

The background of the slide is a close-up, artistic photograph of numerous red blood cells. The cells are biconcave discs, appearing in various shades of red and pink, with some showing a darker center. They are scattered across the frame, creating a textured, organic background.

Patient Blood Management Guidelines: Module 4

Critical Care

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ISBN 978-0-9872519-9-2

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Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the circumstances, clinician's judgement and patient's preferences in each individual case. It is designed to provide information to assist decision making. Recommendations contained herein are based on the best available evidence published up to July 2010 (Question 1), September 2010 (Questions 2 and 3) and March 2011 (Question 4). The relevance and appropriateness of the information and recommendations in this document depend on the individual circumstances. Moreover, the recommendations and guidelines are subject to change over time.

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

Publication approval



Australian Government

National Health and Medical Research Council

These guidelines were approved by the Chief Executive Officer of the National Health and Medical Research Council (NHMRC) on 14 December 2012, under Section 14A of the *National Health and Medical Research Council Act 1992*. In approving these guidelines the NHMRC considers that they meet the NHMRC standard for clinical practice guidelines. This approval is valid for a period of five years.

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

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

Patient Blood Management Guidelines: Module 4 – Critical Care

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



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.

Abbreviations and acronyms

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

Contents

Abbreviations and acronyms

Executive summary	1
Summary of recommendations and practice points	2
1 Introduction	7
1.1 Development of the guidelines	8
1.2 Governance structure	9
1.3 Structure of the document and related materials	9
1.3.1 The document	9
1.3.2 Related materials	10
2 Methods	13
2.1 Clinical research questions – development and details	14
2.2 Review and research	14
2.2.1 Systematic review process	14
2.3 Development of evidence statements, recommendations and practice points	15
3 Clinical guidance	19
3.1 Effect of red blood cell transfusion on outcomes	20
3.2 Effect of non-transfusion interventions to increase haemoglobin concentration	24
3.3 Effect of blood components on outcomes	26
3.3.1 Fresh frozen plasma	26
3.3.2 Fibrinogen concentrate and cryoprecipitate	28
3.3.3 Platelet transfusion	29
3.4 Use of blood conservation strategies	30
3.4.1 Cell salvage	30
3.4.2 Tranexamic acid	32
4 Future directions	35
4.1 Evidence gaps and areas of future research	36
5 Implementing, evaluating and maintaining the guidelines	39
Appendix A Governance	43
Appendix B Transfusion risks in the context of patient blood management	51
Appendix C Blood sectors	55
Appendix D Process report	61
Appendix E Product information	65
References	67
Index	75

Tables

Table 1.1	Phases of development of guideline modules	8
Table 2.1	Body of evidence matrix	16
Table 2.2	Definitions of NHMRC grades for recommendations	16
Table B.1	Transfusion risks	52
Table B.2	Calman Chart (United Kingdom risk per one year)	53

Figures

Figure A.1	Management framework for development of the guidelines	44
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Executive summary

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 3 (Medical) cover all the patient groups addressed by the 2001 document *Clinical Practice Guidelines on the Use of Blood Components*¹ (National Health and Medical Research Council/Australasian Society of Blood Transfusion, NHMRC/ASBT). Thus, the 2001 guidelines have now been replaced.

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

This Executive summary includes:

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

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

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

Summary of recommendations and practice points

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

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

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

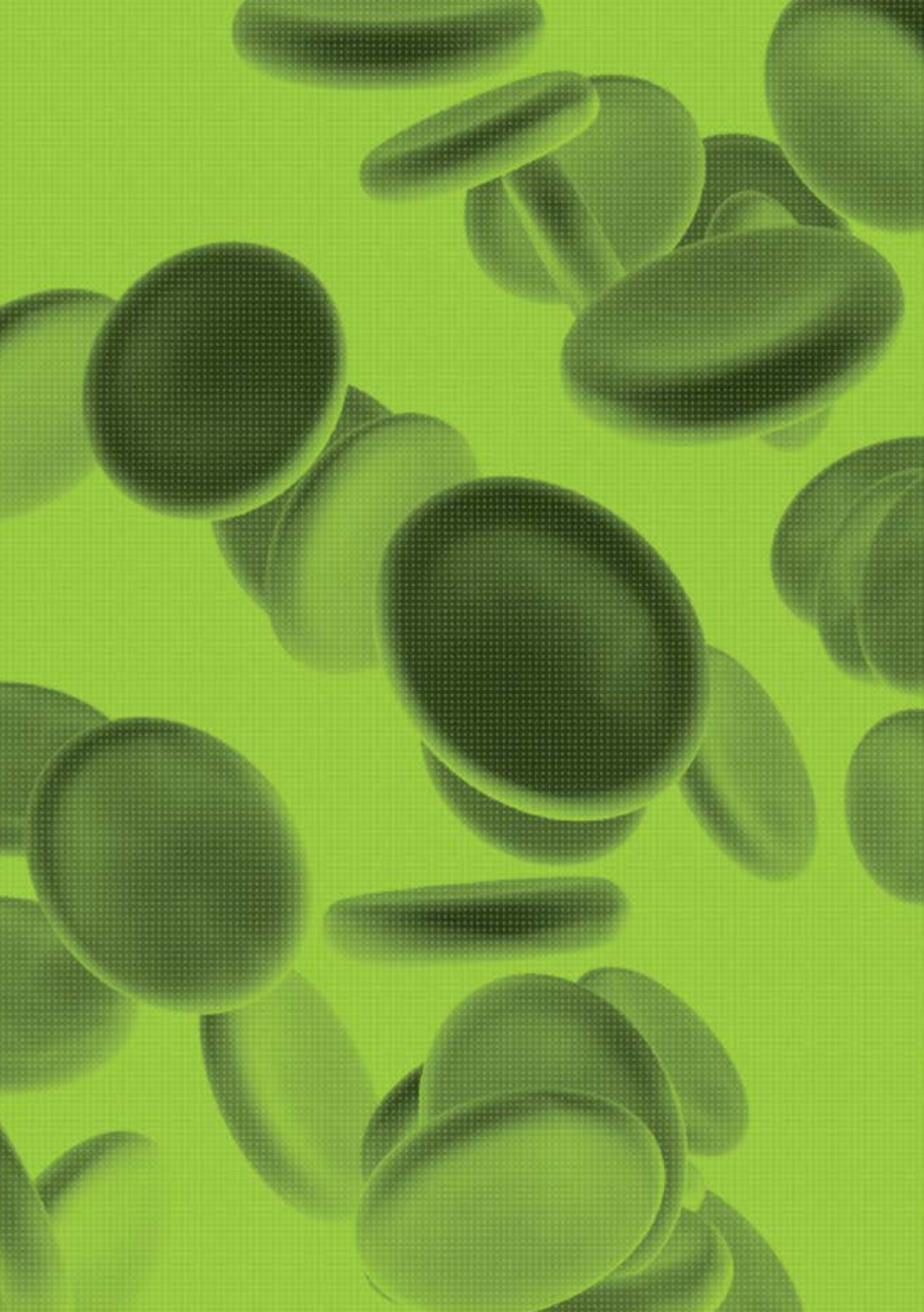
Identifier and grade	Guidance – recommendations and practice points	Relevant section of document
RED CELLS		
R1 GRADE B	In critically ill patients, a restrictive transfusion strategy should be employed.	3.1
PP1	RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.	3.1
PP2	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
PP3	<p>CRG consensus suggests that, with a:</p> <ul style="list-style-type: none"> ▪ Hb concentration <70 g/L, RBC transfusion is likely to be appropriate; however, transfusion may not be required in well-compensated patients or where other specific therapy is available. ▪ Hb concentration of 70–90 g/L, 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. ▪ Hb concentration >90 g/L, RBC transfusion is generally unnecessary. <p>For patients undergoing cardiac surgery, refer to <i>Patient Blood Management Guidelines: Module 2 – Perioperative</i>;² for patients with active bleeding, refer to <i>Patient Blood Management Guidelines: Module 1 – Critical Bleeding/ Massive Transfusion</i>.³</p>	3.1
PP4	<p>For patients with ACS, the following guidance is taken from <i>Patient Blood Management Guidelines: Module 3 – Medical</i>.⁴ In ACS patients with a:</p> <ul style="list-style-type: none"> ▪ Hb concentration <80 g/L, RBC transfusion may be associated with reduced mortality and is likely to be appropriate (see PP5 of Module 3). ▪ 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 (see PP6 of Module 3). ▪ Hb concentration >100 g/L, RBC transfusion is not advisable because of an association with increased mortality (see R1 of Module 3). <p>Any decision to transfuse should be made with caution and based on careful consideration of the risks and benefits (see PP6 of Module 3).</p>	3.1

Identifier and grade	Guidance – recommendations and practice points	Relevant section of document
ERYTHROPOIESIS-STIMULATING AGENTS		
R2 GRADE B	ESAs should not be routinely used in critically ill anaemic patients. ^a	3.2
FRESH FROZEN PLASMA		
PP5	The routine use of FFP in critically ill patients with coagulopathy is not advised. The underlying causes of coagulopathy should be identified.	3.3.1
PP6	The administration of FFP may be independently associated with adverse events, including ARDS and ALI. The decision to transfuse these products to an individual patient should take into account the relative risks and benefits.	3.3.1
PP7	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 an INR ≤2 may not benefit from the administration of FFP and can generally undergo invasive procedures within the ICU without any serious bleeding; higher INRs may be tolerated in certain clinical situations.	3.3.1
FIBRINOGEN AND CRYOPRECIPITATE		
PP8	The routine use of cryoprecipitate and fibrinogen concentrate in critically ill patients with coagulopathy is not advised. The underlying causes of coagulopathy should be identified.	3.3.2
PP9	The effect of cryoprecipitate and fibrinogen on transfusion-related serious adverse events is uncertain. The decision to transfuse cryoprecipitate or fibrinogen to an individual patient should take into account the relative risks and benefits.	3.3.2
PLATELETS		
PP10	The effect of platelet transfusion on transfusion-related serious adverse events is uncertain. The decision to transfuse platelets to an individual patient should take into account the relative risks and benefits.	3.3.3
PP11	In critically ill patients, in the absence of acute bleeding, the administration of platelets may be considered appropriate at a platelet count of $<20 \times 10^9$.	3.3.3

^a This recommendation is based on the lack of effect of ESAs on mortality in a heterogeneous population of critically ill patients.

Identifier and grade	Guidance – recommendations and practice points	Relevant section of document
PP12	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 $\geq 50 \times 10^9$ 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		
PP13	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		
R3 GRADE B	In acutely bleeding critically ill trauma patients, TXA should be administered within 3 hours of injury.	3.4.2
R4 GRADE C	In critically ill patients with upper GI bleeding, consider the use of TXA.	3.4.2
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.	3.4.2
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.	3.4.2

ACS, acute coronary syndrome; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CRASH, Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage; CRG, Clinical/Consumer Reference Group; ESA, erythropoiesis-stimulating agent; FFP, fresh frozen plasma; GI, gastrointestinal; Hb, haemoglobin; ICU, intensive care unit; INR, international normalised ratio; MI, myocardial infarction; PP, practice point; R, recommendation; RBC, red blood cell; RCT, randomised controlled trial; TXA, tranexamic acid



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 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 guidelines¹ 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.

1.1 Development of the guidelines

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 Phases of development of guideline modules

PHASE	MODULES
I	1 – Critical Bleeding/Massive Transfusion 2 – Perioperative
II	3 – Medical 4 – Critical Care
III	5 – Obstetrics 6 – Paediatrics/Neonates

^b The structure of the Australian blood sector is outlined in [Appendix C](#)

1.2 Governance structure

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

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

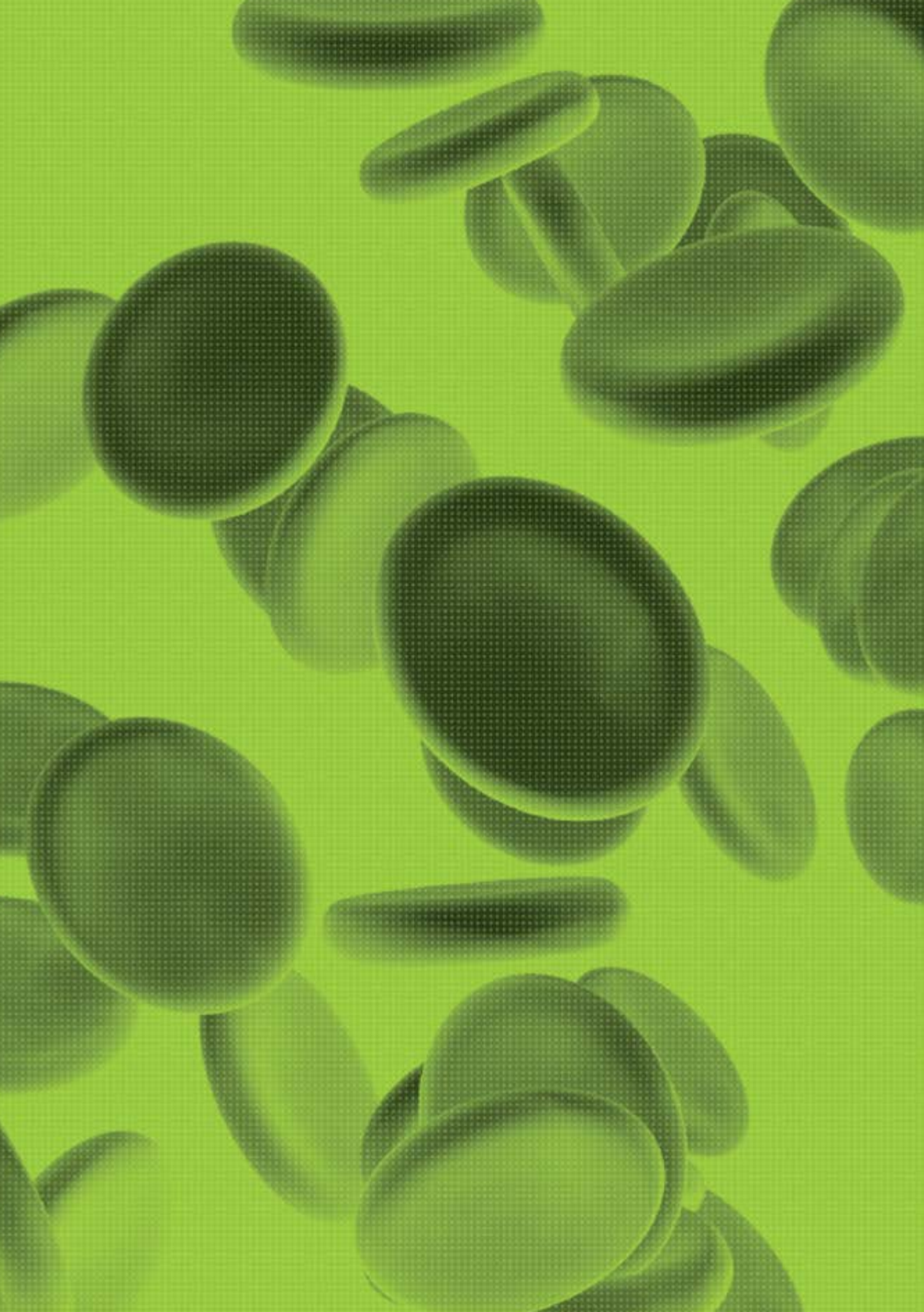
The document also includes appendixes that provide information on membership of the governance bodies for guideline development and transfusion risks; an overview of the blood sectors in Australia and New Zealand; a process report; and information on blood component products. Finally, the document contains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



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.² The methods used in applying this process to the development of this module are outlined below, and are given in full in the accompanying technical report. A summary of the overall process for development of this module is given in [Appendix D](#).

2.1 Clinical research questions – development and details

Between July 2010 and March 2011, the relevant clinical research questions for this module were developed, prioritised, combined and refined by the EWG, the independent systematic review expert and the CRG ([Appendix A](#)). The process resulted in two different types of questions – those that are specific to this module, and those that are generic (i.e. relevant to all six modules that make up the guidelines). The questions included in this module were crafted in such a way that they attempted to provide answers in clinically relevant areas of uncertainty. They were further refined through consultation among the systematic reviewer, CRG, NBA and the independent systematic review expert. Details of research question criteria are presented in Volume 1 of the technical report.⁵

2.2 Review and research

2.2.1 Systematic review process

Systematic reviews were undertaken to attempt to answer the single question specific to patient blood management in a critical care setting, and the three generic questions considered relevant to this module. The systematic review questions are listed in Box 2.1.

To answer these questions, comprehensive search strategies were designed, as detailed in Volume 2 of the technical report.⁶ Searches were conducted in relevant electronic databases, bibliographies of studies identified as relevant and literature recommended by expert members of the CRG. 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 systematic reviews for this module included only data from studies that met the relevant inclusion criteria, were of adequate quality and were published before July 2010 (question 1), September 2010 (questions 2 and 3) and March 2011 (question 4). Identification of relevant evidence and assessment of evidence was conducted in accordance with NHMRC standards and procedures for externally developed guidelines.⁸

Box 2.1 Systematic review questions

Questions 1–3 are relevant to all six modules of these guidelines; question 4 is specific to transfusion in a critical care setting (i.e. to this module).

- **Question 1** – In critically ill patients, what is the effect of RBC transfusion on patient outcomes? (Interventional question)
- **Question 2** – 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? (Interventional question)
- **Question 3** – In critically ill patients, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes? (Interventional question)
- **Question 4** – In critically ill patients, what is the effect of strategies that minimise blood loss on morbidity, mortality and blood transfusion? (Interventional question)

FFP, fresh frozen plasma; RBC, red blood cell

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 (i.e. Levels III or IV) of evidence. This minimised the potential for bias in the evidence base for each systematically reviewed question. However, lower level studies were reviewed where evidence was not available in higher level studies for any of the primary outcomes.

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

- the body of evidence was sufficient – that is, wherever the evidence yielded support for recommendations of at least NHMRC grade C (see [Table 2.2](#), 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.

Table 2.1 Body of evidence matrix

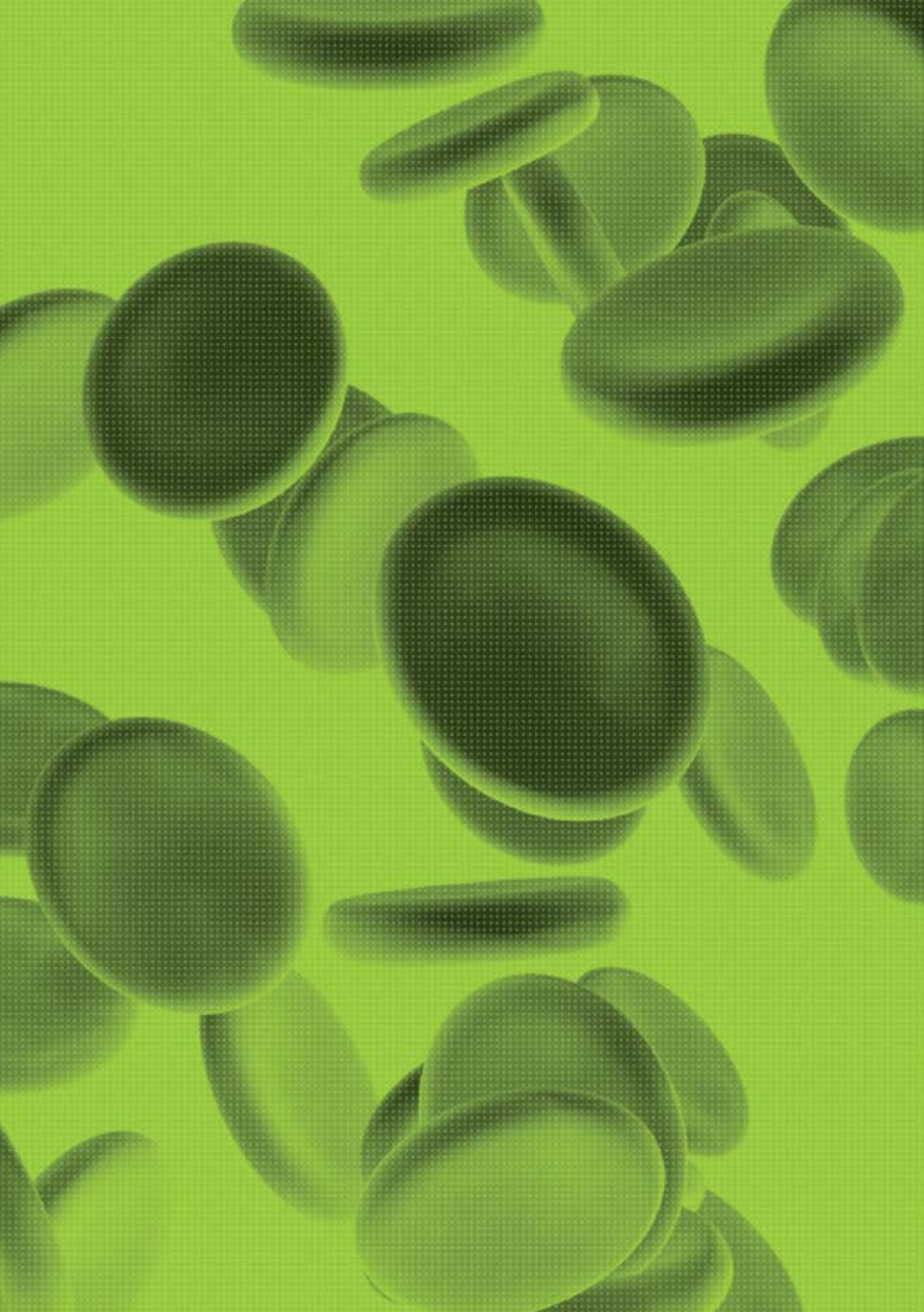
COMPONENT	A (✓✓✓)	B (✓✓)	C (✓)	D (X)
	Excellent	Good	Satisfactory	Poor
Evidence base	Several Level I or II studies with low risk of bias	One or two Level II studies with low risk of bias or a systematic review, or multiple Level III studies with low risk of bias	Level III studies with low risk of bias, 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 2009²

Table 2.2 Definitions of NHMRC grades for recommendations

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

Source: NHMRC 2009²



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 four questions that formed the basis of the systematic review. Full details of the findings of the systematic review are given in the accompanying technical reports.

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 question 'In critically ill patients, is anaemia an independent risk factor for adverse outcomes?' was not included in this review. This was because the systematic review for *Patient Blood Management Guidelines: Module 3 – Medical* found adequate evidence to confirm that anaemia is an independent predictor of poorer patient outcomes.⁴ These results were considered to be generalisable to the critical care population. For further information on the effect of anaemia on patient outcomes refer to Section 3.1 of Module 3.

3.1 Effect of red blood cell transfusion on outcomes

Question 1 (Interventional question)

In critically ill patients, what is the effect of RBC transfusion (allogeneic) on patient outcomes?

RBC, red blood cell

The clinical evidence included for this question falls into two categories. The first category comprises studies that compare red blood cell (RBC) transfusion with no transfusion, or with a different RBC dose. This evidence includes data from observational cohort studies (Level III) with at least 500 participants and adjustment for potential confounding variables using multivariate analysis. The second category consists of studies that compare restrictive and liberal RBC transfusion strategies, based on different transfusion triggers. This evidence includes randomised controlled trial (RCT) (Level II) data.

EVIDENCE STATEMENTS

		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES1.1	In critically ill patients, the effect of RBC transfusion on mortality is uncertain.	✓	✓	X	✓✓✓	✓✓
ES1.2	In critically ill patients, RBC transfusion may be independently associated with an increased risk of ventilator-associated pneumonia.	✓	NA	✓✓	✓✓✓	✓
ES1.3	In critically ill patients, RBC transfusion may be independently associated with an increased risk of infection.	✓	✓✓✓	✓✓	✓✓✓	✓
ES1.4	In critically ill patients, RBC transfusion may be independently associated with an increased risk of ARDS or ALI.	✓	✓✓	✓✓	✓✓✓	✓✓
ES1.5	In critically ill patients, the effect of RBC transfusion on organ failure is uncertain.	X	NA	✓	✓✓✓	✓✓
ES1.6	In critically ill patients, liberal and restrictive RBC transfusion strategies have similar effects on mortality.	✓✓	✓✓✓	NA	✓✓✓	✓✓
ES1.7	In critically ill patients, liberal and restrictive RBC transfusion strategies have similar effects on organ failure and dysfunction.	✓✓	✓✓✓	NA	✓✓✓	✓✓
ES1.8	In critically ill patients, liberal and restrictive RBC transfusion strategies have similar effects on pneumonia and ARDS.	✓✓	NA	NA	✓✓✓	✓✓
ES1.9	In critically ill patients, liberal and restrictive RBC transfusion strategies have similar effects on a broad range of infection outcomes.	✓✓	NA	NA	✓✓✓	✓✓

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ES, evidence statement; RBC, red blood cell

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

RECOMMENDATION

R1

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

GRADE B

PRACTICE POINTS

PP1

RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status.

PP2

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.

PP3

CRG consensus suggests that, with a:

- **Hb concentration <70 g/L**, RBC transfusion is likely to be appropriate; however, transfusion may not be required in well-compensated patients or where other specific therapy is available.
- **Hb concentration of 70–90 g/L**, 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.
- **Hb concentration >90 g/L**, 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

PP4

For patients with ACS, the following guidance is taken from *Patient Blood Management Guidelines: Module 3 – Medical*.⁴ In ACS patients with a:

- **Hb concentration <80 g/L**, RBC transfusion may be associated with reduced mortality and is likely to be appropriate (see PP5 of Module 3).
- **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 (see PP6 of Module 3).
- **Hb concentration >100 g/L**, 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 review¹⁰ 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 review¹⁰ 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.⁴² 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 review¹⁰ 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 analysis¹⁰ and two observational studies^{19,33} reported an increased risk of ARDS or ALI following RBC transfusion. One small, single-centre study²¹ 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 Subgroup analyses of data from this study also found significantly lower mortality in patients aged below 55 years (5.7% vs 13.0%; RD -7.3%; 95% CI -13.5%, -1.1%) or with an APACHE II score below 20 (8.7% vs 16.1%; RD 7.4%; 95% CI -13.6%, -1.0%) when receiving a restrictive transfusion strategy. For the subgroup with ischemic heart disease, a trend towards increased risk of mortality was observed in the restrictive strategy group.³⁷ It should be noted that the TRICC study did not achieve its target sample size, and may therefore have been underpowered to detect a significant difference between treatment arms.

Both restrictive and liberal strategies were shown to have similar effects on organ failure or dysfunction, pneumonia, ARDS and infection rates.

A precautionary approach to the use of red cells using a restrictive transfusion strategy is preferred because liberal transfusion may carry increased risk without delivering commensurate improvements in patient outcomes.

3.2 Effect of non-transfusion interventions to increase haemoglobin concentration

Question 2 (Interventional question)

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.	✓✓✓	✓✓✓	NA	✓✓✓	✓✓
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.	✓✓	✓	NA	✓✓✓	✓✓
ES2.4	In critically ill non-trauma patients, the effect of ESAs on the incidence of RBC transfusion is uncertain.	✓✓✓	✓	NA	✓✓✓	✓✓
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.	X	✓✓✓	NA	✓✓✓	✓✓
ES2.8	In critically ill patients, the effect of oral iron therapy on RBC transfusion is uncertain.	X	X	NA	✓✓✓	✓✓

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

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

RECOMMENDATION

R2

GRADE B

ESAs should not be routinely used in critically ill anaemic patients.^d

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 publication⁴⁴ 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 reported the incidence of thromboembolic events.^{42,43} The updated meta-analysis undertaken for this module (Section 3.2, Volume 1 of the technical report⁵) found no significant difference in deep vein thrombosis (seven trials; 5% vs 4%; RR 1.06; 95% CI 0.69, 1.64), stroke (three trials; 2% vs 3%; RR 0.76; 95% CI 0.41, 1.41) or myocardial infarction (two trials; 2% vs 1%; RR 0.80; 95% CI 0.05, 13.82).

Two RCTs evaluating the use of iron therapy in critically ill patients were identified: both are of poor quality.^{47,48} No effect on mortality was demonstrated and the effect on transfusion requirements was inconsistent.

At the time this Module was submitted to NHMRC for approval, ESAs were registered by the Therapeutic Goods Administration (TGA) and listed on the Pharmaceutical Benefits Scheme (PBS) for anaemia therapy in patients with chronic renal disease.

^d This recommendation is based on the lack of effect of ESAs on mortality in a heterogeneous population of critically ill patients.

3.3 Effect of blood components on outcomes

Question 3 (Interventional)

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.	X	✓	X	✓✓	✓✓
ES3.2	In patients with trauma, FFP may be associated with transfusion-related serious adverse events.	X	✓✓	✓	✓✓	✓✓
ES3.3	In non-trauma patients, FFP may be associated with transfusion-related serious adverse events.	X	NA	X	✓✓	✓✓
ES3.4	In critically ill elderly patients, the effect of FFP on mortality is uncertain.	X	NA	NA	✓✓	✓✓
ES3.5	In critically ill elderly patients, transfusion of FFP may be independently associated with the development of ARDS or ALI.	X	NA	✓✓	✓✓✓	✓✓

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; ES, evidence statement; FFP, fresh frozen plasma

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

PRACTICE POINTS

PP5

The routine use of FFP in critically ill patients with coagulopathy is not advised. The underlying causes of coagulopathy should be identified.

PP6

The administration of FFP may be independently associated with adverse events, including ARDS and ALI. The decision to transfuse these products to an individual patient should take into account the relative risks and benefits.

PP7

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 an INR ≤ 2 may not benefit from the administration of FFP and can generally undergo invasive procedures within the ICU without any serious bleeding; higher INRs may be tolerated in certain clinical situations.

ALI, acute lung injury; ARDS, acute respiratory distress syndrome; FFP, fresh frozen plasma; ICU, intensive care unit; INR, international normalised ratio; PP, practice point

Transfusion of FFP is a therapeutic intervention used in a range of clinical scenarios, including critical bleeding and massive transfusion, surgery, warfarin reversal in patients with and without severe bleeding, liver disease, coagulation factor deficiencies, and thrombotic thrombocytopenic purpura. In critically ill patients, FFP is often used in patients with abnormal coagulation test results, based on two assumptions – that these tests accurately predict bleeding and that transfusion will reduce that risk. The use of plasma is associated with a range of side effects. Therefore the risks and benefits of FFP transfusion in critically ill patients need to be carefully considered before use.

The literature search identified evidence relating to the use of FFP in three critically ill populations:

- trauma patients
- non-trauma patients
- critically ill elderly patients.

Three prospective cohort studies^{12,49,50} and two retrospective cohort studies^{30,51} assessed the use of FFP in trauma populations. Inaba et al (2010)⁵¹ matched 284 trauma patients who were non-massively transfused in the first 12 hours after admission using propensity scores, whereas Bochicchio et al (2008a)⁴⁹ studied 766 trauma patients who had been mechanically ventilated for more than 48 hours. In a second prospective study, Bochicchio et al (2008b)¹² followed up 1172 trauma patients who were admitted to an intensive care unit (ICU) for more than 48 hours. Spinella et al (2008)³⁰ studied 567 combat related trauma patients in Iraq who were transfused FFP, and Watson et al (2009)⁵⁰ followed up 1175 patients with haemorrhagic shock who had been bluntly injured.

Two studies^{30,49} found that FFP transfusion was significantly and independently associated with mortality, whereas one study⁵⁰ reported no significant association between FFP transfusion and mortality and another study⁵¹ reported a trend for greater mortality in patients treated with FFP.

Four studies^{12,49-51} reported that FFP transfusion was significantly and independently associated with a range of transfusion-related adverse events; however, the individual studies reported different specific types of events. None of the studies reported the incidence of bleeding events in patients with trauma receiving different FFP transfusion strategies.

The literature search identified one poor-quality retrospective cohort study (Level II) in 2438 critically ill, non-trauma, surgical patients.⁵² This study found that FFP transfusion was significantly associated with the incidence of infectious complications. Two retrospective cohort studies (Level II) assessed the effects of FFP transfusion in critically ill elderly patients.^{21,53} The first study, which was in 115 coagulopathic medical ICU patients, found no increase in mortality but a greater incidence of ALI.⁵³ The second study, which was in 298 post-surgical ICU patients, found that FFP transfusion was associated with increased incidence of ALI or ARDS.²¹

While interpreting the above data, several limitations need to be considered, including whether the studies adjusted adequately for risk factors, whether the studies were appropriately powered, and whether the results were applicable to Australian trauma patients and standard of care.

3.3.2 Fibrinogen concentrate and cryoprecipitate

EVIDENCE STATEMENTS		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.6	In patients with trauma, the effect of cryoprecipitate on mortality is uncertain.	X	NA	NA	✓✓	✓✓
ES3.7	In patients with trauma, the effect of cryoprecipitate on transfusion-related serious adverse events is uncertain.	X	NA	X	✓✓	✓✓

ES, evidence statement

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

PRACTICE POINTS	
PP8	The routine use of cryoprecipitate and fibrinogen concentrate in critically ill patients with coagulopathy is not advised. The underlying causes of coagulopathy should be identified.
PP9	The effect of cryoprecipitate and fibrinogen on transfusion-related serious adverse events is uncertain. The decision to transfuse cryoprecipitate or fibrinogen to an individual patient should take into account the relative risks and benefits.

PP, practice point

Fibrinogen concentrate and cryoprecipitate are therapeutic interventions used in the correction of low fibrinogen levels. In critically ill patients, fibrinogen concentrate and cryoprecipitate transfusions are used in patients with hypofibrinogenaemia, based on the assumptions that low fibrinogen levels accurately predict bleeding and that transfusion will reduce that risk.

At the time this Module was submitted to NHMRC for approval, fibrinogen concentrate was TGA registered for the treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenaemia and hypofibrinogenaemia. It was not funded under the National Blood Arrangements at this time.

The literature search identified only one poor-quality prospective cohort study.⁵⁰ The study was done in 1175 severely injured, blunt-trauma patients with haemorrhagic shock. Transfusion of cryoprecipitate was not associated with increased mortality, but was independently associated with a higher risk of multiorgan failure. The risk of ARDS and nosocomial infections was not increased.

3.3.3 Platelet transfusion

EVIDENCE STATEMENTS		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.8	In patients with trauma, the effect of platelet transfusion on mortality is uncertain.	X	✓✓✓	NA	✓✓	✓✓
ES3.9	In patients with trauma, the effect of platelet transfusion on transfusion-related serious adverse events is uncertain.	X	✓	✓	✓✓	✓✓
ES3.10	In critically ill elderly patients, the effect of platelet transfusion on transfusion-related serious adverse events is uncertain.	X	NA	✓	✓✓✓	✓✓

ES, evidence statement

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

PRACTICE POINTS	
PP10	The effect of platelet transfusion on transfusion-related serious adverse events is uncertain. The decision to transfuse platelets to an individual patient should take into account the relative risks and benefits.
PP11	In critically ill patients, in the absence of acute bleeding, the administration of platelets may be considered appropriate at a platelet count of $<20 \times 10^9$.
PP12	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 $\geq 50 \times 10^9$ can generally undergo invasive procedures within the ICU without any serious bleeding; lower platelet counts may be tolerated in certain clinical situations.

ICU, intensive care unit; PP, practice point

Platelet transfusion is a therapeutic intervention used for the prevention and treatment of bleeding in patients with thrombocytopenia or significant platelet dysfunction.

The literature search identified evidence relating to the use of platelets in two critically ill populations:

- trauma patients
- critically ill elderly patients.

Three poor-quality prospective cohort studies were identified that assessed the use of platelets in trauma patients.¹²⁴⁹⁵⁰ Of the two studies that reported the association between platelet transfusion and mortality,¹²⁵⁰ neither found a significant association, although one of these studies¹² was probably underpowered. Transfusion-related serious adverse events were reported in all three included studies; however, only one study⁴⁹ reported that platelet transfusion was independently associated with a range of transfusion-related serious adverse events.

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 associated with ARDS or ALI.

3.4 Use of blood conservation strategies

Question 4 (Interventional)

In critically ill patients, what is the effect of strategies that minimise blood loss on morbidity, mortality and blood transfusion?

A systematic review was performed for cell-salvage strategies and antifibrinolytic agents. For this question, the eligible population included critically ill trauma patients and emergency surgery patients. Elective surgical patients are covered in *Patient Blood Management Guidelines: Module 2 – Perioperative*.²

3.4.1 Cell salvage

EVIDENCE STATEMENTS		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES4.1	In trauma patients, the use of cell salvage does not appear to have an effect on mortality.	✓	✓✓	X	✓	✓✓
ES4.2	In trauma patients, the use of cell salvage reduces allogeneic transfusion volume.	✓	✓✓	✓✓✓	✓	✓✓
ES4.3	In patients undergoing emergency surgery for ruptured abdominal aortic aneurysm, the effect of cell salvage on mortality is uncertain.	X	✓✓✓	X	✓✓✓	✓✓
ES4.4	In patients undergoing emergency surgery for ruptured abdominal aortic aneurysm, cell salvage may reduce allogeneic transfusion volume.	X	✓✓	✓	✓✓✓	✓
ES4.5	In patients undergoing emergency surgery for ruptured abdominal aortic aneurysm, the effect of cell salvage on allogeneic RBC transfusion incidence is uncertain.	X	✓	NA	✓✓✓	✓✓

ES, evidence statement; RBC, red blood cell
✓✓✓ = A; ✓✓ = B; ✓ = C; X = D (see Table 2.1); NA, not applicable

PRACTICE POINT

PP13

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 retrieve blood from operative fields and then subsequently re-infuse the recovered blood into the patient. Cell salvage is usually performed intraoperatively. Concerns about the safety and potential shortages of allogeneic blood have resulted in significant interest in this and other technologies or interventions intended to reduce allogeneic blood transfusion.

The research question for this module was designed to evaluate the benefit of cell salvage as a strategy to decrease allogeneic transfusion, while also determining the potential safety of such an intervention. Studies assessing cell salvage in two population groups – trauma and non-trauma patients – were independently evaluated. In each group, the mortality benefit, incidence and volume of allogeneic blood transfused were determined from the evidence. In trauma patients, the use of cell salvage does not appear to have an effect on mortality, but does reduce the volume of allogeneic blood transfused.⁵⁴⁻⁵⁵ The effect of cell salvage on the actual incidence of allogeneic transfusion in this population group is unknown. Despite the potential reduction in the volume of allogeneic blood transfused by employing cell-salvage techniques, concerns remain with respect to both patient selection and safety. In particular, the reinfusion of contaminated blood in the trauma patient may pose a significant risk and hence further research into this area is indicated.

Cell salvage in patients undergoing emergency surgery for ruptured abdominal aortic aneurysms may also reduce allogeneic transfusion volume.⁵⁶⁻⁵⁷ However, the effect of cell salvage on mortality or the incidence of allogeneic red blood cell transfusion is uncertain.⁵⁶⁻⁶² Importantly, in both the trauma and emergency surgery patient populations, the effect of cell salvage on thromboembolic events is unknown.

3.4.2 Tranexamic acid

EVIDENCE STATEMENT		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES4.6	In acutely bleeding critically ill trauma patients, treatment with TXA within three hours of injury reduces the risk of mortality.	✓✓✓	✓✓	✓✓	✓✓✓	✓✓✓
ES4.7	In acutely bleeding critically ill trauma patients, treatment with TXA does not have an effect on allogeneic transfusion incidence.	✓✓✓	NA	X	✓✓✓	✓✓✓
ES4.8	In acutely bleeding critically ill trauma patients, treatment with TXA does not have an effect on allogeneic transfusion volume.	✓✓✓	NA	X	✓✓✓	✓✓✓
ES4.9	In acutely bleeding critically ill trauma patients, treatment with TXA does not have an effect on the risk of stroke, pulmonary embolism or deep vein thrombosis, and reduces the incidence of MI.	✓✓✓	NA	✓	✓✓✓	✓✓✓
ES4.10	In critically ill patients with upper gastrointestinal bleeding, treatment with TXA may reduce the risk of mortality.	✓	✓✓	✓✓	✓✓✓	✓✓
ES4.11	In critically ill patients with upper gastrointestinal bleeding, treatment with TXA does not appear to affect allogeneic transfusion incidence.	✓	✓✓✓	X	✓✓✓	✓✓
ES4.12	In critically ill patients with upper gastrointestinal bleeding, the effect of TXA on the risk of thromboembolic events is uncertain.	✓	✓	NA	✓✓✓	✓✓

ES, evidence statement; MI, myocardial infarction; TXA, tranexamic acid

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

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.

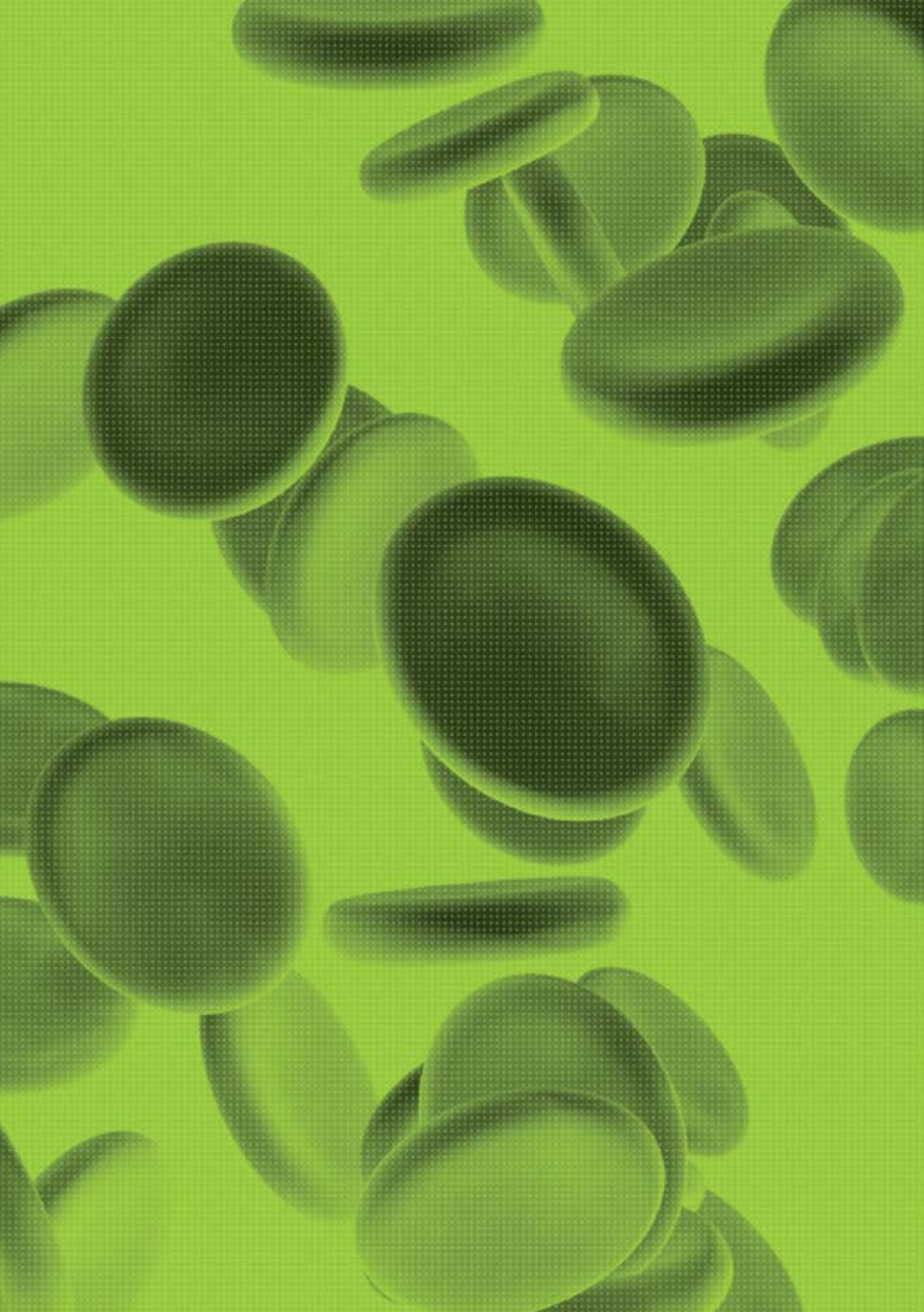
At the time this Module was submitted to NHMRC, intravenous TXA was registered by the TGA and listed on the PBS in:

- 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,⁶³ which included a large RCT with more than 20,000 patients,⁶⁴ has provided the evidence for those recommendations pertaining to trauma patients.

In the acutely bleeding trauma patient, the infusion of 1 g of TXA over 10 minutes, followed by a subsequent 1 g infusion over 8 hours (if commenced within 3 hours of injury) has been associated with a statistically significant reduction in mortality.^{63,64} However, this strategy did not have an effect on RBC allogeneic transfusion incidence or volume.⁶³ 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 administered, and within 3 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.⁶⁵ 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.



4 Future directions

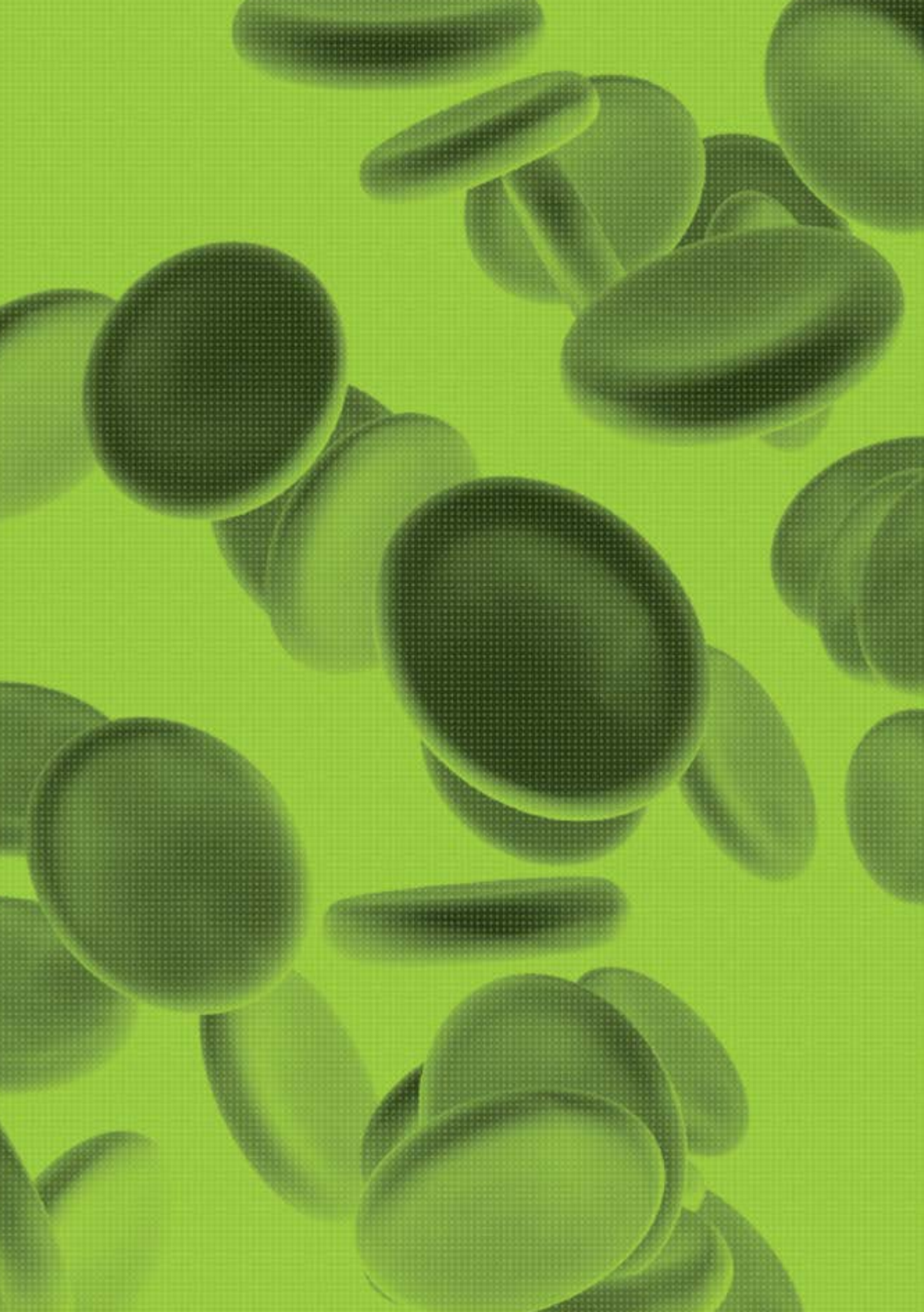
The systematic review for this module found adequate evidence to make recommendations about the use of a restrictive transfusion strategy, ESAs and TXA in critically ill patients.

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.

4.1 Evidence gaps and areas of future research

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.



5 Implementing, evaluating and maintaining the guidelines

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 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 primary and secondary care settings. In addition, the NBA is working with the Australian Commission on Safety and Quality in Health Care (ACSQHC) to develop a hospital guide to support the implementation of the *National Safety and Quality Health Service Standards*.⁶⁷ 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 2018 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.

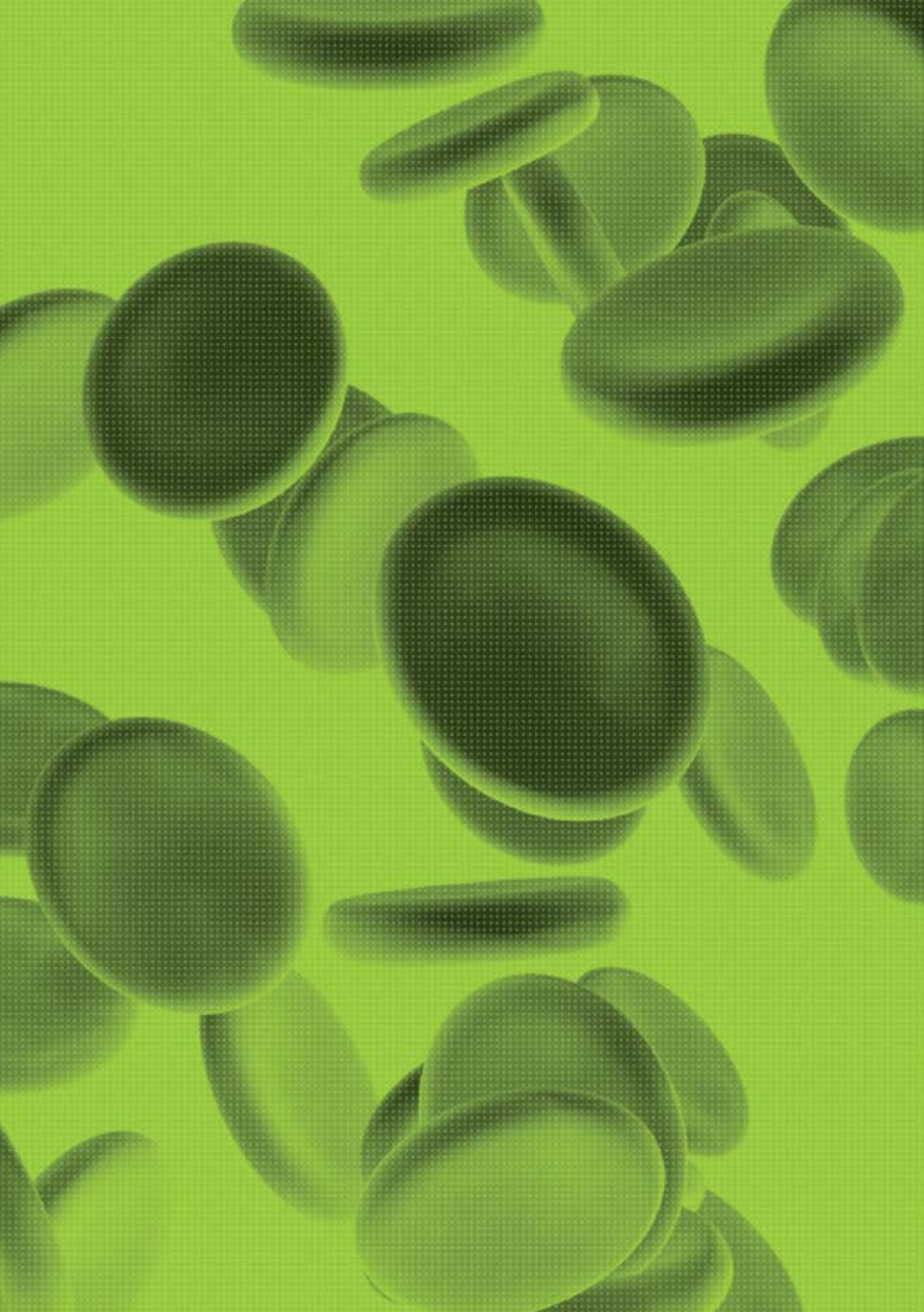
To provide feedback and inform future reviews of this module, please send any comments on its content or implementation, or on the accompanying materials, to:

- Email: guidelines@nba.gov.au
- Mail: Patient Blood Management Guidelines
National Blood Authority
Locked Bag 8430
Canberra ACT 2601
- Fax: +61 2 6211 8330

Any correspondence will be forwarded to the 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.^e

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



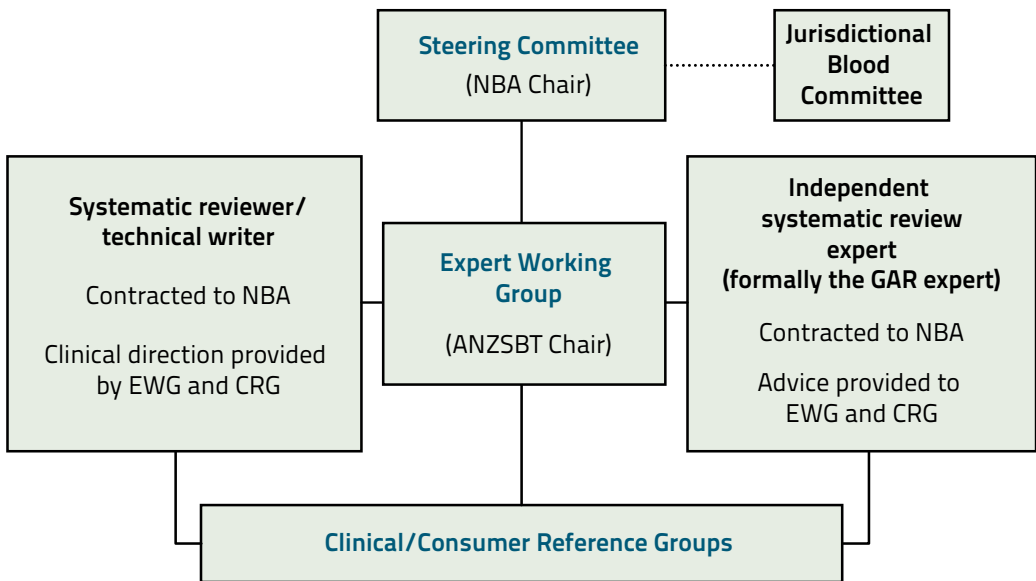
Appendix A

Governance

A1 Management framework for guideline development

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

Figure A1 Management framework for development of the guidelines



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

A2 Terms of reference

Steering Committee

The overarching Steering Committee was established to provide coordination and direction for development of the guidelines. It was chaired by the NBA, with representation from the ANZSBT, the Jurisdictional Blood Committee and a clinical representative from the Australian Government Department of Health and Ageing. The role of the Steering Committee was to:

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

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

Expert Working Group

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

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

Systematic reviewers and technical writers

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

Clinical/Consumer Reference Groups

A CRG was formed to review each phase of the guidelines during development and, with the assistance of technical writers, to formulate recommendations aimed at optimising patient blood management based on systematic review findings or, in the absence of evidence, to develop practice points through a consensus-based process. The 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.

Independent Consumer Advocates

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:

- An acronyms and definitions list (including NHMRC and systematic review terminology)
- A summary of the blood sector governance and major stakeholders
- An overview of the National Blood Authority
- A background on the patient blood management guidelines
- NHMRC Tables:
 - Level of Evidence Hierarchy
 - Grades for body of evidence
 - Grades for recommendations
- The draft Critical Care Module
- A link to the Technical Reports if further information was required.

Overall the module was well received with feedback provided on suggestions for developing useful patient materials. All participants agreed that the module was clear and well presented. Only one participant felt that the module would not be useful for patients and all agreed it was too detailed for patients. These concerns will be addressed with the development of additional materials to be specifically produced for patients, as the module itself is primarily targeted at medical health professionals practicing in the critical care setting. Patient materials will be developed based on the feedback from the survey, input from the Clinical/Consumer Reference Group and PBM Steering Committee members. All participants agreed the recommendations and practice points are easily identifiable, meet their expectations for health professionals and provide sufficient information about the benefits and risks associated with treatments. All participants agreed that the guideline provides clear instructions on how to obtain further information or feedback on the module.

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 & New Zealand and 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 and New Zealand College of Anaesthetists
Prof John Olynyk	University of Western Australia Department of Medicine, Fremantle Hospital
Prof Michael Permezel	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
Dr Kathryn Robinson	Australian Red Cross Blood Service
Dr Helen Savoia	Royal College of Pathologists of Australasia
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 – 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
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Acknowledgements – Consumer input

Mr James Dellit	Independent consumer advocate
Mrs Mollie Littlejohn	Independent consumer advocate
Mr Robert Littlejohn	Independent consumer advocate

Project Management and Committee Secretariat – National Blood Authority

Ms Leia Earnshaw	Assistant Director, Blood Sector Clinical Development
Dr Paul Hyland	Assistant Director, Blood Sector Clinical Development
Ms Jennifer Roberts	Director, Blood Sector Clinical Development
Ms Lyndsay Wall	Project Officer, Blood Sector Clinical Development

Systematic review team – OptumInsight

Ms Nimita Arora	Senior Project Leader, Life Sciences
Dr Briony Jack	Research Analyst, Life Sciences
Dr Kristina Coleman	Principal Analyst, Life Sciences
Mr Gregory Merlo	Senior Analyst, Life Sciences

Medical writing (module only) and technical editing

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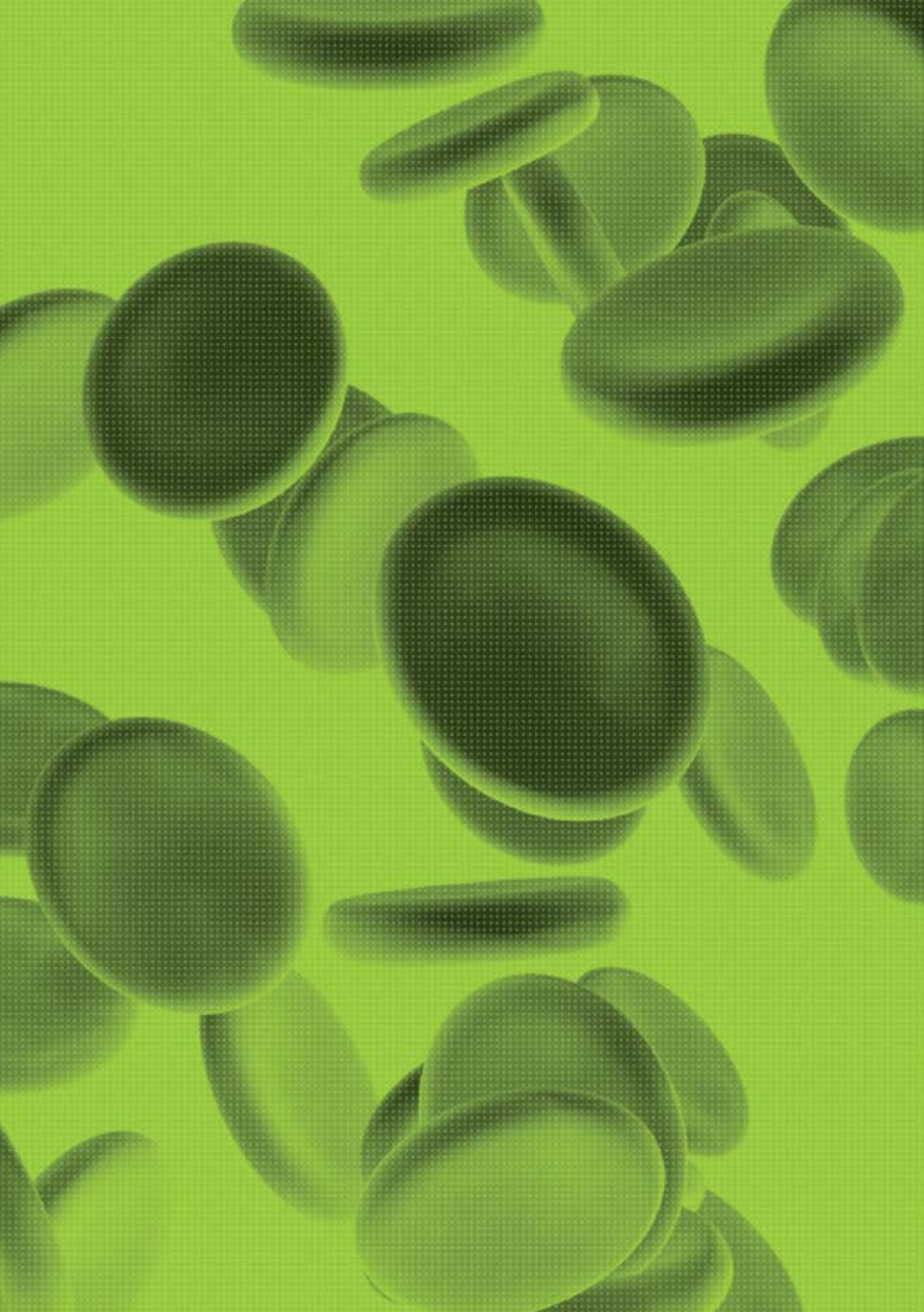
A4 Conflict of interest

All members of the Steering Committee, CRG, EWG and systematic review team declared any interests before starting work on the guidelines. Interests were also reviewed at intervals, and were required to be declared at the start of each meeting. The NBA keeps a register of all declared interests. If an interest is declared, the CRG 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 Australia for a National Cell Salvage Course, Sydney, Australia 2011.
- Dr Anthony Holley declared a study grant from the Royal Australian Navy Reserve, including travel to the Netherlands to assess frozen blood product manufacture and its use in 2010.
- Dr Craig French declared research funding from Wyeth between 2004 and 2008 provided to Western Health whilst he was an employee. He was a chief investigator on the TRANSFUSE and Erythropoietin in Traumatic Brain Injury studies, both of which received project grant funding from the NHMRC. He was appointed to the Australian Red Cross Blood Service Advisory Board in 2011 and as a Blood Service Fellow in 2012.

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 their involvement in 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 transfusion 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, and should:

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

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

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

Table B.1 summarises transfusion risks, and Table B.2 presents the Calman Chart, which may be useful to clinicians for explaining risks to patients.⁶⁹

Table B.1 Transfusion risks

TRANSFUSION RISK	ESTIMATED RATE ^a (HIGHEST TO LOWEST RISK)	CALMAN RATING ^b
Transfusion-associated circulatory overload (iatrogenic)	Up to 1 in 100 transfusions	High
Transfusion-related acute lung injury	1 in 5000–190,000	Low to minimal
Haemolytic reactions	Delayed: 1 in 2500–11,000 Acute: 1 in 12,000–77,000 Fatal: Less than 1 in 1 million	Low to very low Very low Negligible
Anaphylactoid reactions or anaphylaxis (usually due to IgA deficiency)	1 in 20,000–50,000	Very low
Bacterial sepsis: platelets	At least 1 in 75,000	Very low
Bacterial sepsis: red blood cells	At least 1 in 500,000	Minimal
Hepatitis B virus	Approximately 1 in 764,000	Negligible
Hepatitis C virus	Less than 1 in 1 million	Negligible
Human immunodeficiency virus	Less than 1 in 1 million	Negligible
Human T-lymphotropic virus (types 1 and 2)	Less than 1 in 1 million	Negligible

TRANSFUSION RISK	ESTIMATED RATE ^a (HIGHEST TO LOWEST RISK)	CALMAN RATING ^b
Malaria	Less than 1 in 1 million	Negligible
Variant Creutzfeldt-Jakob disease (not tested)	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 1996⁶⁸

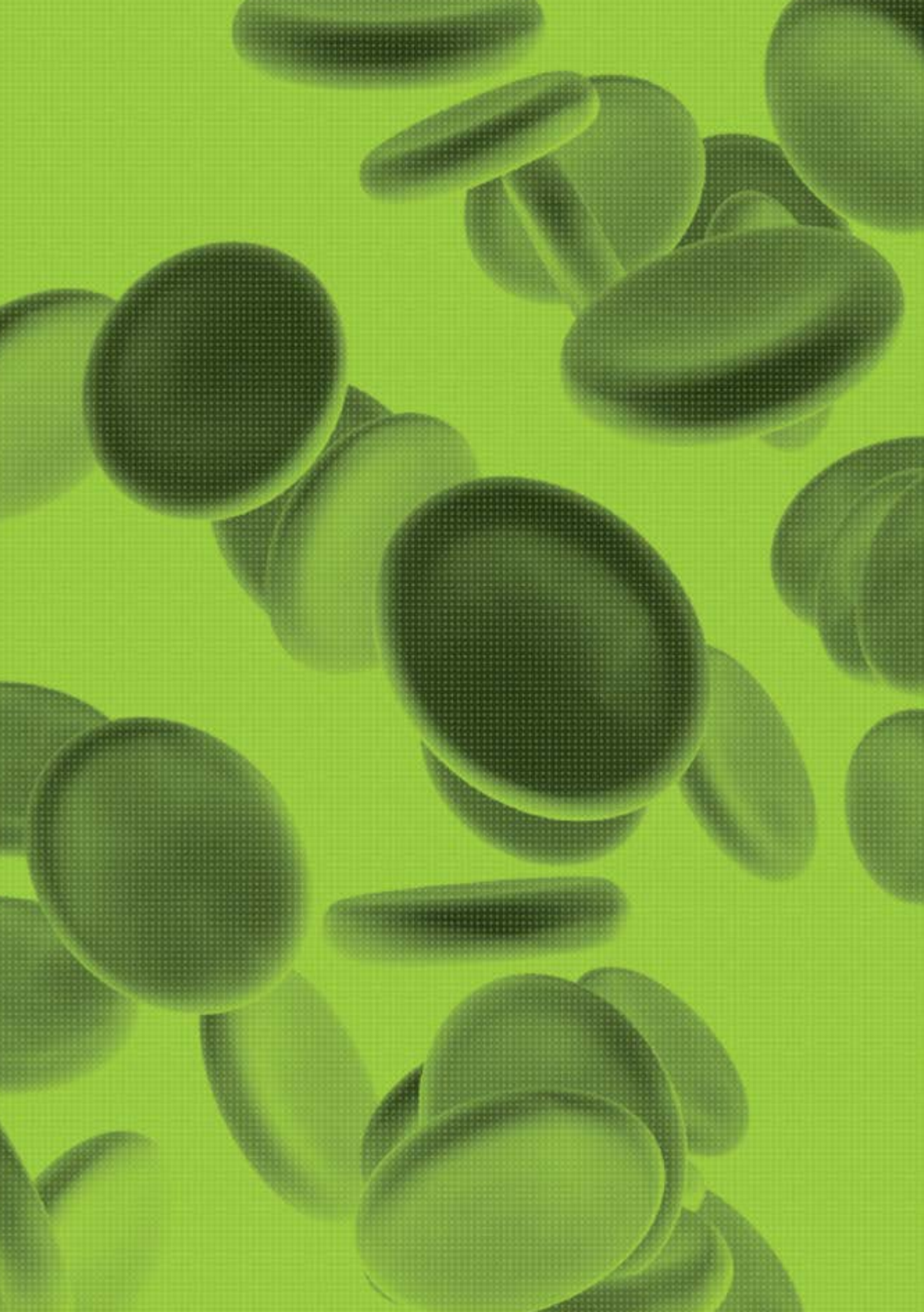
Source: Australian Red Cross Blood Service website (www.transfusion.com.au, accessed 19 June 2012)

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 (United Kingdom risk per one year)

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

^a See Calman 1996⁶⁸



Appendix C

Blood sectors

C1 Australian blood sector

Standing Committee on Health and Australian Health Ministers' Advisory Council

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

Clinical, Technical and Ethical Principal Committee

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

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

Jurisdictional Blood Committee

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

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

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

National Blood Authority

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

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

Therapeutic Goods Administration

The TGA is the regulator for blood and blood products in Australia. The TGA is responsible for:

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

Australian Red Cross Blood Service

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

C2 New Zealand blood sector

Ministry of Health

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

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

Medsafe

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

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

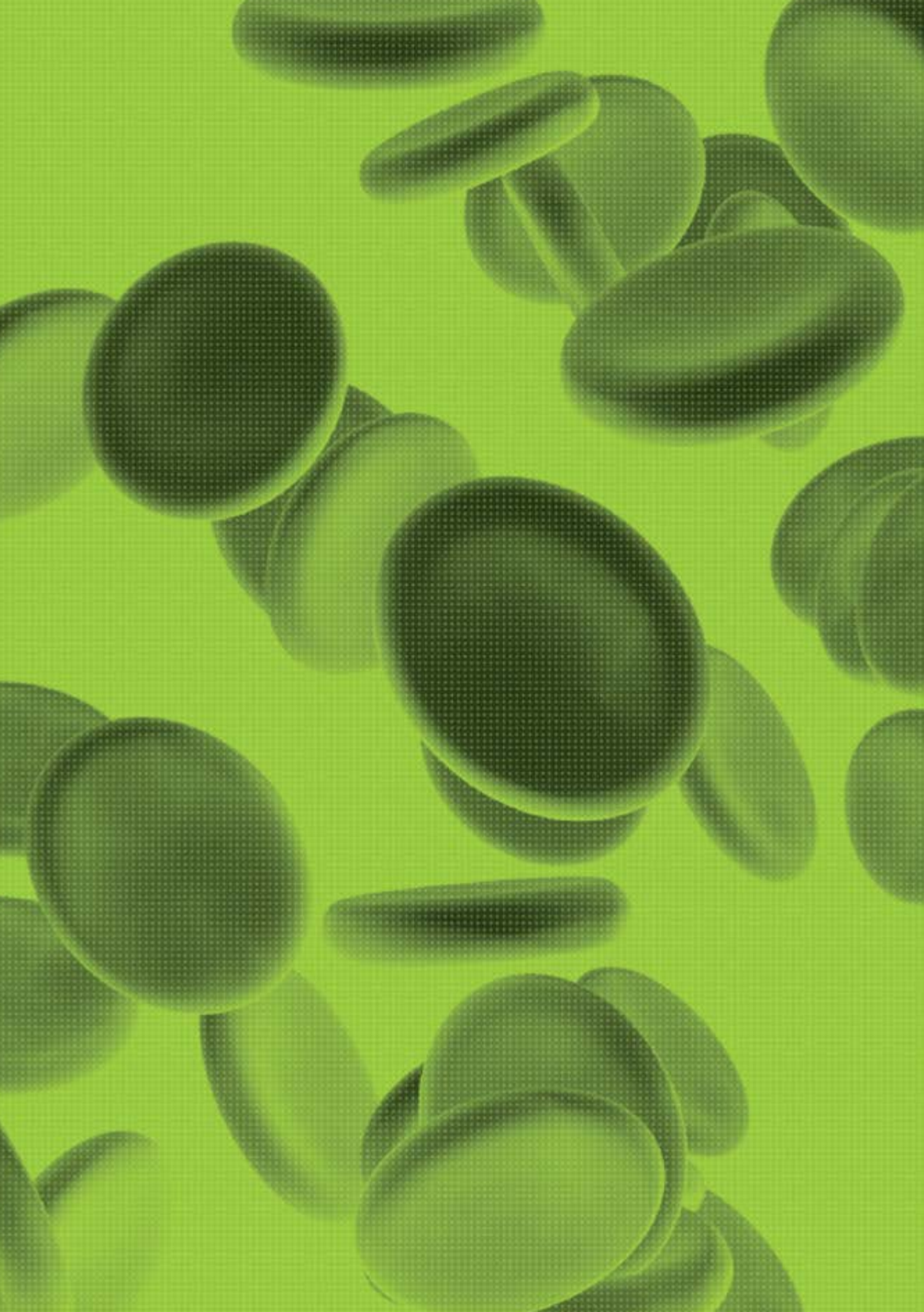
New Zealand Blood Service

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

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

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

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



Appendix D

Process report

D1 Development process

A review by the NBA of the 2001 *Clinical Practice Guidelines on the Use of Blood Components*¹ led to a decision by the NHMRC, ANZSBT and NBA to develop a series of six guidelines on patient blood management, of which this document is the 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](#).

D2 Research phase

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

D3 Methodology

Methods are outlined in Chapter 2, with greater detail given in the technical reports. Briefly, the clinical research questions for systematic review were structured according to three criteria: PICO ('population, intervention, comparator and outcome') for intervention questions, PPO ('population, predictor and outcome') for prognostic questions, or PRO ('population, risk factor and outcome') for aetiology questions. Three main strategies were used to identify potentially relevant literature: electronic database searching, manual searching and use of literature recommended by expert members of the CRG. The primary databases searched were EMBASE, Medline, the Cochrane Library Database and PreMedline. Additional searches were conducted of 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).

Inclusion criteria were determined from the PICO, PPO or PRO criteria that formed the basis of the systematically reviewed research questions. Non-English publications were excluded. Studies that were eligible for inclusion were evaluated according to NHMRC levels of evidence hierarchy, dimensions of evidence and quality assessment criteria.^{2,9} An NHMRC evidence statement form was completed for each systematically reviewed research question. Where there was sufficient evidence to formulate a recommendation, NHMRC grading criteria were applied to indicate the strength of the body of evidence underpinning the recommendation.⁹ Where it was not possible to develop evidence-based recommendations because no evidence was identified, or where additional information was required to supplement recommendations and guide clinical practice, the CRG developed practice points through a consensus-based process.

D4 Public consultation

Public consultation was conducted 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.

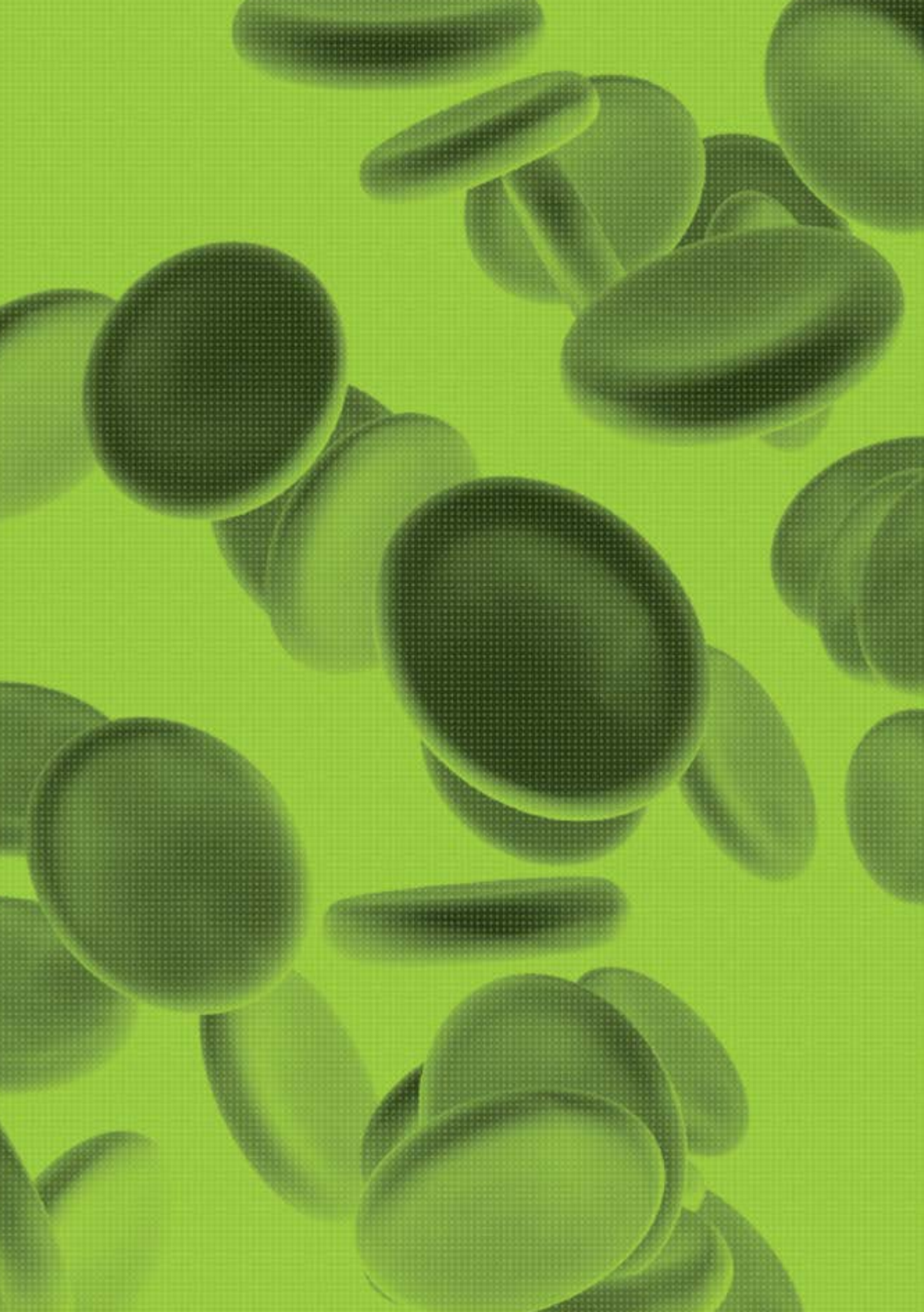
Twelve submissions were received. The CRG met in June 2012 to consider all the public consultation submissions and, where necessary, revise this module in accordance with the submissions. Changes were made to the module to address comments and concerns raised in submissions, and to improve clarity.

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 3 August 2012.

Approval from the NHMRC was received on 14 December 2012.

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

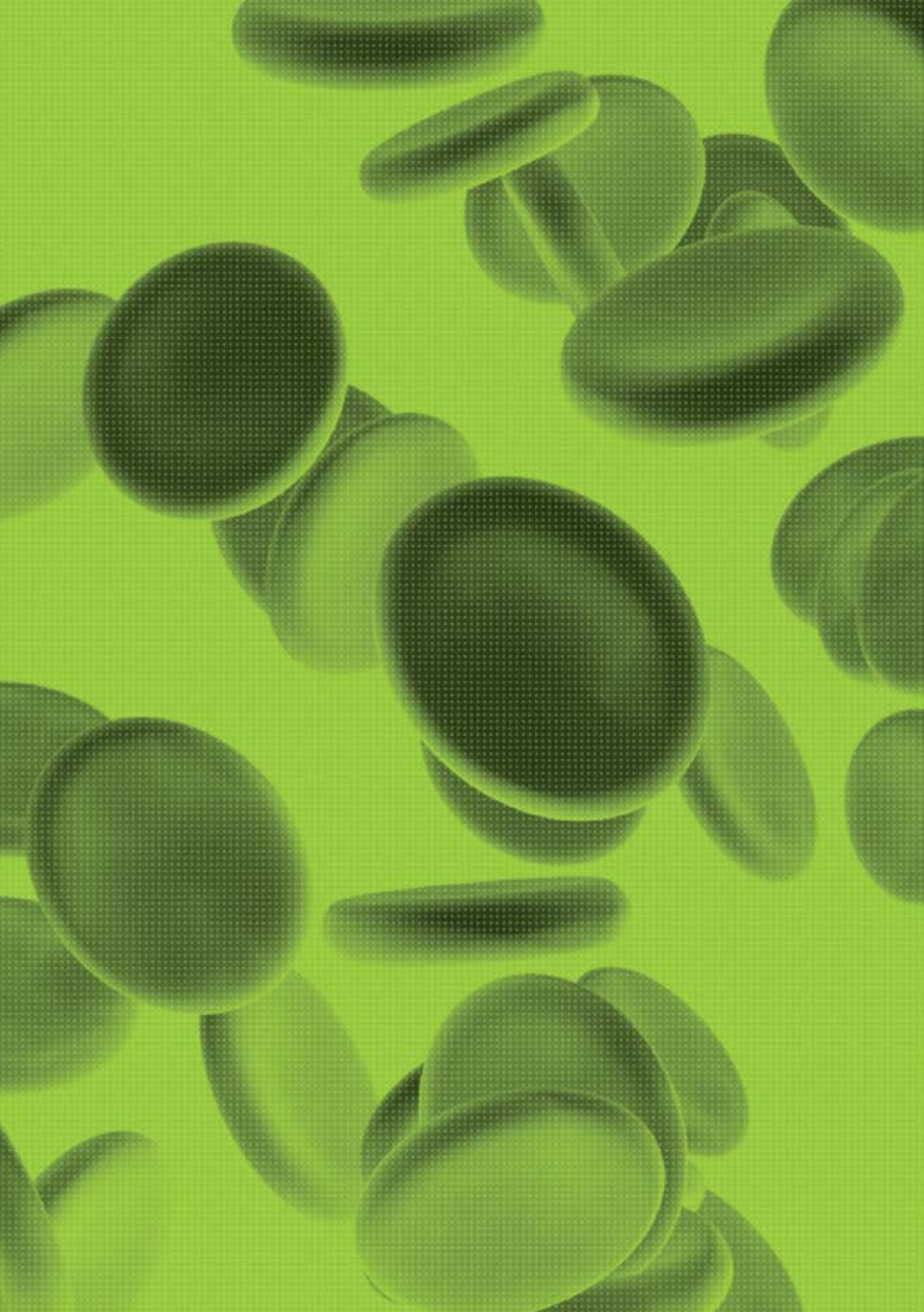


Appendix E

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).



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Index

A

abbreviations and acronyms, *front section*
acute coronary syndrome, 3, 22
acute haemolytic reactions, 52
anaemia, 4, 19
anaphylaxis reactions, 52
Australian & New Zealand Society of Blood Transfusion, 8
Australian blood sector, 56–7
Australian Commission on Safety and Quality in Health Care, 40
Australian Health Ministers' Advisory Council, 56
Australian Red Cross Blood Service, 57, 65
autotransfusion *see* cell salvage

B

bacterial sepsis risks, 52
bleeding risk assessment, 4
blood component transfusions, 26–30
blood conservation strategies, 30, 31
blood sectors, 55–8
BloodSafe eLearning program, 40
body of evidence matrix, 16

C

Calman chart, 53
cell salvage, 5, 31
Clinical, Technical & Ethical Principal Committee, 56
clinical practice guidance, 10, 19–33
Clinical Practice Guidelines on the Use of Blood Components, 8
clinical research questions, development of, 14
Clinical/Consumer Reference Groups, 1, 9, 46, 48
coagulopathy, use of FFP not recommended, 4
conflict of interest declarations, 49
Consumer input, 48
coordinated patient blood management approach, 40
Creutzfeldt-Jakob disease, 53
critically ill patients, clinical guidance question, 26–30
cryoprecipitate, 4, 28

D

development process, 62

E

erythropoiesis-stimulating agent therapy, 4–5, 24–5
evaluating guidelines, 39–40
evidence gaps, 36
evidence statements
 development of, 15–16
 non-transfusal interventions, 24
 red blood cell transfusions, 21
 executive summary, 1
Expert Working Group, 9, 45, 47

F

fibrinogen concentrate, 4, 28
fresh frozen plasma
 evidence statements, 26
 practice points, 4, 27–8
 summary recommendations, 4
future directions, 35–6

G

governance framework, 43–9
governance of blood products supply, 9
grading scheme for recommendations, 2, 16
guidelines
 development of, 8–9
 finalisation of, 63
 implementation of, 39–40

H

haemoglobin concentration
 non-transfusal interventions, 24–5
 red blood cell transfusions, 22
 summary practice points, 3
haemolytic reactions, 52
hepatitis, risks of, 52
human immunodeficiency virus (HIV), risks of, 52
human T-lymphotropic virus, as transfusion risk, 52

I

implementing guidelines, 39–40
Independent Consumer Advocates, 46
introduction, 7–11
iron therapy, recommendations, 25
ischaemic heart disease, 23

J

Jurisdictional Blood Committee, 40, 56

M

maintenance of guidelines, 39–40
malaria risks, 53
management framework for guideline development, 44
medical writing and technical editing, 48
Medsafe (NZ), 57
memberships, 47–8
methods, 13–16, 62
Ministry of Health (NZ), 57
mortality risk, red blood cell transfusions and, 23

N

National Blood Authority, 8, 48, 56–7
National Safety and Quality Health Service Standards, 40
New Zealand Blood Service, 58, 65
non-transfusional interventions, 24–5

O

OptumInsight, 48
organ failure, red blood cell transfusions and, 23

P

patient blood management programs, transfusion risks, 51–3
platelet transfusions, 4–5, 29–30
practice points
 basis for, 9
 development of, 15–16
 fresh frozen plasma, 4, 27–8
 haemoglobin concentration, 3
 platelet transfusions, 4–5
 red blood cell transfusions, 3, 22–3
 tranexamic acid, 5, 33
process report, 61–2
product information, 65
Project Management and Committee Secretariat, 48
public consultation, 63

R

recommendations
 basis for, 9
 development of, 15–16
 erythropoiesis-stimulating agent therapy, 25
 fresh frozen plasma, 4
 grading scheme, 2, 16
 iron therapy, 25
 red blood cell transfusions, 3, 22
 tranexamic acid, 33
red blood cell transfusions, 3, 20–3
references, 67–74
related materials, 10
research
 future goals for, 36
 research phase, 62
 review and, 14–15
respiratory conditions, transfusions associated with, 23
review, research and, 14–15

S

Standing Committee on Health, 56
Steering Committee, 9, 44–6, 47
structure of the document, 9–10
summary recommendations and practice points, 2
systematic review process, 9, 14–15, 45, 48

T

technical writers, terms of reference, 45
terms of reference, 44–6
Therapeutic Goods Administration, 57
tissue plasminogen activator, 33
tranexamic acid
 evidence statements, 32
 recommendations and practice points, 33
 summary practice points, 5
Transfusion Requirements in Critical Care trial, 23
transfusion-related adverse events, 23, 51–3
 acute lung injury, 52
 circulatory overload, 52
 graft-versus-host disease, 53
 immunomodulation, 5

