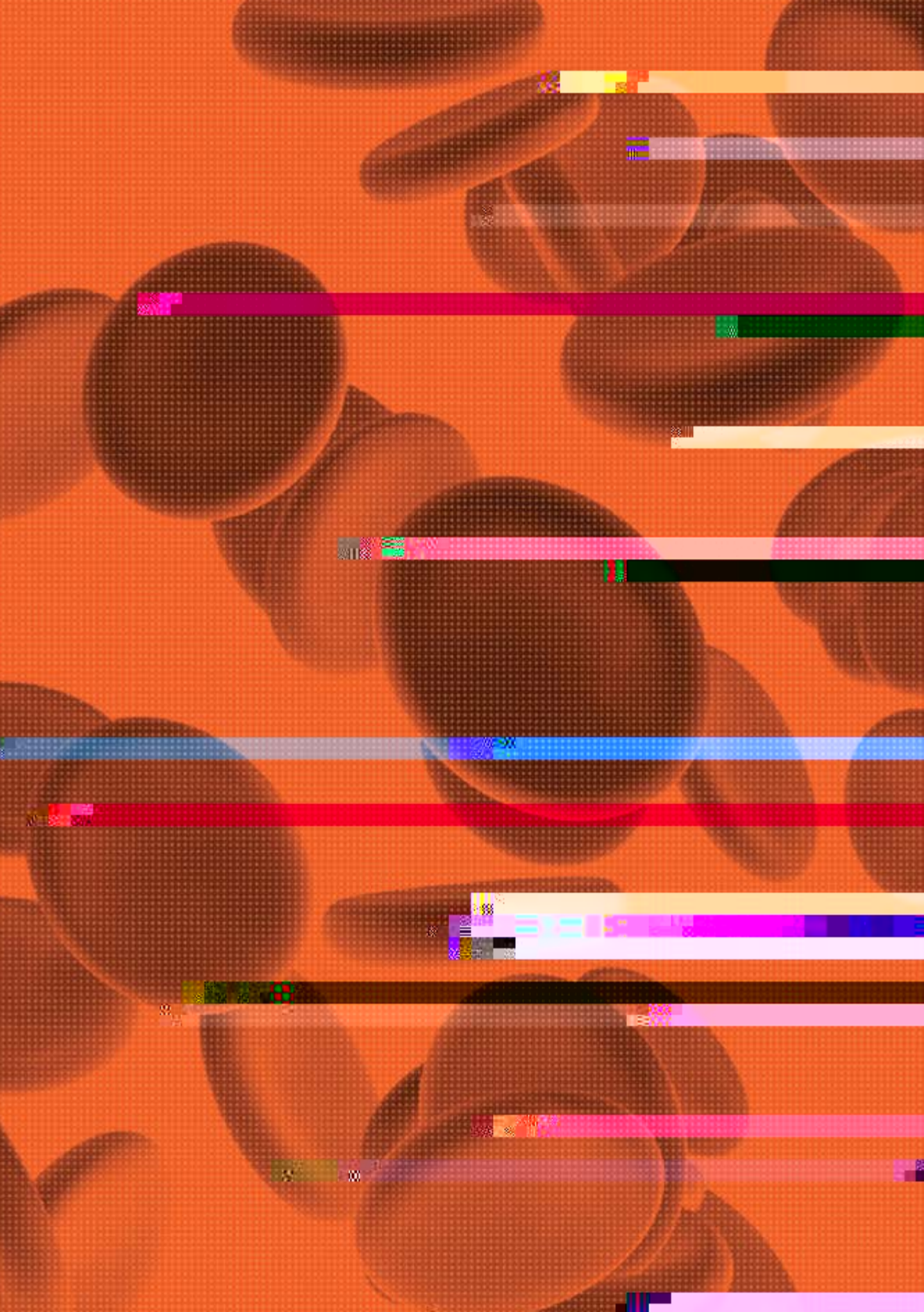
Appendix B
Transfusion risks in the context of patient blood management

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, thrombocytopaenia or coagulopathy, transfusion should not be a default decision. Instead, the decision on whether to transfuse should be carefully considered,



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.

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 o5 TgTllstrategiecdisrctinn ior che peovision of blood and blood

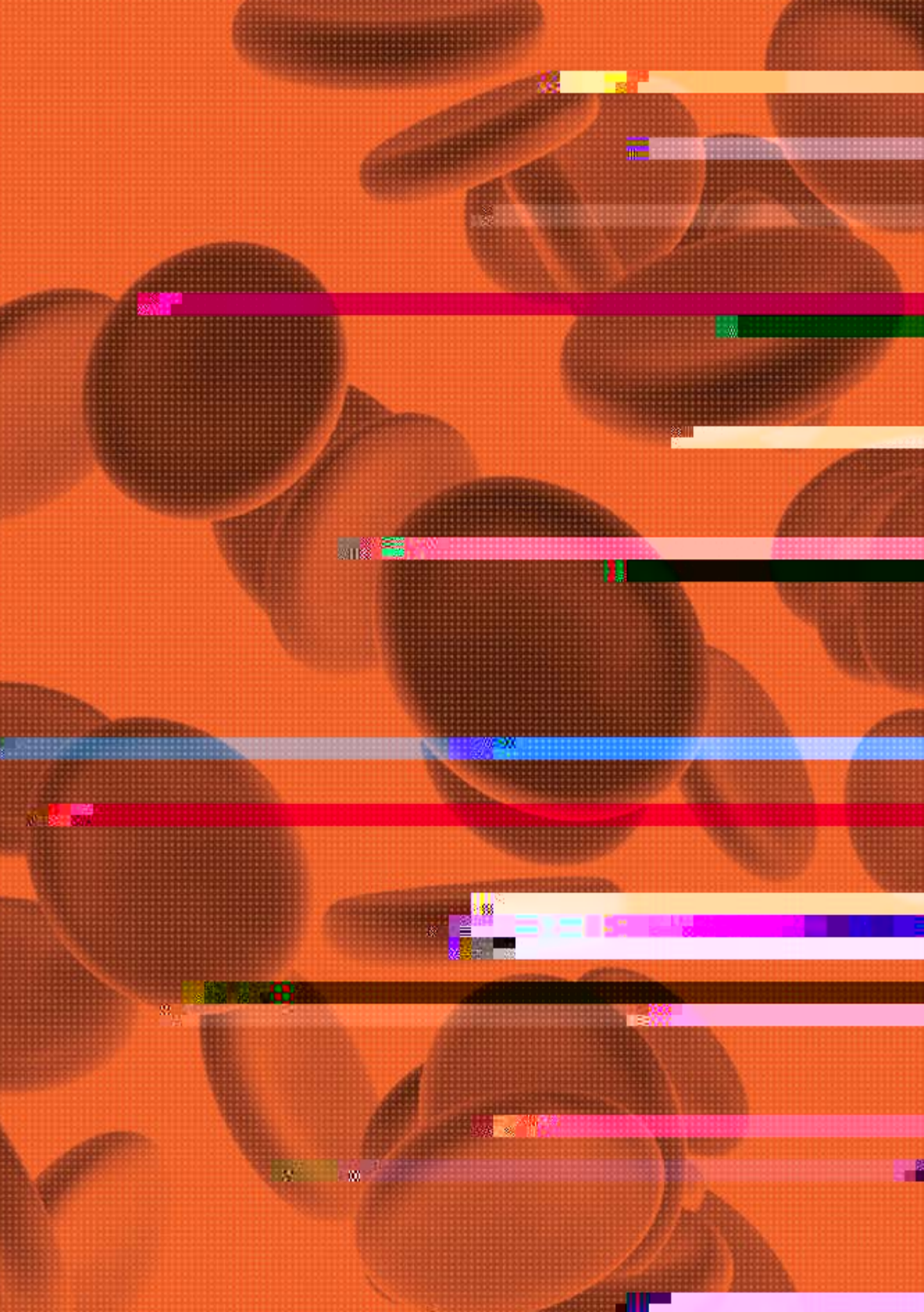
New Zealand Blood Service

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



Appendix D
Process report

D1 Development process

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.

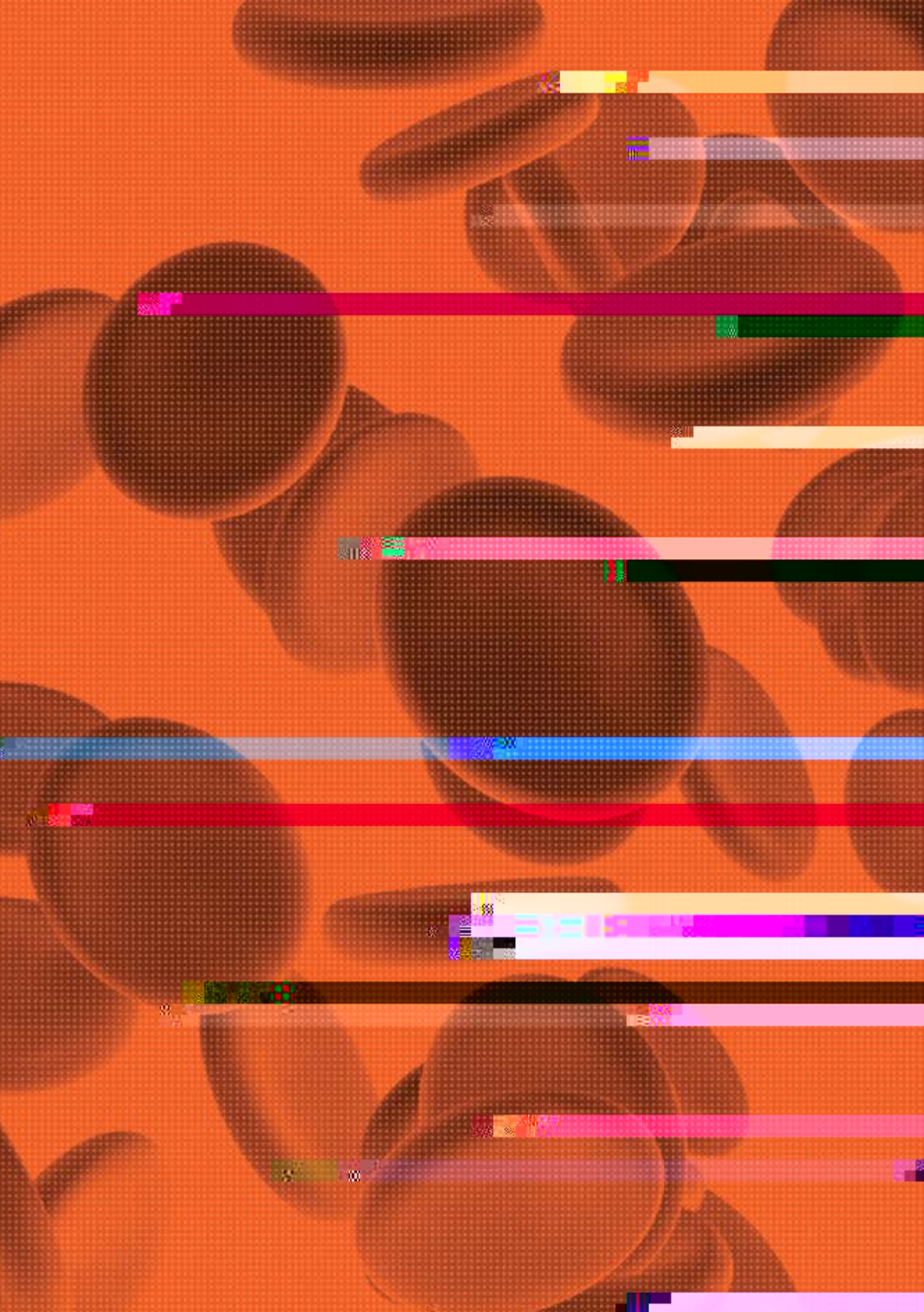
Eleven submissions were received. The CRG met in April 2012 to consider all the public consultation submissions and, where necessary, revise this module in accordance with the submissions. Changes were made to the module to address comments and concerns raised in submissions, and to improve clarity.

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.

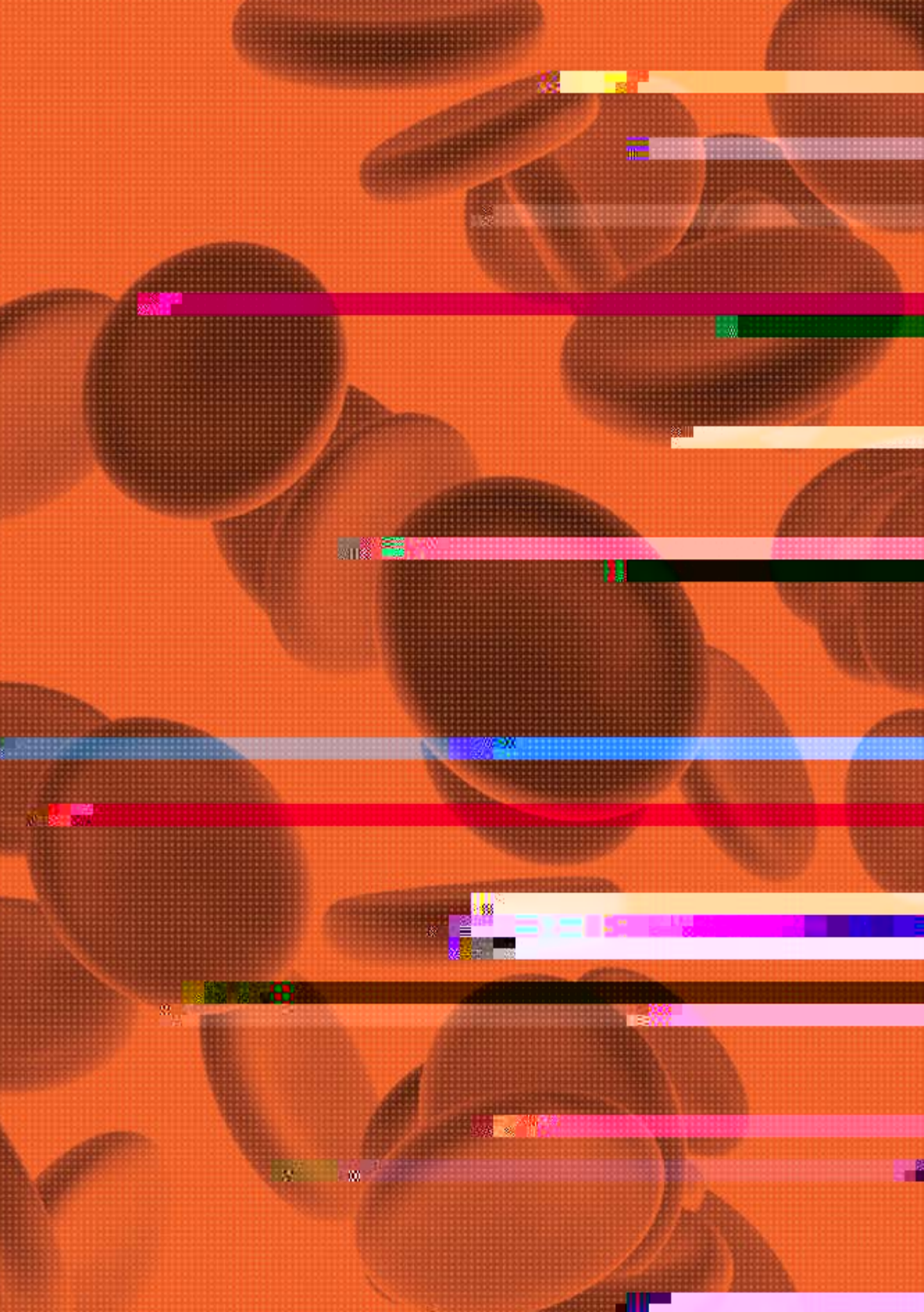
[d] http://www.nba.gov.au/



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		
	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
	Direct evidence is not available in general medical patients.[a] Evidence from other patient groups and CRG consensus suggests that, with a: • b on\ ıt a ‡ on , 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. • b on\ ıt a ‡ on o , 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. • b on\ ıt a ‡ on , RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with ACS. [a] Recommendations and practice points for medical patients in a critical care setting will be found in the *Patient Blood Management Guidelines: Module 4 – Critical Care*.[3] Recommendations and practice points for specific medical subgroups (ACS, CHF, cancer, acute upper gastrointestinal bleeding and chronically transfused) appear elsewhere in this module.	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

ACS, acute coronary syndrome; CHF, chronic heart failure; CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; PP, practice point; RBC, red blood cell

F2 Cardiac – acute coronary syndrome

Identifier and grade[e]	Guidance – recommendations and practice points	Relevant section of document
RED CELLS		
GRADE C	**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
	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
	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.	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.	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 GRADE	**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.**	3.3.2
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

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

Identifier and grade[e]	Guidance – recommendations and practice points	Relevant section of document
RED CELLS		
	Direct evidence is not available in general medical patients.[a] Evidence from other patient groups and CRG consensus suggests that, with a: • b on\ ‡ a on , 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. • b on\ ‡ a on o , 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. • b on\ ‡ a on\ , RBC transfusion is likely to be unnecessary and is usually inappropriate. Transfusion has been associated with increased mortality in patients with ACS. [a] Recommendations and practice points for medical patients in a critical care setting will be found in the *Patient Blood Management Guidelines: Module 4 – Critical Care*.[3] Recommendations and practice points for specific medical subgroups (ACS, CHF, cancer, acute upper gastrointestinal bleeding and chronically transfused) appear elsewhere in this module.	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
	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

ACS, acute coronary syndrome; CHF, chronic heart failure; CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; NYHA, New York Heart Association; PP, practice point; R, recommendation; RBC, red blood cell

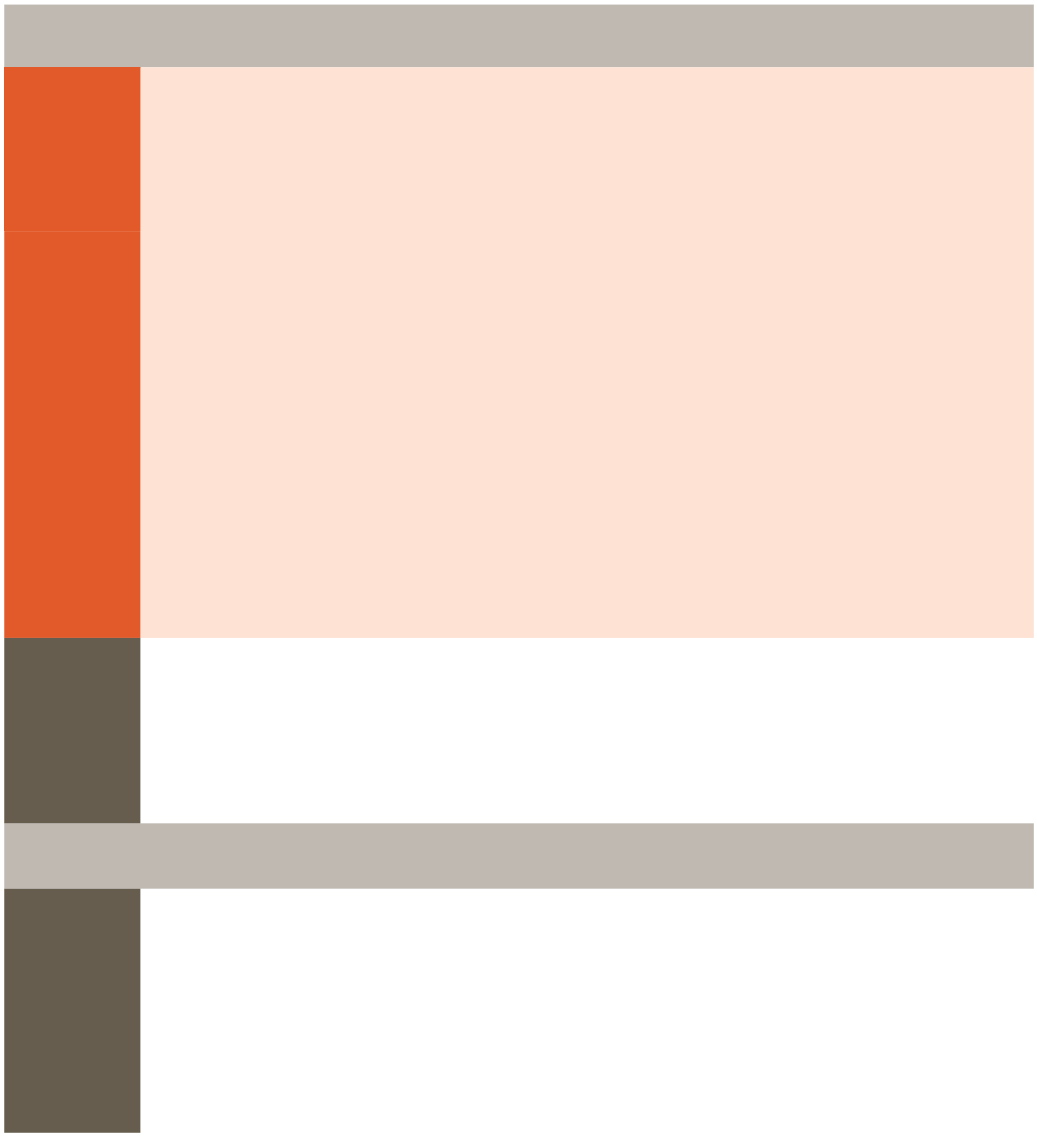
F4 Cancer

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	

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	

Identifier		

F6 Chronic kidney disease

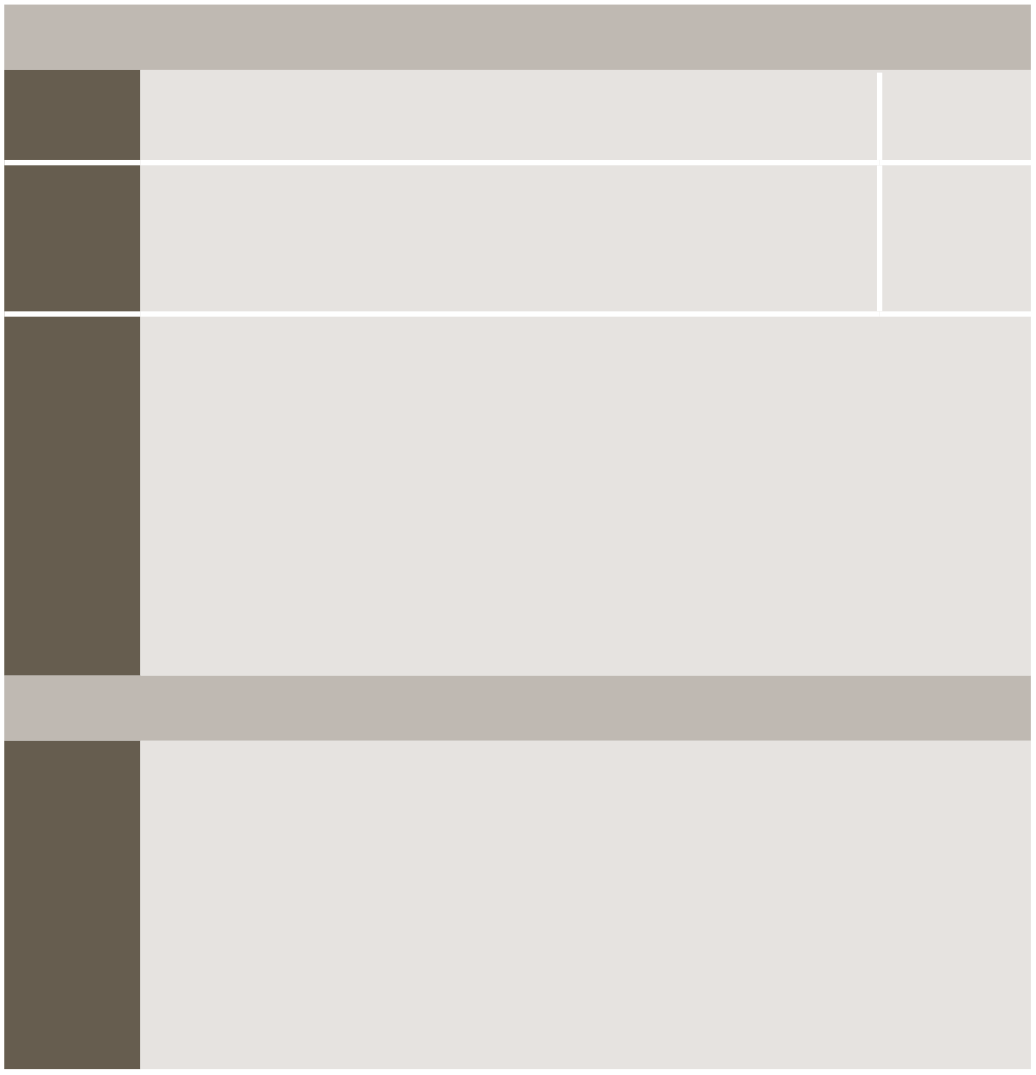


Identifier and grade[e]	Guidance – recommendations and practice points	Relevant section of document
	Direct evidence is not available in general medical patients.[a] Evidence from other patient groups and CRG consensus suggests that, with a: • b on\ rf ‡ on , RBC transfusion may be associated with reduced mortality and is likely to be appropriate. However, transfusion may not be required in well-compensated patients or where other specific therapy is available. • b on\ rf ‡ on o , 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. • b on\ rf ‡ on , 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

F8 Thalassaemia and myelodysplasia



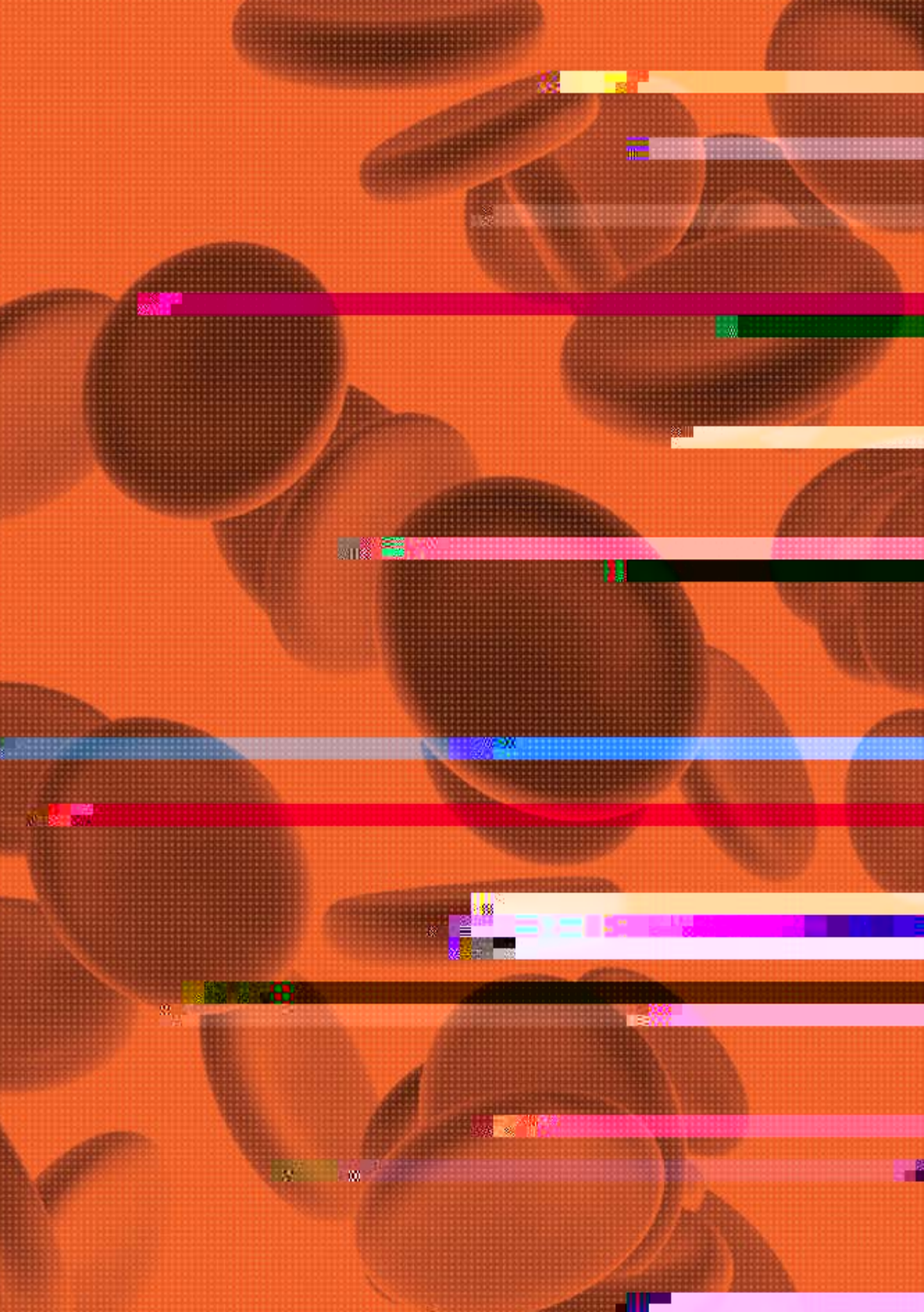
F9 Coagulopathy

Identifier	Guidance – recommendations and practice points	Relevant section of document
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.	3.4.1
	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 (http://www.ahcdo.org.au) • TTP: *Guidelines for the Use of Fresh-Frozen Plasma, Cryoprecipitate and Cryosupernatant* (2004).[8]	3.4.1
CRYOPRECIPITATE OR FIBRINOGEN CONCENTRATE		
	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.	3.4.2
	For guidance on the use of cryoprecipitate or fibrinogen concentrate in specific patient groups, refer to: • *Patient Blood Management Guidelines: Module 1 – Critical Bleeding / Massive Transfusion* (2011)[4] • 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]	

F10 Thrombocytopenia

Identifier	Guidance – recommendations and practice points	Relevant section of document
PLATELETS		
	Platelet transfusion may be indicated for the prevention and treatment of haemorrhage in patients with thrombocytopenia or platelet function defects. Platelet transfusions are not indicated in all causes of thrombocytopenia, and may be contraindicated in certain conditions (e.g. TTP and HIT). Thus, the cause of the thrombocytopenia should be established and expert opinion sought.	3.4.3
	In patients with chronic failure of platelet production (e.g. myelodysplasia or aplastic anaemia), a specific threshold for transfusion may not be appropriate. These patients are best managed on an individual basis, in consultation with a relevant expert.[9] Long-term prophylactic platelet transfusions may be best avoided because of the risk of complications (e.g. alloimmunisation and platelet refractoriness). Therapeutic platelet transfusions could be considered for treatment of bleeding.	3.4.3

HIT, heparin-induced thrombocytopaenia; PP, practice point; TTP, thrombotic thrombocytopenic purpura



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