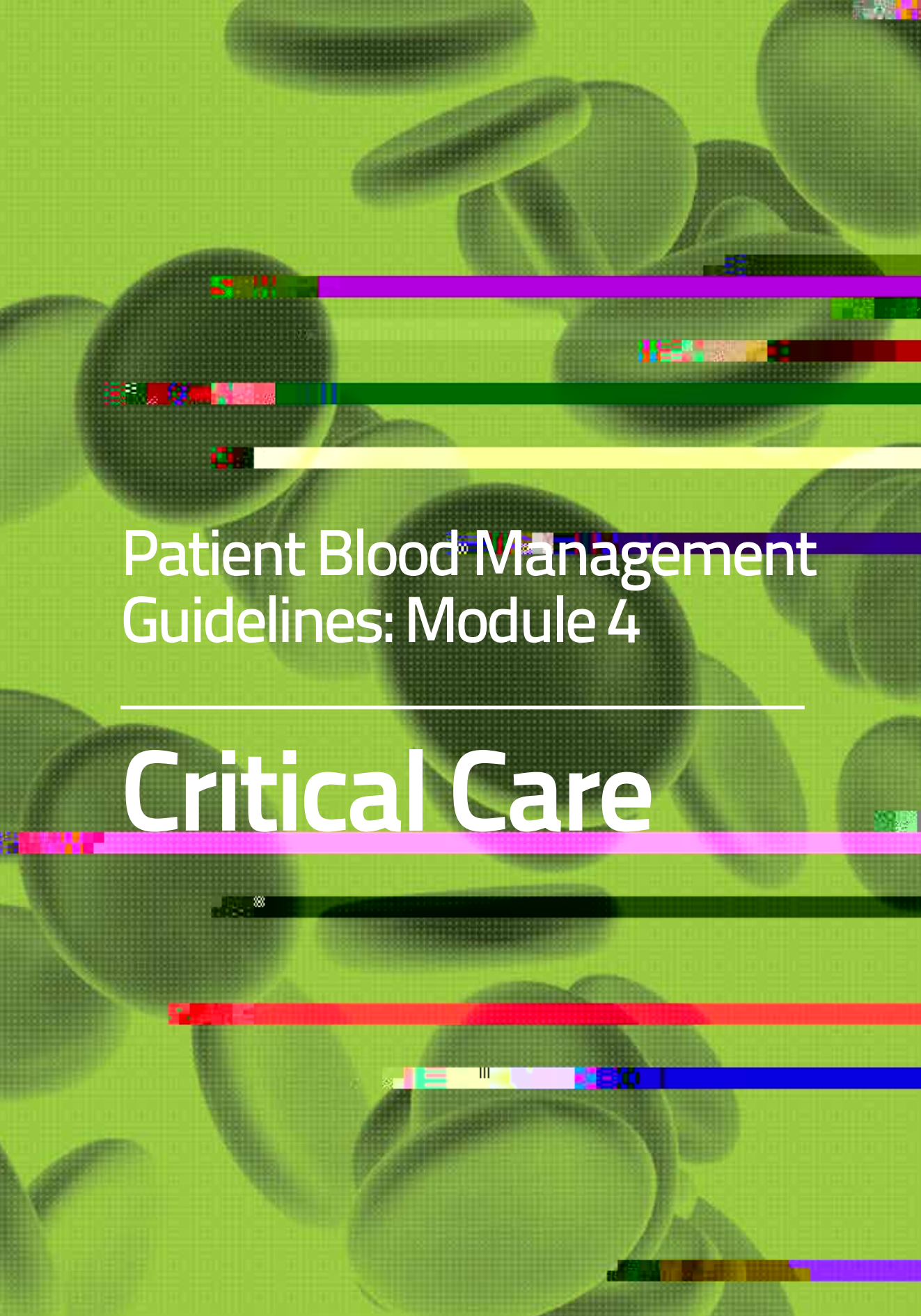

Patient Blood Management Guidelines: Module 4

Critical Care

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Development of this module was achieved through clinical input and expertise of representatives from the colleges and societies listed below and a patient blood management advocate (see Appendix A).

Australian and New Zealand College of Anaesthetists

Australian and New Zealand Intensive Care Society

College of Intensive Care Medicine of Australia and New Zealand

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

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Funding, secretariat and project management was provided by the National Blood Authority, Australia. The development of the final recommendations has not been influenced by the views or interests of the funding body.

A r on n ron

ACS	acute coronary syndrome
AHMAC	Australian Health Ministers' Advisory Council
ALI	acute lung injury
ANZSBT	Australian & New Zealand Society of Blood Transfusion
APACHE	acute physiology and chronic health evaluation
ARDS	acute respiratory distress syndrome
ASBT	Australasian Society of Blood Transfusion
CI	confidence interval
COI	conflict of interest
CRASH	Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage
CRG	Clinical/Consumer Reference Group
CTEPC	Clinical, Technical and Ethical Principal Committee
ES	evidence statement
ESA	erythropoiesis-stimulating agent
EWG	Expert Working Group
FFP	fresh frozen plasma
GI	gastrointestinal
Hb	haemoglobin
ICU	intensive care unit
INR	international normalised ratio
JBC	Jurisdictional Blood Committee
MI	myocardial infarction
NBA	National Blood Authority
NHMRC	National Health and Medical Research Council
NZBS	New Zealand Blood Service
PICO	population, intervention, comparator and outcome
PP	practice point
PPO	population, predictor and outcome
PRO	population, risk factor and outcome
R	recommendation
RBC	red blood cell
RCT	randomised controlled trial

RD	risk difference
RR	relative risk
SCOH	Standing Committee on Health
TGA	Therapeutic Goods Administration
TRICC	transfusion requirements in critical care
TXA	tranexamic acid

Con n

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This document, *Patient Blood Management Guidelines: Module 4 – Critical Care*, is the fourth in a series of six modules that focus on evidence-based patient blood management. The other five modules are critical bleeding/massive transfusion, perioperative, medical, obstetrics and paediatrics (including neonates). Together, Module 2 (Perioperative) and Module 3erig Mv212doerioperative, medical, obstetrics and paediatrics (including n

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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:

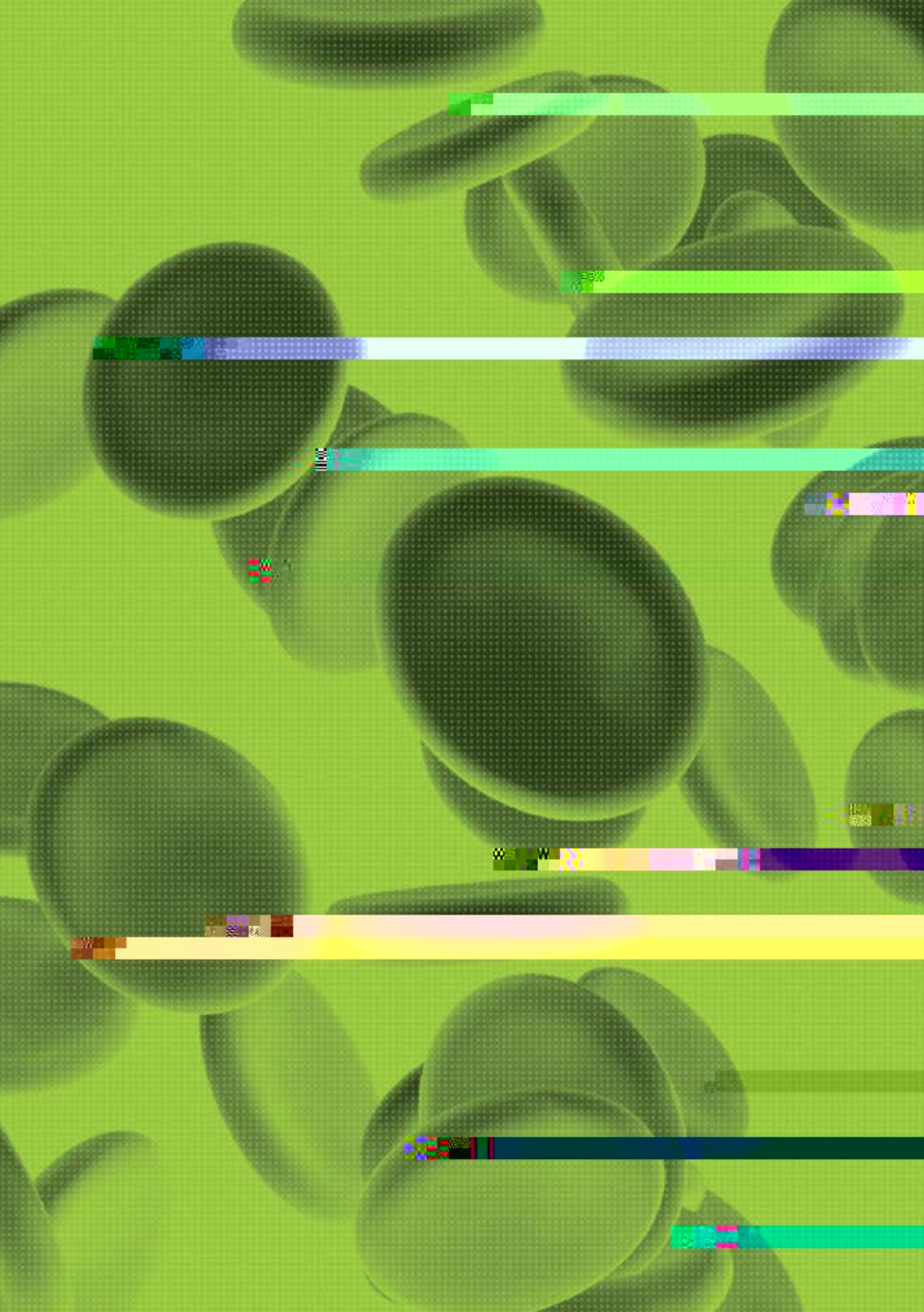
G ADE A	Body of evidence can be trusted to guide practice
G ADE	Body of evidence can be trusted to guide practice in most situations
G ADE C	Body of evidence provides some support for recommendation(s), but care should be taken in its application
G ADE D	Body of evidence is weak and recommendations must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

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

Identifier and grade	Guidance – recommendations and practice points	Relevant section of document
RED CELLS		
R1	**In critically ill patients, a restrictive transfusion strategy should be employed.**	**3.1**
	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.	**3.1**
	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.	**3.1**
	CRG consensus suggests that, with a: • **b on\ n ‡ a on , RBC transfusion is likely to be appropriate; however, transfusion may not be required in well-compensated patients or where other specific therapy is available.** • **b on\ n ‡ 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.** • **b on\ n ‡ a on\ , RBC transfusion is generally unnecessary.** **For patients undergoing cardiac surgery, refer to *Patient Blood Management Guidelines: Module 2 – Perioperative*;[2] for patients with active bleeding, refer to *Patient Blood Management Guidelines: Module 1 – Critical Bleeding / Massive Transfusion*.[3]**	**3.1**
	For patients with ACS, the following guidance is taken from *Patient Blood Management Guidelines: Module 3 – Medical*.[4] In ACS patients with a: • **b on\ n ‡ a on , RBC transfusion may be associated with reduced mortality and is likely to be appropriate (see PP5 of Module 3).** • **b on\ n ‡ a on o , the effect of RBC transfusion on mortality is uncertain and may be associated with an increased risk of recurrence of MI (see PP6 of Module 3).** • **b on\ n ‡ a on\ , RBC transfusion is not advisable because of an association with increased mortality (see R1 of Module 3).** **Any decision to transfuse should be made with caution and based on careful**	

Identifier and grade	Guidance –	

Identifier and grade	Guidance – recommendations and practice points	Relevant section of document
	Assessment of bleeding risk is complex and requires careful consideration of patients' clinical status and laboratory parameters. Specialist haematology advice may also be required. However, patients with a platelet count ≥50 × 10^9 can generally undergo invasive procedures within the ICU without any serious bleeding; lower platelet counts may be tolerated in certain clinical situations.	3.3.3
CELL SALVAGE		
	In critically ill trauma patients and patients undergoing emergency surgery for ruptured abdominal aortic aneurysm, the use of cell salvage may be considered.	3.4.1
TRANEXAMIC ACID		
	In acutely bleeding critically ill trauma patients, TXA should be administered within 3 hours of injury.	3.4.2
	In critically ill patients with upper GI bleeding, consider the use of TXA.	3.4.2
	TXA should be given as early as possible, preferably within 3 hours of injury. The late administration of TXA is less effective and may be harmful.	3.4.2
	The suggested dose of TXA administered is a 1 g bolus followed by a 1 g infusion over 8 hours. This is the dose administered in the large	



n ro on

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 blood components are likely to be indicated, transfusion should not be a default decision. Instead, the decision on whether to transfuse should be carefully considered, taking into account the full range of available therapies, and balancing the evidence for efficacy and improved clinical outcome against the potential risks (Appendix B). 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 4 – Critical Care*, is the fourth in a series of six modules that focus on evidence-based patient blood management. The other five modules are listed in Table 1.1, below. Together, Module 2 (Perioperative) and Module 3 (Medical) cover all the patient groups addressed by the 2001 document *Clinical Practice Guidelines on the Use of Blood Components*[1] (National Health and Medical Research Council/Australasian Society of Blood Transfusion, NHMRC/ASBT).

This document is intended to assist and guide health-care professionals in making clinical decisions when managing patients requiring critical care. Transfusion decisions for patients should also take into account each individual's clinical circumstances and physiological status, and their treatment preferences and choices.

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

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

D op n o n

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

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

Table 1.1 Phaseselinwhen mavidence guThe six nwhen mavisagr en mavidencea6t ncn 5.mmendationon, csfines f(dea6t

1.2 Governance structure

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

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

The NBA sought advice from a consumer advocate, and subsequently considered convening a small consumer forum to review and provide input on the draft module as part of the transition to the *Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines.* As a result, the CRG members and an intensive care specialist provided consumer representative nominees to participate in an online survey. Of the nominations received, three individuals were selected by the NBA to complete the survey based on their experiences as either a patient or a carer of a patient in a critical care setting. Consumers were required to read the module and answer a series of questions relating to how the module provides consumers with sufficient information about the benefits and risks of treatments within the recommendations and practice points and whether the module meets their expectations for health professionals.

The NBA provided the secretariat, project funding and project management. The NBA website includes a list of colleges and societies that have endorsed these guidelines.[c] Appendix A lists the membership of the bodies involved in governance of the guidelines. Details of how the guidelines will be implemented and updated are provided in Chapter 5.

1.3 Structure of the document and related materials

1.3.1 The document

This module includes:

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

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

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

The remainder of this document includes:

- an outline of the methods used to develop the clinical research questions, undertake a systematic review of the literature, and develop recommendations and practice points (Chapter 2)
- clinical practice guidance, setting out the main findings of the systematic review and other considerations documented by the CRG, and recommendations and practice points, as appropriate (Chapter 3)
- recommendations for future directions (Chapter 4)
- information on implementing, evaluating and maintaining the guidelines (Chapter 5).

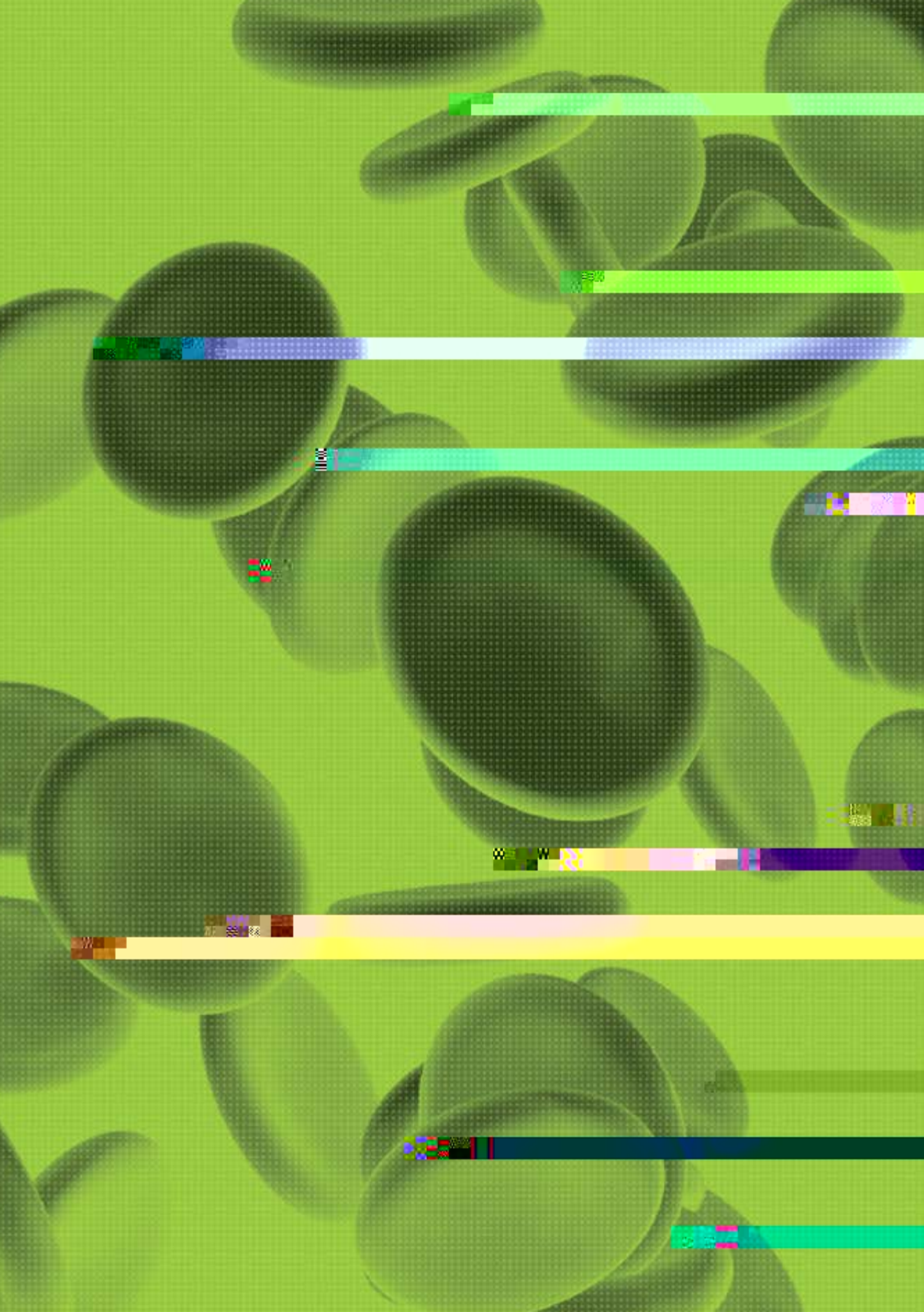
The document also includes appendixes that provide information on membership of the governance bodies for guideline development and transfusion risks; an overview of the blood sectors in Australia and New Zealand; a process report; and information on blood component products. Finally, the document contains 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 also available online, in two volumes:

- *Volume 1*[5]
  This volume contains background information and the results of the systematic reviews pertaining to the clinical questions posed within this guideline.
- *Volume 2*[6]
  This volume contains appendixes that document the literature searches, study-quality appraisal, NHMRC evidence statement forms and evidence summaries for the individual studies.



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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

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Box 2.1 Systematic review questions

Table 2.1 Body of evidence matrix

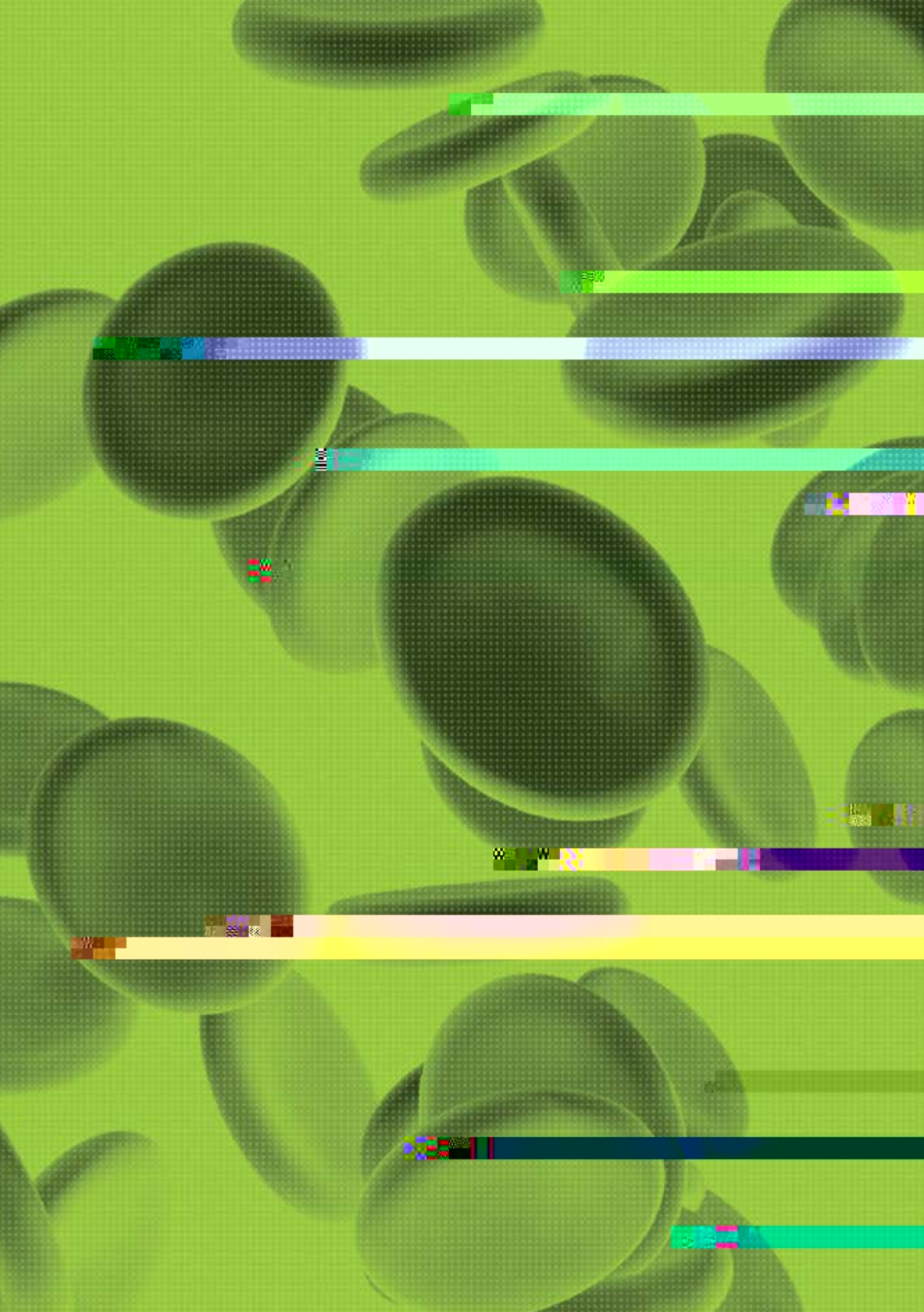
COMPONENT	A (✓✓✓)	B (✓✓)	C (✓)	D (X)
	Excellent	**Good**	**Satisfactory**	**Poor**
Evidence base	Several Level I or II studies with low risk of bias	One or two Level II studies with low risk of bias or a systematic review, or multiple Level III studies with low risk of bias	Level III studies with low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

Source: NHMRC 2009[9]

Table 2.2 Definitions of NHMRC grades for recommendations

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

Source: NHMRC 2009[9]



C n n

This chapter provides clinical guidance in the form of recommendations (based on evidence) and practice points (based on CRG consensus). The guidance is

RECOMMENDATION

G ADE	**In critically ill patients, a restrictive transfusion strategy should be employed.**

PRACTICE POINTS

	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.
	Where indicated, transfusion of a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.
	CRG consensus suggests that, with a: • **b on\ rt a on RBC transfusion is likely to be appropriate; however, transfusion may not be required in well-compensated patients or where other specific therapy is available.** • **b on\ rt 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.** • **b on\ rt a on RBC transfusion is generally unnecessary.** **For patients undergoing cardiac surgery, refer to *Patient Blood Management Guidelines: Module 2 – Perioperative*;[2] for patients with active bleeding, refer to *Patient Blood Management Guidelines: Module 1 – Critical Bleeding / Massive Transfusion*.[3]**
	For patients with ACS, the following guidance is taken from *Patient Blood Management Guidelines: Module 3 – Medical*.[4] In ACS patients with a: • **b on\ rt a on RBC transfusion may be associated with reduced mortality and is likely to be appropriate (see PP5 of Module 3).** • **b on\ rt a on o , the effect of RBC transfusion on mortality is uncertain and may be associated with an increased risk of recurrence of MI (see PP6 of Module 3).** • **b on\ rt a on RBC transfusion is not advisable because of an association with increased mortality (see R1 of Module 3).** **Any decision to transfuse should be made with caution and based on careful consideration of the risks and benefits (see PP6 of Module 3).**

ACS, acute coronary syndrome; CRG, Clinical/Consumer Reference Group; Hb, haemoglobin; MI, myocardial infarction; PP, practice point; R, recommendation; RBC, red blood cell

For the comparison of RBC transfusion with no transfusion or with a different RBC dose, 1 systematic review[10] and 24 observational (Level III) studies were identified.[11-34]

Overall, the effect of RBC transfusion on mortality in critically ill patients remains uncertain. A systematic review[10] identified four studies that all showed RBC transfusion to be associated with an increase in mortality.[15,17,23,31] Since that review, an additional six studies have been identified, and the results are mixed. One study demonstrated an increased risk of mortality when adjusting for admission characteristics only; however, this association was lost when additional variables reflecting the extent of organ dysfunction were included in the analysis.[27] The three studies that observed an association between RBC transfusion and mortality did not adjust for all of these variables.[26,28,34] The remaining two studies showed that RBC transfusion was associated with decreased mortality.[18,32] These studies included adjustment for organ failure and acute physiology and chronic health evaluation (APACHE) II score, plus various other organ dysfunction variables.

The effect of RBC transfusion on organ failure is also uncertain. The literature search identified only one prospective cohort study (Level III-2) reporting the effect of RBC transfusion on organ failure or dysfunction.[13] This study demonstrated that RBC transfusion was associated with an increased risk of organ failure; however, it was a single-centre study with at least a moderate level of bias.

There is evidence to suggest that RBC transfusion may be associated with a range of transfusion-related adverse events. The transfusion-related adverse events reported in the eligible studies included pneumonia, infection and acute respiratory distress syndrome (ARDS) or acute lung injury (ALI). One prospective cohort study (Level III-2) demonstrated that RBC transfusion was significantly associated with an increased risk of ventilator-associated pneumonia and late-onset ventilator-associated pneumonia.[29] One systematic review[10] and six cohort studies[11,12,14,16,25,26] found a significant association between infection and RBC transfusion, with four studies demonstrating a dose-dependent relationship.[11,12,16,25] A pooled analysis[10] and two observational studies[19,33] reported an increased risk of ARDS or ALI following RBC transfusion. One small, single-centre study[21] did not demonstrate an increased risk; however, this study may have been underpowered to detect a significant association.

For the comparison of restrictive versus liberal transfusion strategies, the evidence was drawn from five publications derived from two RCTs (Level II).[35-39]

Neither RCT demonstrated a statistically significant difference in mortality between restrictive and liberal transfusion at any of the follow-up time periods; however, the larger Transfusion Requirements in Critical Care (TRICC) trial reported a reduction in favour of restrictive transfusion for in-hospital mortality (22.2% vs 28.1%; risk difference [RD] 5.8%; 95% confidence interval [CI] –11.7%, 0.3%).[35]

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

RBC, red blood cell

The transfusion of RBCs is resource intensive, and has been associated with morbidity in recipients. Recombinant erythropoiesis-stimulating agents (ESAs) promote bone-marrow production of RBCs. However, ESAs have been associated with complications of therapy in some patients, particularly where the baseline haemoglobin (Hb) is near normal. In some patients, iron administration may also be effective. The systematic review examined the effectiveness of ESAs or iron supplementation in critically ill patients.

EVIDENCE STATEMENTS		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.1	In a heterogeneous population of critically ill patients, ESAs have no effect on mortality.	✓✓✓	✓✓✓	A	✓✓✓	✓✓
ES2.2	In critically ill trauma patients, ESAs may be associated with decreased mortality.	✓✓✓	✓✓✓	✓✓	✓✓	✓✓
ES2.3	In a heterogeneous population of critically ill patients, ESAs do not appear to reduce the incidence of RBC transfusion when a restrictive transfusion strategy is employed.	✓✓	✓	A	✓✓✓	✓✓
ES2.4	In critically ill non-trauma patients, the effect of ESAs on the incidence of RBC transfusion is uncertain.	✓✓✓	✓	A	✓✓✓	✓✓
ES2.5	In critically ill trauma patients, ESAs appear to have no effect on the incidence of RBC transfusion.	✓✓✓	✓	✓	✓✓✓	✓✓
ES2.6	In a heterogeneous population of critically ill patients, ESAs may increase the risk of thromboembolic events.	✓✓	✓	✓	✓✓✓	✓✓
ES2.7	In critically ill patients, the effect of iron therapy on mortality is uncertain.		✓✓✓	A	✓✓✓	✓✓
ES2.8	In critically ill patients, the effect of oral iron therapy on RBC transfusion is uncertain.			A	✓✓✓	✓✓

ES, evidence statement; ESA, erythropoiesis-stimulating agent; RBC, red blood cell

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

R2	[illegible]

ESA, erythropoiesis-stimulating agent; R, recommendation

For ESAs, the evidence was obtained from two systematic reviews (Level I)[40,41] and two RCTs (Level II)[42,43] that were published subsequently. Further evidence was obtained from a publication[44] that provided a subgroup analysis of the trauma patients from the two largest RCTs[45,46] included in the review by Zarychanski et al (2007)[41] assessing ESAs in critically ill patients. This meta-analysis demonstrated no survival benefit (odds ratio [OR] 0.86; 95% CI 0.71, 1.05) in critically ill patients.[41] Neither of the subsequent RCTs was able to demonstrate an improvement in mortality. The subgroup analysis by Napolitano et al (2008) found that, in trauma patients specifically, mortality was lower in patients treated with ESAs compared with no ESA treatment (three trials; 4% vs 8%; relative risk [RR] 0.51; 95% CI 0.33, 0.80).[44]

Zarychanski et al (2007) also evaluated the effect of ESAs on transfusion requirement in critically ill patients.[41] The review found no significant difference in RBC transfusion incidence when restrictive (Hb ≤80 g/L) transfusion practice was used (three trials; 44% vs 50%; RR 0.68; 95% CI 0.43, 1.07); although there was significant heterogeneity due to differences in setting and treatment.[41] In studies with less restrictive (Hb >80 g/L) transfusion practices; however, ESAs significantly reduced RBC transfusion incidence compared with the control (three trials; 50% vs 60%; RR 0.83; 95% CI 0.76, 0.91).[41]

The two studies published after Zarychanski et al (2007)[41]

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

FFP, fresh frozen plasma

The aim of this question was to determine the effect of using fresh frozen plasma (FFP), cryoprecipitate, fibrinogen and platelet concentrates on mortality, bleeding events and transfusion-related adverse events. For this question, the search was limited to studies that could be categorised as Level III or above. Studies that were eligible for inclusion could either compare blood product transfusion with no transfusion or compare different strategies for blood product transfusion. All of the studies identified in the systematic review compared blood product transfusion with no transfusion. To minimise bias, the eligible cohort studies were limited to those that adjusted for confounding variables using multivariate logistic regression.

3.3.1 Fresh frozen plasma

EVIDENCE STATEMENTS		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.1	In patients with trauma, the effect of FFP on mortality is uncertain.		✓		✓✓	✓✓
ES3.2	In patients with trauma, FFP may be associated with transfusion-related serious adverse events.		✓✓	✓	✓✓	✓✓
ES3.3	In non-trauma patients, FFP may be associated with transfusion-related serious adverse events.		A		✓✓	✓✓
ES3.4						

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3.3.2 Fibrinogen concentrate and cryoprecipitate

EVIDENCE STATEMENTS		Evidence	Consistency	Clinical impact	Generalisability	Applicability
E	In p t nts w t tr u , t to r opr p t t on ort t s un rt n	X	NA	NA	✓✓	✓✓
E	In p t nts w t tr u , t to r opr p t t on tr ns us on r t s r ous v rs v nts s un rt n	X	NA	X	✓✓	

3.3.3 Platelet transfusion

One retrospective cohort study (Level III) studied the effects of platelet transfusion in 122 medical ICU patients.[21] This study found that platelet transfusion was significantly and independently

PRACTICE POINT

In critically ill trauma patients and patients undergoing emergency surgery for ruptured abdominal aortic aneurysm, the use of cell salvage may be considered.

PP, practice point

Cell salvage, also referred to as 'autotransfusion', is a term that covers a range of techniques designed to

3.4.2 Tranexamic acid

	EVIDENCE STATEMENT	Evidence	Consistency	Clinical impact	Generalisability	Applicability

RECOMMENDATIONS	
R3 **GRADE B**	In acutely bleeding critically ill trauma patients, TXA should be administered within 3 hours of injury.
R4 **GRADE C**	In critically ill patients with upper GI bleeding, consider the use of TXA.

PRACTICE POINTS	
PP14	TXA should be given as early as possible, preferably within 3 hours of injury. The late administration of TXA is less effective and may be harmful.
PP15	The suggested dose of TXA administered is a 1 g bolus followed by a 1 g infusion over 8 hours. This is the dose administered in the large multicentre RCT CRASH-2.

CRASH, Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage, GI, gastrointestinal, PP, practice point, R, recommendation, RCT, randomised controlled trial, TXA, tranexamic acid

Tissue plasminogen activator is a major enzyme responsible for conversion of plasminogen into active plasmin, which in turn is responsible for fibrinolysis or the breakdown of thrombus Tranexamic acid (TXA) is an antifibrinolytic that inhibits both plasminogen activation and plasmin activity, thereby preventing thrombus lysis

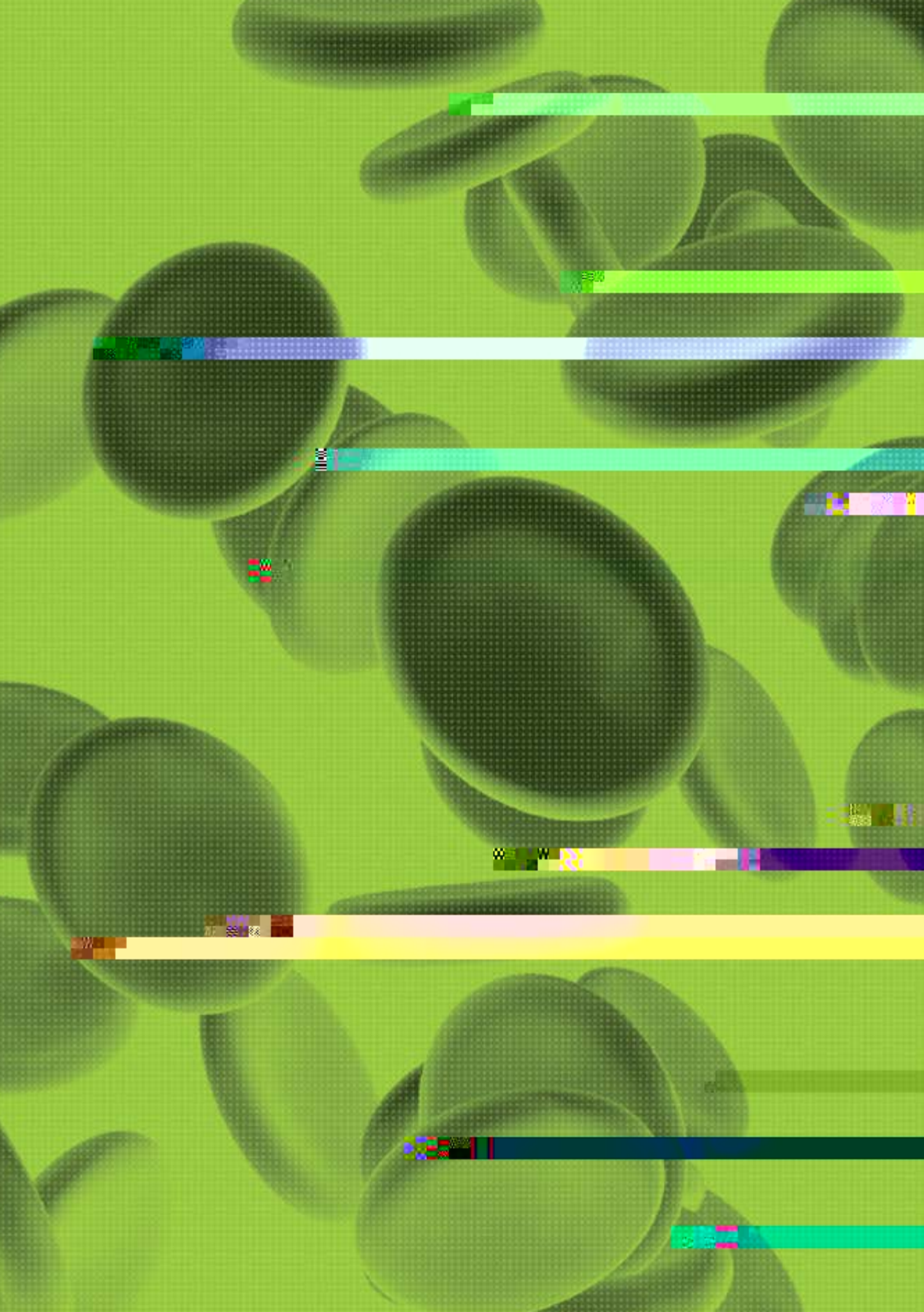
At the time this Module was submitted to NHMRC, intravenous TXA was registered by the TGA and listed on the PBS in·

- adults (for the reduction of peri and post operative blood loss and the need for blood transfusion in patients undergoing cardiac surgery or total knee arthroplasty or total hip arthroplasty) and
- children (for the reduction of peri and post operative blood loss and the need for blood transfusion in patients undergoing cardiac surgery)

The systematic review evaluated the effect of TXA infusion in both trauma and non trauma populations The potential benefit of TXA infusion on mortality, transfusion incidence and volume was determined A recent systematic review, which included a large RCT with more than patients, has provided the evidence for those recommendations pertaining to trauma patients

In the acutely bleeding trauma patient, the infusion of g of TXA over minutes, followed by a subsequent g infusion over hours (if commenced within hours of injury) has been associated with a statistically significant reduction in mortality However, this strategy did not have an effect on RBC allogeneic transfusion incidence or volume This work has also provided the evidence that the use of TXA in trauma is safe and does not result in an increase in either venous or arterial thrombotic complications Therefore, it is reasonable to recommend that in the acutely bleeding trauma patient TXA should be should be administered, and within hours of injury

The evidence for the use of TXA in upper gastrointestinal (GI) bleeding is less convincing A systematic review of seven RCTs suggests that TXA may reduce the risk of mortality, but it does not appear to affect the incidence of allogeneic red blood cell transfusion · The risk of thromboembolic events in this setting remains uncertain Therefore, it is reasonable for the clinician caring for the critically ill patient with an upper GI haemorrhage to consider the use of TXA The dosing, safety and efficacy of TXA administration in GI bleeding needs to be established through well designed RCTs



F r r on

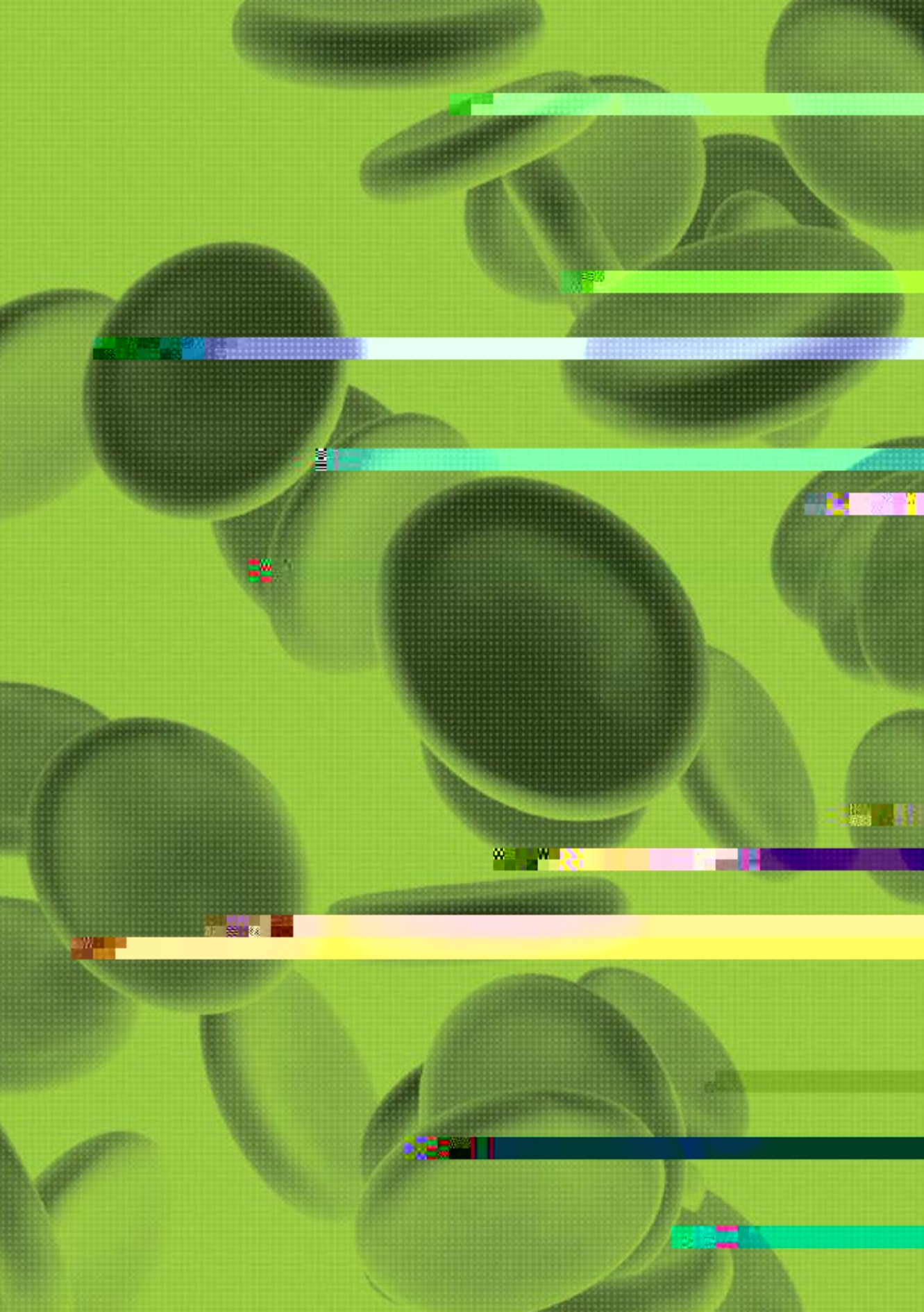
The systematic review for this module found adequate evidence to make recommendations about the use of a restrictive transfusion strategy, ESAs and TXA in critically ill patients.

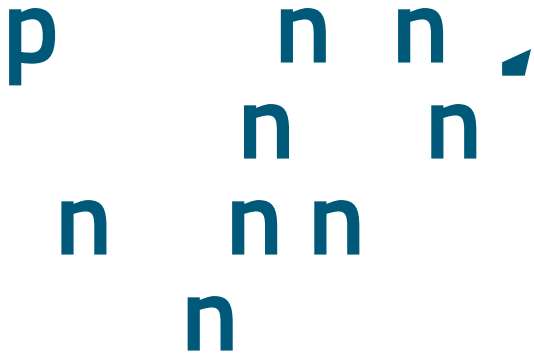
The benefit of RBC transfusions in the critically ill has not been established. Thus, it has been difficult to provide guidance on RBC transfusion thresholds while ensuring a patient focus. The systematic review identified little evidence regarding the use of FFP, cryoprecipitate, fibrinogen concentrate and platelets in this population.

E n p n r o r r r

In this review, there were a number of areas where there was insufficient evidence to generate recommendations. These areas may present avenues for further research:

- identifying the clinical factors, including Hb concentration, that should guide RBC transfusion in critically ill patients
- RBC transfusion in critically ill patients with acute coronary syndrome (ACS)
- the role of ESAs in patients with traumatic brain injury
- the diagnosis and management of iron deficiency and suboptimal iron stores in the critically ill
- the safety and efficacy of FFP, cryoprecipitate, fibrinogen concentrate and platelets in the critically ill
- the role of point-of-care testing in guiding coagulation management
- the role of cell-salvage techniques in critically ill trauma patients and in those undergoing emergency surgery
- the optimal dose of TXA
- the role of strategies to reduce iatrogenic blood loss.





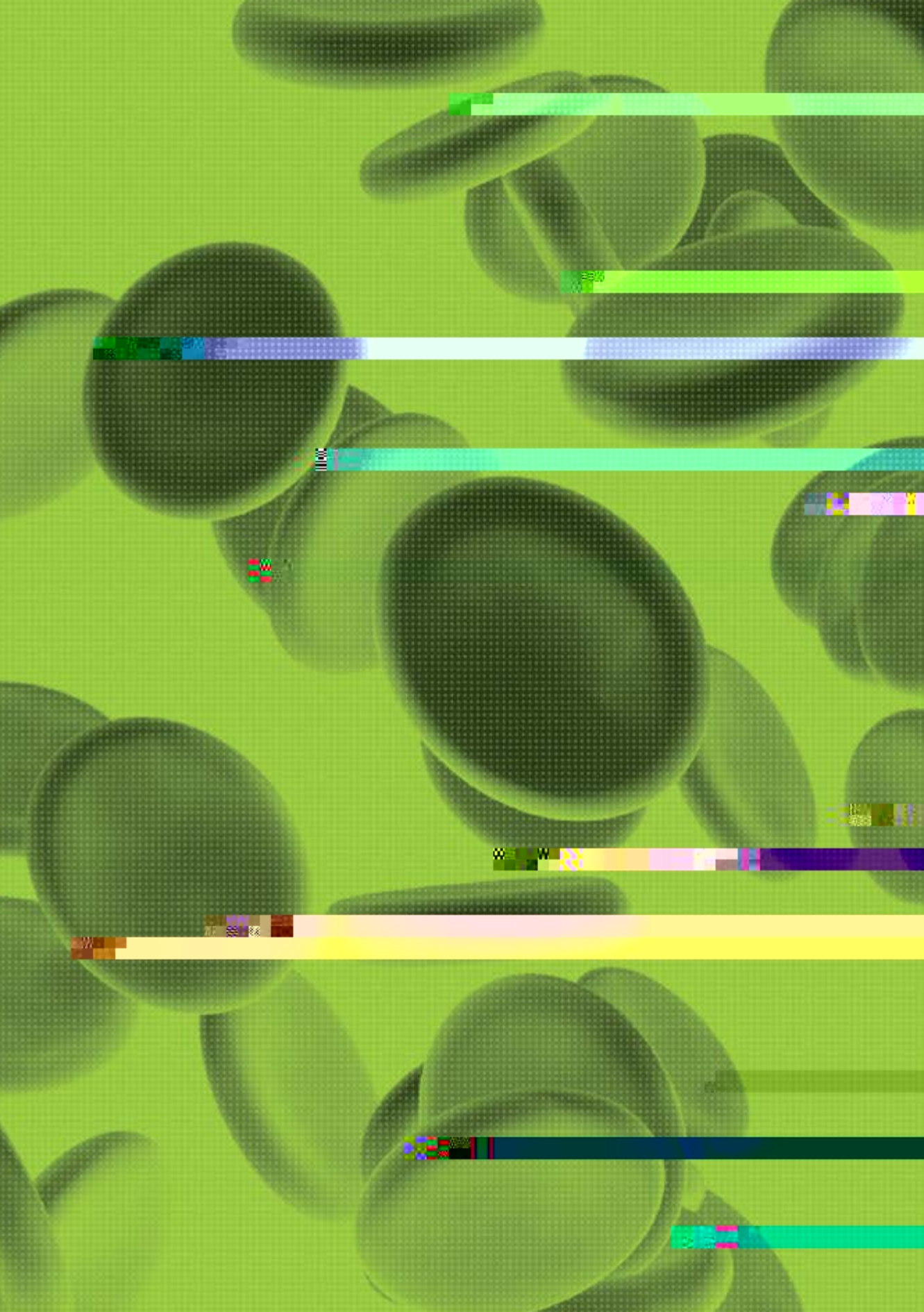
The NBA, in collaboration with the Steering Committee, developed a plan to guide appropriate communication on the implementation of this module. The plan identifies target audiences for the module, strategies and tools for effective implementation, communication channels and key messages.

Continued re-evaluation of the guidelines is necessary to reduce variation in practice patterns, support appropriate use of blood component therapy and reduce inappropriate exposure of patients to blood components.[66] A plan was designed to evaluate implementation of the six modules of the guidelines and to determine:

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

The results of the evaluation will be used to inform future review of the guidelines. Economic issues were considered when formulating the evidence-based recommendations. The recommendations have the potential to reduce product associated expenditure and the burden on health services through reduced complications and reduced length of stay. All recommendations within this Module constrain the use of expensive products (such as blood and blood products and erythropoietin stimulating agents).

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 a coorA, tts gram e useinc



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

n n n

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

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

n n n n A

During the development of this module, the PBM guideline development process was transitioning to the *Procedures and requirements for meeting the 2011 NHMRC standard for clinical practice guidelines*. In order to achieve an increasing focus on consumer involvement in clinical practice guidelines, the NBA sought advice from a consumer advocate, and subsequently sought the participation of consumers in an online survey to review and provide input on the draft module in order to meet the new procedures and requirements.

A recruitment process resulted in the selection of three consumers to undertake the survey. Consumers had experience as an intensive care unit patient, or were a carer of a patient in the critical care setting. The NBA (in considering advice previously received from an independent consumer advocate and an intensive care specialist) developed eight specific questions to focus consumer input and included two optional questions for suggestions on patient materials and an opportunity for personal comments.

The consumers were provided with the following documentation prior to completing the survey:

Clinical / Consumer Reference Group – critical care module

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 Anthony Holley	Intensive care physician	College of Intensive Care Medicine of Australia and New Zealand, and Australian & New Zealand Intensive Care Society
Dr Santosh Verghese	Intensive care physician	College of Intensive Care Medicine of Australia and New Zealand, and Australian & New Zealand Intensive Care Society

Independent systematic review expert

Ms Tracy Merlin	Adelaide Health Technology Assessment, University of Adelaide

Acknowledgements – Consumer input

A Con o n r

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 decides by consensus whether 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. Mr Farmer also declared travel grants and honoraria from Johnson & Johnson ETHICON Biosurgery for lectures at Cardiothoracic Surgery PBM Workshop Singapore in 2011, Annual Australian Training Meeting Melbourne 2011, Pan European Anaesthesia Summit on Patient Blood Management Barcelona Spain 2010, Asia Pacific Patient Blood Management Surgical Workshop, Tokyo, Japan 2010, Global Webcast on Surgical Patient Blood Management, Somerville New Jersey USA 2010. He also received a travel grant and lecture honorarium from the Queensland Department of Health for a lecture on patient advocacy at the Transfusion Forum Brisbane Queensland 2011. He also received a lecture travel grant from the Haematology Society of Australia and New Zealand South Australia Branch Annual Blood Club Meeting, Victor Harbour, South Australia, 2010. A lecture travel grant and honorarium from Medtel
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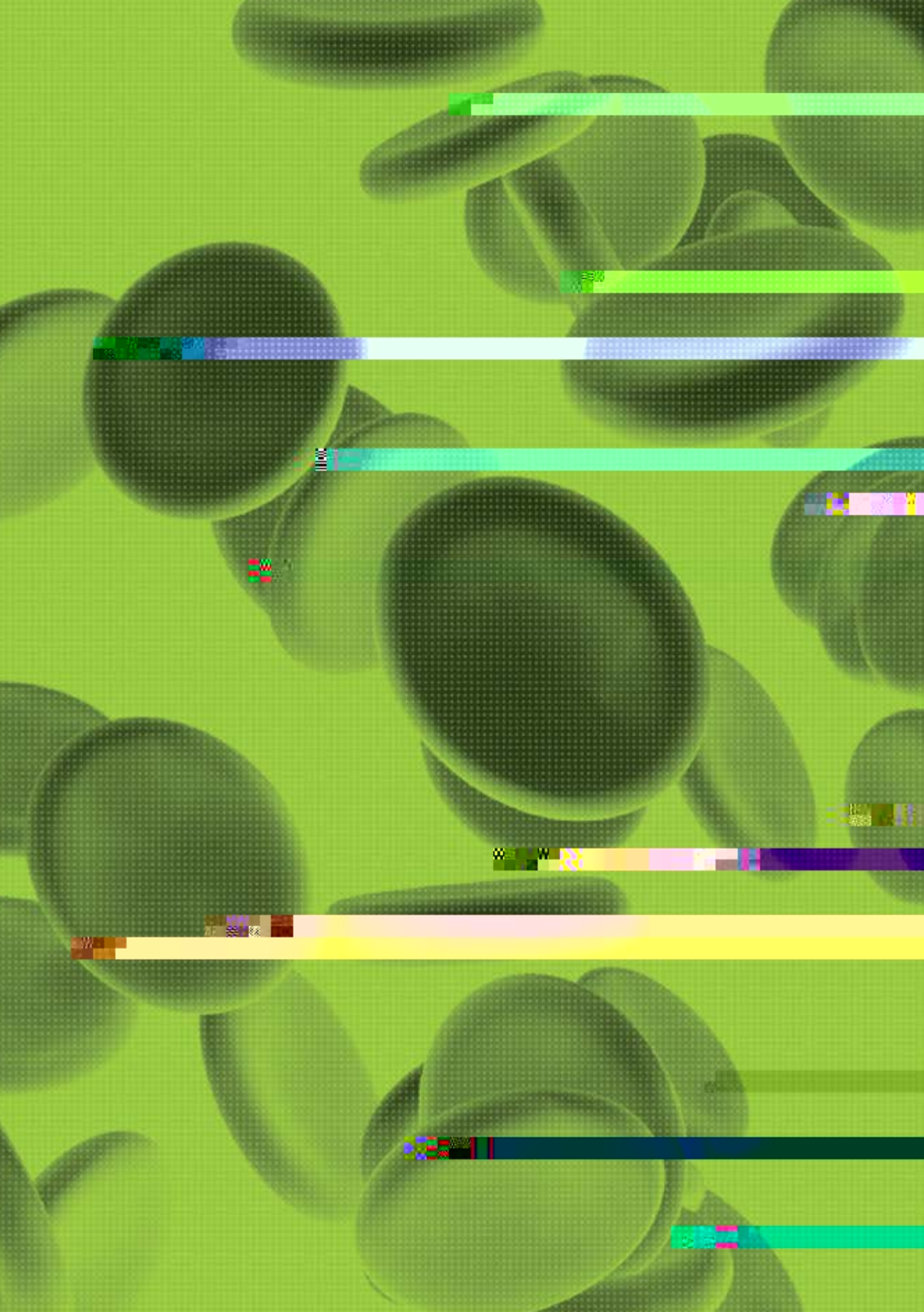

App n B

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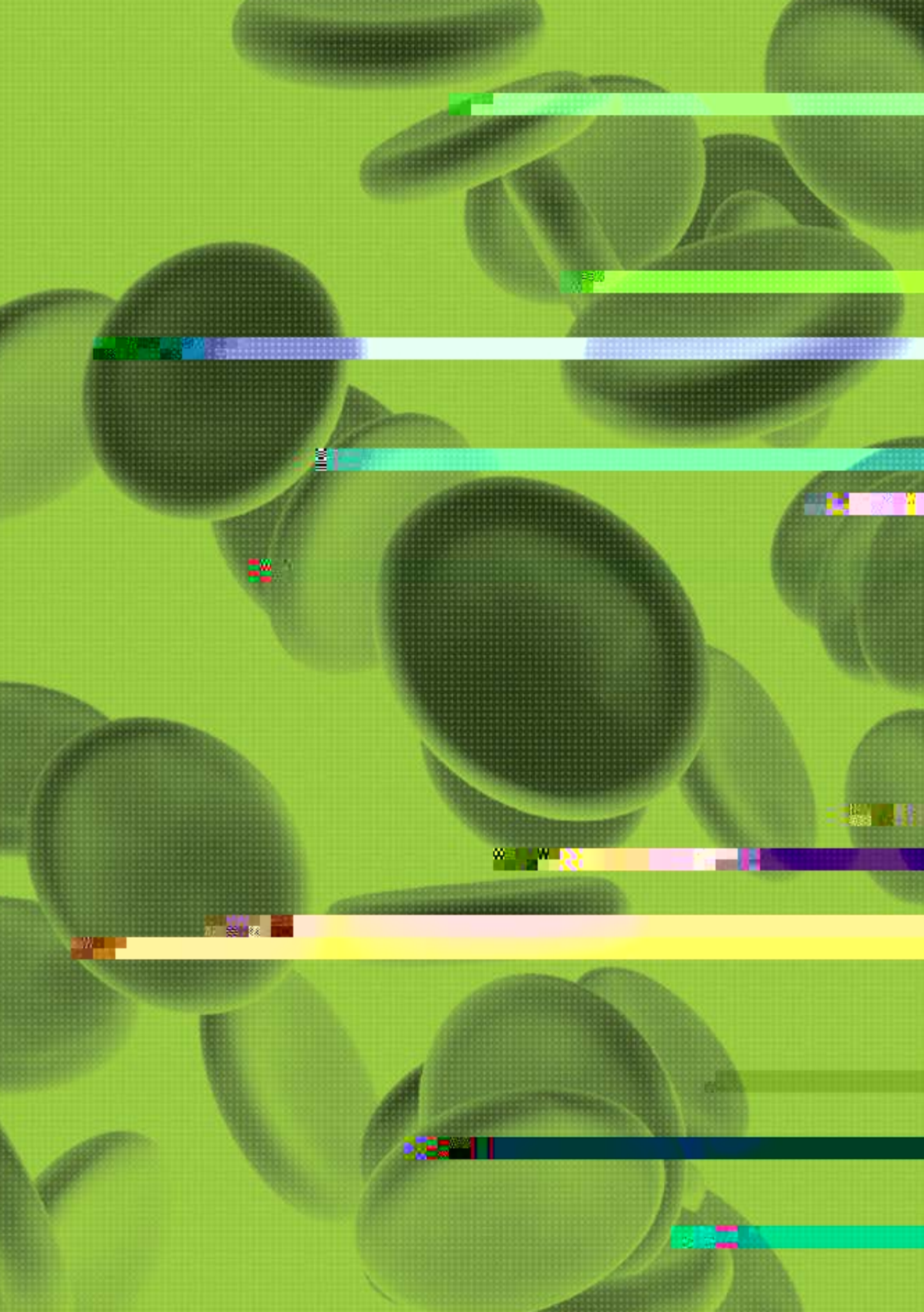
TRANSFUSION RISK	ESTIMATED RATE[a] (HIGHEST TO LOWEST RISK)	CALMAN RATING[b]
Malaria	Less than 1 in 1 million	Negligible
Variant Creutzfeldt-Jakob disease (not tested)	Possible, not yet reported in Australia	Negligible
Transfusion-associated graft-versus-host disease	Rare	Negligible
Transfusion-related immunomodulation	Not quantified	Unknown

IgA, immunoglobulin A
[a] Risk per unit transfused unless otherwise specified
[b] See Calman 1996[68]

Source: Australian Red Cross Blood Service website (www.transfusion.com.au, accessed 19 June 2012)

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

Table B.2 Calman Chart[a]



App n C

B oo or

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.

C Z n oo or

Ministry of Health

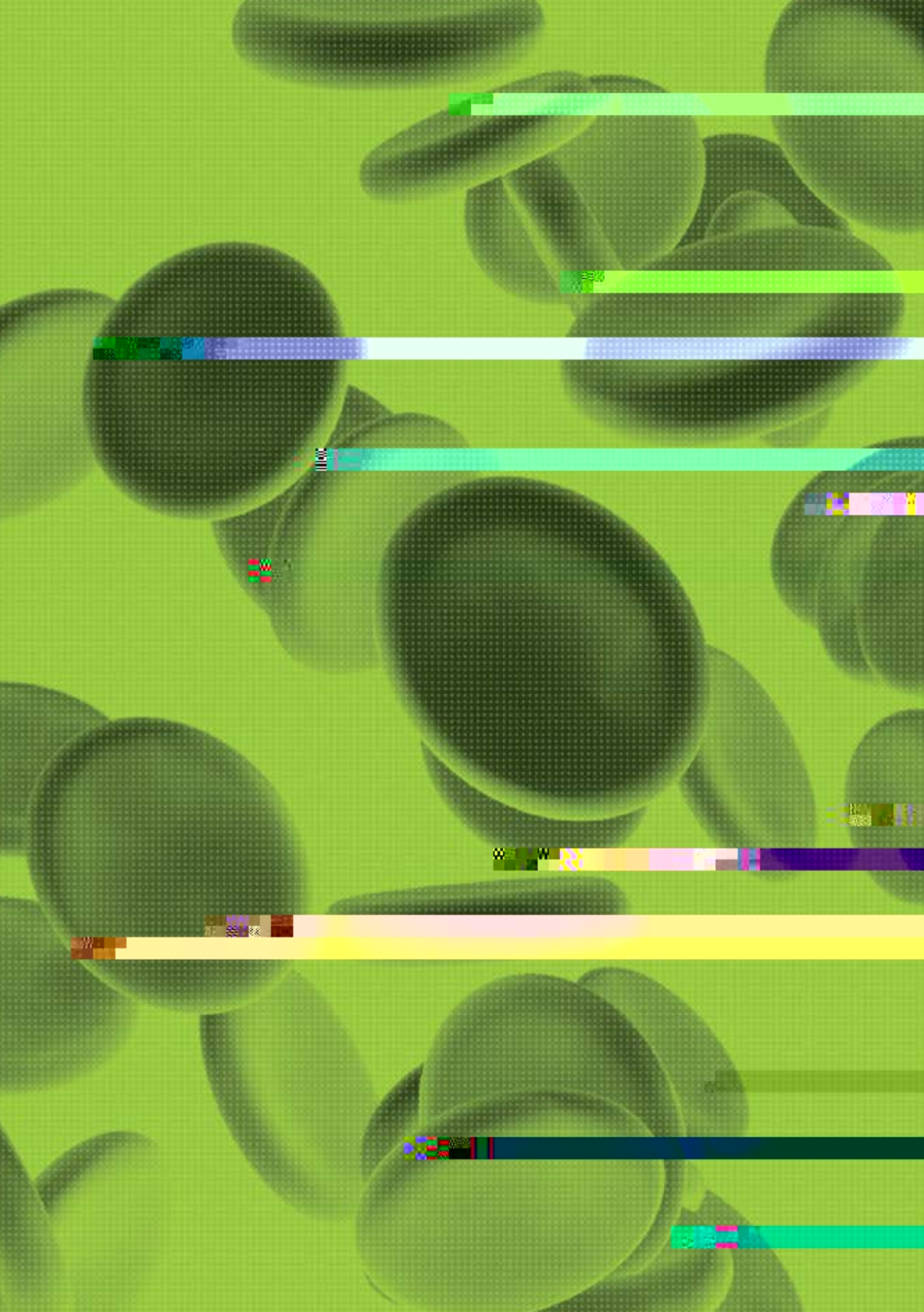
The New Zealand Minister of Health is the government owner of the New Zealand Blood Service (NZBS). The Minister appoints the NZBS Board and approves the Statement of Intent and Output Agreement.

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

Medsafe

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

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



D D op n pro

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

A CRG, with membership including a patient blood management advocate and representation from relevant colleges and societies, was established to develop this critical care module, with assistance from systematic reviewers and a technical writer, and advice and mentoring from an independent systematic review expert. Further details of the governance framework are provided in Section 1.2 and Appendix A.

D r p

Relevant clinical research questions were developed, prioritised, combined and refined by the EWG and the CRG for this guideline, and further refined through consultation among the systematic reviewer, CRG, NBA and independent systematic review expert.

D o o o

Methods are outlined in Chapter 2, with greater detail given in the technical reports. Briefly, the clinical research questions for systematic review were structured according to three criteria: PICO ('population, intervention, comparator and outcome') for intervention questions, PPO ('population, predictor and outcome') for prognostic questions, or PRO ('population, risk factor and outcome') for aetiology questions. Three main strategies were used to identify potentially relevant literature: electronic database searching, manual searching and use of literature recommended by expert members of the CRG. The primary databases searched were EMBASE, Medline, the Cochrane Library Database and PreMedline. Additional searches were conducted of the Cumulative Index to Nursing and Allied Health Literature and Australasian Medical Index. The electronic searches included articles published between 1966 and July 2010 (Question 1), September 2010 (Questions 2 and 3) and March 2011 (Question 4).

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Public consultation was conducted from 26 March to 18 May 2012, during which time the draft module was available on the NBA website.[f] 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.

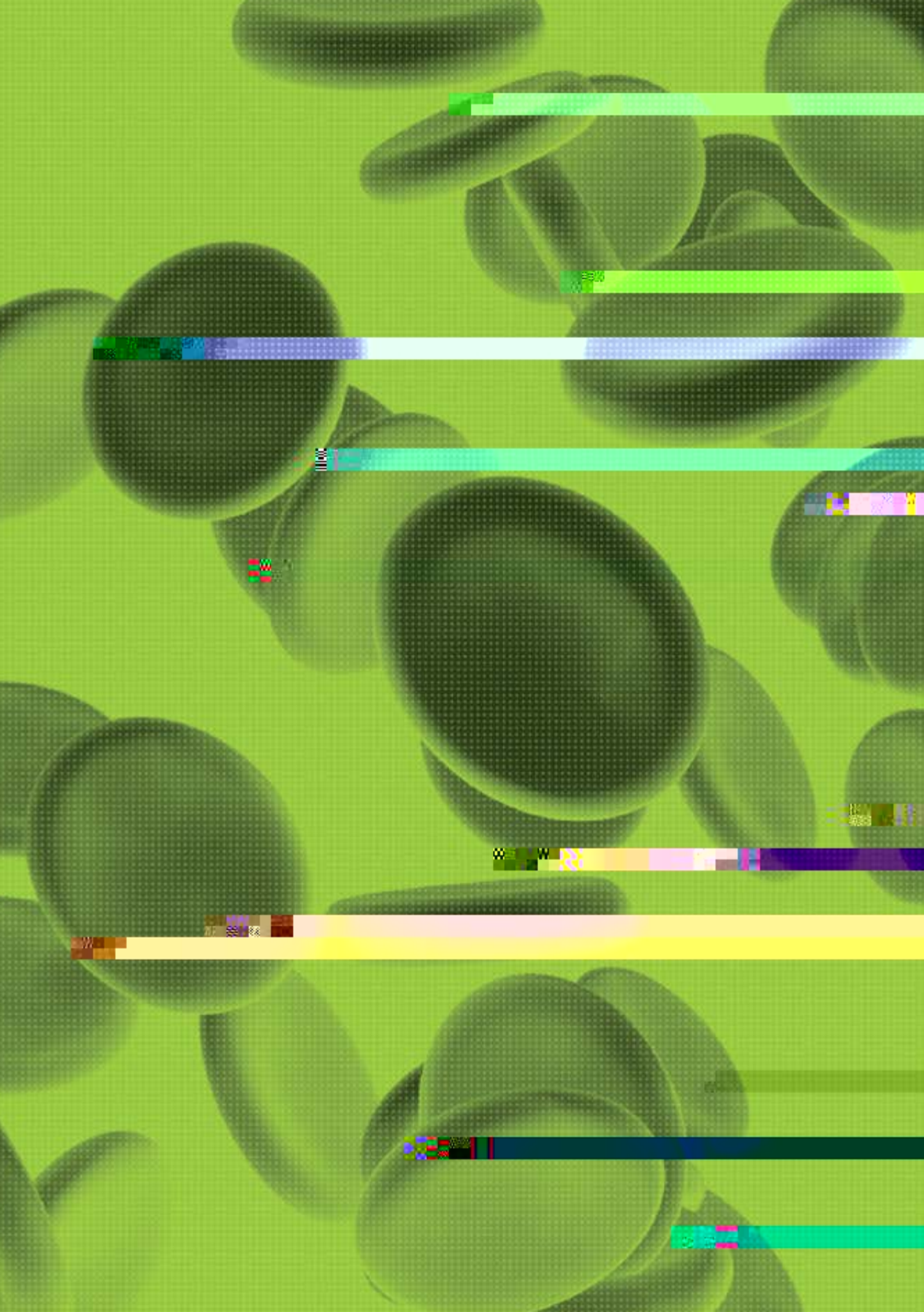
Twelve submissions were received. The CRG met in June 2012 to consider all the public consultation submissions and, where necessary, revise this module in accordance with the submissions. Changes were made to the module to address comments and concerns raised in submissions, and to improve clarity.

D F n n n

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 3 August 2012.

Approval from the NHMRC was received on 14 December 2012.

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



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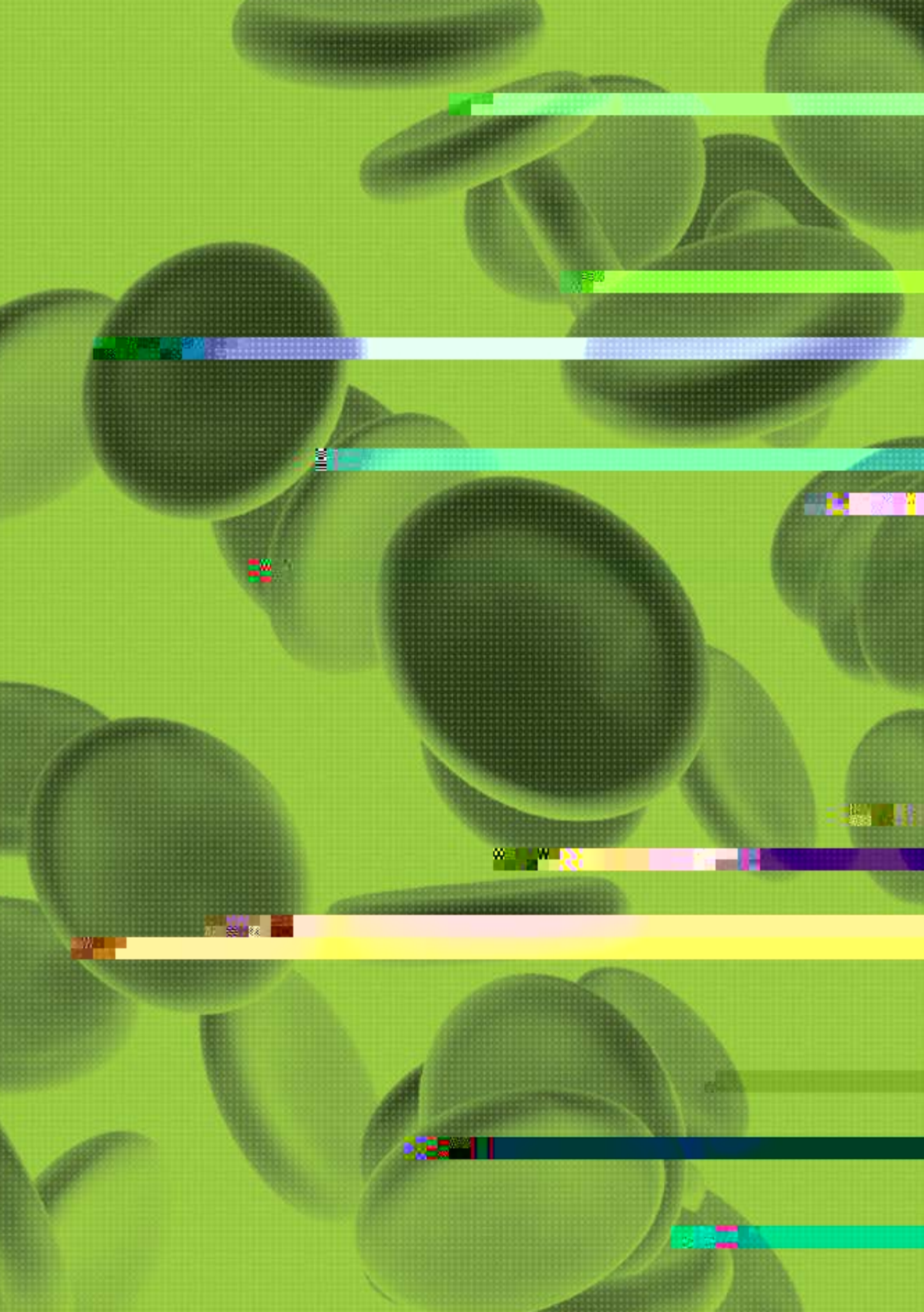
For information on blood products available in Australia, see the website of the Australian Red Cross Blood Service (www.transfusion.com.au).

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



r n

13 Ciesla DJ, Moore EE, Johnson JL, Burch JM, Cothren CC and Sauaia A (2005). A 12-year prospective study of postinjury multiple organ failure: has anything changed? *Archives of Surgery* 140:432-440.

http://www.ncbi.nlm.nih.gov/pubmed/15897438

14 Claridge JA, Sawyer RG, Schulman AM, McLemore EC and Young JS (2002). Blood transfusions correlate with infections in trauma patients in a dose-dependent manner. *American Surgeon* 68(7):566–572.

http://www.ncbi.nlm.nih.gov/pubmed/12132734

15 Corwin HL, Gettinger A, Pearl RG, Fink MP, Levy MM, Abraham E, et al. (2004). The CRIT Study: anemia and blood transfusion in the critically ill - current clinical practice in the United States. *Critical Care Medicine* 32:39–52.

http://www.ncbi.nlm.nih.gov/pubmed/14707558

16 Duane TM, Mayglothling J, Grandhi R, Warrier N, Aboutanos MB, Wolfe LG, et al. (2008). The effect of anemia and blood transfusions on mortality in closed head injury patients. *Journal of Surgical Research* 147:163–167.

http://www.ncbi.nlm.nih.gov/pubmed/18498864

17 Dunne JR, Malone DL, Tracy JK and Napolitano LM (2004). Allogenic blood transfusion in the first 24 hours after trauma is associated with increased systemic inflammatory response syndrome (SIRS) and death. *Surgical Infections* 5(4):395–404.

http://www.ncbi.nlm.nih.gov/pubmed/15744131

18 Engoren M and Arslanian-Engoren C (2009). Long-term survival in the intensive care unit after erythrocyte blood transfusion. *American Journal of Critical Care* 18(2):124–131.

http://www.ncbi.nlm.nih.gov/pubmed/19255102

19 Gong NJ, Thompson BT, Williams P, Pothier L, Boyce PD and Chistiani DC (2005). Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. *Critical Care Medicine* 33(6):1191–1198.

http://www.ncbi.nlm.nih.gov/pubmed/15942330

20 Hébert PC, Wells G, Tweeddale M, Martin C, Marshall J, Pham B, et al. (1997). Does transfusion practice affect mortality in critically ill patients? Transfusion Requirements in Critical Care (TRICC) Investigators and the Canadian Critical Care Trials Group. *American Journal of Respiratory and Critical Care Medicine* 155:1618–1623.

http://www.ncbi.nlm.nih.gov/pubmed/9154866

21 Khan H, Belsher J, Yilmaz M, Afessa B, Winters JL, Moore SB, et al. (2007). Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. *Chest* 131(5):1308–1314.

http://www.ncbi.nlm.nih.gov/pubmed/17400669

22 Leal-Noval SR, Rincon-Ferrari MD and Garcia-Curiel A (2001). Transfusion of blood components and postoperative infection in patients undergoing cardiac surgery. *Chest* 119:1461–1468.

http://www.ncbi.nlm.nih.gov/pubmed/11348954

23 Malone DL, Dunne J, Tracy JK, Putnam AT, Scalea TM and Napolitano LM (2003). Blood transfusion, independent of shock severity, is associated with worse outcome in trauma. *Journal of Trauma – Injury, Infection and Critical Care* 54:898–907.

http://www.ncbi.nlm.nih.gov/pubmed/12777902

24 Muller MH, Moubarak P, Wolf H, Kuchenhoff H, Jauch KW and Hartl WH (2008). Independent determinants of early death in critically ill surgical patients. *Shock* 30(1):11–16.

http://www.ncbi.nlm.nih.gov/pubmed/18323738

25 Palmieri TL, Caruso DM, Foster KN, Cairns BA, Peck MD, Gamelli RL, et al. (2006). Effect of blood transfusion on outcome after major burn injury: A multicenter study. *Critical Care Medicine* 34(6):1602-1607.

http://www.ncbi.nlm.nih.gov/pubmed/16607231

26 Rachoin JS, Daher R, Schorr C, Milcarek B, Parrillo JE and Gerber DR (2009). Microbiology, time course and clinical characteristics of infection in critically ill patients receiving packed red blood cell transfusion. *Vox Sanguinis* 97(4):294–302.

http://www.ncbi.nlm.nih.gov/pubmed/19682350

27 Ruttinger D, Wolf H, Kuchenhoff H, Jauch KW and Hartl WH (2007). Red cell transfusion: An essential factor for patient prognosis in surgical critical illness? *Shock* 28(2):165–171.

http://www.ncbi.nlm.nih.gov/pubmed/17529904

28 Salim A, Hadjizacharia P, DuBose J, Brown C, Inaba K, Chan L, et al. (2008). Role of anemia in traumatic brain injury. *Journal of the American College of Surgeons* 207:398–406.

http://www.ncbi.nlm.nih.gov/pubmed/18722946

29 Shorr AF, Duh MS, Kelly KM and Kollef MH (2004). Red blood cell transfusion and ventilator-associated pneumonia: A potential link? *Critical Care Medicine* 32(3):666–674.

http://www.ncbi.nlm.nih.gov/pubmed/15090945

30 Spinella PC, Perkins JG, Grathwohl KW, Beekley AC, Niles SE, McLaughlin DF, et al. (2008). Effect of plasma and red blood cell transfusions on survival in patients with combat related traumatic injuries. *Journal of Trauma - Injury, Infection and Critical Care* 64:S69–S78.

http://www.ncbi.nlm.nih.gov/pubmed/18376175

31 Vincent JL, Baron JF, Reinhart K, Gattioni L, Thijs L, Webb A, et al. (2002). Anemia and blood transfusion in critically ill patients. *Journal of the American Medical Association* 288(12):1499–1507.

http://www.ncbi.nlm.nih.gov/pubmed/12243637

32 Vincent JL, Sakr Y, Sprung C, Harboe S and Damas P (2008). Are blood transfusions associated with greater mortality rates? Results of the sepsis occurrence in acutely ill patients study. *Anesthesiology* 108(1):31–39.

54 Bowley DM, Barker P and Boffard KD (2006). Intraoperative blood salvage in penetrating abdominal trauma: A randomised, controlled trial. *World Journal of Surgery* 30(6):1074-1080.

http://www.ncbi.nlm.nih.gov/pubmed/16736339

55 Brown G, Bookallil M and Herkes R (1991). Use of the cell saver during elective abdominal aortic aneurysm surgery – influence on transfusion with bank blood. A retrospective survey. *Anaesthesia and Intensive Care* 19(4):546-550.

http://www.ncbi.nlm.nih.gov/pubmed/1750636

56 Markovic M, Davidovic L, Savic N, Sindjelic R, Ille T and Dragas M (2009). Intraoperative cell salvage versus allogeneic transfusion during abdominal aortic surgery: Clinical and financial outcomes. *Vascular* 17(2):83–92.

http://www.ncbi.nlm.nih.gov/pubmed/19426638

57

65 Gluud LL, Klingenberg SL and Langholz SE (2008). Tranexamic acid for upper gastrointestinal bleeding. *Alimentary Pharmacology and Therapeutics* 27(9):752–758.

http://www.ncbi.nlm.nih.gov/pubmed/22258969

66 Snyder-Ramos SA, Mohnle P, Weng YS, Bottiger BW, Kulier A, Levin J, et al. (2008). The ongoing variability in blood transfusion practices in cardiac surgery. *Transfusion* 48(7):1284–1299.

http://www.ncbi.nlm.nih.gov/pubmed/18422857

67 Australian Commission on Safety and Quality in Health Care (ACSQHC) (2011). *National sh Care (as333uTut0 cma7*

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