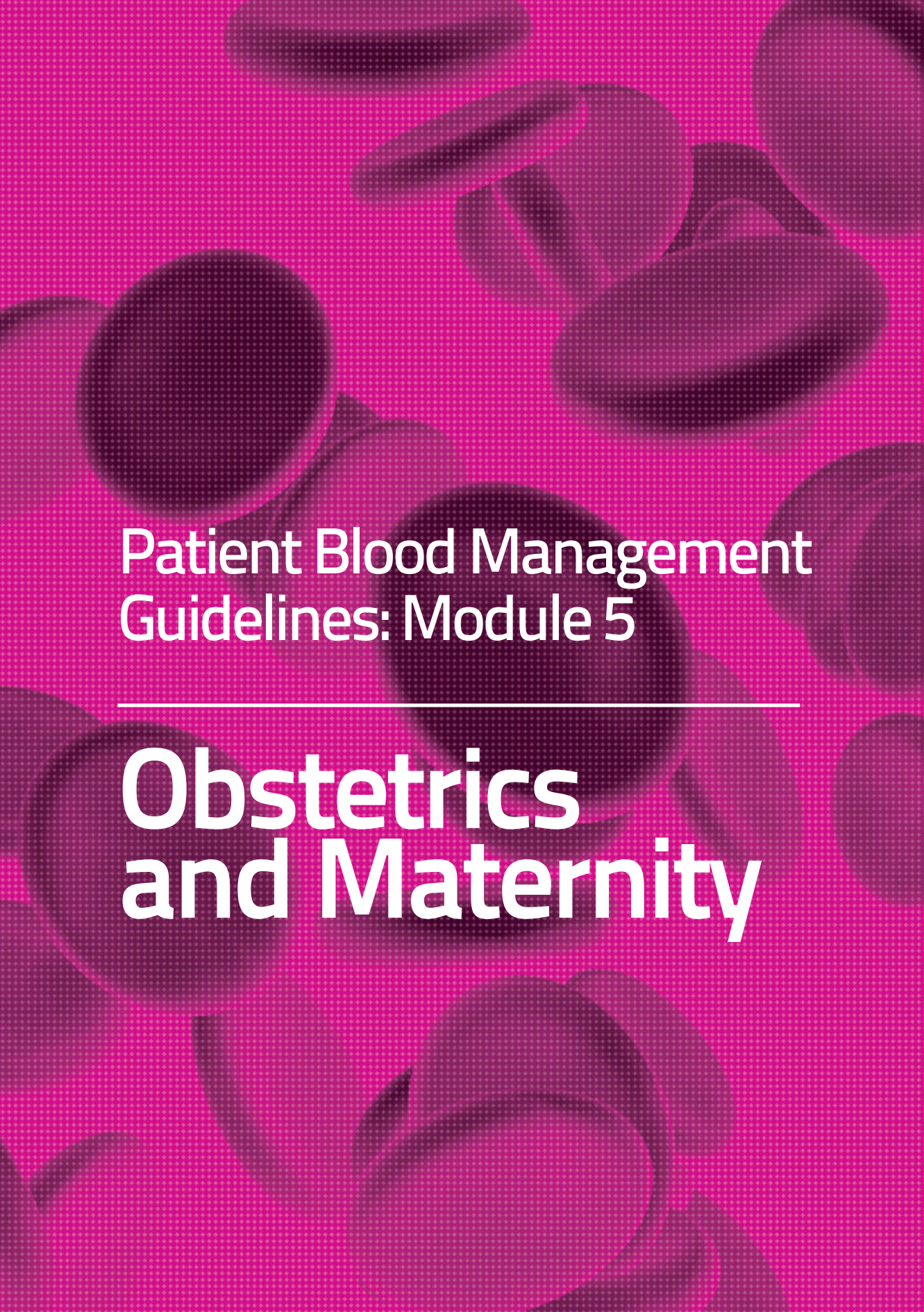

Patient Blood Management Guidelines: Module 5

Obstetrics and Maternity

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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 12 June 2013. 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.

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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 22 December 2014, 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.

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

Patient Blood Management Guidelines: Module 5 – Obstetrics and Maternity

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

Australian and New Zealand College of Anaesthetists

Australian and New Zealand Intensive Care Society

Australian and New Zealand Society of Blood Transfusion

Australian College of Midwives

Australasian Society of Haemostasis and Thrombosis

College of Intensive Care Medicine of Australia and New Zealand

Perinatal Society of Australia and New Zealand

Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Society of Obstetric 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.blood.gov.au.

NATIONAL BLOOD AUTHORITY
AUSTRALIA

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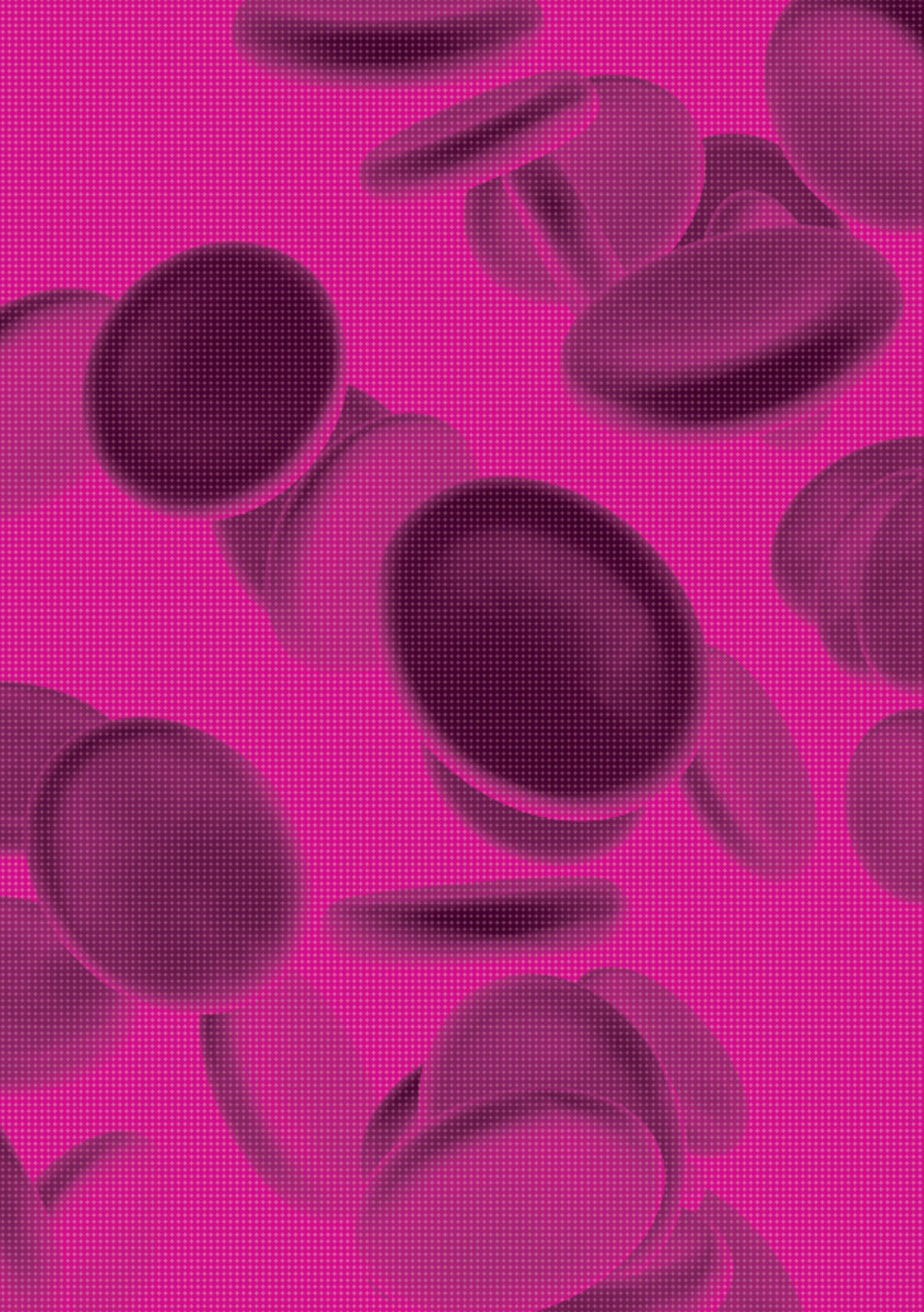


Abbreviations and acronyms

ACOG	American Congress of Obstetricians and Gynaecologists
ACSQHC	Australian Commission on Safety and Quality in Health Care
ACS	acute coronary syndrome
AGREE	Appraisal of Guidelines for REsearch & Evaluation
AHMAC	Australian Health Ministers' Advisory Committee
ANZSBT	Australian & New Zealand Society of Blood Transfusion
APACHE	acute physiology and chronic health evaluation
APTT	activated partial thromboplastin time
ASBT	Australasian Society of Blood Transfusion
CDC	Centers for Disease Control and Prevention
CHC	Council of Australian Governments (COAG) Health Council
CI	confidence interval
CMV	cytomegalovirus
COAG	Council of Australian Governments
COI	conflict of interest
CRASH	Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage
CRG	Clinical/Consumer Reference Group
EOP	expert opinion point
ES	evidence statement
ESA	erythropoiesis stimulating agent
EWG	Expert Working Group
FBC	full blood count
FFP	fresh frozen plasma
GI	gastrointestinal
Hb	haemoglobin
HDN	haemolytic disease of the newborn
HPC	Hospitals Principal Committee
ICU	intensive care unit
IM	intramuscular
INR	international normalisation ratio
IR	interventional radiology
IV	intravenous
JBC	Jurisdictional Blood Committee
MI	myocardial infarction

MTP	massive transfusion protocol
NBA	National Blood Authority
NHMRC	National Health and Medical Research Council
NSQHS	National Safety and Quality Health Service Standards
NSW	New South Wales
NZBS	New Zealand Blood Service
PBM	patient blood management
PBS	Pharmaceutical Benefits Scheme
PICO	population, intervention, comparator and outcome
POC	point of care
PP	practice point
PPH	postpartum haemorrhage
PPO	population, predictor and outcome
PRO	population, risk factor and outcome
PT	prothrombin time
R	recommendation
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RBC	red blood cell
RCT	randomised controlled trial
RCOG	Royal College of Obstetricians and Gynaecologists
RD	risk difference
rFVIIa	recombinant activated factor VII
RR	relative risk
SAE	serious adverse event
SD	standard deviation
TACO	transfusion-related circulatory volume overload
TGA	Therapeutic Goods Administration
TRALI	transfusion-related acute lung injury
TTP	thrombocytopenic purpura
TRICC	transfusion requirements in critical care
UAB	uterine artery balloon
TXA	tranexamic acid
WHO	World Health Organization

Contents

Abbreviations and acronyms

Plain English summary 1

Summary of recommendations, practice points and expert opinion points 2

1 Introduction 13
1.1 Development of the guidelines 14
1.1.1 Clinical need for these guidelines 14
1.2 Structure of the document and related materials 15
1.2.1 The document 15
1.2.2 Related materials 16

2 Methods 19
2.1 Clinical research questions 20
2.1.1 Question development summary 20
2.1.2 Background material 20
2.2 Review and research 21
2.2.1 Systematic review process 21
2.2.2 Literature search dates 21
2.2.3 Inclusion and exclusion criteria 21
2.3 Development of evidence statements, recommendations and practice points 22

3 Clinical guidance 25
3.1 Introduction 26
3.1.1 Purpose and audience 26
3.1.2 Scope 26
3.1.3 Patient population and setting 26
3.1.4 Formation of evidence statements 27
3.2 Effect of red blood cell transfusion on outcomes 28
3.2.1 General maternity 31
3.2.2 Sickle cell disease 31
3.2.3 Functional and performance status 31
3.2.4 Clinical commentary 31
3.3 Effect of non-transfusion interventions to increase haemoglobin concentration 32
3.3.1 Oral and/or parenteral iron 32
3.3.2 Erythropoiesis stimulating agents 41
3.4 Effect of blood components on outcomes 44
3.5 Use of blood conservation strategies 49
3.5.1 Point-of-care testing 49
3.5.2 Intraoperative cell salvage 50
3.5.3 Interventional radiology 51
3.5.4 Recombinant activated factor VII 53
3.5.5 Tranexamic acid 55
3.6 Considerations for Aboriginal and Torres Strait Islander women 58

4 Background questions 61
4.1 Anaemia as a risk factor 62

4.1.1 Definition of anaemia 62
4.1.2 The optimal haemoglobin range 63
4.1.3 Causes of anaemia 63
4.2 Transfusion support for maternity services 64
4.2.1 Access to transfusion support 65
4.2.2 High-risk populations 66
4.2.3 Guidelines for pretransfusion laboratory testing 66
4.2.4 Role of blood group and antibody screening before birth 67
4.2.5 Red cell selection for maternity patients requiring transfusion 67
4.3 Adapting or modifying a massive transfusion protocol 68
4.3.1 Trigger and activation of massive transfusion protocol 68
4.3.2 Administration of blood products 68
4.3.3 Permissive hypotension 69
4.4 Care of patients in whom transfusion is not an option 70
4.4.1 Antenatal care 70
4.4.2 Management in labour 71
4.4.3 Management of haemorrhage 71
4.4.4 Management of postpartum anaemia 71
4.4.5 Legal and ethical aspects 71

5 Future directions 73
5.1 Evidence gaps and areas of future research 74

6 Implementing, evaluating and maintaining the guidelines 77
6.1 Implementation strategies 78
6.2 Endorsement 78
6.3 Scheduled review and update 79

Appendix A Governance 81
Appendix B Process report 91
Appendix C Transfusion risks in the context of patient blood management 99
Appendix D Blood sectors 103
Appendix E Product information 109

References 111

Index 125

Tables

Table 1.1 Phases of development of guideline modules 14
Table 2.1 Body of evidence matrix 23
Table 2.2 Definitions of NHMRC grades for recommendations 23
Table 3.1 Structure of evidence statements 27
Table 3.2 Description of interventions 28
Table 4.1 Haemoglobin levels in pregnancy, United States population 62
Table 4.2 Haemoglobin levels in pregnancy, Danish population 63
Table C.1 Transfusion risks 100
Table C.2 Calman Chart (United Kingdom risk per one year) 101

Figure

Figure A1 Management framework for development of the guidelines 83

Plain English summary

This document, *Patient Blood Management Guidelines: Module 5 – Obstetrics and Maternity*, is the fifth in a series of six modules that focus on evidence-based patient blood management. The other five modules are critical bleeding/massive transfusion,[1] perioperative,[2] medical,[3] critical care[4] 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*[5] (National Health and Medical Research Council/Australasian Society of Blood Transfusion, NHMRC/ASBT). Thus, the 2001 guidelines have now been replaced.

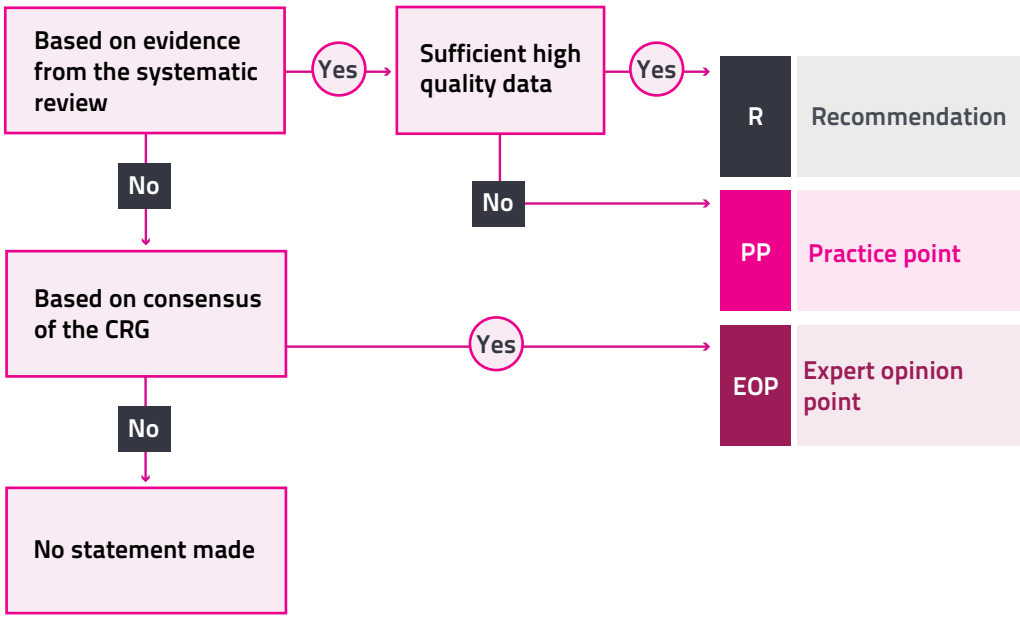
This document was developed by a Clinical/Consumer Reference Group (CRG) representing specialist colleges, organisations and societies, with the active participation of the clinical community.

This plain English summary includes:

- a summary of the *recommendations* that were developed by the CRG, based on evidence from a systematic review
- a summary of the *practice points* that were developed by the CRG through consensus decision making
- a summary of the *expert opinion 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.[6,7]

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



Summary of recommendations, practice points and expert opinion 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	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

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. The CRG also developed expert opinion points related to the material covered in the background questions. Both the practice points and the expert opinion points are based on consensus among the members of the CRG.

Identifier and grade	Guidance – recommendations, practice points and expert opinion points	Relevant section of document
ORAL AND/OR PARENTERAL IRON		
R1 GRADE C	The routine administration of iron supplementation to all pregnant women is not recommended.[a] [a] In accordance with *Clinical practice guidelines: Antenatal care – Module 1*[8]	3.3.1
R2 GRADE C	The administration of iron to pregnant women with iron deficiency anaemia is recommended; IV iron is preferred when rapid restoration of Hb and iron stores is required.	3.3.1
R3 GRADE C	In maternity patients who require iron therapy for the treatment of anaemia, the routine addition of folic acid is not recommended.[a] [a] Folic acid should be administered for the prevention of neural tube defects, in accordance with *Clinical practice guidelines: Antenatal care – Module 1*[8]	3.3.1
PP9	In maternity patients with iron deficiency anaemia, a therapeutic dose of elemental iron (100–200 mg daily) should be prescribed, and the response to therapy monitored. If the response to oral iron is inadequate, IV iron should be used.	3.3.1
PP10	In maternity patients with iron deficiency without anaemia, a low dose of elemental iron (e.g. 20–80 mg daily) may be considered, and may be better tolerated than higher doses.	3.3.1
PP11	In maternity patients requiring iron, IV iron is preferred when oral iron is poorly tolerated (affecting compliance), or absorption is likely to be impaired.	3.3.1
PP12	When IV iron is prescribed, calculation of the dose should take into consideration the iron deficit.	3.3.1
PP13	The routine use of IM iron is not advised where alternatives are available.	3.3.1
ERYTHROPOIESIS STIMULATING AGENTS		
R4 GRADE C	ESAs should not be routinely used in maternity patients.	3.3.2
PP14	In maternity patients with anaemia, where an ESA is used, it should be combined with iron therapy.[a] [a] ESAs are currently registered with the TGA for anaemia therapy in patients with chronic renal disease, non-myeloid malignancies and those scheduled for elective surgery with an expected moderate blood loss.	3.3.2

Identifier and grade	Guidance – recommendations, practice points and expert opinion points	Relevant section of document
BLOOD GROUP AND SCREEN DURING PREGNANCY		
EOP9	All women should be offered routine blood group and antibody testing during pregnancy, with follow-up testing for Rh D negative women and women with alloantibodies capable of causing HDN. Women with antibodies associated with moderate and severe HDN (-D, -c, -K) should consult with a specialist obstetrician with relevant expertise.[a] [a] In accordance with *Guidelines for blood grouping & antibody screening in the antenatal & perinatal setting*[a]	4.2
EOP10	Women with clinically significant alloantibodies should have a blood group and antibody screen on admission, in labour or prior to vaginal or caesarean birth, to avoid potential delays in blood provision. Where complex antibodies or rare red cell phenotypes are identified, and provision of compatible blood may be difficult, the management plan should include timely access to specialist blood product support.	4.2
EOP11	Decisions regarding blood group and antibody screen prior to vaginal or caesarean birth should include a risk assessment for peripartum haemorrhage, and the presence of any factors that may delay access to blood, should it be required. Such factors include the presence of red cell alloantibodies, and the local arrangements for provision of testing and blood products.	4.2
ANAEMIA		
EOP1	In women at high risk of anaemia, ferritin should be tested along with FBC early in pregnancy to assess iron stores and anaemia. Other factors contributing to anaemia, such as deficiencies in folic acid and vitamin B12, or hookworm, should be screened for in selected women.	3.6 4.1
EOP2	Women should be provided with information and advice in relation to minimising anaemia, for example, by adequate spacing of pregnancies, consumption of a healthy diet and optimal management of any medical comorbidities.	3.6 4.1
WHEN TRANSFUSION IS NOT AN OPTION		
EOP16	In all maternity patients, it is good clinical practice to optimise Hb during the antenatal period, minimise blood loss during birth and, in the event of haemorrhage, secure haemostasis as a matter of urgency. This is vital in patients for whom transfusion is not an option.	4.4
EOP17	To arrest significant and life-threatening haemorrhage, when transfusion is not an option, the definitive procedure to minimise ongoing blood loss is hysterectomy, which must be considered and acted upon early.	4.4

Identifier and grade	Guidance – recommendations, practice points and expert opinion points	Relevant section of document
EOP18	Early identification of women for whom transfusion is not an option is vital, to enable a comprehensive multidisciplinary plan to be developed and implemented.	4.4
WOMEN WHO ARE NOT ACTIVELY BLEEDING		
PP4	In maternity patients who are not actively bleeding, RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status (e.g. the risk of further haemorrhage). Most maternity patients are otherwise healthy and can generally tolerate moderate degrees of anaemia while medical therapies take effect.	3.2
PP5	In maternity patients who are not actively bleeding, non-transfusion therapies, including iron, should be considered as part of the treatment of anaemia. (See recommendations R2 and R3, and practice points PP9–PP14)	3.2
PP6	In maternity patients who are not actively bleeding, where transfusion is indicated, a single unit of RBC, followed by clinical reassessment to determine the need for further transfusion, is appropriate. This reassessment will also guide the decision on whether to retest the Hb level.	3.2
PP7	In maternity patients, the risk of RBC alloimmunisation and potential clinical impact should be considered when balancing the risks and benefits of RBC transfusion.	3.2
PP8	Direct evidence of the efficacy of RBC transfusion for treatment of anaemia is not available in maternity patients. Evidence from other patient groups and CRG consensus suggests that, with a: ▪ Hb concentration >90 g/L, RBC transfusion is usually inappropriate. ▪ 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, the availability of other therapies for the treatment of anaemia, the expected timeframe to giving birth and the presence of risk factors for haemorrhage. ▪ Hb concentration <70 g/L, RBC transfusion may be associated with reduced mortality and may be appropriate. However, transfusion may not be required in well-compensated patients, or where other specific therapy is available.	3.2

Identifier and grade	Guidance – recommendations, practice points and expert opinion points	Relevant section of document
BLOOD COMPONENT TRANSFUSION – MODIFIED BLOOD COMPONENTS (CMV SERONEGATIVE AND PHENOTYPED)		
EOP12	CMV safe blood products should be offered to all pregnant women, regardless of CMV status, when transfusion occurs in the antenatal setting in the context of an ongoing pregnancy. Preference is for CMV seronegative blood products, where available; however, life-saving transfusion should not be withheld if CMV seronegative products are not available. **CMV 'safe' means through leucodepletion or antibody testing of donor blood. Neither process excludes the possibility of transfusion-transmitted infection; rather, they both provide a significant risk reduction. It is unknown whether CMV seronegative blood products provide significant additional protection over routine leucodepletion.*	4.2
EOP13	Where possible, K negative RBC should be selected for transfusion for all females of child-bearing potential who are K negative or whose K antigen status is unknown.	4.2
COAGULOPATHIC PATIENTS AT RISK OF BLEEDING		
PP19	In general, a platelet count ≥50 × 10^9/L is considered acceptable for vaginal or caesarean birth; however, lower platelet counts may be tolerated.	3.4
PP20	In maternity patients with abnormal coagulation tests who are not bleeding (note: concealed bleeding should be excluded), the *routine* use of cryoprecipitate or FFP is not supported. There was no evidence to define a threshold fibrinogen level or prothrombin ratio/INR that is associated with significant adverse events.	3.4
PP21	In maternity patients, underlying causes of coagulopathy should be assessed and treated. Where transfusion of platelets, cryoprecipitate or FFP is considered necessary, the risks and benefits should be considered for each patient, and expert guidance sought.	3.4
PP22	Maternity patients with pre-existing haematological conditions (e.g. thrombocytopenia, inherited or acquired disorders of coagulation) should have their condition optimised before giving birth, and have a multidisciplinary plan in place for birth and the postnatal period.	3.4
OBSTETRIC HAEMORRHAGE/CRITICAL BLEEDING		
PP1	Major blood loss can develop rapidly around the time of giving birth in the absence of haemodynamic compromise; hence, close monitoring of all women, and early recognition and rapid response, are critical.	3.2

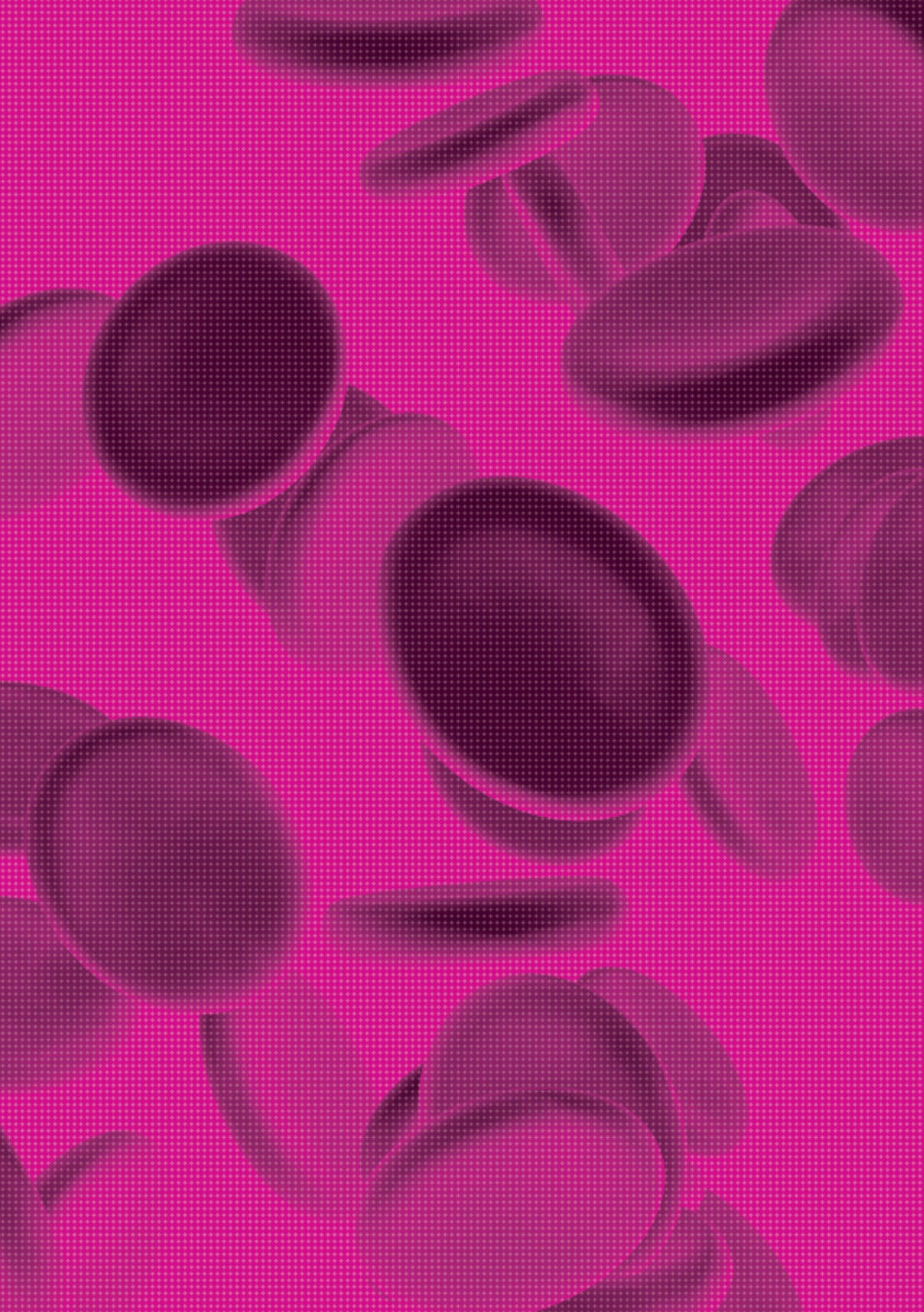
Identifier and grade	Guidance – recommendations, practice points and expert opinion points	Relevant section of document
PP2	In maternity patients requiring massive transfusion, the use of RBC and other blood components may be life-saving. However, in non-maternity patients, transfusion of RBC and other blood components is independently associated with increased morbidity and mortality.	3.2
PP3	In maternity patients with critical bleeding, a structured approach to patient care that includes escalation procedures, and timely and appropriate use of RBC and other blood components (e.g. an MTP), may reduce the risk of morbidity and mortality.	3.2
PP15	All providers of birthing services should develop a plan to manage obstetric haemorrhage. The plan should give consideration to local resources, transport and access to relevant specialist advice, blood products and equipment.	3.4
PP16	In women with major obstetric haemorrhage, in addition to clinical observations, the following parameters should be measured early and frequently: ▪ temperature ▪ acid–base status ▪ ionised calcium ▪ haemoglobin ▪ platelet count ▪ PT/INR ▪ APTT ▪ fibrinogen level With successful treatment, values should trend towards normal.	3.4
PP17	Values indicative of critical physiologic derangement include: ▪ temperature <35°C ▪ pH <7.2, base excess worse than –6, lactate >4 mmol/L ▪ ionised calcium <1.1 mmol/L ▪ platelet count <50 × 10^9/L ▪ PT >1.5 × normal ▪ INR >1.5 ▪ APTT >1.5 × normal ▪ fibrinogen level <2.0 g/L.	3.4

Identifier and grade	Guidance – recommendations, practice points and expert opinion points	Relevant section of document
PP18	In women with major obstetric haemorrhage requiring massive transfusion, suggested doses of blood components are:[a] ▪ FFP: 15 mL/kg ▪ platelets: 1 adult therapeutic dose ▪ cryoprecipitate: 3–4 g. [a] Or as directed by the haematologist/transfusion specialist. See Appendix E for dose equivalents.	3.4
EOP7	In pregnant women at risk of major obstetric haemorrhage (e.g. women with placenta accreta or major placenta previa), a multidisciplinary management plan is strongly advised.	4.2
MASSIVE TRANSFUSION PROTOCOL FOR MATERNITY CARE		
EOP8	It is strongly advised that maternity services develop an MTP that includes access to RBC and the dose, timing and ratio of blood component therapy, for use in maternity patients with critical bleeding requiring massive transfusion.	4.2
EOP14	In the maternity population, activate MTPs early.	4.3
EOP15	The MTP should be modified for the maternity patient, because fibrinogen levels approaching 2 g/L are indicative of critical physiological derangement and are associated with severe haemorrhage.	4.3
OBSTETRIC HAEMORRHAGE/CRITICAL BLEEDING – TRANSFUSION SUPPORT FOR MATERNITY SERVICES		
EOP3	All maternity services must have procedures in place to manage the critically bleeding maternity patient. This includes agreed communication and transport arrangements, access to transfusion medicine expertise and defined escalation strategies.	4.2
EOP4	All maternity services should liaise with their local pathology provider to ensure that information on local blood access arrangements is available to all clinicians (e.g. time to process 'group and hold' and cross-match blood, and availability of products).	4.2
EOP5	Maternity services in rural and remote areas should develop management plans to minimise any delay in accessing specialist health-care services and resources, including blood products.	3.6 4.2
EOP6	Women with identifiable risk factors for obstetric haemorrhage should, wherever possible, give birth in a maternity service capable of providing the appropriate level of care.	4.2

Identifier and grade	Guidance – recommendations, practice points and expert opinion points	Relevant section of document
RECOMBINANT ACTIVATED FACTOR VII		
PP29	The administration of rFVIIa may be considered in maternity patients with life-threatening haemorrhage, but only after conventional measures (including surgical haemostasis and appropriate blood component therapy) have failed.[a] [a] Refer to PP8, PP9 in *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion*[1] and PP20 in *Patient Blood Management Guidelines: Module 2 – Perioperative*[2] NB: rFVIIa is not licensed for this use. Its use should only be considered in exceptional circumstances.	3.5.4
PP30	Ideally, rFVIIa should only be administered to maternity patients as part of a locally adapted MTP. The MTP should include strict attention to the control of bleeding, physiological and metabolic parameters, coagulation status and temperature maintenance.	3.5.4
PP31	When rFVIIa is administered to maternity patients with life-threatening haemorrhage, an initial dose of 90 µg/kg is suggested.	3.5.4
TRANEXAMIC ACID		
PP32	In maternity patients with significant blood loss, the early use (within 3 hours of the onset of haemorrhage) of TXA may be considered.[a] [a] The use of TXA in this context is considered off label.	3.5.5
PP33	TXA should only be administered in the context of overall patient management; the protocol should include strict attention to the control of bleeding, physiological and metabolic parameters, coagulation status and temperature maintenance.	3.5.5
CELL SALVAGE		
PP23	In maternity patients, cell salvage should be considered if anticipated blood volume loss is likely to result in transfusion.[a] [a] In accordance with *Guidance for the provision of intraoperative cell salvage.*[10]	3.5.2
PP24	In maternity patients who are at increased risk of bleeding and in whom transfusion is not an option, cell salvage should be considered.	3.5.2
PP25	Cell salvage requires a local procedural guideline that should include patient selection, use of equipment and reinfusion. All staff operating cell salvage devices should receive appropriate training, to ensure that they are familiar with and proficient in the technique.	3.5.2

Identifier and grade	Guidance – recommendations, practice points and expert opinion points	Relevant section of document
PP26	In Rh D negative maternity patients receiving salvaged blood where the cord blood group is Rh D positive, a dose of Rh D immunoglobulin is required, with additional doses based on the result of assessment of fetomaternal haemorrhage test.	3.5.2
INTERVENTIONAL RADIOLOGY		
PP27	Preventative IR may be appropriate in selected maternity patients; however, the risk of complications from this procedure should be balanced against the potential benefits.	3.5.3
PP28	Although the role of therapeutic IR in the treatment of major obstetric haemorrhage is unknown, it may be considered in the overall approach to management.	3.5.3

APTT, activated partial thromboplastin time; CMV, cytomegalovirus; CRG, Clinical/Consumer Reference Group; EOP, expert opinion point; ESA, erythropoiesis stimulating agent; FBC, full blood count; FFP, fresh frozen plasma; Hb, haemoglobin; HDN, haemolytic disease of the newborn; IM, intramuscular; INR, international normalisation ratio; IR, interventional radiography; IV, intravenous; MTP, massive transfusion protocol; PP, practice point; PT, prothrombin time; R, recommendation; RBC, red blood cell; rFVIIa, recombinant activated factor VII; TGA, Therapeutic Goods Administration; 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 (PBM) improves patient outcomes by ensuring that the focus of the patient's medical and surgical management is on improving and conserving the patient's own blood. As a consequence of the better management, patients usually require fewer transfusions of donated blood components, thus avoiding transfusion-associated complications.

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.

1.1 Development of the guidelines

This document, *Patient Blood Management Guidelines: Module 5 – Obstetrics and Maternity*, is the fifth in a series of six modules that focus on evidence-based PBM. 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*[5] (National Health and Medical Research Council/Australasian Society of Blood Transfusion, NHMRC/ASBT).

1.1.1 Clinical need for these guidelines

Revision of the 2001 guidelines[5] 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.

In response to the situation outlined above, the NHMRC, the Australian and New Zealand Society of Blood Transfusion (ANZSBT) and the National Blood Authority (NBA)[a] agreed to develop a series of six patient-focused, evidence-based modules that together will comprise new PBM 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[1] 2 – Perioperative[2]
II	3 – Medical[3] 4 – Critical care[4]
III	5 – Obstetrics and maternity 6 – Paediatric/neonatal

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

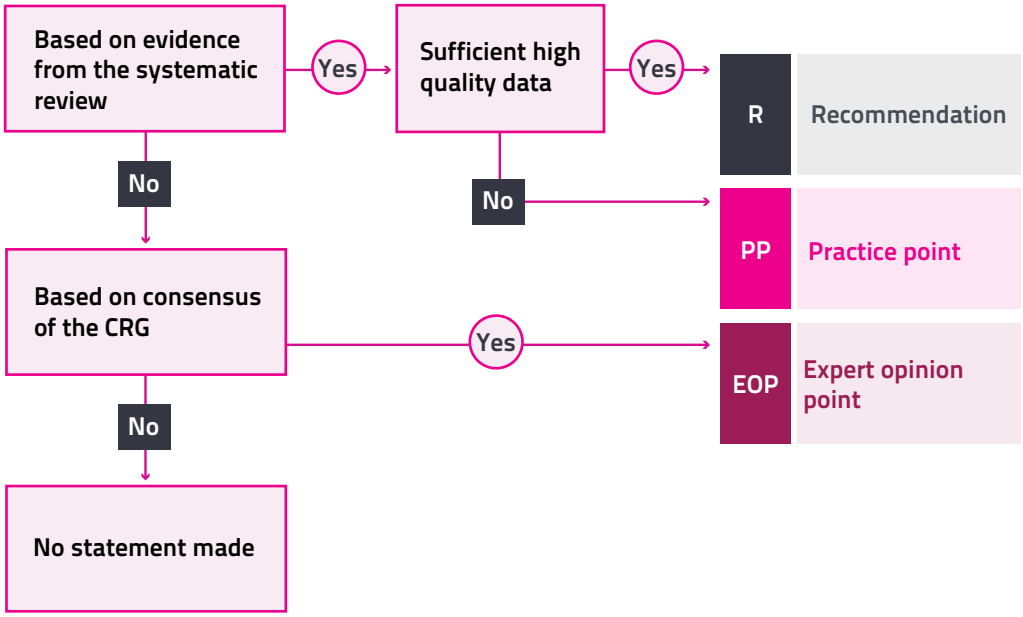
1.2 Structure of the document and related materials

1.2.1 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
- **expert opinion points** – based on consensus decision making, where relevant guidance that is outside of the scope of the systematic review is required.

The recommendations, practice points and expert opinion points are summarised in the plain English summary.



The remainder of this document includes:

- an outline of the methods used to develop the clinical research questions, undertake a systematic review of the literature, and develop recommendations and practice points (Chapter 2)
- clinical practice guidance, setting out the main findings of the systematic review and other considerations documented by the CRG, and recommendations and practice points, as appropriate (Chapter 3)
- background questions (Chapter 4)
- recommendations for future directions (Chapter 5)
- information on implementing, evaluating and maintaining the guidelines (Chapter 6).

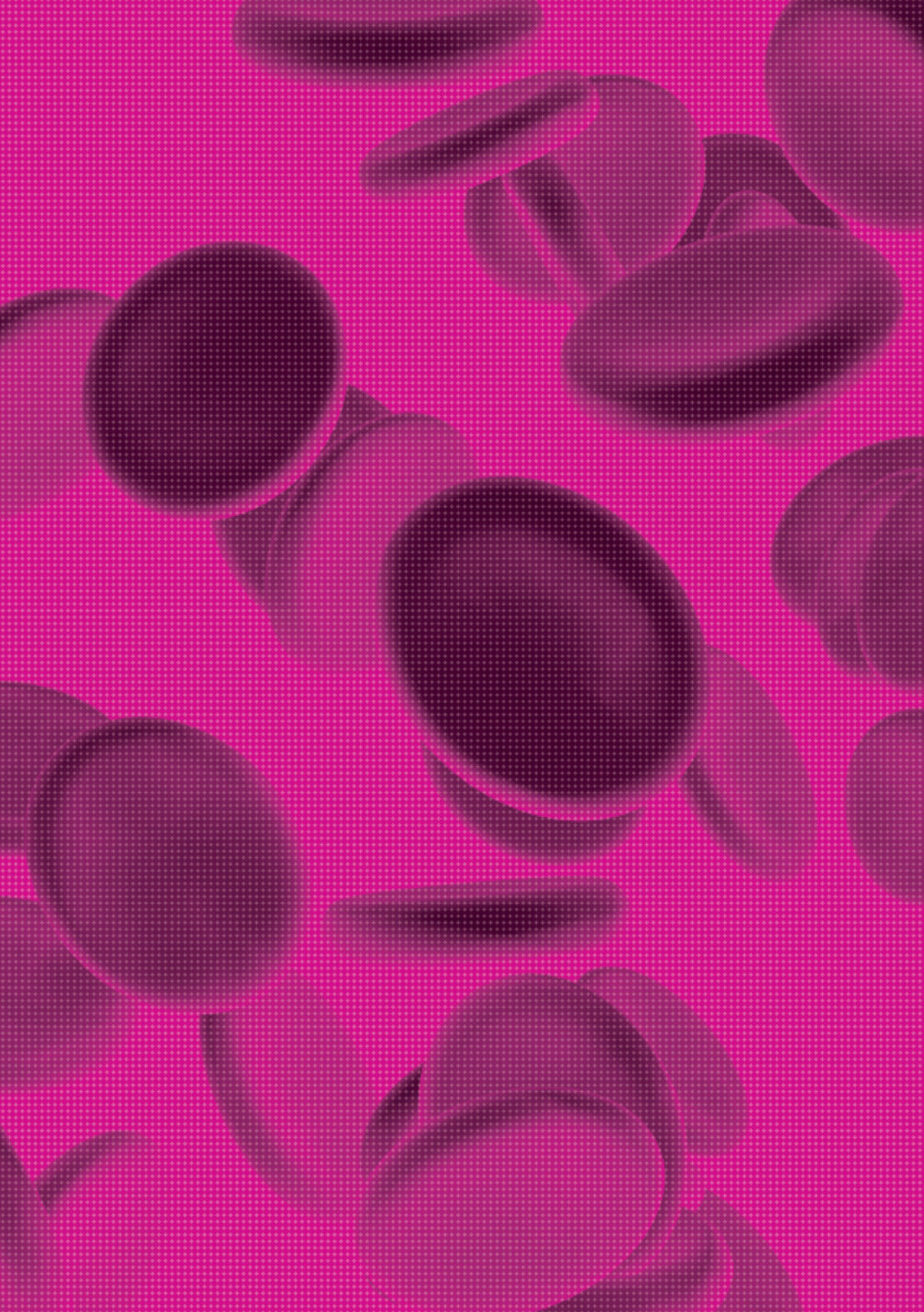
The document also includes appendixes that provide information on membership of the governance bodies for guideline development; transfusion risks; an overview of the blood sectors in Australia and New Zealand; a process report; and information on blood component products. Finally, the document contains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

1.2.2 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*[6]
  This volume contains background information and the results of the systematic reviews pertaining to the clinical questions posed within this guideline.
- *Volume 2*[7]
  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.[11] 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

2.1.1 Question development summary

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 is described in greater detail in the technical reports.[6,7] The clinical research questions for systematic review (Box 2.1) were all intervention questions structured according to PICO (population, intervention, comparator and outcome) criteria. Three main strategies were used to identify potentially relevant literature: electronic database searching, manual searching and use of literature recommended by expert members of the CRG. The primary databases searched were EMBASE, Medline, the Cochrane Library Database and PreMedline. Additional searches were conducted on Health Technology Assessment and guideline websites (e.g. NICE, CADTH) and clinical trial registries.

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 maternity setting (i.e. to this module).

- Question 1 – In maternity patients, what is the effect of RBC transfusion on patient outcomes? (Interventional question)
- Question 2 – In maternity patients, what is the effect of non-transfusion interventions to increase Hb concentration on morbidity, mortality and need for RBC blood transfusion? (Interventional question)
- Question 3 – In maternity patients, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes? (Interventional question)
- Question 4 – In maternity patients, what is the effect of non-obstetric strategies that aim to minimise maternal blood loss in the peripartum period on transfusion and clinical outcomes? (Interventional question)

FFP, fresh frozen plasma; Hb, haemoglobin; RBC, red blood cell

2.1.2 Background material

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

Box 2.2 Background research questions

- **Background Question 1** – Is anaemia an independent risk factor for adverse pregnancy outcomes? What recommendations should be made for the detection, diagnosis and management of anaemia during pregnancy?
- **Background Question 2** – What guidance can be given regarding transfusion support for maternity services?
- **Background Question 3** – What obstetric-specific factors should be considered in adapting and/or modifying a massive transfusion protocol?
- **Background Question 4** – What guidance can be provided to assist in the care of maternity patients for whom transfusion is not an option?

2.2 Review and research

2.2.1 Systematic review process

Systematic reviews were undertaken to attempt to answer the single question specific to PBM in a maternity 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.[7] 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. However, implications for rural and remote areas, and the Indigenous population, have been considered and documented in the clinical guidance (Chapter 3).

2.2.2 Literature search dates

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 12 June 2013. Identification of relevant evidence and assessment of evidence was conducted in accordance with the *Procedures and requirements for meeting the 2011 standard for clinical practice guidelines*.[12]

2.2.3 Inclusion and exclusion criteria

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.[7]

Briefly, inclusion criteria were determined from the PICO criteria that formed the basis of the systematically reviewed research questions. Non-English publications were excluded.

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. For all recommendations, practice points and expert opinion points, consensus was achieved. There were no dissenting views.

Table 2.1 Body of evidence matrix

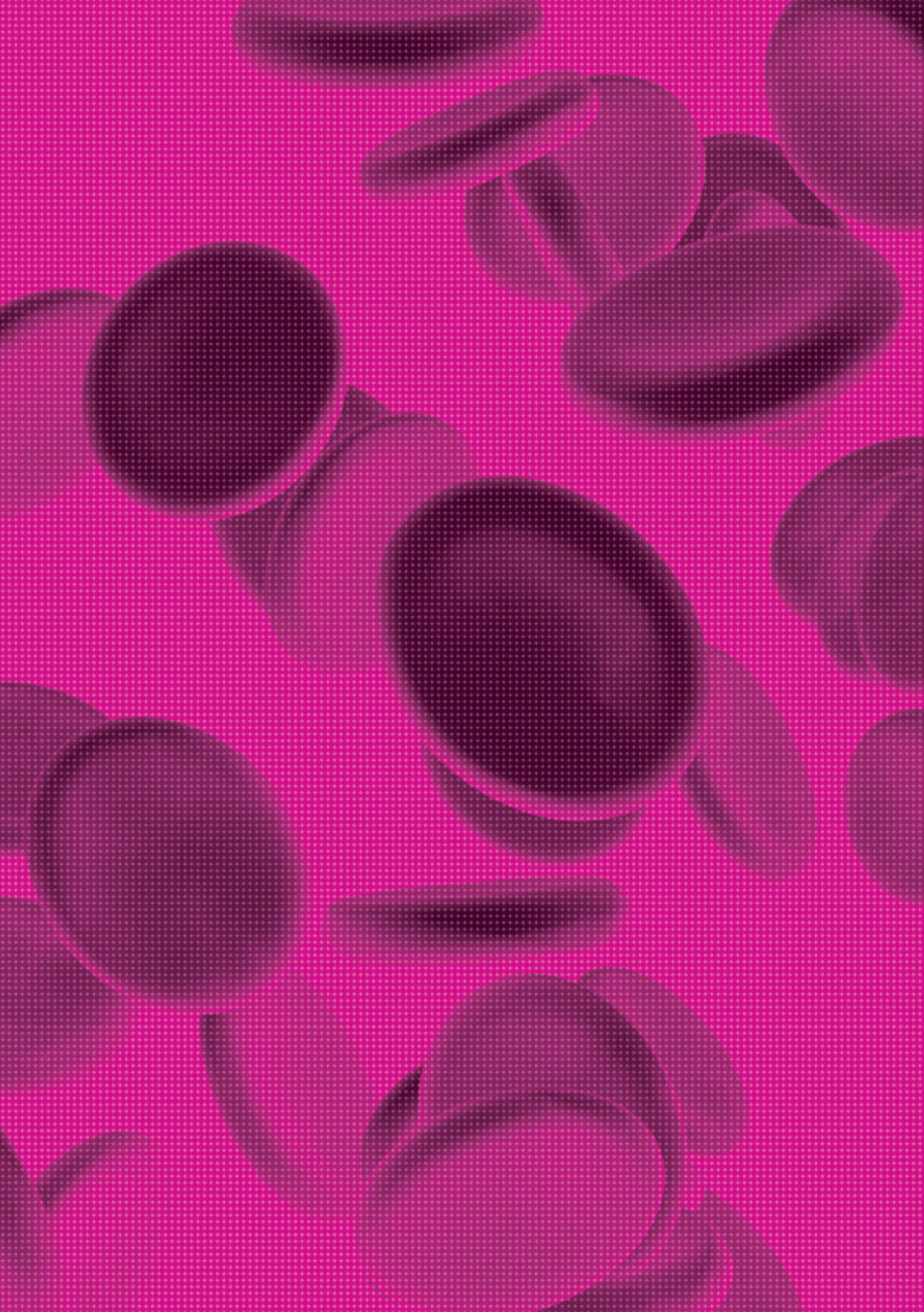
COMPONENT	A (✓✓✓)	B (✓✓)	C (✓)	D (X)	NA
	Excellent	Good	Satisfactory	Poor	Not applicable
Evidence base	Several Level I or II studies with low risk of bias	One or two Level II studies with low risk of bias or a systematic review, or multiple Level III studies with low risk of bias	Level III studies with 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	One study only
Clinical impact	Very large	Substantial	Moderate	Slight or restricted	
Generalisability	Population/s studied in the body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in the body of evidence are different to the target population, but it is clinically sensible to apply this evidence to the target population for the guideline	Population/s studied in the body of evidence are different to the target population and it is hard to judge whether it is sensible to generalise to the target population for the guideline	
Applicability	Directly applicable to the Australian health-care context	Applicable to the Australian health-care context, with a few caveats	Probably applicable to the Australian health-care context, with some caveats	Not applicable to the Australian health-care context	

Source: NHMRC 2009[13]

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 2009[13]



3 Clinical guidance

3.1 Introduction

3.1.1 Purpose and audience

This document is intended to assist and guide health-care professionals in making clinical decisions when managing pregnant and postpartum women. Transfusion rates have been reported to be increasing in such women.[14] Both the incidence and severity of obstetric haemorrhage is increasing,[15] with the most recent reported incidence of postpartum haemorrhage ranging from 3.8% in Tasmania,[16] to 24.7% in primiparous and 18.4% in multiparous women in Victoria.[17] In New South Wales, 1.3% of all women giving birth in 2010 received a blood transfusion for postpartum haemorrhage.[18] Transfusion decisions for these women should take into account each woman's clinical circumstances, physiological status, treatment preferences and choices.

3.1.2 Scope

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.[6,7]

A diagnostic approach to anaemia in maternity patients is outside the scope of these guidelines.

In the context of PPH, the information given here should be used as an adjunct to standard treatment protocols (e.g. use of uterotonics, uterine tamponade, and obstetric and surgical interventions).[19,20]

3.1.3 Patient population and setting

Patient population

Definitions

For the purpose of this guideline, *maternity patients* are defined as women who are pregnant or postpartum (within 6 weeks of the end of pregnancy), whereas the term *pregnant women* relates to the antenatal period. Fetal and neonatal populations will be considered in Module 6.

It can be argued that because the majority of pregnant women are not sick, they are not patients. However, for ease of reading and clarity, the CRG agreed to use the term 'women' where possible and the term 'maternity patients' rather than the more cumbersome 'women who use maternity services' or 'pregnant and postpartum women' throughout. This also prevents limiting the guideline to obstetric care. An exception is 'women with major obstetric haemorrhage' as this is a specific sub-group of patients that needed to be defined. The terms in the evidence statements reflect the populations identified in the underlying evidence.

'Critical bleeding' may be defined as major haemorrhage that is life-threatening and likely to result in the need for massive transfusion. In maternity patients, 'massive transfusion' may be defined as a transfusion of five or more units within 4 hours.[21]

Specific management issues

In general, young healthy women tolerate blood loss associated with childbirth and do not require transfusion. However, antenatal anaemia is a risk factor for transfusion. Therefore, to minimise RBC transfusion and improve patient outcomes, anaemia should be identified, and Hb and iron stores optimised. The optimal haemoglobin for best maternal and fetal outcomes is poorly defined; further research is indicated. Anaemia diagnosis and management is discussed further in Section 4.1.

The management of obstetric haemorrhage and postpartum haemorrhage (PPH) is challenging because blood loss and the transition from apparently well to decompensated with life-threatening haemorrhage is often rapid.

Some aspects of the recommendations and practice points described in *Patient Blood Management: Module 1 – Critical Bleeding/Massive Transfusion*[1] are generalisable to maternity patients; however, in obstetric bleeding, disseminated intravascular coagulation (DIC) is frequently an early manifestation. Maternity patients, in general, are fit and healthy, and, if haemorrhage occurs, clinical signs of deterioration often develop late in the course of the haemorrhage. Suggested modifications to the management of critical bleeding in maternity patients are described in Section 4.2.

Thromboembolism is a leading cause of maternal death,[22] and appears to occur more frequently in patients receiving transfusion of blood products.[23] While some studies reported thromboembolism, it was rarely a predefined outcome measure.

Aboriginal and Torres Strait Islander populations

The research protocol required the systematic reviewers to isolate included papers that addressed Aboriginal or Torres Strait Islander subgroups. No papers have been published that addressed the research questions in this population. The experience of clinicians working in this area suggests the rate of anaemia is high.[24] Research is urgently required to inform targeted care. Specific issues relating to the maternity care of Aboriginal or Torres Strait Islander women are addressed in Section 3.6 with expert opinion points provided.

Settings

The guidance given here applies to all settings where birth is planned to occur; that is, home or hospital; and metropolitan, rural or remote areas. In all settings, the composition of a *multidisciplinary team* should reflect the woman's clinical need. Where access to a haematologist or transfusion medicine specialist is limited, early consultation or referral is warranted.

3.1.4 Formation of evidence statements

The evidence statements given here and in Volume 1 of the technical report[7] were created using a standard sentence structure, as shown in Table 3.1. This sentence structure was used where possible. However, in some cases, the order of the components was changed for clarity and to maintain correct grammar.

Table 3.1 Structure of evidence statements

CONTENT	EXAMPLE
1. A definition of the relevant population.	In bleeding maternity patients during the peripartum period…
2. A description of the intervention.	In bleeding maternity patients during the peripartum period, cell salvage…
3. A description of the effect on the outcome of interest.	In bleeding maternity patients during the peripartum period, cell salvage reduces/does not reduce the risk of maternal mortality…
4. Where appropriate, a description of the comparator.	In bleeding maternity patients during the peripartum period, cell salvage reduces/does not reduce the risk of maternal mortality compared with no cell salvage.

The description of the effect of the intervention was also standardised, as shown in Table 3.2.

Table 3.2 Description of interventions

EVIDENCE	STRUCTURE OF STATEMENT	EXAMPLE
Sufficiently powered, consistent evidence of an effect or no effect.	States strongly that there **is** an effect or no effect.	In bleeding maternity patients during the peripartum period, cell salvage reduces/does not reduce the risk of maternal mortality compared with no cell salvage.
Evidence of an effect, but a slight concern about underpowering or consistency.	States that there **may be** an effect.	In bleeding maternity patients during the peripartum period, cell salvage may reduce the risk of maternal mortality compared with no cell salvage.
Little evidence available, or evidence is conflicting or clearly underpowered.	States that the effect is **uncertain**.	In bleeding maternity patients during the peripartum period, the effect of cell salvage compared with no cell salvage on maternal mortality risk is uncertain.
No evidence available for a particular question or outcome.	States that the effect is **unknown**.	In bleeding maternity patients during the peripartum period, the effect of cell salvage compared with no cell salvage on maternal mortality risk is unknown.

3.2 Effect of red blood cell transfusion on outcomes

Question 1 (Interventional question)

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

RBC, red blood cell

Maternity patients are transfused to reduce morbidity and mortality, and improve their quality of life. The literature search for this question sought studies that compared red blood cell (RBC) transfusion with no transfusion, or with a different RBC dose; and studies that compared liberal and restrictive transfusion strategies.

Despite a comprehensive systematic review and hand searching process, only one multicentre randomised controlled trial (RCT) was identified.[25] This RCT examined the effect of prophylactic RBC transfusion in pregnant women, and was restricted to women with sickle cell disease. Consequently, the clinical guidance for this section, which applies to maternity patients in general, is based on expert CRG consensus and other modules in this series.[1-4]

EVIDENCE STATEMENTS – red blood cell transfusion		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES1.1	In maternity patients, the effect of RBC transfusion on maternal and perinatal mortality, functional and performance status, and measures of fetal outcome is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES1.2	In pregnant women with sickle cell disease, the effect of prophylactic RBC transfusion on maternal and perinatal mortality is uncertain. (See evidence matrix D1.A in Volume 2 of the technical report)	✓	**NA**	**NA**	✓✓✓	✓
ES1.3	In pregnant women with sickle cell disease, the effect of prophylactic RBC transfusion on measures of fetal outcome is uncertain. (See evidence matrix D1.B in Volume 2 of the technical report)	✓	**NA**	**NA**	✓✓✓	✓
ES1.4	In pregnant women with sickle cell disease, the effect of RBC transfusion on functional and performance status is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**

ES, evidence statement; RBC, red blood cell

✓✓✓=A; ✓✓=B; ✓=C; **X**=D; **NA**, not applicable

PRACTICE POINTS – red blood cell transfusion	
PP1	Major blood loss can develop rapidly around the time of giving birth in the absence of haemodynamic compromise; hence, close monitoring of all women, and early recognition and rapid response, are critical.
PP2	In maternity patients requiring massive transfusion, the use of RBC and other blood components may be life-saving. However, in non-maternity patients, transfusion of RBC and other blood components is independently associated with increased morbidity and mortality.
PP3	In maternity patients with critical bleeding, a structured approach to patient care that includes escalation procedures, and timely and appropriate use of RBC and other blood components (e.g. an MTP), may reduce the risk of morbidity and mortality.
PP4	In maternity patients who are not actively bleeding, RBC transfusion should not be dictated by a Hb concentration alone, but should also be based on assessment of the patient's clinical status (e.g. the risk of further haemorrhage). Most maternity patients are otherwise healthy and can generally tolerate moderate degrees of anaemia while medical therapies take effect.
PP5	In maternity patients who are not actively bleeding, non-transfusion therapies, including iron, should be considered as part of the treatment of anaemia. (See recommendations R2 and R3, and practice points PP9–PP14)
PP6	In maternity patients who are not actively bleeding, where transfusion is indicated, 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.
PP7	In maternity patients, the risk of RBC alloimmunisation and potential clinical impact should be considered when balancing the risks and benefits of RBC transfusion.
PP8	Direct evidence of the efficacy of RBC transfusion for treatment of anaemia is not available in maternity patients. Evidence from other patient groups and CRG consensus suggests that, with a: ▪ Hb concentration >90 g/L, RBC transfusion is usually inappropriate. ▪ 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, the availability of other therapies for the treatment of anaemia, the expected timeframe to giving birth and the presence of risk factors for haemorrhage. ▪ Hb concentration <70 g/L, RBC transfusion may be associated with reduced mortality and may be appropriate. However, transfusion may not be required in well-compensated patients, or where other specific therapy is available.

RBC, red blood cell; Hb, haemoglobin; MTP, massive transfusion protocol

3.2.1 General maternity

The systematic review and hand searching process identified no studies that reported the effect of RBC transfusion on maternal or perinatal mortality, functional or performance status (e.g. postnatal depression and breastfeeding rates), or measures of fetal outcome within a general maternity population.

3.2.2 Sickle cell disease

The systematic review and hand searching process identified one study on women with sickle cell disease that compared prophylactic transfusion with transfusion only for obstetric or medical complications (restrictive group).[25] That study reported fewer perinatal deaths in the restrictive transfusion group. However, the difference was not statistically significant, and the trend was removed after adjustment for multiple births. There were no maternal deaths, but the study was underpowered to measure the effect of treatment on mortality. Although the study reported a statistically significant difference in fetal outcomes (gestation) favouring the restrictive transfusion strategy arm, this effect was removed after adjustment for previous perinatal mortality and multiple births.

3.2.3 Functional and performance status

The systematic review and hand searching process identified no studies that reported the effect of RBC transfusion on measures of functional and performance status (e.g. postnatal depression and breastfeeding rates).

3.2.4 Clinical commentary

In the context of critical bleeding, there is no question that blood transfusion can save lives. However, less certain is whether blood transfusion is of benefit to maternity patients who are not actively bleeding. Interpreting and applying general blood transfusion research findings to maternity patients is challenging, given the adapted physiology of pregnancy and the presence of the fetus, and the influence of blood management on mortality outcomes and on retaining the uterus (and thus preserving future fertility).

Normal physiology in pregnancy includes an increase in the red cell mass of 20–40%, while the plasma volume increases 40–50%. The end result is a 40–50% increase in blood volume.[26] The resultant physiological haemodilution produces a relative anaemia that is thought to be beneficial for utero-placental perfusion. As outlined in Section 4.1, the World Health Organization (WHO) defines anaemia as a Hb level of less than 110 g/L during pregnancy. However, we do not have a sound understanding of a clinically relevant degree of anaemia for treatment purposes. The degree of anaemia associated with adverse perinatal outcomes (e.g. preterm birth, low birth weight, perinatal mortality and maternal morbidity) is unknown.

The lack of research in maternal blood transfusion management means that practice is based on extrapolation of evidence from other patient populations. For example, *Blood Transfusion in Obstetrics*,[27] produced by the Royal College of Obstetricians and Gynaecologists (RCOG) is based mainly on expert consensus, because of the lack of high-level research to inform best practice. The RCOG guidelines aim for appropriate use of blood products (i.e. use that does not compromise the woman or expose her to unnecessary risk).

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) provides guidance on blood transfusion in the management of PPH[19] and placenta accreta.[28] This guidance emphasises appropriate choice of birth place (i.e. that takes into account the woman's clinical condition). Thus, if a woman is considered to be at high risk for a severe PPH (e.g. she has a known placenta accreta), the guidance suggests that her care be transferred to a facility with adequate blood transfusion capabilities.

Limited or no evidence regarding secondary harm outcomes was identified.

3.3 Effect of non-transfusion interventions to increase haemoglobin concentration

Question 2 (Interventional question)

In maternity 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

In pregnancy, iron is required for expansion of maternal red cell mass, and the red cell mass of the fetal and placental circulation. Anaemia is one of the most common medical disorders in pregnancy; most cases are caused by red blood cell iron deficiency, associated with depleted iron stores and inadequate iron intake. Anaemia during pregnancy is a risk factor for transfusion, and is linked to adverse maternal and perinatal outcomes.

Universally, there is advice to actively screen for anaemia in pregnancy, and to treat iron deficiency anaemia with iron. However, the optimal Hb level to be achieved through treatment during pregnancy has not been established.

This section examines the evidence for iron (oral and/or parenteral iron) and erythropoiesis stimulating agents (ESAs).

3.3.1 Oral and/or parenteral iron

The evidence base comprised two Level I studies of good quality, 17 Level II studies of poor to fair quality and two Level III studies of poor quality.[29,30] However, it was difficult to evaluate the effect of iron on RBC transfusion and perinatal and maternal outcomes because the studies varied with respect to:

- definitions of anaemia (with varying cut-offs for Hb, haematocrit and ferritin determining inclusion in the study)
- intervention; for example:
  - oral, intravenous (IV) and intramuscular (IM) iron
  - combination therapy versus placebo or an alternate route of administration
  - combination of iron with folic acid
  - concurrent treatment with anti-helminthic agents
- dosing schedules
- timing of assessment of laboratory outcomes
- reporting of side effects

- patient population; for example, all pregnant women (of any gestational age and parity), or pregnant or postpartum women with:
  - a specified degree of anaemia
  - iron deficiency (with or without anaemia)
  - those with anaemia from any cause
- their applicability to the Australian health care setting.

Also, most studies were underpowered, did not report compliance with therapy, and focused on laboratory measures rather than more clinically relevant outcomes. These inconsistencies made the results difficult to apply to practice, and this is reflected in the guidance given here.

Gastrointestinal (GI) side effects of oral iron frequently lead to patient non-adherence, which limits efficacy. For example, in a clinical trial setting, Westad (2008)[31] reported significant numbers of study withdrawals due to GI side effects of oral iron; for those women who remained in the study, compliance was poor, with participants taking less than half the prescribed dose of oral iron. Based on clinical experience, CRG members suggested that compliance may be even lower than that reported in clinical trials. Also, efficacy of oral iron may be impaired by reduced absorption for other reasons: surgical (e.g. bariatric surgery), medications (e.g. calcium supplementation) and medical conditions (e.g. acute and chronic inflammatory states, and *Helicobacter pylori* infection).

One RCT[32] included in the Pena-Rosas (2012)[33] study was excluded from our review because the RCT compared routine with selective iron supplementation during pregnancy, and 20% of women in the selective iron group received iron if their haematocrit and Hb dropped below a certain level. Our protocol required the comparator arm to receive placebo or iron administered by a different route. The impact of excluding this RCT is reflected in the data presented in the relevant analyses.

There were numerous studies examining the role of micronutrient supplementation on maternal and perinatal outcomes, with some supplements containing iron. However, this literature, as well as the Pena-Rosas (2012)[34] Level I study on intermittent oral iron in pregnancy, was determined by the CRG to be out of scope for this review.

The literature results for iron are presented according to the outcomes examined:

- transfusion incidence
- laboratory measures
- measures of fetal outcome
- mortality (maternal, perinatal and neonatal).

The recommendations and practice points for iron combine the evidence for these four outcomes.

EVIDENCE STATEMENTS – oral and/or parenteral iron (transfusion incidence)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.1	In pregnant women, the effect of routine oral iron compared to no treatment or placebo on transfusion incidence is uncertain. (See evidence matrix D2.E in Volume 2 of the technical report)	✓	**NA**	**NA**	✓✓	✓
ES2.2	In pregnant women, the effect of oral iron plus folic acid compared to no treatment or placebo on transfusion incidence is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES2.3	In maternity patients with iron deficiency anaemia, the effect of IV iron compared to oral iron on transfusion incidence is uncertain. (See evidence matrix D2.F in Volume 2 of the technical report)	✓	✓✓✓	**NA**	✓✓	✓
ES2.4	In maternity patients with anaemia, the effect of IV iron plus oral iron compared to oral iron alone on transfusion incidence is uncertain. (See evidence matrix D2.G in Volume 2 of the technical report)	✓	✓✓✓	**NA**	✓✓	✓
ES2.5	In maternity patients, the effect of IV iron plus folic acid compared to oral iron plus folic acid on transfusion incidence is uncertain. (See evidence matrix D2.H in Volume 2 of the technical report)	✓	✓✓✓	**NA**	✓✓✓	✓✓
ES2.6	In pregnant women with iron deficiency anaemia, the effect of IM iron compared to oral iron on transfusion incidence is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES2.7	In maternity patients with iron deficiency anaemia, the effect of IV iron compared to IM iron plus oral iron on transfusion incidence is uncertain. (See evidence matrix D2.I in Volume 2 of the technical report)	**X**	**NA**	**NA**	✓✓✓	✓

ES, evidence statement; IM, intramuscular; IV, intravenous

✓✓✓=A; ✓✓=B; ✓=C; **X**=D; **NA**, not applicable

EVIDENCE STATEMENTS – oral and/or parenteral iron (laboratory measures)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.8	In pregnant women, oral iron reduces maternal anaemia (Hb <110 g/L) at 34 weeks gestation or more compared to no treatment or placebo. (See evidence matrix D2.J in Volume 2 of the technical report)	✓✓✓	✓✓	✓	✓	✓
ES2.9	In pregnant women, oral iron reduces maternal iron deficiency anaemia (Hb <110 g/L) at 34 weeks gestation or more compared to no treatment or placebo. (See evidence matrix D2.J in Volume 2 of the technical report)	✓✓✓	✓✓	✓	✓	✓
ES2.10	In pregnant women, the effect of oral iron compared to no treatment or placebo on postpartum anaemia (Hb <110 g/L) is uncertain. (See evidence matrix D2.J in Volume 2 of the technical report)	✓✓✓	X	NA	✓✓	✓
ES2.11	In pregnant women with iron deficiency anaemia, oral iron improves laboratory measures (Hb and ferritin) and reduces anaemia (Hb <110 g/L) compared to no treatment or placebo. (See evidence matrix D2.K in Volume 2 of the technical report)	✓	✓✓✓	✓	✓	✓
ES2.12	In pregnant women, oral iron plus folic acid reduces maternal anaemia (Hb <110 g/L) at 34 weeks gestation or more compared to no treatment or placebo. (See evidence matrix D2.L in Volume 2 of the technical report)	✓✓✓	✓✓	✓	✓✓✓	✓
ES2.13	In pregnant women, the effect of oral iron plus folic acid compared to no treatment or placebo on maternal iron deficiency anaemia is uncertain. (See evidence matrix D2.L in Volume 2 of the technical report)	✓	NA	NA	✓✓✓	✓
ES2.14	In pregnant women, oral iron plus folic acid reduces moderate anaemia postpartum (Hb between 80 g/L and 110 g/L) compared to no treatment or placebo. (See evidence matrix D2.L in Volume 2 of the technical report)	X	✓✓	NA	✓✓	X
ES2.15	In pregnant women, the effect of oral iron plus folic acid compared to no treatment or placebo on severe anaemia (Hb <80 g/L) is uncertain. (See evidence matrix D2.L in Volume 2 of the technical report)	✓	✓✓	NA	✓✓	X
ES2.16	In maternity patients with iron deficiency anaemia, IV iron may lead to more rapid correction of laboratory measures (Hb and ferritin) than oral iron; however, at completion of therapy Hb levels were similar in both groups but ferritin continued to be higher with IV iron. (See evidence matrix D2.M in Volume 2 of the technical report)	✓	✓✓	✓	✓✓	✓

EVIDENCE STATEMENTS – oral and/or parenteral iron (laboratory measures)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.17	In maternity patients with anaemia, the superiority of IV iron plus oral iron compared to oral iron alone in increasing Hb or ferritin levels is uncertain. (See evidence matrix D2.N in Volume 2 of the technical report)	✓	✓✓	✓	✓✓	✓✓
ES2.18	In maternity patients with iron deficiency anaemia, IV iron is more effective at increasing Hb and ferritin levels than oral iron plus folic acid. (See evidence matrix D2.O in Volume 2 of the technical report)	✓	**NA**	✓	✓✓✓	✓
ES2.19	In non-anaemic pregnant women, prophylactic IV iron plus folic acid compared to oral iron plus folic acid does not improve Hb levels but does increase ferritin level before delivery. (See evidence matrix D2.P in Volume 2 of the technical report)	✓	**NA**	**X**	✓✓✓	✓✓
ES2.20	In pregnant women with iron deficiency anaemia, IV iron plus folic acid was more effective than oral iron plus folic acid at increasing Hb and ferritin levels. (See evidence matrix D2.P in Volume 2 of the technical report)	✓	✓✓	✓	✓✓✓	✓✓
ES2.21	In women with postpartum iron deficiency anaemia, IV iron plus folic acid was no more effective than oral iron plus folic acid at increasing Hb levels but was more effective at increasing ferritin levels. (See evidence matrix D2.P in Volume 2 of the technical report)	✓	**NA**	**X**	✓✓✓	✓✓✓
ES2.22	In pregnant women with iron deficiency anaemia, the effect of IM iron compared to oral iron plus folic acid on laboratory measures is uncertain. (See evidence matrix D2.T in Volume 2 of the technical report)	**X**	**NA**	**X**	✓✓✓	**X**
ES2.23	In pregnant women with iron deficiency anaemia, IM iron may increase maternal Hb and haematocrit compared to oral iron. (See evidence matrix D2.S in Volume 2 of the technical report)	**X**	✓✓✓	**X**	✓✓✓	✓
ES2.24	In pregnant women with iron deficiency anaemia, IV iron is more effective than IM iron in increasing Hb levels. (See evidence matrix D2.Q in Volume 2 of the technical report)	**X**	**NA**	✓	✓✓✓	✓
ES2.25	In pregnant women with iron deficiency anaemia, IV iron increases Hb levels more than IM iron plus oral iron. (See evidence matrix D2.R in Volume 2 of the technical report)	**X**	✓✓✓	✓	✓✓✓	✓

ES, evidence statement; Hb, haemoglobin; IM, intramuscular; IV, intravenous

✓✓✓=A; ✓✓=B; ✓=C; **X**=D; **NA**, not applicable

EVIDENCE STATEMENTS – oral and/or parenteral iron (measures of fetal outcome)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.26	In pregnant women, the effect of oral iron compared to no treatment or placebo on the incidence of low birth weight (<2500 g), very low birth weight (<1500 g) and preterm birth is uncertain. (See evidence matrix D2.U in Volume 2 of the technical report)	✓✓	✓✓✓	**NA**	✓✓✓	✓✓
ES2.27	In pregnant women, the effect of oral iron plus folic acid compared to no treatment or placebo on measures of fetal outcomes (low birth weight, incidence of preterm birth and small-for-gestational age) is uncertain. (See evidence matrix D2.V in Volume 2 of the technical report)	✓✓	✓	**NA**	✓	**X**
ES2.28	In maternity patients with iron deficiency anaemia, the effect of IV iron compared to oral iron on measures of fetal outcomes is uncertain. (See evidence matrix D2.W in Volume 2 of the technical report)	✓	✓✓✓	**NA**	✓✓	✓
ES2.29	In non-anaemic pregnant women, the effect of prophylactic IV iron plus folic acid compared to oral iron plus folic acid on measures of fetal outcomes is uncertain. (See evidence matrix D2.X in Volume 2 of the technical report)	✓	**NA**	**NA**	✓✓✓	✓✓
ES2.30	In pregnant women with iron deficiency anaemia, the effect of IV iron plus folic acid compared to oral iron plus folic acid on measures of fetal outcomes is uncertain. (See evidence matrix D2.X in Volume 2 of the technical report)	✓	**NA**	**NA**	✓✓✓	✓✓
ES2.31	In pregnant women, the effect of IV iron plus oral iron compared to oral iron on fetal outcomes is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES2.32	In pregnant women, the effect of IV iron compared to IM iron on measures of fetal outcomes is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES2.33	In pregnant women with iron deficiency anaemia, the effect of IM iron compared to oral iron on measures of fetal outcome is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES2.34	In pregnant women with iron deficiency anaemia, the effect of IM iron compared to iron plus folic acid on birth weight is uncertain. (See evidence matrix D2.Y in Volume 2 of the technical report)	**X**	**NA**	**NA**	✓✓✓	**X**

ES, evidence statement; RBC, red blood cell

✓✓✓=A; ✓✓=B; ✓=C; **X**=D; **NA**, not applicable

EVIDENCE STATEMENTS – oral and/or parenteral iron (mortality)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.35	In pregnant women, the effect of oral iron compared to no treatment or placebo on maternal mortality is uncertain. (See evidence matrix D2.Z in Volume 2 of the technical report)	✓	**NA**	**NA**	✓✓✓	✓✓
ES2.36	In pregnant women, the effect of oral iron compared to no treatment or placebo on perinatal and neonatal mortality is uncertain. (See evidence matrix D2.Z in Volume 2 of the technical report)	✓	**NA**	✓	✓	✓
ES2.37	In pregnant women, the effect of oral iron plus folic acid compared to no treatment or placebo on maternal and neonatal mortality is uncertain. (See evidence matrix D2.AA in Volume 2 of the technical report)	✓	✓	**NA**	✓	✓
ES2.38	In maternity patients with iron deficiency anaemia, the effect of IV iron compared to oral iron on maternal and perinatal mortality is uncertain. (See evidence matrix D2.AB in Volume 2 of the technical report)	✓✓	✓✓✓	**NA**	✓✓	✓✓
ES2.39	In pregnant women, the effect of IV iron plus oral iron compared to oral iron alone on maternal and perinatal mortality is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES2.40	In pregnant women, the effect of IV iron compared to IM iron on maternal and perinatal mortality is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES2.41	In pregnant women with iron deficiency anaemia, the effect of IM iron compared to oral iron on perinatal mortality is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES2.42	In maternity patients, the effect of IM iron compared to oral iron plus folic acid on maternal and perinatal mortality is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**

ES, evidence statement; RBC, red blood cell

✓✓✓=A; ✓✓=B; ✓=C; **X**=D; **NA**, not applicable

RECOMMENDATIONS – oral and/or parenteral iron	
R1 GRADE C	The routine administration of iron supplementation to all pregnant women is not recommended.[a] [a] In accordance with *Clinical practice guidelines: Antenatal care – Module 1* [8]
R2 GRADE C	The administration of iron to pregnant women with iron deficiency anaemia is recommended; IV iron is preferred when rapid restoration of Hb and iron stores is required.
R3 GRADE C	In maternity patients who require iron therapy for the treatment of anaemia, the routine addition of folic acid is not recommended.[a] [a] Folic acid should be administered for the prevention of neural tube defects, in accordance with *Clinical practice guidelines: Antenatal care – Module 1* [8]

Hb, haemoglobin; IV, intravenous; R, recommendation

PRACTICE POINTS – oral and/or parenteral iron	
PP9	In maternity patients with iron deficiency anaemia, a therapeutic dose of elemental iron (100–200 mg daily) should be prescribed, and the response to therapy monitored. If the response to oral iron is inadequate, IV iron should be used.
PP10	In maternity patients with iron deficiency without anaemia, a low dose of elemental iron (e.g. 20–80 mg daily) may be considered, and may be better tolerated than higher doses.
PP11	In maternity patients requiring iron, IV iron is preferred when oral iron is poorly tolerated (affecting compliance), or absorption is likely to be impaired.
PP12	When IV iron is prescribed, calculation of the dose should take into consideration the iron deficit.
PP13	The routine use of IM iron is not advised where alternatives are available.

IM, intramuscular; IV, intravenous; PP, practice point

Transfusion incidence – oral and/or parenteral iron

One Level I study[33] identified a single study[35] that compared oral iron to no treatment, in which transfusion incidence was reported; no difference was observed.

One Level I study[36] and three Level II studies[37-39] compared IV iron to oral iron, and reported transfusion incidence. Two studies[38,39] showed no transfusion event in either group, and the remaining studies[36,37] showed no significant difference.

Two Level II studies[31,40] compared IV iron plus oral iron to oral iron alone, and reported transfusion incidence. Neither study reported any significant difference between the groups.

Three Level II studies[41-43] compared IV iron plus folic acid to oral iron plus folic acid, and reported transfusion incidence in both pregnant and postpartum groups. None reported any significant difference between the groups.

One Level II study[44] compared IV iron to IM iron plus oral iron, and reported transfusion incidence; no transfusion events were reported in either arm.

It was not possible to pool results reporting transfusion incidence, because of the heterogeneity of patient populations and interventions. Numbers in individual studies were small, and studies were underpowered to detect a significant difference in transfusion incidence. No studies defined triggers for transfusion, and transfusion decision making is likely to be influenced by many factors, including clinician practices, and the cost, safety and availability of blood.

Laboratory measures – oral and/or parenteral iron

One Level I study[33] that compared oral iron to placebo or no treatment reported significant differences:

- maternal anaemia at term (Hb < 110g/L at 37 weeks gestation or more) (14 trials)
- maternal iron deficiency anaemia at term (Hb < 110g/L with at least one additional laboratory marker) (6 trials)
- maternal anaemia at 34 weeks gestation or more (16 trials)
- within 6 weeks postpartum (6 trials).

In all cases, the studies favoured oral iron.

One Level I study[33] that compared oral iron plus folic acid to placebo or no treatment reported results similar to oral iron versus placebo or no treatment. The studies favoured oral iron plus folic acid, with the exception of a single trial[45] that demonstrated no significant difference.

Various laboratory measures (e.g. Hb, ferritin, haematocrit or numbers of subjects achieving a specified laboratory measure) were reported in the single Level I study[36] and nine Level II studies that compared IV iron to oral iron.[37-39,46-51] Most studies favoured IV iron treatment. The studies in postpartum women with anaemia consistently demonstrated clinically relevant differences in Hb at early time points (days to weeks), and a sustained difference in ferritin, favouring IV iron.

Three Level II studies[31,40,52] that compared IV iron plus oral iron to oral iron alone reported laboratory measures that favoured IV iron plus oral iron. However, Westad (2008)[31] reported that Hb levels were similar in both treatment arms after 4 weeks.

One Level II study[53] that compared IV iron to oral iron plus folic acid reported results favouring IV iron at 2, 4 and 6 weeks following treatment.

A single poor-quality Level II study[54] that compared IV iron to IM iron reported results favouring IV iron at 2 and 4 weeks following treatment.

One Level I study[36] and one Level II study[44] that compared IV iron to IM iron plus oral iron showed significant improvements in Hb, favouring IV iron in the measured outcomes.

The Level I study[36] that compared IM iron to oral iron reported two trials: one[55] favoured IM iron and one[56] showed no significant difference in measured outcomes.

The Level I study[36] that compared IM iron to oral iron plus folic acid included one trial[57] with a high risk of bias that favoured oral iron plus folic acid based on mean Hb at 36 weeks gestation, although the difference in Hb was not clinically meaningful.

It was not possible to pool results from all studies reporting laboratory measures, because of the heterogeneity of patient populations, type and timing of interventions, and timing of outcome measures. As expected, administration of iron generally led to an increase in iron stores and Hb.

Measures of fetal outcome – oral and/or parenteral iron

Measures of fetal outcome were assessed by multiple treatment comparisons, with evidence available for oral iron versus placebo or no treatment,[33] oral iron with folic acid versus placebo or no treatment,[33] IV iron versus oral iron,[36] IV iron with folic acid versus oral iron with folic acid,[41,43] and IM iron versus oral iron with folic acid.[36] Birth weight, incidence of low and very low birth weight, and premature birth (<37 weeks gestation) were variously reported. There were no significant differences in any of the measures of fetal outcome reported, with the exception of two trials[58,59] that favoured oral iron and folic acid over no iron, based on a mean difference in birth weight of 57.7 g (which may not be of clinical significance).

Mortality – oral and/or parenteral iron

The two systematic reviews[33,36] both reported mortality for oral iron versus placebo or no treatment, oral iron plus folic acid versus placebo or no treatment, and IV iron versus oral iron. No maternal deaths were reported, but studies were underpowered (n=278) for this outcome. The two Level III studies[29,30] reported an effect favouring the use of iron or iron plus folic acid during pregnancy for prevention of perinatal or neonatal deaths, but the evidence-base was small or inconsistent.

3.3.2 Erythropoiesis stimulating agents

Recombinant ESAs promote bone marrow production of RBCs; however, ESA use is associated with complications of therapy, particularly where the baseline Hb is near normal. Accordingly, the effectiveness of ESAs in treating anaemia must be balanced against these risks.

ESAs are currently registered with the Therapeutic Goods Administration (TGA) for anaemia therapy in patients with chronic renal disease, non-myeloid malignancies and those scheduled for elective surgery with an expected moderate blood loss.

Limited or no evidence regarding the secondary outcome of functional performance status was identified.

EVIDENCE STATEMENTS – erythropoiesis stimulating agents		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES2.43	In women with iron deficiency anaemia in pregnancy, the effect on transfusion incidence of adding ESAs to iron is uncertain. (See evidence matrix D2.A in Volume 2 of the technical report)	✓✓	**NA**	**NA**	✓	✓✓
ES2.44	In women with postpartum iron deficiency anaemia, the effect on transfusion incidence of adding ESAs to iron is uncertain. (See evidence matrix D2.A in Volume 2 of the technical report)	✓✓	✓✓	**NA**	✓	✓✓
ES2.45	In women with iron deficiency anaemia in pregnancy, the effect on laboratory measures of adding ESAs to iron is uncertain. (See evidence matrix D2.B in Volume 2 of the technical report)	✓✓	**NA**	**NA**	✓	✓✓
ES2.46	In women with postpartum iron deficiency anaemia, the effect on laboratory measures of adding ESAs to iron is uncertain. (See evidence matrix D2.B in Volume 2 of the technical report)	✓✓	✓	**X**	✓✓	✓✓
ES2.47	In women with iron deficiency anaemia in pregnancy, the effect on thromboembolic events of adding ESAs to iron is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES2.48	In women with postpartum iron deficiency anaemia, the effect on thromboembolic events of adding ESAs to iron is uncertain. (See evidence matrix D2.C in Volume 2 of the technical report)	✓✓	✓✓✓	**NA**	✓✓	✓✓
ES2.49	In women with iron deficiency anaemia in pregnancy, the effect on fetal outcomes of adding ESAs to iron is uncertain. (See evidence matrix D2.D in Volume 2 of the technical report)	✓✓	**NA**	**NA**	✓	✓✓
ES2.50	In women with postpartum iron deficiency anaemia, the effect on fetal outcomes of adding ESAs to iron is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES2.51	In pregnant women, the effect on maternal and perinatal mortality of adding ESAs to iron is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**

ES, evidence statement; ESA, erythropoiesis stimulating agent

✓✓✓=A; ✓✓=B; ✓=C; **X**=D; **NA**, not applicable

RECOMMENDATION – erythropoiesis stimulating agents	
R4 **GRADE C**	**ESAs should not be routinely used in maternity patients.**

ESA, erythropoiesis stimulating agent; R, recommendation

PRACTICE POINT – erythropoiesis stimulating agents	
PP14	**In maternity patients with anaemia, where an ESA is used, it should be combined with iron therapy.[a]** [a] ESAs are currently registered with the TGA for anaemia therapy in patients with chronic renal disease, non-myeloid malignancies and those scheduled for elective surgery with an expected moderate blood loss.

ESA, erythropoiesis stimulating agent; PP, practice point; TGA, Therapeutic Goods Administration

The systematic review and hand searching process did not identify any studies that compared ESAs with placebo in maternity patients with anaemia.

Two Level I studies[36,60] and two subsequent Level II studies[61,62] that compared ESAs and iron to iron alone were identified by the systematic review and hand searching process. The systematic reviews were of good quality and included up to five RCTs that were assessed as having a low or uncertain risk of bias.

Mortality – erythropoiesis stimulating agents

No studies reporting mortality were identified.

Transfusion Incidence – erythropoiesis stimulating agents

No difference was observed in the incidence of transfusion between maternity patients with anaemia treated with ESAs plus iron and those treated with iron alone; however, the total number of events was low (2 patients transfused from a total of 180 patients studied) and wide confidence limits were observed. The studies are therefore underpowered to detect any difference, and no conclusion may be drawn.

Laboratory measures – erythropoiesis stimulating agents

Laboratory measures were reported by all four of the included studies.[36,60-62] One study[37] demonstrated an increase in Hb measured within 2 weeks of treatment, favouring iron alone, but these differences were not sustained at 6 weeks. One fair-quality RCT[61] demonstrated the opposite, and the remaining studies found no effect. This inconsistency reflects genuine uncertainty around the question.

Thromboembolic events – erythropoiesis stimulating agents

Two studies[60,61] reported thromboembolic complications. No difference was observed, but the studies were underpowered to detect any difference, and no conclusions can be drawn.

Fetal outcomes – erythropoiesis stimulating agents

One study[36] reported fetal outcomes: birth before 37 weeks and birth weight. No differences were observed, but the studies were underpowered to detect any difference and no conclusion can be drawn.

Summary – erythropoiesis stimulating agents

It was not possible to pool results reporting outcomes relating to administration of ESAs, because of the heterogeneity of patient populations and interventions. Numbers in individual studies were small, and studies were underpowered to detect a significant difference in outcomes.

3.4 Effect of blood components on outcomes

Question 3 (Interventional)

In maternity 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 platelets on mortality, bleeding events and transfusion-related adverse events in maternity patients.

FFP contains all the coagulation factors present in normal plasma. It is primarily transfused in the maternity setting to correct coagulation during PPH. Other situations may include the maternity patient requiring medical management for liver disease, coagulation factor deficiencies or thrombotic thrombocytopenic purpura (TTP); for these indications, refer to *Patient Blood Management Guidelines: Module 3 – Medical*.[3] Cryoprecipitate and fibrinogen concentrate are therapeutic interventions used in the correction of low fibrinogen levels.[a]

EVIDENCE STATEMENTS – fresh frozen plasma (bleeding patients)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.1	In patients with postpartum haemorrhage, the effect of FFP on maternal mortality is uncertain. (See evidence matrix D3.A in Volume 2 of the technical report)	**X**	✓✓✓	**NA**	✓✓	✓✓
ES3.2	In patients with postpartum haemorrhage, the effect of FFP on transfusion requirements is uncertain. (See evidence matrix D3.B in Volume 2 of the technical report)	**X**	**NA**	**X**	✓✓	✓✓
ES3.3	In patients with postpartum haemorrhage, the effect of FFP on transfusion-related SAEs (TACO, TRALI, other[a]) is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES3.4	In patients with postpartum haemorrhage, the effect of FFP on the need for additional interventions to control bleeding is uncertain. (See evidence matrix D3.C in Volume 2 of the technical report)	**X**	**NA**	**NA**	✓✓	✓✓

ES, evidence statement; FFP, fresh frozen plasma; SAE, serious adverse event; TACO, transfusion-related circulatory volume overload; TRALI, transfusion-related acute lung injury

✓✓✓=A; ✓✓=B; ✓=C; **X**=D; **NA**, not applicable

[a] The Jurisdictional Blood Committee (JBC) recently approved the addition of fibrinogen concentrate for patients with congenital fibrinogen deficiency to the list of products funded and supplied under the national blood arrangements administered by the NBA. Fibrinogen concentrate became available for treatment of congenital fibrinogen deficiency under the NBA arrangements from 1 July 2014.

EVIDENCE STATEMENTS – fresh frozen plasma (coagulopathic patients at risk of bleeding)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.5	In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of FFP on maternal mortality is uncertain. (See evidence matrix D3.A in Volume 2 of the technical report)	**X**	✓✓✓	**NA**	✓✓	✓✓
ES3.6	In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of FFP on transfusion requirements is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES3.7	In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of FFP on transfusion-related SAEs (TACO, TRALI, other[a]) is unknown (no evidence). [a] 'Other' includes haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease, anaphylactic reactions.	**NA**	**NA**	**NA**	**NA**	**NA**
ES3.8	In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of FFP on additional interventions to control bleeding is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**

ES, evidence statement; FFP, fresh frozen plasma; SAE, serious adverse event; TACO, transfusion-related circulatory volume overload; TRALI, transfusion-related acute lung injury

✓✓✓=A; ✓✓=B; ✓=C; **X**=D; **NA**, not applicable

EVIDENCE STATEMENTS – cryoprecipitate, fibrinogen concentrate, or platelet transfusion (bleeding patients)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.9	In patients with PPH, the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion on maternal mortality is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES3.10	In patients with PPH, the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion on transfusion requirements is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES3.11	In patients with PPH, the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion on transfusion-related SAEs (TACO, TRALI, other[a]) is unknown (no evidence). [a] 'Other' includes haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease and anaphylactic reactions.	**NA**	**NA**	**NA**	**NA**	**NA**
ES3.12	In patients with PPH, the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion on the need for additional interventions to control bleeding is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**

ES, evidence statement; PPH, postpartum haemorrhage; SAE, serious adverse event; TACO, transfusion-related circulatory volume overload; TRALI, transfusion-related acute lung injury

✓✓✓=A; ✓✓=B; ✓=C; **X**=D; **NA**, not applicable

EVIDENCE STATEMENTS – cryoprecipitate, fibrinogen concentrate, or platelet transfusion (coagulopathic patients at risk of bleeding)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.13	In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion on maternal mortality is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES3.14	In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion on transfusion requirements is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES3.15	In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion on transfusion-related SAEs (TACO, TRALI, other[a]) is unknown (no evidence). [a] 'Other' includes haemolytic transfusion reactions, transfusion transmitted infections, transfusion-induced graft-versus-host-disease and anaphylactic reactions.	**NA**	**NA**	**NA**	**NA**	**NA**
ES3.16	In maternity patients with an abnormal coagulation profile who are at risk of bleeding, the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion on the need for additional interventions to control bleeding is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**

ES, evidence statement; PPH, postpartum haemorrhage; SAE, serious adverse event; TACO, transfusion-related circulatory volume overload; TRALI, transfusion-related acute lung injury

✓✓✓=A; ✓✓=B; ✓=C; **X**=D; **NA**, not applicable

EVIDENCE STATEMENTS – combination or fixed ratio therapy (bleeding patients)		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES3.17	In patients with postpartum haemorrhage, the effect of combination or fixed ratio therapy (FFP, cryoprecipitate, fibrinogen concentrate and/or platelet transfusion), on transfusion requirements is uncertain. (See evidence matrix D3.D in Volume 2 of the technical report)	**X**	**NA**	**NA**	✓✓	✓✓
ES3.18	In patients with postpartum haemorrhage, the effect of combination or fixed ratio therapy (FFP, plasma, cryoprecipitate, fibrinogen concentrate and/or platelet transfusion), on the need for additional interventions to control bleeding is uncertain. (See evidence matrix D3.E in Volume 2 of the technical report)	**X**	**NA**	**X**	✓✓	✓✓

ES, evidence statement; FFP, fresh frozen plasma

✓✓✓=A; ✓✓=B; ✓=C; **X**=D; **NA**, not applicable

PRACTICE POINTS – bleeding maternity patients	
PP15	All providers of birthing services should develop a plan to manage obstetric haemorrhage. The plan should give consideration to local resources, transport and access to relevant specialist advice, blood products and equipment.
PP16	In women with major obstetric haemorrhage, in addition to clinical observations, the following parameters should be measured early and frequently: ▪ temperature ▪ acid–base status ▪ ionised calcium ▪ haemoglobin ▪ platelet count ▪ PT/INR ▪ APTT ▪ fibrinogen level With successful treatment, values should trend towards normal.
PP17	Values indicative of critical physiologic derangement include: ▪ temperature <35°C ▪ pH <7.2, base excess worse than –6, lactate >4 mmol/L ▪ ionised calcium <1.1 mmol/L ▪ platelet count <50 × 10^9/L ▪ PT >1.5 × normal ▪ INR >1.5 ▪ APTT >1.5 × normal ▪ fibrinogen level <2.0 g/L.
PP18	In women with major obstetric haemorrhage requiring massive transfusion, suggested doses of blood components are:[a] ▪ FFP: 15 mL/kg ▪ platelets: 1 adult therapeutic dose ▪ cryoprecipitate: 3–4 g. [a] Or as directed by the haematologist/transfusion specialist. See Appendix E for dose equivalents

PRACTICE POINTS – coagulopathic patients at risk of bleeding	
PP19	In general, a platelet count ≥50 × 10^9/L is considered acceptable for vaginal or caesarean birth; however, lower platelet counts may be tolerated.
PP20	In maternity patients with abnormal coagulation tests who are not bleeding (note: concealed bleeding should be excluded), the *routine* use of cryoprecipitate or FFP is not supported. There was no evidence to define a threshold fibrinogen level or prothrombin ratio/INR that is associated with significant adverse events.
PP21	In maternity patients, underlying causes of coagulopathy should be assessed and treated. Where transfusion of platelets, cryoprecipitate or FFP is considered necessary, the risks and benefits should be considered for each patient, and expert guidance sought.
PP22	Maternity patients with pre-existing haematological conditions (e.g. thrombocytopenia, inherited or acquired disorders of coagulation) should have their condition optimised before giving birth, and have a multidisciplinary plan in place for birth and the postnatal period.

APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalisation ratio; PP, practice point; PT, prothrombin time

The literature search was limited to Level III studies or above, and the results are based on two retrospective cohort studies. The guidance is also based on consideration of previous modules in this series of guidelines.[1-4]

The search identified no Level 1 or Level II studies. Two retrospective cohort studies of fair quality were identified from the systematic review and hand searching process.

No maternal deaths were reported; the increased transfusion volume (of RBC and platelets) and the requirement for additional procedures in patients receiving FFP is likely to have been influenced by patient selection bias.

There were no studies that reported on transfusion-related serious adverse events, and no studies that examined the effect of cryoprecipitate, fibrinogen concentrate, or platelet transfusion in bleeding patients.

One Level III study examining combination or fixed ratio therapy was identified.[63] Although subgroup analysis reported a reduction in the use of additional interventions in women with a high FFP: RBC ratio (compared to a low ratio), the numbers were small (n=41); thus, the study was underpowered to be confident of this result.

There are limited clinical data to guide management of transfusion in maternity patients. In particular, it is unclear whether the approach to transfusion using blood components and plasma products should be different to use in other clinical populations.

Limited or no evidence on the secondary outcomes of laboratory measures or functional performance status was identified.

In Australia, fibrinogen concentrate is listed on the Australian Register of Therapeutic Goods for the treatment of acute bleeding in people with an absence or low level of human fibrinogen (congenital lack of fibrinogen). Its use in a maternity patient who has an abnormal coagulation profile without a congenital fibrinogen deficiency, would be considered 'off-label'.

3.5 Use of blood conservation strategies

Question 4 (Interventional)

In maternity patients, what is the effect of non-obstetric strategies that aim to minimise maternal blood loss in the peripartum period on transfusion and clinical outcomes?

The systematic review investigated the following strategies in maternity patients:

- point-of-care (POC) testing
- cell salvage
- interventional radiology (IR)
- recombinant activated factor VII (rFVIIa)
- tranexamic acid (TXA).

Limited or no evidence regarding secondary harm outcomes was identified for any of the strategies.

3.5.1 Point-of-care testing

EVIDENCE STATEMENTS – point-of-care testing		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES4.1	In maternity patients, the effect of POC testing (thromboelastography and rotational thromboelastometry) on transfusion requirements is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES4.2	In maternity patients, the effect of POC testing (thromboelastography and rotational thromboelastometry) on the need for additional interventions to control bleeding is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES4.3	In maternity patients, the effect of POC testing (thromboelastography and rotational thromboelastometry) on maternal mortality is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES4.4	In maternity patients, the effect of POC testing (thromboelastography and rotational thromboelastometry) on thromboembolic events is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**

ES, evidence statement; POC, point-of-care

✓✓✓=A; ✓✓=B; ✓=C; **X**=D; **NA**, not applicable

Historically, POC testing (also known as 'near-patient testing') has included testing of Hb, arterial blood gases and blood glucose. More recently, developments in thromboelastography and thromboelastometry techniques have enabled POC testing of clot formation and lysis to guide clinical decision making, including blood component therapy. These techniques are the focus of this question.

The systematic review and hand searching process did not identify any studies that examined the use of POC testing in maternity patients.

Clinical commentary – point-of-care testing

There is evidence to show that the use of algorithms based on platelet analysis used intraoperatively in cardiac surgery reduces the incidence of transfusion with FFP and platelets, and may reduce the incidence of RBC transfusion (R16 of Module 2[2]). It remains to be seen whether this type of POC testing in the maternity setting would have similar effects.

3.5.2 Intraoperative cell salvage

Cell salvage involves the collection of blood lost during surgery, followed by reinfusion of the washed RBCs. One of the key aims is to reduce allogeneic transfusion, and thus reduce transfusion-related adverse events. In the maternity setting, cell salvage is generally only considered in women with, or at risk of, major blood loss likely to result in transfusion.

Theoretical concerns over cell salvage for obstetric surgery have not been borne out in clinical practice.

EVIDENCE STATEMENTS – intraoperative cell salvage		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES4.5	In maternity patients who have placenta previa or refuse transfusion, the effect of intraoperative cell salvage compared with no intraoperative cell salvage on transfusion requirements is uncertain. (See evidence matrix D4.A in Volume 2 of the technical report)	**X**	**NA**	**NA**	**X**	✓
ES4.6	In maternity patients who have placenta previa or refuse transfusion, the effect of intraoperative cell salvage compared with no intraoperative cell salvage on the need for additional interventions to control bleeding is uncertain. (See evidence matrix D4.B in Volume 2 of the technical report)	**X**	**NA**	**NA**	**X**	✓
ES4.7	In maternity patients the effect of intraoperative cell salvage on maternal mortality is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES4.8	In maternity patients who have placenta previa or refuse transfusion, the effect of intraoperative cell salvage compared with no intraoperative cell salvage on thromboembolic events is uncertain. (See evidence matrix D4.C in Volume 2 of the technical report)	**X**	**NA**	**NA**	**X**	✓

ES, evidence statement

✓✓✓=A; ✓✓=B; ✓=C; **X**=D; **NA**, not applicable

PRACTICE POINTS – intraoperative cell salvage	
PP23	In maternity patients, cell salvage should be considered if anticipated blood volume loss is likely to result in transfusion.[a] [a] In accordance with *Guidance for the provision of intraoperative cell salvage*.[10]
PP24	In maternity patients who are at increased risk of bleeding and in whom transfusion is not an option, cell salvage should be considered.
PP25	Cell salvage requires a local procedural guideline that should include patient selection, use of equipment and reinfusion. All staff operating cell salvage devices should receive appropriate training, to ensure that they are familiar with and proficient in the technique.
PP26	In Rh D negative maternity patients receiving salvaged blood where the cord blood group is Rh D positive, a dose of Rh D immunoglobulin is required, with additional doses based on the result of assessment of fetomaternal haemorrhage test.

PP, practice point

The systematic review and hand searching process identified no Level I evidence for cell salvage in the maternity setting. One Level II study of poor quality[64] and one Level III study of poor quality were identified.[65] The Level II study reported a significant difference in the incidence of homologous RBC transfusion between women who had blood salvaged during caesarean birth and those who did not have blood salvaged. There was no significant difference in the transfusion rates between the two groups in the Level III study, suggesting that the use of cell salvage did not correspond to a reduction in the use of blood transfusion. No thromboembolic events were reported in the intervention group (and no information was provided about such events in the comparator group).

Clinical commentary – intraoperative cell salvage

Based on experience in other patient groups, cell salvage has been endorsed by a number of bodies (e.g. the American Congress of Obstetricians and Gynaecologists [ACOG] and RCOG) as a reasonable intervention in patients at increased risk of major blood loss likely to require transfusion.

Further guidance on cell salvage is available from the NBA.[10]

3.5.3 Interventional radiology

In maternity patients, IR typically includes iliac balloon catheters and transcatheter arterial embolisation, which are used to block the principal vessels supplying the uterus as a means to control bleeding and preserve fertility. IR is used in two scenarios – to treat major bleeding or (prophylactically) as part of the management of morbidly adherent placenta.

These techniques may be less efficacious in maternity patients than in other groups because of the extensive collateral pelvic circulation in the former. Also, they require access to imaging technology and an experienced interventional radiologist. Potential safety concerns include fetal exposure to radiation if catheterisation occurs before birth, and direct complications of arterial thrombosis and dissection.

EVIDENCE STATEMENTS – interventional radiology		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES4.9	In women with suspected morbidly adherent placenta, the effect of preventative interventional radiology (iliac balloon catheters or embolisation only) on transfusion requirements is uncertain. (See evidence matrix D4.D in Volume 2 of the technical report)	**X**	✓	**X**	✓✓	✓✓
ES4.10	In women with suspected morbidly adherent placenta, the effect of preventative interventional radiology (iliac balloon catheters or embolisation only) on the need for additional interventions to control bleeding is uncertain. (See evidence matrix D4.E in Volume 2 of the technical report)	**X**	✓	**X**	✓✓	✓✓
ES4.11	In women with suspected morbidly adherent placenta, the effect of preventative interventional radiology (iliac balloon catheters or embolisation only) on maternal mortality is uncertain. (See evidence matrix D4.F in Volume 2 of the technical report)	✓	**NA**	**NA**	✓✓	✓✓
ES4.12	In women with suspected morbidly adherent placenta, the effect of preventative interventional radiology (iliac balloon catheters or embolisation) on thromboembolic events is uncertain. (See evidence matrix D4.G in Volume 2 of the technical report)	✓	**X**	**NA**	✓✓	✓✓
ES4.13	In women with major obstetric haemorrhage, the effect of interventional radiology (iliac balloon catheters or embolisation only) on transfusion requirements is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES4.14	In women with major obstetric haemorrhage, the effect of interventional radiology (iliac balloon catheters or embolisation only) on the need for additional interventions to control bleeding is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES4.15	In women with major obstetric haemorrhage, the effect of interventional radiology (iliac balloon catheters or embolisation only) on maternal mortality is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**
ES4.16	In women with major obstetric haemorrhage, the effect of interventional radiology (iliac balloon catheters or embolisation only) on thromboembolic events is unknown (no evidence).	**NA**	**NA**	**NA**	**NA**	**NA**

ES, evidence statement

✓✓✓=A; ✓✓=B; ✓=C; **X**=D; **NA**, not applicable

PRACTICE POINTS – interventional radiology	
PP27	Preventative IR may be appropriate in selected maternity patients; however, the risk of complications from this procedure should be balanced against the potential benefits.
PP28	Although the role of therapeutic IR in the treatment of major obstetric haemorrhage is unknown, it may be considered in the overall approach to management.

IR, interventional radiology; PP, practice point

The systematic review identified two Level I reviews[66,67] containing only Level III and IV evidence, but did not include any pooled analysis; hence, the primary Level III retrospective cohort studies of fair quality were assessed.[68-70] An additional poor-quality prospective Level III study was identified.[71]

Incidence and volume – interventional radiology

The studies reporting transfusion incidence[69,71] and volume[68-70] did not find a statistically significant difference between intervention and comparator arms.

Ballas et al (2012)[71] found no significant difference between the mean units of packed RBC or FFP transfused in patients who underwent uterine artery balloon (UAB) catheterisation compared to those who did not (p=0.14 and p=0.17, respectively). Although significantly fewer women who underwent UAB catheterisation required a massive transfusion (31% vs 52%; p=0.03), intervention and treatment arms were subject to selection bias (i.e. most women who underwent UAB catheterisation had an antenatal diagnosis of abnormal placentation).

The three cohort studies that examined the effect of IR on the use of additional interventions such as hysterectomy, uterine artery ligation and pelvic artery embolisation to control bleeding were underpowered to determine a treatment effect.[68-70]

One study,[68] reported on maternal deaths, but was underpowered to determine a treatment effect.

Two studies[68,70] reported on thromboembolic events, but reporting was incomplete. Thus, it was not possible to compare the occurrence of such events between those patients who received IR and those that did not.

Clinical commentary – interventional radiology

When considering the use of IR techniques to arrest haemorrhage, the risks associated with delay in arranging access to these procedures must be carefully balanced against the benefits of preserving fertility. IR techniques do not appear to affect subsequent menstruation and fertility.[72]

Guidelines are available from New South Wales and South Australia.[20,73]

3.5.4 Recombinant activated factor VII

rFVIIa is used for the control of bleeding and prophylaxis for surgery in patients with inhibitors to coagulation factors FVIII or FIX, congenital factor VII deficiency and Glanzmann's thrombasthenia. Its use as an additional haemostatic agent in management of severe haemorrhage has not been associated with significantly improved clinical outcomes, and has the potential to increase the risk of thromboembolism.

EVIDENCE STATEMENTS – recombinant activated factor VII		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES4.17	In women with massive PPH, the effect of rFVIIa compared with no rFVIIa on transfusion requirements is uncertain. (See evidence matrix D4.H in Volume 2 of the technical report)	X	✓	NA	✓✓	✓
ES4.18	In women with massive PPH, the effect of rFVIIa compared with no rFVIIa on the need for additional interventions to control bleeding (hysterectomy and uterine artery embolisation) is uncertain. (See evidence matrix D4.I in Volume 2 of the technical report)	X	✓✓	NA	✓✓	✓
ES4.19	In women with massive PPH, the effect of rFVIIa compared with no rFVIIa on maternal mortality is uncertain. (See evidence matrix D4.J in Volume 2 of the technical report)	X	✓	NA	✓✓	✓
ES4.20	In women with massive PPH, the effect of rFVIIa compared with no rFVIIa on thromboembolic events is uncertain. (See evidence matrix D4.K in Volume 2 of the technical report)	X	✓	NA	✓✓	✓

ES, evidence statement; PPH, postpartum haemorrhage; rFVIIa, recombinant activated factor VII

✓✓✓=A; ✓✓=B; ✓=C; **X**=D; **NA**, not applicable

PRACTICE POINTS – recombinant activated factor VII

PP29	The administration of rFVIIa may be considered in maternity patients with life-threatening haemorrhage, but only after conventional measures (including surgical haemostasis and appropriate blood component therapy) have failed.[a] [a] Refer to PP8, PP9 in *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion*[1] and PP20 in *Patient Blood Management Guidelines: Module 2 – Perioperative*[2] NB: rFVIIa is not licensed for this use. Its use should only be considered in exceptional circumstances.
PP30	Ideally, rFVIIa should only be administered to maternity patients as part of a locally adapted MTP. The MTP should include strict attention to the control of bleeding, physiological and metabolic parameters, coagulation status and temperature maintenance.
PP31	When rFVIIa is administered to maternity patients with life-threatening haemorrhage, an initial dose of 90 µg/kg is suggested.

MTP, massive transfusion protocol; PP, practice point; rFVIIa, recombinant activated factor VII

The systematic review examined the evidence for the use of rFVIIa in maternity patients. Three Level III studies were identified from the systematic review and hand searching process, all of which were subject to selection bias.[74-76]

Two studies found that patients who received rFVIIa were given more RBC, fibrinogen and platelets than comparator groups; however, the women who received rFVIIa had more severe haemorrhage.[74,76]

The authors reported no difference in the need for hysterectomy,[75,76] maternal mortality[75,76] or thromboembolic events[74,75] in women who received rFVIIa and those who did not.

Clinical commentary – recombinant activated factor VII

There are no data from an RCT that assess the impact of rFVIIa in the management of obstetric haemorrhage. Studies that are available are prone to bias, with rFVIIa generally being given to women with more severe bleeding. In Australia, rFVIIa is not licensed for use in major bleeding and its role should be limited to major ongoing bleeding where standard obstetric, surgical and transfusion approaches have been unsuccessful.

3.5.5 Tranexamic acid

TXA acts as an antifibrinolytic by competitively inhibiting the activation of plasminogen to plasmin, a molecule responsible for the degradation of fibrin. There is strong evidence to support the use of TXA to reduce blood loss in the surgical and trauma population. Its mechanism of action is such that it may also be of benefit in the obstetric population in the control of PPH.

EVIDENCE STATEMENTS – tranexamic acid		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES4.21	In women giving birth by caesarean delivery, the effect of the routine use of antifibrinolytic therapy (TXA only) on transfusion requirements is uncertain. (See evidence matrix D4.L in Volume 2 of the technical report)	✓✓	✓	**NA**	✓✓	✓
ES4.22	In women giving birth by vaginal delivery, the effect of the routine use of antifibrinolytic therapy (TXA only) on transfusion requirements is uncertain. (See evidence matrix D4.M in Volume 2 of the technical report)	✓✓	**NA**	**NA**	✓✓	✓
ES4.23	In women with postpartum haemorrhage after vaginal delivery, the effect of antifibrinolytic therapy (TXA only) on transfusion requirements is uncertain. (See evidence matrix D4.N in Volume 2 of the technical report)	✓✓	**NA**	**X**	✓✓	✓✓
ES4.24	In women giving birth by caesarean delivery, the effect of the routine use of antifibrinolytic therapy (TXA only) on the need for additional interventions to prevent bleeding is uncertain. (See evidence matrix D4.O in Volume 2 of the technical report)	✓✓	✓✓✓	**NA**	✓✓	✓
ES4.25	In women giving birth by vaginal delivery, the effect of the routine use of antifibrinolytic therapy (TXA only) on the need for additional interventions to control bleeding is uncertain. (See evidence matrix D4.P in Volume 2 of the technical report)	✓✓	NA	NA	✓✓	✓

EVIDENCE STATEMENTS – tranexamic acid		Evidence	Consistency	Clinical impact	Generalisability	Applicability
ES4.26	In women with postpartum haemorrhage after vaginal delivery, the effect of antifibrinolytic therapy (TXA only) on the need for additional interventions to control bleeding is uncertain. (See evidence matrix D4.Q in Volume 2 of the technical report)	✓✓	**NA**	**NA**	✓✓	✓✓
ES4.27	In women giving birth by caesarean delivery, the effect of the routine use of antifibrinolytics (TXA only) on maternal mortality is uncertain. (See evidence matrix D4.R in Volume 2 of the technical report)	✓	**NA**	**NA**	✓✓	✓
ES4.28	In women giving birth by vaginal delivery, the effect of the routine use of antifibrinolytic therapy (TXA only) on maternal mortality is uncertain. (See evidence matrix D4.S in Volume 2 of the technical report)	✓✓	**NA**	**NA**	✓✓	✓
ES4.29	In women with postpartum haemorrhage after vaginal delivery, the effect of antifibrinolytic therapy (TXA only) on maternal mortality is uncertain. (See evidence matrix D4.T in Volume 2 of the technical report)	✓✓	**NA**	**NA**	✓✓	✓✓
ES4.30	In women giving birth by caesarean delivery, the effect of the routine use of antifibrinolytic therapy (TXA only) on thromboembolic events is uncertain. (See evidence matrix D4.U in Volume 2 of the technical report)	✓✓	✓✓✓	**NA**	✓✓	✓
ES4.31	In women giving birth by vaginal delivery, the effect of the routine use of antifibrinolytic therapy (TXA only) on thromboembolic events is uncertain. (See evidence matrix D4.V in Volume 2 of the technical report)	✓✓	**NA**	**NA**	✓✓	✓
ES4.32	In women with postpartum haemorrhage after vaginal delivery, the effect of antifibrinolytic therapy (TXA only) on thromboembolic events is uncertain. (See evidence matrix D4.W in Volume 2 of the technical report)	✓✓	**NA**	**NA**	✓✓	✓✓
ES4.33	In women with placenta problems or unspecified antepartum haemorrhage, the effect of antifibrinolytic therapy (TXA only) on thromboembolic events is uncertain. (See evidence matrix D4.X in Volume 2 of the technical report)	**X**	**NA**	**NA**	✓✓	✓✓

ES, evidence statement; TXA, tranexamic acid

✓✓✓=A; ✓✓=B; ✓=C; **X**=D; **NA**, not applicable

PRACTICE POINTS – tranexamic acid	
PP32	**In maternity patients with significant blood loss, the early use (within 3 hours of the onset of haemorrhage) of TXA may be considered.[a]** [a] The use of TXA in this context is considered off label
PP33	**TXA should only be administered in the context of overall patient management; the protocol should include strict attention to the control of bleeding, physiological and metabolic parameters, coagulation status and temperature maintenance.**

PP, practice point; TXA, tranexamic acid

The literature search identified no systematic reviews that reported the effect of TXA in maternity patients and that also reported on the outcomes of interest in our research protocol. However, individual RCTs were included if they met the relevant criteria. Although many studies reported blood loss as a primary outcome, the CRG did not include this as an outcome measure because it is subjective, and is less reliable than transfusion incidence.

The literature search identified seven RCTs that examined the effect of tranexamic acid in maternity patients: five in women giving birth by caesarean,[77-81] one in women giving birth vaginally,[82] and one in women with PPH after vaginal birth.[83]

The literature search identified one Level III study that examined the effect of tranexamic acid in maternity patients.[84]

Transfusion incidence or volume of transfusion

The use of TXA on the incidence of transfusion or volume of transfusion in women following vaginal or caesarean birth was examined. The incidence of transfusion was reported in five studies and transfusion volume was reported in two studies.

Three studies examined the effect of comparable doses of TXA, administered prior to incision, in maternity patients who underwent elective or urgent caesarean section.[79-81] One reported no transfusions in either the TXA or placebo groups.[80] Another reported no significant difference in transfusion incidence between those who received TXA and those who did not.[79] In contrast, the other study reported a significantly higher incidence of RBC transfusion in patients who received placebo (22%) compared with those who were treated with TXA (9%).[81] The transfusion rate in both the TXA and placebo arms of the study by Xu et al (2013)[81] seemed very high, and the authors did not provide any explanation for this finding.

No significant difference in the incidence of transfusion was found in the one study that examined the effect of prophylactic administration of TXA around the time of vaginal birth.[82] The study included women at risk of PPH.

One RCT examined the effect of TXA on transfusion volume and incidence in women with active, severe PPH (>800 mL within 2 hours) after vaginal birth. There was no significant difference in the incidence of RBC transfusion.[83] However, the total RBC transfusion volume and the use of other blood components (fibrinogen, FFP) was significantly lower in the TXA group compared with the no TXA group.

Additional interventions to control bleeding

Five studies reported the use of additional interventions to control bleeding. Four studies reported that no women in either group required additional interventions.[79,80,82] The other reported no significant differences in the use of additional interventions between the two groups.[83]

Maternal mortality

No maternal deaths were observed in the three RCTs reporting on maternal mortality, but the studies were not powered to detect differences.[81-83]

Thromboembolic events

No significant difference in thromboembolic events was reported in the seven RCTs[78-83] and one retrospective cohort study[84] that examined such events.

Clinical commentary

TXA is currently licensed for use in Australia in a number of surgical and trauma indications, including cardiac and orthopaedic surgery, and patients with coagulopathies undergoing minor surgery.[a]

The effect of the use of TXA on the volume and incidence of transfusion, and on additional interventions for PPH to control bleeding following vaginal or caesarean birth is uncertain.

In the non-obstetric (surgical and trauma) population, there is strong evidence to support the use of TXA to control haemorrhage.[85] Therefore, it seems reasonable to consider this agent in the context of the overall management of the maternity patient with critical bleeding. The optimal timing of administration in maternity patients is unknown; however, in other populations, early administration appears to be beneficial.

3.6 Considerations for Aboriginal and Torres Strait Islander women

Aboriginal and Torres Strait Islander women are more likely to have a spontaneous vaginal birth than other Australians; however, they experience a much higher prevalence of factors that contribute to anaemia and iron deficiency, and their adverse effects.[86] Such factors include:

- higher fertility rate (2.6% Indigenous vs 1.9% non-Indigenous in 2009)[86] and higher parity
- more frequent teenage births (21% Indigenous vs 4% non-Indigenous in 2009)[86]
- more limited access to affordable nutritious food[86]
- higher rates of medical comorbidities, such as chronic renal disease, diabetes, chronic vascular disease and rheumatic heart disease[86]
- higher rates of hookworm in certain communities[87]
- higher rate of *H. pylori*.[88]

Other factors that disproportionately affect Indigenous Australians include:

- more likely to live in remote communities[86,89]
- less likely to participate in preventative health care[86] and less engagement in antenatal care (due to a variety of factors including lack of culturally safe services, financial barriers, transport issues and other community or family commitments that take priority)[89]
- more frequent single-parent families[86]
- higher smoking rate.[86,89]

[a] 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).

These factors may contribute to the:

- higher frequency of low birth weight and preterm birth than in non-Indigenous women (13.8% vs 8.1%)[86,89]
- higher perinatal mortality rate (13 per 1000 for Indigenous babies vs 9 per 1000 for other Australian babies).[86,89]

All the recommendations, practice points and expert opinion points contained in this guideline apply to Aboriginal and Torres Strait Islander women. Of particular importance in this population is the early detection and treatment of iron deficiency and iron deficiency anaemia (especially EOP1 and EOP2).

EXPERT OPINION POINTS – anaemia	
EOP1	In women at high risk of anaemia, ferritin should be tested along with FBC early in pregnancy to assess iron stores and anaemia. Other factors contributing to anaemia, such as deficiencies in folic acid and vitamin B12, or hookworm, should be screened for in selected women.

FBC, full blood count

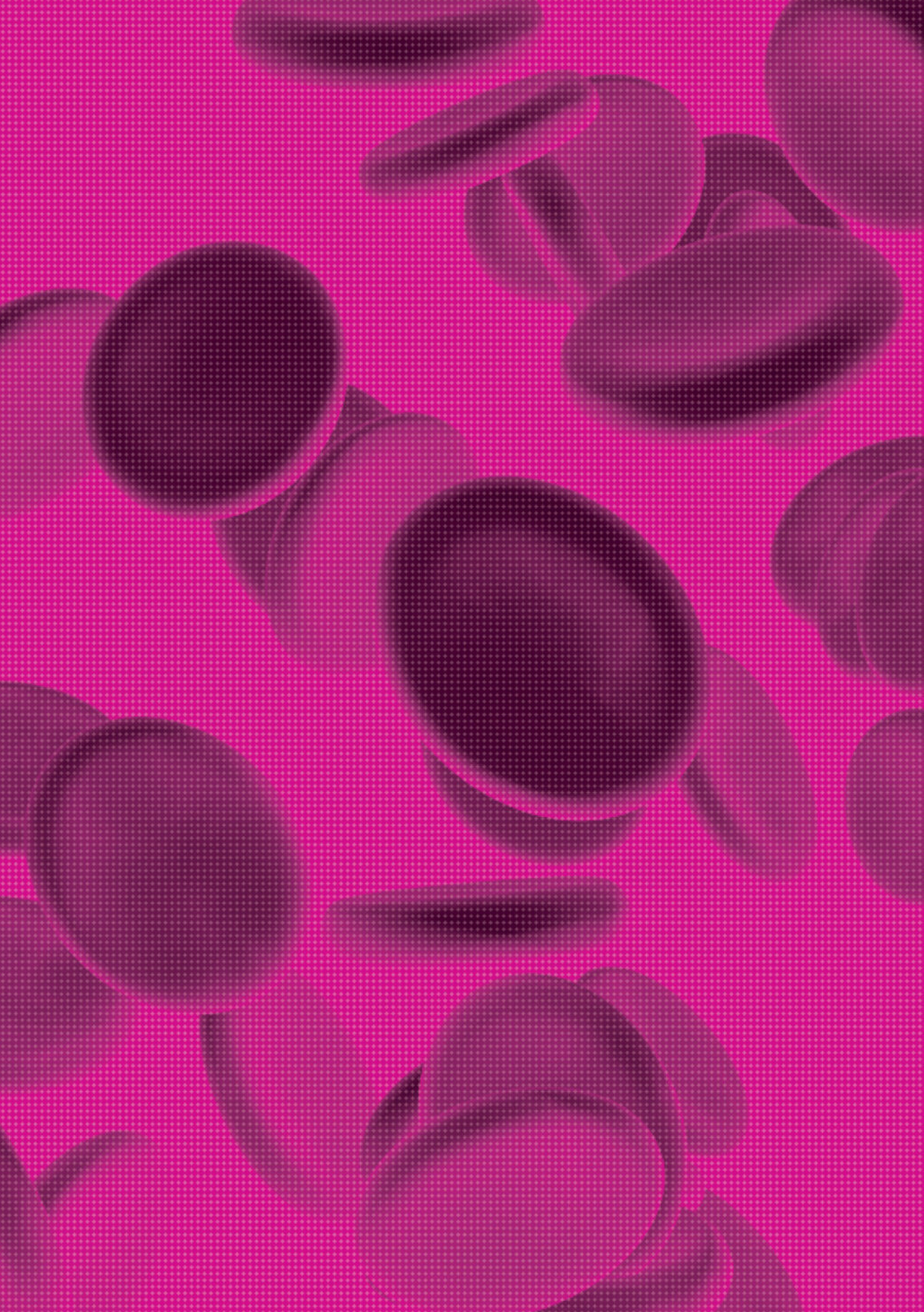
EOP2	Women should be provided with information and advice in relation to minimising anaemia, for example, by adequate spacing of pregnancies, consumption of a healthy diet and optimal management of any medical comorbidities.

EOP, expert opinion point; FBC, full blood count

EXPERT OPINION POINT – maternity services	
EOP5	Maternity services in rural and remote areas should develop management plans to minimise any delay in accessing specialist health-care services and resources, including blood products.

PRACTICE POINT – oral and/or parenteral iron	
PP13	The routine use of IM iron is not advised where alternatives are available.

IM, intramuscular; IV, intravenous; PP, practice point



4 Background questions

The CRG developed background questions in relation to PBM for maternity patients. The first pillar of PBM is optimisation of blood volume and red cell mass, and yet for maternity patients the level of Hb associated with best maternal and fetal outcomes remains unknown. The first question explores anaemia and its causes in pregnant women.

Blood transfusion is an uncommon intervention in maternity care;[90] however, since critical bleeding may occur rapidly and unexpectedly, all maternity services require procedures to respond appropriately to this event. Technical, logistical and planning aspects of transfusion support for maternity patients are explored further in background questions 2 to 4.

4.1 Anaemia as a risk factor

Background question 1

Is anaemia an independent risk factor for adverse pregnancy outcomes? What recommendations should be made for the detection, diagnosis and management of anaemia during pregnancy?

The purpose of this section is to explore the definitions and causes of anaemia, and the impact of anaemia on pregnancy outcomes.

EXPERT OPINION POINTS – anaemia	
EOP1	In women at high risk of anaemia, ferritin should be tested along with FBC early in pregnancy to assess iron stores and anaemia. Other factors contributing to anaemia, such as deficiencies in folic acid and vitamin B12, or hookworm, should be screened for in selected women.
EOP2	Women should be provided with information and advice in relation to minimising anaemia, for example, by adequate spacing of pregnancies, consumption of a healthy diet and optimal management of any medical comorbidities.

EOP, expert opinion point; FBC, full blood count

4.1.1 Definition of anaemia

There is no agreed normal range for Hb concentration in pregnant women in Australia. Although total red cell mass and plasma volume both increase during pregnancy, the relative changes result in Hb levels slightly below those found in age-matched non-pregnant women. Maternal Hb levels reach a nadir near the end of the second trimester. As outlined in Table 4.1, the US Centers for Disease Control and Prevention (CDC) have established that the lower limit for the normal range of Hb in the latter part of the second trimester is 103 g/L (two standard deviations [SD] below the mean of 116 g/L).[91]

Table 4.1 Haemoglobin levels in pregnancy, United States population

GESTATION (WEEKS)							
12	16	20	24	28	32	36	40
HAEMOGLOBIN (g/L), MEAN ± 2 STANDARD DEVIATIONS							
122 (±14)	118 (±14)	116 (±13)	116 (±13)	118 (±13)	121 (±13)	125 (±13)	129 (±13)

Source: CDC 1989[91]

Anaemia may be defined as a Hb concentration less than two SD below the mean for a specific population. In 1968, WHO determined that, in pregnant women, this equates to a Hb level of less than 110 g/L and/or a haematocrit of less than 0.33.[92] More recent WHO guidelines have maintained this definition; in addition, they classify Hb levels of less than 70 g/L as severe anaemia (requiring medical treatment), and those of less than 40 g/L as a medical emergency on account of the risk of maternal congestive cardiac failure.[93] Postpartum anaemia is defined by the WHO as a Hb level of less than 100 g/L.

The populations from which the WHO definition of normal Hb and anaemia is derived are predominantly from developing countries, which limits their applicability to the Australian population. More recently, normal reference ranges for Hb levels from a healthy, iron-replete Danish maternity population have been described; these are shown in Table 4.2.[94]

Table 4.2 Haemoglobin levels in pregnancy, Danish population

GESTATION (WEEKS)			
13–20	21–28	29–34	35–42
HAEMOGLOBIN (g/L), REFERENCE RANGE			
113–147	111–143	109–145	110–147

Source: Klainbard et al (2010)[94]

Although data are limited, the haematological parameters of Indigenous Australians are thought to be similar to those of non-Indigenous Australians, although a high prevalence of iron deficiency anaemia is noted in this population.[95]

4.1.2 The optimal haemoglobin range

There is evidence indicating an association between maternal anaemia and adverse pregnancy outcomes, including:

- low birth weight and preterm birth when mothers are anaemic in the first or second trimester[96]
- placental abruption,[97] maternal mortality[98] and postnatal depression.[99]

Studies that have generated this evidence have used the statistical definitions of anaemia outlined above; however, many confounding factors are present. A more specific Hb range that results in optimal maternal and perinatal outcomes (other than absence of statistically determined anaemia) has not been established. In light of evidence that higher Hb levels may also be associated with adverse pregnancy outcomes,[100] it would seem reasonable to assume that normal pregnancy haemoglobin levels lie between 103 and 146 g/L.

4.1.3 Causes of anaemia

Iron deficiency is the most common cause of anaemia in pregnancy, in both the developed and developing world.[93] Other causes of anaemia include megaloblastic anaemias due to vitamin B12 and folic acid deficiency, thalassaemias, haemolytic states (sickle cell disease, malaria and pre-eclampsia), helminthic infection and underlying malignancy or chronic disease.[101] The treatment of anaemia requires an accurate assessment of its underlying cause, but this can be difficult in pregnancy, where multiple factors may be responsible.

The preferred test of maternal iron status is the serum ferritin level,[93] although because ferritin is an acute phase reactant, levels can be elevated in inflammatory states. Other measures of iron status (e.g. serum iron, transferrin, transferrin receptors and erythrocyte protoporphyrin) have a limited role in pregnancy, due to restricted availability, cost and interpretive difficulties arising from non-standardised reference ranges and diurnal variation.

Women who have previously completed one or more pregnancies are at risk of iron deficiency at the start of any subsequent gestation, especially if the inter-pregnancy interval is short or their deliveries have been complicated by PPH. Other groups at special risk include adolescents,[102] Indigenous Australians,[24] and recent immigrants.[103,104] Low socioeconomic status confers an odds ratio of 1.419 for iron deficiency anaemia (95% CI 1.05–1.90).[105]

These and other at-risk groups should be targeted for assessment of iron status at the start of pregnancy.

4.2 Transfusion support for maternity services

Background question 2

What guidance can be given regarding transfusion support for maternity services?

The purpose of this section is to provide guidance on both the technical aspects of transfusion medicine related to pregnancy and the practicalities of blood product accessibility.

EXPERT OPINION POINTS – maternity services	
EOP3	All maternity services must have procedures in place to manage the critically bleeding maternity patient. This includes agreed communication and transport arrangements, access to transfusion medicine expertise and defined escalation strategies.
EOP4	All maternity services should liaise with their local pathology provider to ensure that information on local blood access arrangements is available to all clinicians (e.g. time to process 'group and hold' and cross-match blood, and availability of products).
EOP5	Maternity services in rural and remote areas should develop management plans to minimise any delay in accessing specialist health-care services and resources, including blood products.
EOP6	Women with identifiable risk factors for obstetric haemorrhage should, wherever possible, give birth in a maternity service capable of providing the appropriate level of care.
EOP7	In pregnant women at risk of major obstetric haemorrhage (e.g. women with placenta accreta or major placenta previa), a multidisciplinary management plan is strongly advised.

EXPERT OPINION POINTS – maternity services	
EOP8	It is strongly advised that maternity services develop an MTP that includes access to RBC and the dose, timing and ratio of blood component therapy, for use in maternity patients with critical bleeding requiring massive transfusion.
EOP9	All women should be offered routine blood group and antibody testing during pregnancy, with follow-up testing for Rh D negative women and women with alloantibodies capable of causing HDN. Women with antibodies associated with moderate and severe HDN (-D, -c, -K) should consult with a specialist obstetrician with relevant expertise.[a] [a] In accordance with *Guidelines for blood grouping & antibody screening in the antenatal & perinatal setting*[a]
EOP10	Women with clinically significant alloantibodies should have a blood group and antibody screen on admission, in labour or prior to vaginal or caesarean birth, to avoid potential delays in blood provision. Where complex antibodies or rare red cell phenotypes are identified, and provision of compatible blood may be difficult, the management plan should include timely access to specialist blood product support.
EOP11	Decisions regarding blood group and antibody screen prior to vaginal or caesarean birth should include a risk assessment for peripartum haemorrhage, and the presence of any factors that may delay access to blood, should it be required. Such factors include the presence of red cell alloantibodies, and the local arrangements for provision of testing and blood products.
EOP12	CMV safe blood products should be offered to all pregnant women, regardless of CMV status, when transfusion occurs in the antenatal setting in the context of an ongoing pregnancy. Preference is for CMV seronegative blood products, where available; however, life-saving transfusion should not be withheld if CMV seronegative products are not available. ** CMV 'safe' means through leucodepletion or antibody testing of donor blood. Neither process excludes the possibility of transfusion-transmitted infection; rather, they both provide a significant risk reduction. It is unknown whether CMV seronegative blood products provide significant additional protection over routine leucodepletion.*
EOP13	Where possible, K negative RBC should be selected for transfusion for all females of child-bearing potential who are K negative or whose K antigen status is unknown.

CMV, cytomegalovirus; EOP, expert opinion point; HDN, haemolytic disease of the newborn; RBC, red blood cell

4.2.1 Access to transfusion support

The National Maternity Services Capability Framework[106] establishes the minimum requirements of service provision for the six specified levels of maternity services in Australia, and thus determines the clinical complexity that can be managed at each level. The clinical complexity of each pregnancy requires ongoing evaluation because it often evolves through gestation, birth and the postnatal period. The discerning characteristics that relate to transfusion medicine include the scope of testing provided by a supporting pathology service, the location and hours of operation of the pathology service, and blood product access arrangements. The framework specifies on-site access to blood products for maternity services at or above Level 3.[106]

Major obstetric haemorrhage poses a challenge because it is rarely predictable. When risk factors are present, identification and escalation to the appropriate level of maternity care minimises the potential for morbidity and mortality. However, for a significant proportion of women, major obstetric haemorrhage occurs in the absence of identifiable risk factors.

4.2.2 High-risk populations

From a transfusion medicine perspective, maternity patients in the following categories are at increased risk:

- women at increased risk of obstetric haemorrhage[19]
- women with bleeding disorders
- women who will be difficult to transfuse because of the presence of complex antibodies or rare red cell phenotypes.

Each of these categories is discussed below.

Obstetric haemorrhage

Obstetric haemorrhage remains a significant cause of maternal mortality in Australia; it contributes to maternal morbidity, and complicates 3–6% of pregnancies.[107] Its impact on maternal health and resource use has not been adequately measured.[108] Identifiable risk factors, when present, are generally those that contribute to uterine atony, lacerations or the need for surgical intervention. Those identifiable before the onset of labour include placental abruption, placenta previa, multiple pregnancy and pre-eclampsia. Those that usually become apparent during labour and birth include emergency caesarean section, retained placenta, assisted vaginal birth, prolonged labour and macrosomia.

Bleeding disorders

Inherited and acquired bleeding disorders increase the risk of PPH and the complexity of transfusion management. Acquired conditions include severe pre-eclampsia, HELLP syndrome (the acronym is derived from a combination of haemolysis, elevated liver enzymes and low platelet count), PPH itself (where DIC is often an early feature), amniotic fluid embolism and anticoagulant therapy. Women with inherited bleeding disorders – including von Willebrand disease, haemophilia carrier state and Factor XI deficiency – are at greater risk of PPH, and thus require specialist care.[109-111]

Complex antibodies or rare phenotypes

Red cell alloantibodies can develop in response to previous transfusions or pregnancy, and have the potential to cause haemolytic transfusion reactions and haemolytic disease of the newborn (HDN). Pretransfusion testing involves the detection and identification of alloantibodies, with provision of cross-match compatible, antigen-negative blood. Depending on the complexity of antibodies involved, this testing may take several hours to days to complete.

Rare red cell phenotypes occur when a person lacks an antigen or antigens that are usually present in the population. Finding compatible blood may pose a significant challenge, depending on the antigen involved, and it may include the following strategies: use of autologous blood, or use of stored or frozen RBC sourced from local, national or international blood services.

Routine testing during pregnancy will identify the presence of alloantibodies or rare red cell phenotypes, so that appropriate specialty testing, referral and provision of compatible blood can occur.

4.2.3 Guidelines for pretransfusion laboratory testing

Laboratory transfusion support for maternity services takes into account issues affecting both the fetus and the mother, in the index pregnancy and any future pregnancy. The aim is to provide safe, appropriate transfusion strategies and minimise the incidence and severity of HDN.

The Australian and New Zealand Society for Blood Transfusion (ANZSBT), in conjunction with relevant parties, has produced two guidelines:

- *Guidelines for Blood Grouping & Antibody Screening in the Antenatal & Perinatal Setting*[9]
- *Guidelines for Pretransfusion Laboratory Practice*.[112]

These documents guide testing, timing of tests and interpretation of results in relation to all maternity patients, to identify:

- Rh D negative women who will benefit from immunoprophylaxis
- pregnancies complicated by alloantibodies that may cause HDN, or have the potential to impact on blood availability in the event that transfusion is required.

4.2.4 Role of blood group and antibody screening before birth

The *Guidelines for Blood Grouping & Antibody Screening in the Antenatal & Perinatal Setting*[9] stipulate that blood group and antibody screening must be performed as part of pretransfusion testing. Beyond this indication, there is no general consensus about the role of routine blood group and antibody screening at time of giving birth. Opinions vary, depending on the complexity of the pregnancy and mode of giving birth.

Vaginal birth

Consensus from the literature suggests that performance of blood group and antibody screening at the time of giving birth should be reserved for women at increased risk of peripartum haemorrhage as defined by the presence of identifiable risk factors.

Caesarean birth

There is controversy about the role of blood group and antibody screening prior to caesarean birth. A coronial inquiry into a maternal death associated with PPH in New South Wales (NSW) recommended routine blood group and antibody screening prior to caesarean birth.[113] However, recent Australian data suggest that the likelihood of transfusion following elective caesarean birth is low for women without established risk factors, and that routine blood group and antibody screening is not cost effective.[114]

4.2.5 Red cell selection for maternity patients requiring transfusion

Cytomegalovirus

Cytomegalovirus (CMV) infection is the most common cause of congenital infection, affecting about 1% of neonates worldwide; the infection has significant long-term sequelae and a fatality rate of about 20%.[115,116] Congenital CMV infection can occur in the context of maternal primary infection, reinfection with a new strain of the virus or (less commonly) reactivation of latent infection. Although most congenital CMV infection is community acquired rather than transfusion related, the potential serious impact of exposure to CMV during pregnancy underscores the need for transfusion of CMV 'safe' (leucodepleted) blood products to pregnant women.

The ANZSBT guidelines recommend the provision of CMV antibody negative or CMV 'safe' blood products for pregnant women who receive cellular transfusion in the context of an ongoing pregnancy.[112] Neither of these methods completely eliminates the risk of transfusion transmitted CMV infection, with 'breakthrough' rates of infection reported to occur in about 1–3% of transfused high-risk patients.[117] Breakthrough infections are currently thought to be the result of transfusion of cell-free CMV.

Kell antigen system

Within the Kell system, the K antigen is the antigen of greatest clinical relevance in pregnancy. K isoimmunisation in pregnancy is the most common cause of severe HDN outside the Rh system, with an incidence of 1 per 1000 pregnancies. K sensitization is associated with a high risk of severe HDN, with up to 50% of cases developing severe HDN requiring intervention.[118] It is estimated that 50–88% of anti-K antibodies develop as a result of previous blood transfusion. Where possible, K negative RBC should be selected for transfusion for all females of child-bearing potential who are K negative or whose K antigen status is unknown. In the Australian context, donor K status is generally indicated on the blood product label.

4.3 Adapting or modifying a massive transfusion protocol

Background question 3

What obstetric-specific factors should be considered in adapting and/or modifying a massive transfusion protocol?

This question focuses on the areas of an MTP that could be modified to better manage critical bleeding in maternity patients.

EXPERT OPINION POINTS – adapting or modifying a massive transfusion protocol	
EOP14	In the maternity population, activate MTPs early.
EOP15	The MTP should be modified for the maternity patient, because fibrinogen levels approaching 2 g/L are indicative of critical physiological derangement and are associated with severe haemorrhage.

EOP, expert opinion point; MTP, massive transfusion protocol

4.3.1 Trigger and activation of massive transfusion protocol

The purpose of the MTP is to trigger a multidisciplinary response to critical bleeding. Transfusion support needs to occur simultaneously with measures to arrest bleeding.[20] Obstetric haemorrhage is often underestimated and may be concealed; delays in recognition and response contribute to the severity of haemorrhage, and to maternal morbidity and mortality; and profound coagulopathy and DIC may develop rapidly and early.

4.3.2 Administration of blood products

Red blood cells

In the context of rapid bleeding, RBC transfusion is given in response to haemodynamic changes and estimated blood loss, rather than to a Hb trigger. Most women will tolerate blood loss of up to 1000 mL without requiring immediate RBC transfusion.

Platelets

Standard MTPs suggest platelet transfusion once the platelet count falls below 50 × 10^9/L. This level is also suggested by the RCOG guidelines.[27] It is uncertain what the optimal platelet count should be, or whether early transfusion is beneficial.[119]

Fresh frozen plasma

There is no evidence to suggest that dose and timing of FFP in the critically bleeding maternity patient should differ from standard MTPs, except when DIC is present.

Cryoprecipitate and fibrinogen concentrate

In maternity patients, fibrinogen levels increase to an average of 5–6 g/L by term (compared to non-pregnant levels of 2.0–4.5 g/L).[120,121] Low fibrinogen levels are an independent risk factor for development of severe PPH,[122–124] with one study showing levels below 2 g/L having a 100% positive predictive value for development of severe PPH.[122] In their review, de Lloyd et al (2011) also showed a correlation between fibrinogen levels and blood loss.[123] This has led some authors to propose a change in the trigger for supplementing fibrinogen to <2.0 g/L,[119] or a rapidly falling level in the context of ongoing bleeding.

In Australia, the most common way of increasing plasma fibrinogen levels is to transfuse cryoprecipitate. This plasma-derived blood product contains high levels of fibrinogen, factor VIII, von Willebrand factor, factor XIII and fibronectin. To provide a dose of 3–4 g of fibrinogen, about 8–10 bags (normally 30–40 mL), which require thawing, have to be given.[1]

Case reports[125,126] of fibrinogen concentrate use during obstetric bleeding have recently been published. The FIB-PPH trial recently completed assessed the role of 2 g of fibrinogen in PPH.[121] Although available in Australia, fibrinogen concentrate is not currently licensed for use in obstetric haemorrhage.

Tranexamic acid

There is no evidence to suggest that dose and timing of TXA in the critically bleeding maternity patient should differ from standard MTPs.

Recombinant activated factor VII

There is no evidence to suggest that dose and timing of rFVIIa in the critically bleeding maternity patient should differ from standard MTPs.

4.3.3 Permissive hypotension

The role of permissive hypotension in the maternity patient is uncertain, because there is concern that it may compromise fetal well-being and uterine contractility in the postpartum patient.

4.4 Care of patients in whom transfusion is not an option

Background question 4

What guidance can be provided to assist in the care of maternity patients in whom transfusion is not an option?

Blood transfusion may not be a management option in some situations (e.g. due to personal choice, religious and/or cultural beliefs, the presence of rare blood groups or complex antibodies, or the unavailability of blood products). Observational studies suggest an increased risk of maternal morbidity and mortality in such circumstances, with substandard care (including delayed decision making) contributing to poorer outcomes.[127,128]

EXPERT OPINION POINTS – care of patients in whom transfusion is not an option	
EOP16	In all maternity patients, it is good clinical practice to optimise Hb during the antenatal period, minimise blood loss during birth and, in the event of haemorrhage, secure haemostasis as a matter of urgency. This is vital in patients for whom transfusion is not an option.
EOP17	To arrest significant and life-threatening haemorrhage, when transfusion is not an option, the definitive procedure to minimise ongoing blood loss is hysterectomy, which must be considered and acted upon early.
EOP18	Early identification of women for whom transfusion is not an option is vital, to enable a comprehensive multidisciplinary plan to be developed and implemented.

EOP, expert opinion point; Hb, haemoglobin

4.4.1 Antenatal care

- Early in the antenatal period, identify women for whom provision of transfusion support is likely to be difficult (e.g. rare blood groups).
- A multidisciplinary team should provide maternity care and counsel the woman about the increased risk of maternal morbidity and mortality associated with not receiving a transfusion when it is indicated. The discussion needs to be individualised, to determine the specific blood products and alternatives to blood products that are acceptable to the woman. Document the advice provided and the woman's preferences in the antenatal record and in a legally valid format.
- Identify and manage anaemia and iron deficiency according to established guidelines.
- Assess women for bleeding risk, including established obstetric risk factors for bleeding, use of anticoagulants, a personal history of an inherited or acquired bleeding disorder, and family history of bleeding disorder.
- Advise women at high risk of bleeding to give birth at a site that has access to surgical expertise, IR and cell salvage if this is an acceptable option.

- Prescribe antenatal iron therapy for women in whom substantial blood loss is expected and who have suboptimal iron stores (i.e. ferritin <100 µg/L).[2]
- Consider ESAs in selected women at high risk of substantial blood loss. When an ESA is used, it must be combined with iron therapy.

4.4.2 Management in labour

- Inform appropriate senior staff when the woman is admitted in labour.
- Active management of the third stage of labour with oxytocics is advised.
- Careful observation and monitoring of the woman – including recording of blood loss and fundal assessment in the first hours after giving birth – is advised, to ensure early detection and appropriate management of abnormal bleeding.

4.4.3 Management of haemorrhage

Early definitive management may be life-saving when blood products are not available to assist in optimising oxygen delivery, cardiac output and haemostasis.

- Involve senior staff and activate postpartum bleeding protocols with rapid progression to the next intervention if haemorrhage is not rapidly controlled.
- Consider operative management (including balloon tamponade) and IR earlier than usual.
- Consider cell salvage if available and acceptable to the woman.
- Consider pharmacologic agents, including topical haemostatic agents, to assist in haemostasis.
- Consider cryoprecipitate, fibrinogen concentrate or prothrombin complex concentrate when available and acceptable to the woman.

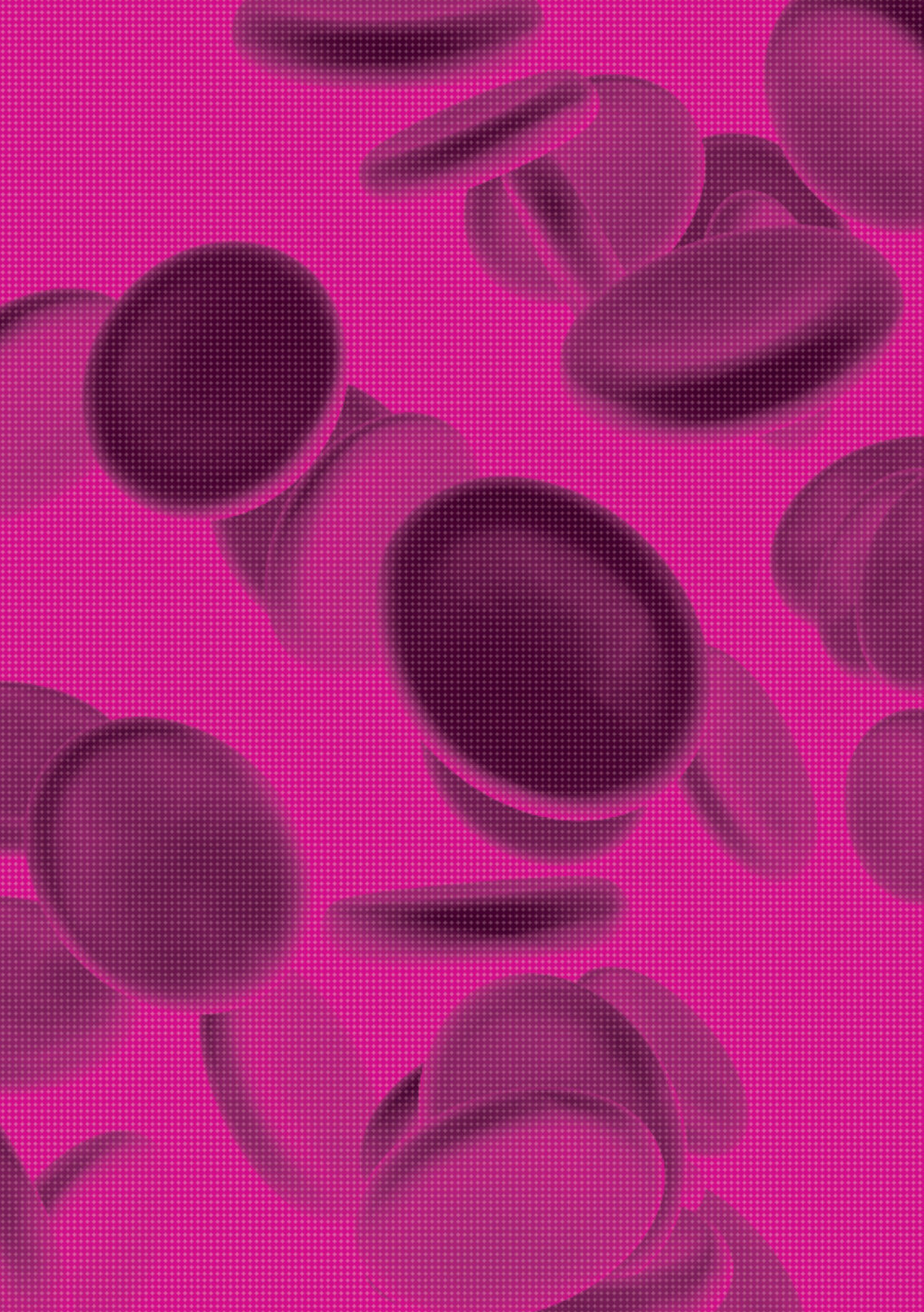
4.4.4 Management of postpartum anaemia

Use IV iron in women with moderate postpartum anaemia, and consider the addition of ESAs where anaemia is severe.

In the case of severe acute postpartum anaemia, management should be guided by early and ongoing expert advice.

4.4.5 Legal and ethical aspects

In any situation where refusal of transfusion may affect the health of a fetus (e.g. profound maternal antenatal anaemia, intrauterine transfusion), obtain legal advice and complete relevant documentation, as per jurisdictional requirements.



5 Future directions

The systematic review for this module found sufficient evidence to make recommendations on the use of iron and ESA therapy in the maternity patient.

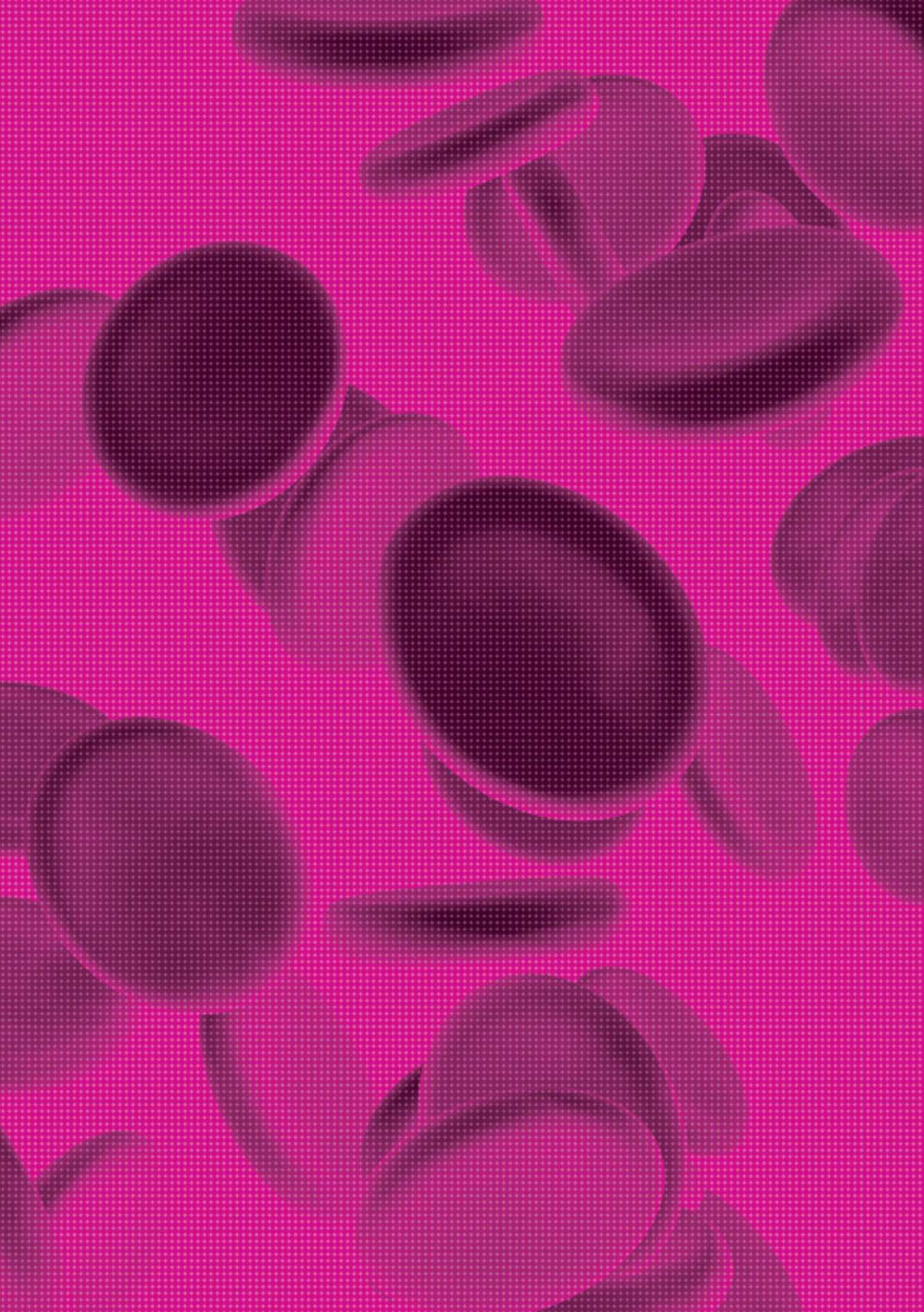
There were a number of areas where there was insufficient evidence to generate recommendations. These areas, which are outlined below, may present avenues for further research.

5.1 Evidence gaps and areas of future research

- in maternity patients in general:
  - the Hb and ferritin levels that are associated with optimal maternal and fetal outcomes
  - the clinically relevant degree of anaemia that equates to 'optimisation' of Hb
  - the degree of anaemia that is clinically relevant
  - the relationship between different levels of anaemia and functional and performance levels
  - when and how frequently iron stores should be assessed during pregnancy
- in the bleeding maternity patient:
  - the effect of transfusion on patient-centred outcomes, including mortality, morbidity, postnatal recovery, quality of life, functional status, breastfeeding and psychological health
  - the place of an MTP, and the need to adapt the MTP to match the specific needs of this population; for example, 'permitted hypotension' may be a contraindication in management of obstetric haemorrhage if the uterus is still in situ and the aim is to optimise the chance for the uterus to contract (and respond to medical management)
- in anaemic women who are not actively bleeding, the effect of transfusion on patient outcomes
- the impact of routine iron supplementation in pregnancy and in iron deficiency anaemia (studies should focus on patient-centred outcomes as well as laboratory measures, and should report on compliance)
- the effect of giving birth on hepcidin levels and iron absorption
- in women with moderate to severe postpartum anaemia, the comparative efficacy of IV iron versus RBC transfusion on short and long-term patient outcomes
- studies should include sufficient iron because studies show that IV iron makes a difference to the response to ESA (most studies of ESAs do not include sufficient iron)
- optimal strategies for using blood components and plasma products in the management of obstetric haemorrhage
- the effect of early administration of fibrinogen on progression to severe PPH, and whether there is an advantage to having access to fibrinogen concentrate
- what is the optimal strategy for use of blood components and plasma products including cryoprecipitate, fibrinogen concentrate and platelet transfusion in women with obstetric haemorrhage?
- at what level of thrombocytopenia is there an increase in bleeding risk for vaginal and caesarean birth?
- determining the values of laboratory measures of haemostasis which are associated with adverse outcomes
- the haemostatic changes that occur during normal birth and in the context of PPH, and the role of POC testing in the management of PPH
- the role (if any) of cell salvage in maternity patients, and if there is a role, in which groups

- the safety of IR techniques in maternity patients (direct procedural complications of arterial thrombosis and dissection have been reported, but rates and outcomes following complications are unknown)
- whether the administration of rFVIIa, in addition to standard obstetric, surgical and transfusion approaches, reduces morbidity and mortality in women with severe haemorrhage
- whether early administration of rFVIIa can prevent hysterectomy in women with severe haemorrhage
- the role (if any) for TXA in the management of PPH
- whether there is a role for prophylactic administration of TXA in women at high risk of major haemorrhage[a]
- the role of TXA in management of antepartum haemorrhage
- research to inform targeted care of Aboriginal and Torres Strait Islander maternity populations.

[a] The World Maternal Antifibrinolytic Trial (The WOMAN Trial) is a large, multicentre, randomised, double-blinded, placebo controlled trial currently underway to investigate the effect of TXA administration early in the course of PPH



6 Implementing, evaluating and maintaining the guidelines

6.1 Implementation strategies

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.[129] 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 non-compliance with the guidelines.

The results of the evaluation will be used to inform future development and review of the guidelines. Economic issues were considered when formulating the evidence-based recommendations, and these recommendations will have cost implications. The NBA, together with the Jurisdictional Blood Committee (JBC) and key stakeholders, developed the *National Patient Blood Management Guidelines Implementation Strategy 2013–17*[130] to facilitate uptake of the guidelines.

The implementation strategy includes the development of tools to support the introduction of PBM practices in the clinical setting. The tools are being developed with the help of a network of clinicians with an interest in PBM. The NBA has also funded the development of online courses within the BloodSafe eLearning Australia Program (e.g. iron deficiency anaemia, PBM, Critical Bleeding and Perioperative). In addition, the NBA, in collaboration with the Australian Commission on Safety and Quality in Health Care (ACSQHC), has developed a hospital guide to support the implementation of the *National Safety and Quality Health Service Standards*.[131] The guide provides links to the PBM guidelines and tools, and the BloodSafe eLearning Australia courses. These resources provide tools to support uptake of the recommendations in this module.

6.2 Endorsement

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

[a] http://www.blood.gov.au/

6.3 Scheduled review and update

This module will be reviewed and amended in 2019 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.

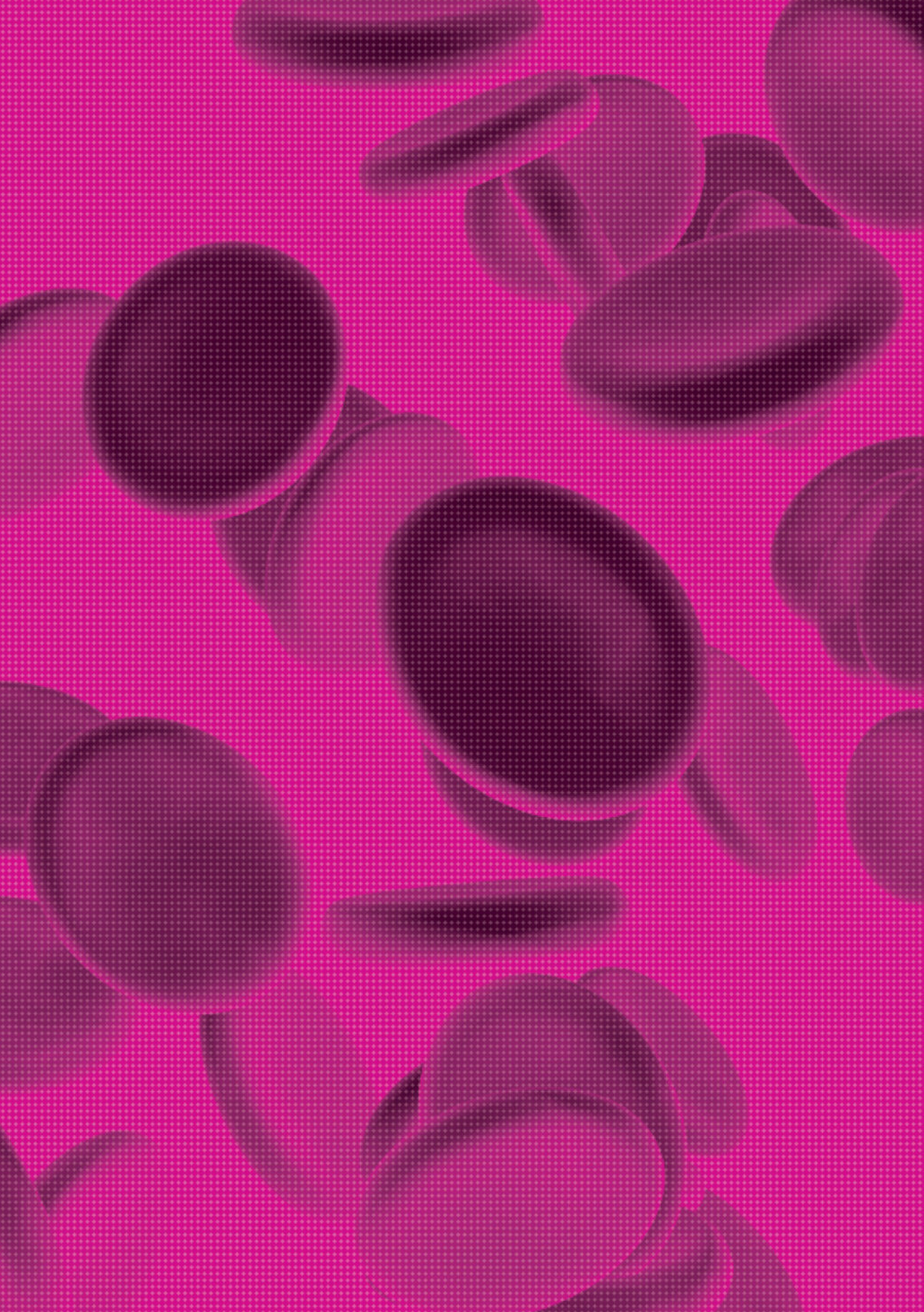
To provide feedback and inform future reviews of this module, please send any comments on its content, implementation, or the accompanying materials, to:

Email: guidelines@blood.gov.au

Mail: Patient Blood Management Guidelines
National Blood Authority
Locked Bag 8430
Canberra ACT 2601

Fax: +61 2 6151 5300

Any correspondence will be forwarded to the project manager for consideration in the next scheduled review.



Appendix A
Governance

A1 Governance structure

A multilevel management framework was established by the NBA to coordinate the development of the new PBM guidelines. The management framework consists of:

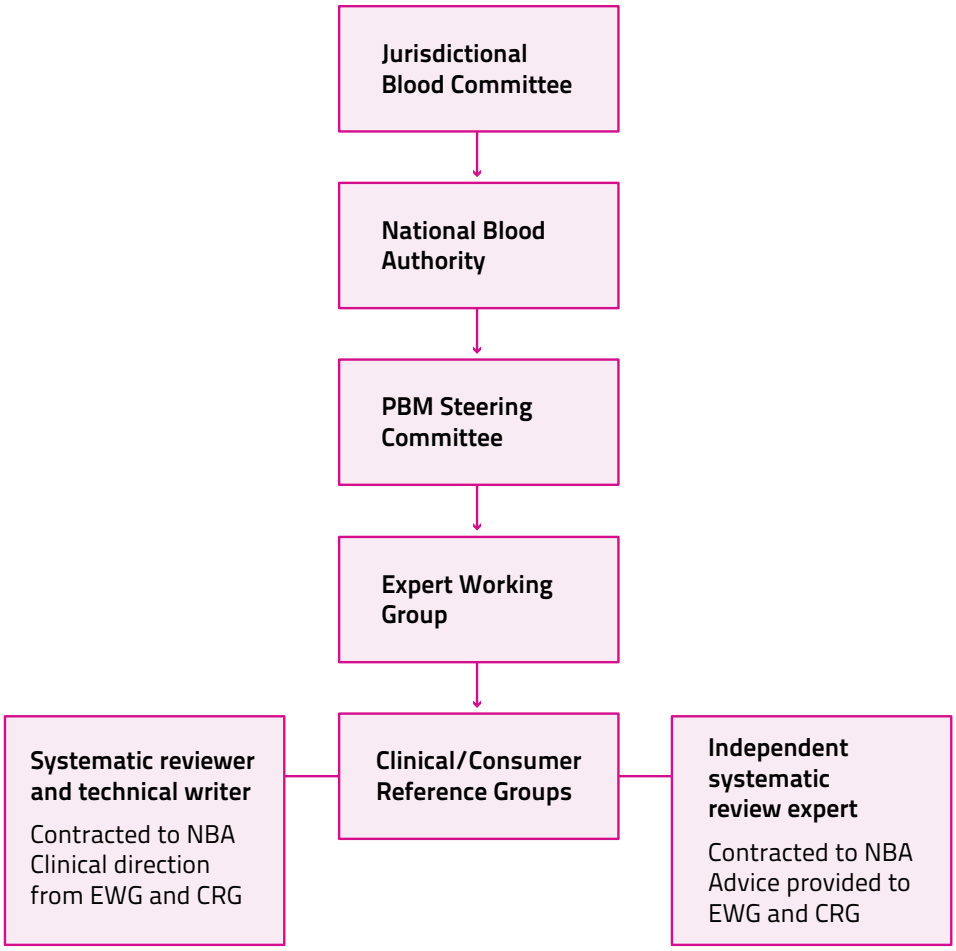
- a Steering Committee, which was responsible for the initial development and governance of the entire project; this has now become the PBM Steering Committee, which oversees the implementation strategy for the PBM Guidelines
- an Expert Working Group (EWG), responsible for providing advice on scope, 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 provided the secretariat, project funding and project management. Appendix A3 lists the membership of the bodies involved in governance of the guidelines. Details of how the guidelines will be implemented and updated are provided in Chapter 6.

A1.1 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



CRG, Clinical/Consumer Reference Group; EWG, Expert Working Group; NBA, National Blood Authority; PBM, Patient Blood Management

A2 Terms of reference

Steering Committee

The overarching Steering Committee was originally established in 2009 to provide coordination and direction for development of the guidelines. In 2012–13, its role and membership was reviewed and a PBM Steering Committee was established to:

- provide information through the NBA to the JBC
- review resources that are developed as part of the PBM Guidelines implementation strategy
- provide expert advice on:
  - the design and delivery of PBM activities
  - PBM implementation and evaluation initiatives
  - system based approaches to sustain PBM practices
  - the management, administration and use of fresh and other blood products excluding normal polyvalent immunoglobulin and clotting factors
  - education and training priorities
  - practice performance improvement
  - data and system requirements
- influence the uptake of PBM practice
- improve intergovernmental coordination and cooperation on PBM implementation activities
- monitor guideline development projects to ensure they meet their objectives
- link the PBM program activities to deliver the priorities for the *National Safety and Quality Health Service (NSQHS) Standards*[131]
- integrate the PBM program with the ACSQHC initiatives for delivery to health providers and their safety and quality framework
- network with other NBA committees to share information.

Expert Working Group

The EWG was established in 2009 to advise the original steering committee about the scope and structure of the guidelines, and determine the focus the systematic review of the literature. In 2012-13, its role and membership was reviewed and the new terms of reference were to provide advice to the NBA on the scope of the modules, and approve the focus of the systematic review questions and literature search strategies. Each member of the EWG is responsible for overseeing the conduct of the systematic review in relation to their area of practice as either a member or Chair of the relevant CRG. Each EWG member is responsible for ensuring that the scope of the modules is appropriate, and that they address areas of clinical need.

The role of the EWG is to:

- formulate the generic clinical questions to be answered in all modules by the literature review (under the guidance of the systematic reviewers)
- identify the need for CRGs, participating in or chairing these groups as required, and identifying and nominating additional CRG members as required
- consider the specific clinical questions and systematic review specifications developed by the CRGs and, if necessary, make recommendations to the NBA on revisions
- consider the scope of the project as referred by the CRGs and, if necessary, make recommendations to the NBA on revisions
- consider and provide advice to the NBA as to whether interests declared by Chairs of the CRGs present a conflict and suggest strategies to manage these declarations
- consider and provide advice, as requested by CRG Chairs, about interests declared by members of the CRG, to assist the Chair to manage declared interests to minimise potential bias in clinical practice guidance.

Clinical/Consumer Reference Groups

The CRGs provide clinical and consumer input to the systematic review, draft the module and provide guidance on relevant additional clinician and consumer information. The role of each CRG is to:

- under the guidance of the systematic reviewers, formulate the specific clinical question for their module
- under the guidance of the systematic reviewers, define the literature search strategies for all the clinical questions
- review the medical literature
- provide advice on current practice in their area of expertise
- under the guidance of the systematic reviewers and medical writer, formulate evidence-based recommendations based on the results of the review
- under the guidance of the systematic reviewers and medical writer, formulate practice points based on expert consensus opinion
- under the guidance of the systematic reviewers, ensure their analysis and grading of the literature and recommendations follows NHMRC procedures and meets the 2011 standards
- define the structure of the module
- take responsibility for drafting content of the module in their area of expertise (as assigned by the Chair and agreed by all members)
- under the guidance of the systematic reviewers and medical writer, draft the content of the module
- review public consultation feedback and make changes as required
- propose relevant additional clinician and consumer materials
- propose tools and strategies to support implementation.

Consumer selection process

An open recruitment process was used to seek interested consumers to participate on the CRG. The consumer representative and Indigenous representative positions were advertised on the NBA website, and forwarded to the Consumer Health Forum and major consumer organisations in each state and territory in Australia. Applications were reviewed by the NBA Executive Director – Fresh, Data and Clinical Development, Director – Blood Sector Clinical Development, PBM Guidelines Project Manager, and the Chair of the CRG. Upon notification and acceptance of their selection on the group, the representatives were provided with an orientation pack, and a face-to-face meeting was held (where possible) before the first meeting. The following documentation was provided:

- 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 Australian health-care system
- FAQs: 'What are the PBM Guidelines?'
- an overview of the NBA
- a background on the PBM guidelines
- NHMRC tables:
  - levels of evidence hierarchy
  - ratings for the body of evidence
  - grades for recommendations
- hard copies of each previous module
- links to relevant pages and documents about PBM on the NBA website.

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.

A3 Membership of bodies involved in governance of the guidelines

Steering Committee

Dr Lilon Bandler	General Practice and community medicine
Ms Karen Carey	Consumers Health Forum
Dr Steve Flecknoe-Brown	Haematology
Ms Trudi Gallagher	Jurisdictional PBM coordinator/Clinical Nurse Consultant
Prof James Isbister	Clinical Academic Expert
Ms Kathy Meleady	Australian Commission on Quality and Safety in Healthcare
Dr Beverley Rowbotham	Private pathology
Dr Ben Saxon	Australian Red Cross Blood Service
Dr Amanda Thomson	Australian & New Zealand Society of Blood Transfusion
Prof Simon Towler	Patient Blood Management Expert and Chair

Expert Working Group

A/Prof Mark Dean	Royal Australasian College of Physicians and Haematology Society of Australia & New Zealand
A/Prof Craig French	Australian and New Zealand Intensive Care Society and College of Intensive Care Medicine of Australia and New Zealand
A/Prof Helen Liley	Royal Australasian College of Physicians (Paediatrics and Child Health Division) and Perinatal Society of Australia and New Zealand
A/Prof Larry McNicol	Australian and New Zealand College of Anaesthetists
Dr Helen Savoia	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
Dr Amanda Thomson	Australian & New Zealand Society of Blood Transfusion

Clinical/Consumer Reference Group – Obstetrics and Maternity module

Dr Weragoda Abeypala	Obstetric anaesthetist	Australian and New Zealand College of Anaesthetists
Dr Daniel Challis	Obstetrician and Maternal fetal medicine sub-specialist	Royal Australian and New Zealand College of Obstetricians and Gynaecologists and Perinatal Society of Australia and New Zealand
Dr Marilyn Clarke	Indigenous representative	Not applicable
Mr Shannon Farmer	PBM consultant	Not applicable

A/Prof Craig French	Intensive care physician	Australian and New Zealand Intensive Care Society and College of Intensive Care Medicine of Australia and New Zealand
Dr Claire McLintock	Haematologist and obstetric physician	Australasian Society of Thrombosis & Haemostasis and Society of Obstetric Medicine of Australia and New Zealand
Prof Michael Permezel	Obstetrician and gynaecologist	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
Dr Wendy Pollock	Critical care nurse and midwife	Australian College of Midwives
Dr Shelley Rowlands	Obstetrician and Maternal fetal medicine sub-specialist	Royal Australian and New Zealand College of Obstetricians and Gynaecologists and Perinatal Society of Australia and New Zealand
Dr Helen Savoia	Haematologist	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
Dr Amanda Thomson	Haematologist	Australian & New Zealand Society of Blood Transfusion
Ms Catherine Whitby	Consumer representative	Not applicable

Background Researchers

Dr Carin Black	Obstetric & Gynaecology trainee, Royal Women's Hospital, Melbourne (Supervisors Dr Shelley Rowlands, Dr Marilyn Clarke, Dr Wendy Pollock, A/Prof Craig French, Dr Helen Savoia)
Dr Lisa Clarke	Haematology Registrar, Prince of Wales Hospital, Sydney (Supervisors Dr Helen Savoia and Dr Amanda Thomson)
Dr Stefan Kane	Obstetric & Gynaecology trainee, Royal Women's Hospital, Melbourne (Supervisors Dr Shelley Rowlands, Dr Marilyn Clarke, Dr Wendy Pollock, A/Prof Craig French, Dr Helen Savoia)
Dr Giselle Kidson-Gerber	Consultant Haematologist, Prince of Wales Hospital and Royal Hospital for Women, Sydney (Supervisors Dr Daniel Challis, Dr Helen Savoia, Mr Shannon Farmer)
Dr Patrick Nelmes	Anaesthetic Registrar, Royal Brisbane and Women's Hospital (Supervisors Dr Weragoda Abeypala, Dr Helen Savoia, Dr Claire McLintock)

Independent systematic review expert

A/Prof Tracy Merlin	Adelaide Health Technology Assessment, University of Adelaide

Project Management and Committee Secretariat – National Blood Authority

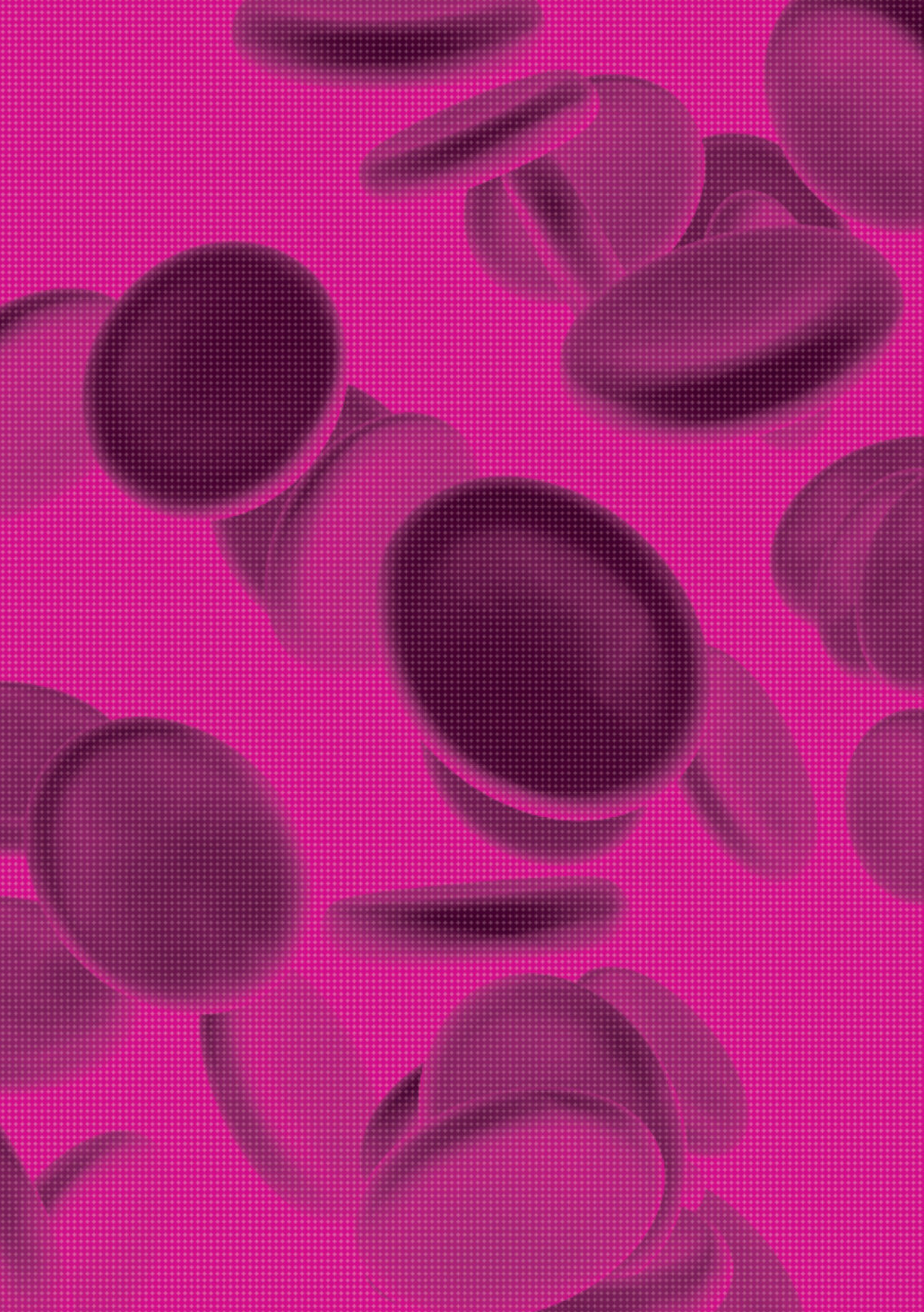
Ms Donna Cassoni	Project Officer, Blood Sector Clinical Development
Ms Leia Earnshaw	Assistant Director, Blood Sector Clinical Development
Ms Jennifer Roberts	Director, Blood Sector Clinical Development

Systematic review team – Optum

Ms Katherine Applegarth	Research Analyst, Life Sciences
Dr Margaret Jorgensen	Senior Project Leader, Life Sciences
Ms Alison Mahony	Research Analyst, Life Sciences
Ms Gabrielle Mears	Research Analyst, Life Sciences

Medical writing (module only) and technical editing

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



Appendix B
Process report

B1 Development process and methodology

Further information on the development process and methods is included in Chapters 1 and 2, and Appendix A.

B2 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. These processes are outlined in further detail in Chapter 1 and Appendix A.

B3 Methodology

Methods are outlined in Chapter 2, with greater detail given in the technical reports.[6,7]

B4 Consensus process

Consensus process for developing practice points and expert opinion

In circumstances where no evidence was identified, practice points were developed by the CRG through a consensus-based process. Where relevant guidance that was outside of the scope of the systematic review was required, consensus-based 'expert opinion' was included (e.g. background research in Chapter 4).

Guiding principles and values, and 'ground rules' were established, and the following process was used to develop practice points and expert opinion through consensus.

Stage 1 – Introduction. The Chair described the consensus process, participants' roles and responsibilities, ground rules and the guiding principles.

Stage 2 – Open discussion. The Chair opened the floor to a general discussion and suggestions for practice point/expert opinion wording. The Chair provided an opportunity for concerns or issues to be raised.

Stage 3 – Resolve concerns. The Chair has the first option to resolve the listed concerns by clarifying or changing the wording, or seeing whether those with concerns will stand aside (i.e. 'had concerns, but could live with them'). Where concerns were not resolved and the time was short, the discussion was carried over to a later meeting.

Stage 4 – First call for consensus. The Chair called for consensus.

Stage 5 – Second call for consensus. If consensus was not reached, the CRG considered the consensus process guiding principles and values, and:

- the member withdrew the concern and consensus was reached
- the member stood aside and the differing schools of thought were documented
- the member was not willing to withdraw the concern or stand aside, and the CRG declared itself blocked – the practice point or expert opinion was not accepted.

B5 Conflict of interest

All members of the Steering Committee, CRG, EWG and systematic review team declared any interests before starting work on the guidelines. Declarations were also reviewed at intervals, as new declarations were required to be declared to the Chair prior to the start of each meeting as a standing agenda item on each day of a meeting. The NBA keeps a register of all declared interests. If an interest is declared, and the Chair decides it should be considered by the CRG, 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.

The following declarations were made during the guideline development process:

Dr Weragoda Abeypala	Nil.
Dr Carin Black	Nil.
Dr Daniel Challis	Nil.
Dr Lisa Clarke	Nil.
Dr Marilyn Clarke	Nil.
Mr Shannon Farmer	Mr Farmer is a consultant in PBM. He has received lecturing/consulting honoraria/travel support from: ▪ AdvancMed (USA) ▪ Australian JBC ▪ Australian NBA ▪ Australia Pacific Health Group ▪ Australian Red Cross Blood Service ▪ Beijing Municipal Health Bureau (China) ▪ Department of Health NSW ▪ Department of Health Queensland ▪ Department of Health SA ▪ Department of Health Western Australia ▪ Janssen-Cilag (Australia) ▪ Johnson & Johnson, ETHICON Biosurgery (Australia, Europe, Asia Pacific & USA) ▪ Medical Society for Blood Management (Europe) ▪ Medtel Pty Ltd (Australia) ▪ Novo Nordisk (Australia) ▪ Society for the Advancement of Blood Management (USA) ▪ Vifor Pharma (Europe)

Mr Shannon Farmer (cont.)	In 2008 he served on J&J ETHICON Biosurgery International Ad Board for PBM. He is a chief investigator and a principal investigator for two State Health Research Advisory Council (SHRAC) research grants: ▪ Primary care and tertiary care clinicians working with patients to ensure they are "Fit for Surgery" ▪ **I**ntravenous i**R**on or placeb**O** for a**N**ae**M**i**A** in i**N**tensive care: a randomised controlled study: The IRONMAN Study. He is also an associate investigator for one NHMRC research grant: ▪ Patient Blood Management in Critical Illness and Trauma. He is a Board Member and General Secretary for the Medical Society for Blood Management and a member of two international professional societies: Society for the Advancement of Blood Management (SABM) and Network for the Advancement of Transfusion Alternatives (NATA). He has received lecture honorarium. Fremantle General Practice Network, Western Australia. Honorarium for Book Chapter, Thieme, Stuttgart, Germany. Honorarium for Book Chapter, Elsevier Science USA. Mr Farmer was also on an Expert Panel, European Commission, European Guide on "Good Practices in the Field of Blood" and "European Union Guide for Member States on Good Practices for Patient Blood Management (EU-PBM)." Consumers, Health and Food Executive Agency (CHAFEA) of the European Commission.
A/Prof Craig French	A/Prof French received research funding from Wyeth between 2004 and 2008 provided to Western Health while 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 has also received research grants from Lily and Bayer. He was appointed to the Australian Red Cross Blood Service Advisory Board in 2011 and as a Blood Service Fellow in 2012.
Dr Stefan Kane	Dr Kane holds shares in CSL Limited.
Dr Giselle Kidson-Gerber	Nil.
Dr Claire McLintock	Dr McLintock has received support from CSL Behring Australia for educational meetings and registration fees. She was a consultant for CSL regarding the use of fibrinogen concentrate in post-partum haemorrhage and has participated in CSL supported meetings to develop publications on bleeding disorders, recommending the use of rFVIIa in post-partum haemorrhage. She has previously received honoraria and funding for educational meetings from Novonordisk. She acted as a consultant for Novonordisk during the TGA's consideration of a submission for the use of rFVIIa in obstetric haemorrhage and recommended its use. She was part of a rFVIIa registry group supported by an unrestricted grant from Novonordisk. Dr McLintock has been invited to attend a meeting by Bayer on strategies and new agents to manage PPH.
Prof Michael Permezel	Prof Permezel is the current President of RANZCOG and Director of the RANZCOG Research Foundation.

Dr Wendy Pollock	Dr Pollock is Director of the Australian College of Critical Care Nurses. She has participated on the Haemostasis Registry obstetric subcommittee and was a guest speaker on behalf of Cividien at an obstetrics special interest group on VTE (both unsupported).
Dr Shelley Rowlands	Nil.
Dr Helen Savoia	Dr Savoia is an employee of the Australian Red Cross Blood Service. She has attended a conference as a guest speaker supported by Bayer Australia in 2012.
Dr Amanda Thomson	Dr Thomson is an employee of the Australian Red Cross Blood Service and BloodSafe eLearning Australia.
Ms Catherine Whitby	Nil.

The Chair considered these declarations and determined that they did not constitute a conflict. Members were not asked to leave the room at any time during their involvement in the guideline development process.

None of the NBA and Optum staff had any declarations.

B6 Public consultation

Public consultation was conducted for six weeks from Monday 16th June to Friday 25th July, 2014, during which time the draft module was available on the NBA website.[a] 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 via email. A full list is detailed in the public consultation submissions report.

A formal letter advising of public consultation was sent to the organisations with a representative on the CRG. An email was sent to the following:

- members of each of the previous and current EWG, CRGs and PBM Steering Committee
- relevant colleges, societies and other health organisations
- individuals registered to receive PBM Guideline updates
- TGA
- Director General/Chief Executive/Secretary of each state, territory and health department
- Pharmaceutical Benefits Advisory Committee
- Medical Services Advisory Committee
- Australian Red Cross Blood Service
- Consumers Health Forum of Australia and the major consumer organisation in each state and territory.

Twenty-one submissions were received. The CRG met in August 2014 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.

[a] http://www.blood.gov.au/

B7 Finalising the guidelines

AGREE II assessment

The *Appraisal of Guidelines for REsearch & Evaluation* (AGREE) II instrument was developed to address the issue of variability in guideline quality and assesses the methodological rigour and transparency in which a guideline is developed.[132] The post-public consultation version of the module was sent to two Australian reviewers, independent to the guideline development process, who used the AGREE II tool to assess the quality and usability of the module against international quality standards.

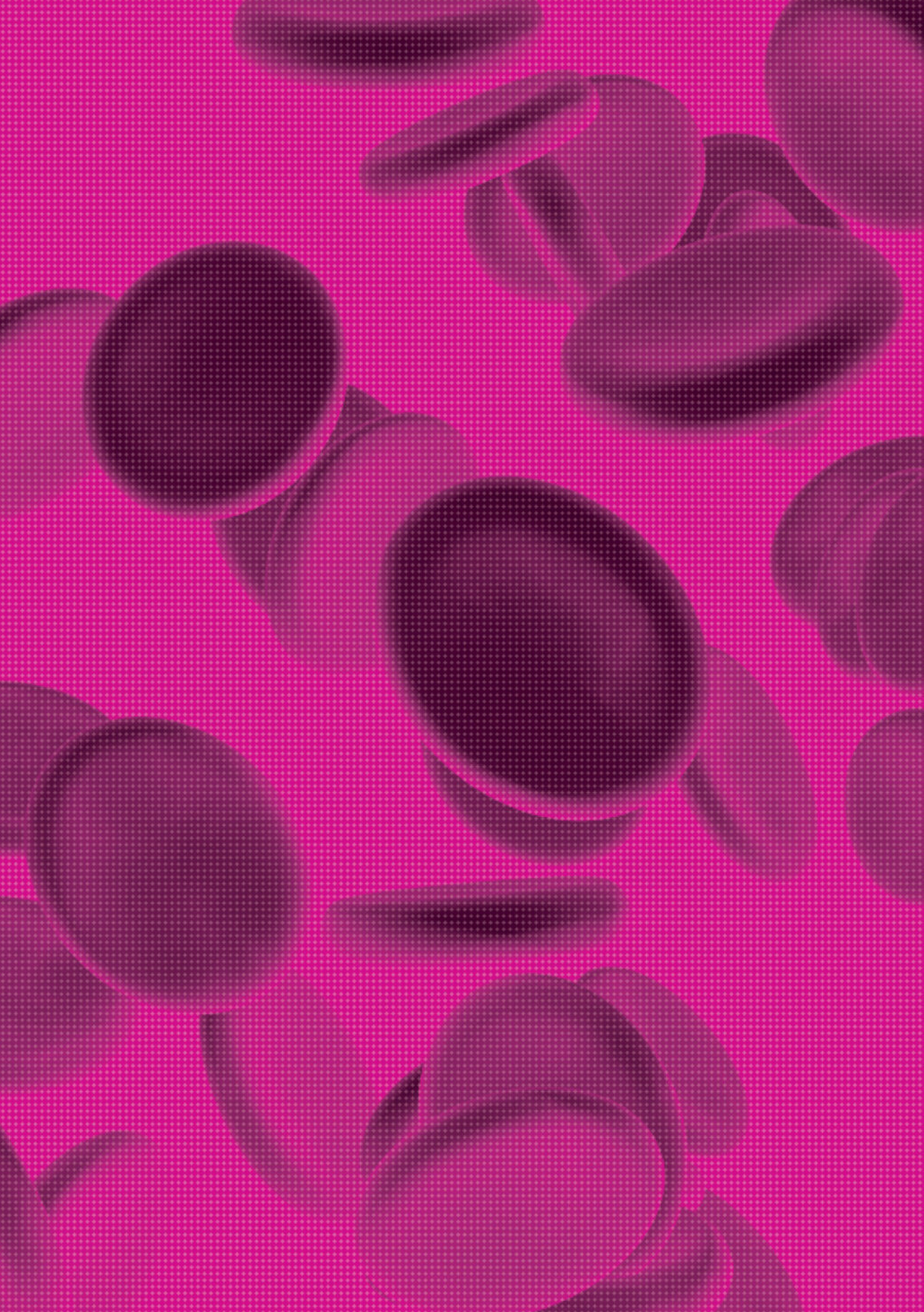
Both AGREE II assessors would recommend the guideline for use, and gave a rating of six out of seven for its overall quality (with seven being the highest possible quality rating).

Additional review

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 and accompanying documents were then sent to the NHMRC for methodological and independent peer review on 26 September 2014.

NHMRC approval

Approval from the Council was received on 22 December 2014.



Appendix C
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 C.1 summarises transfusion risks, and Table C.2 presents the Calman Chart, which may be useful to clinicians for explaining risks to patients.[133]

Table C.1 Transfusion risks

TRANSFUSION RISK	ESTIMATED RATE[a] (HIGHEST TO LOWEST RISK)	CALMAN RATING[b]
Transfusion-associated circulatory overload (iatrogenic)	Up to 1 in 100 transfusions	High
Transfusion-related acute lung injury	1 in 1200–190,000	Low to minimal
Haemolytic reactions	Delayed: 1 in 2500–11,000 Acute: 1 in 76,000 Fatal: Less than 1 in 1.8 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 468,000	Minimal
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 immune modulation	Not quantified	Unknown

IgA, immunoglobulin A

[a] Risk per unit transfused unless otherwise specified

[b] See Calman 1996[133]

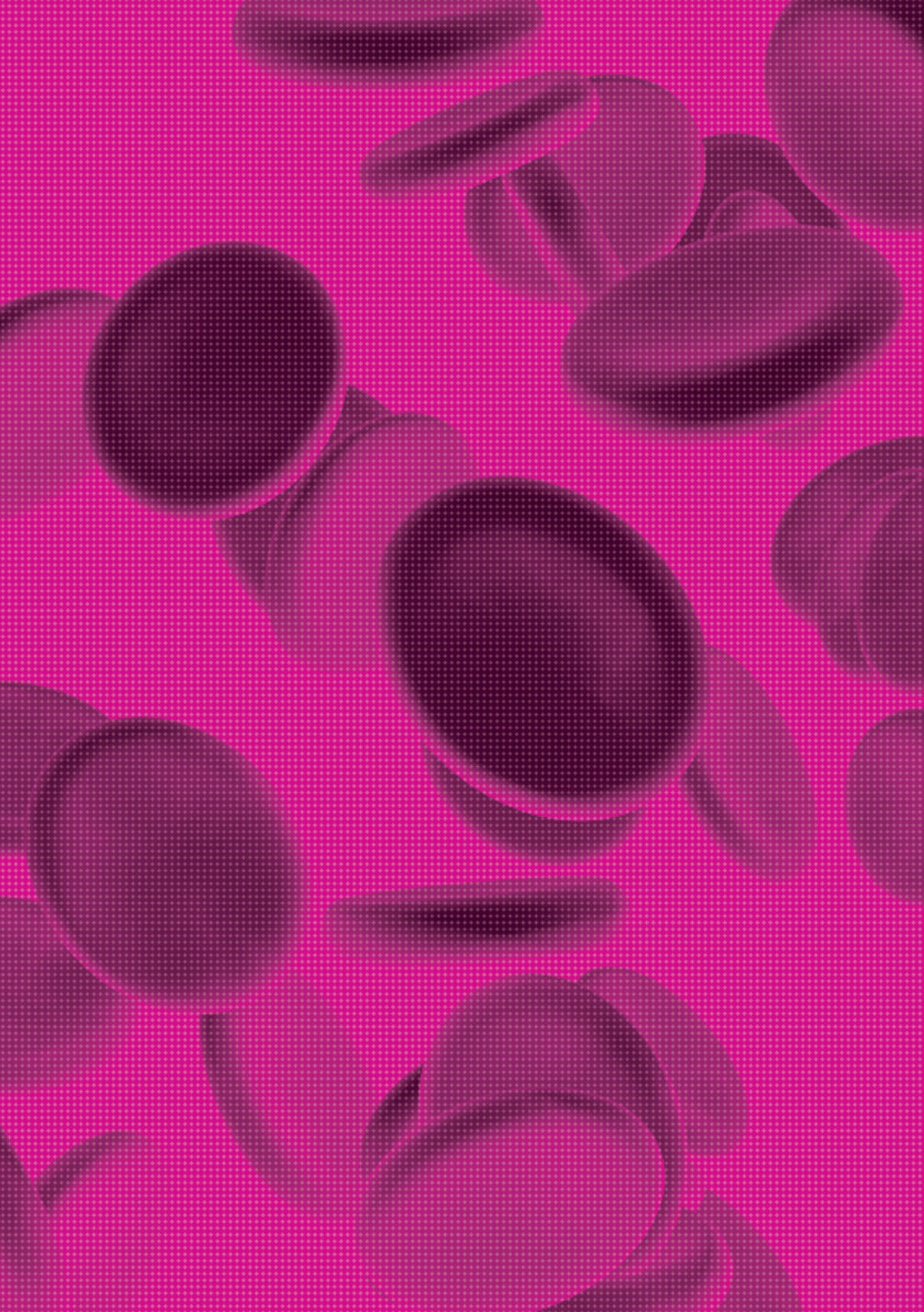
Source: Australian Red Cross Blood Service website (www.transfusion.com.au, accessed 28 July 2014)

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 C.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
Moderate	1 in 100–1,000	Death from smoking 10 cigarettes per day
High	≥1 in 100	Transmission of chicken pox to susceptible household contacts

[a] See Calman 1996 [133]



Appendix D
Blood sectors

D1 Australian blood sector

Council of Australian Governments Health Council

The Council of Australian Governments (COAG) promotes policy reforms that are of national significance, or that need coordinated action by all Australian governments. The COAG Health Council (CHC) (formerly the Standing Committee on Health) comprises health ministers from all jurisdictions, and is one of eight COAG Councils. The Commonwealth and state and territory health ministers on the CHC work in partnership to improve health outcomes for all Australians, and ensure the sustainability of the Australian health system.

The CHC's responsibilities include the oversight and management of the Australian blood sector, including 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. The CHC oversees the implementation of the National Blood Agreement (described below), and is supported in its roles by the Australian Health Ministers' Advisory Council (AHMAC).

Australian Health Ministers' Advisory Council

The Australian Health Ministers' Advisory Council (AHMAC) provides support to the CHC. It advises the health ministers on strategic matters relating to the coordination of health services across the nation and, as necessary, with New Zealand. The AHMAC considers blood sector matters referred to it by the Jurisdictional Blood Committee (JBC) through the Hospitals Principal Committee (HPC), and reports as necessary to the CHC. The AHMAC has no statutory power, and decisions are reached by consensus.

Hospitals Principal Committee

The Hospitals Principal Committee (HPC) considers and provides advice to the AHMAC on a range of issues. Areas covered include:

- all activities that largely relate to hospital care including emergency departments, outpatient care, inpatient care and alternatives to hospital care
- implementation of the health reform agenda as it applies to hospital care
- clinical, technical and medico–ethical developments
- the appropriateness, likely impact, policy implications, effectiveness and safety of clinical and technical developments.

Jurisdictional Blood Committee

All Australian governments are represented on the Jurisdictional Blood Committee (JBC), which was established by the National Blood Agreement in 2003.[134] 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 CHC through the HPC (of which it has been a subcommittee since September 2006) and the AHMAC.

National Blood Authority

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

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

Therapeutic Goods Administration

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

- regulating the sector in terms of the safety and quality of blood and blood products under the *Therapeutic Goods Act 1989*
- auditing 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 (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 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 Blood Service also has significant transfusion medicine expertise and clinical involvement.

D2 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.

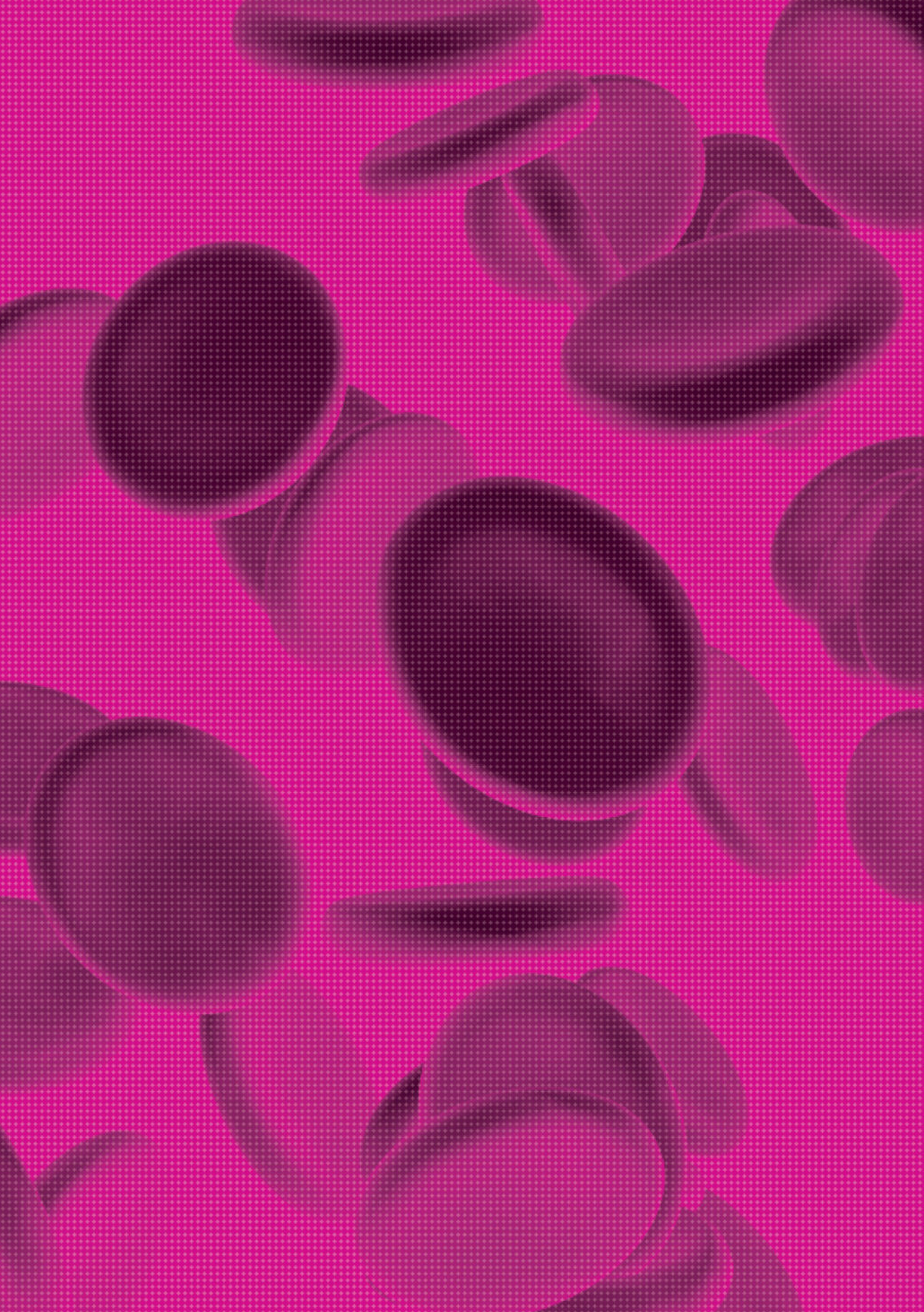
New Zealand Blood Service

The New Zealand Blood Service (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.

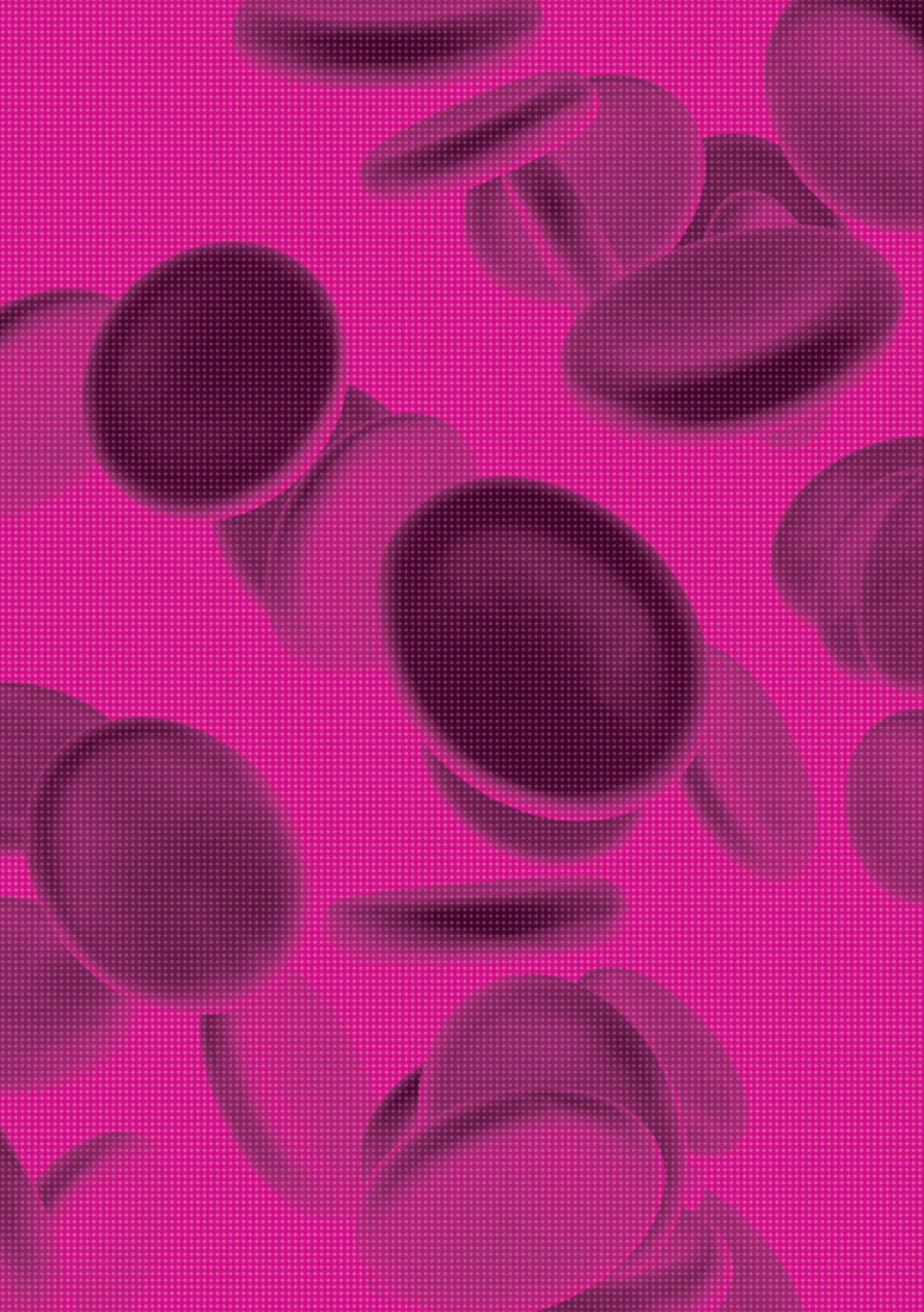
In addition to its role in collecting, processing and distribution of blood and blood products, the NZBS is actively involved in the provision of blood banking and clinical services within New Zealand's major hospitals.



Appendix 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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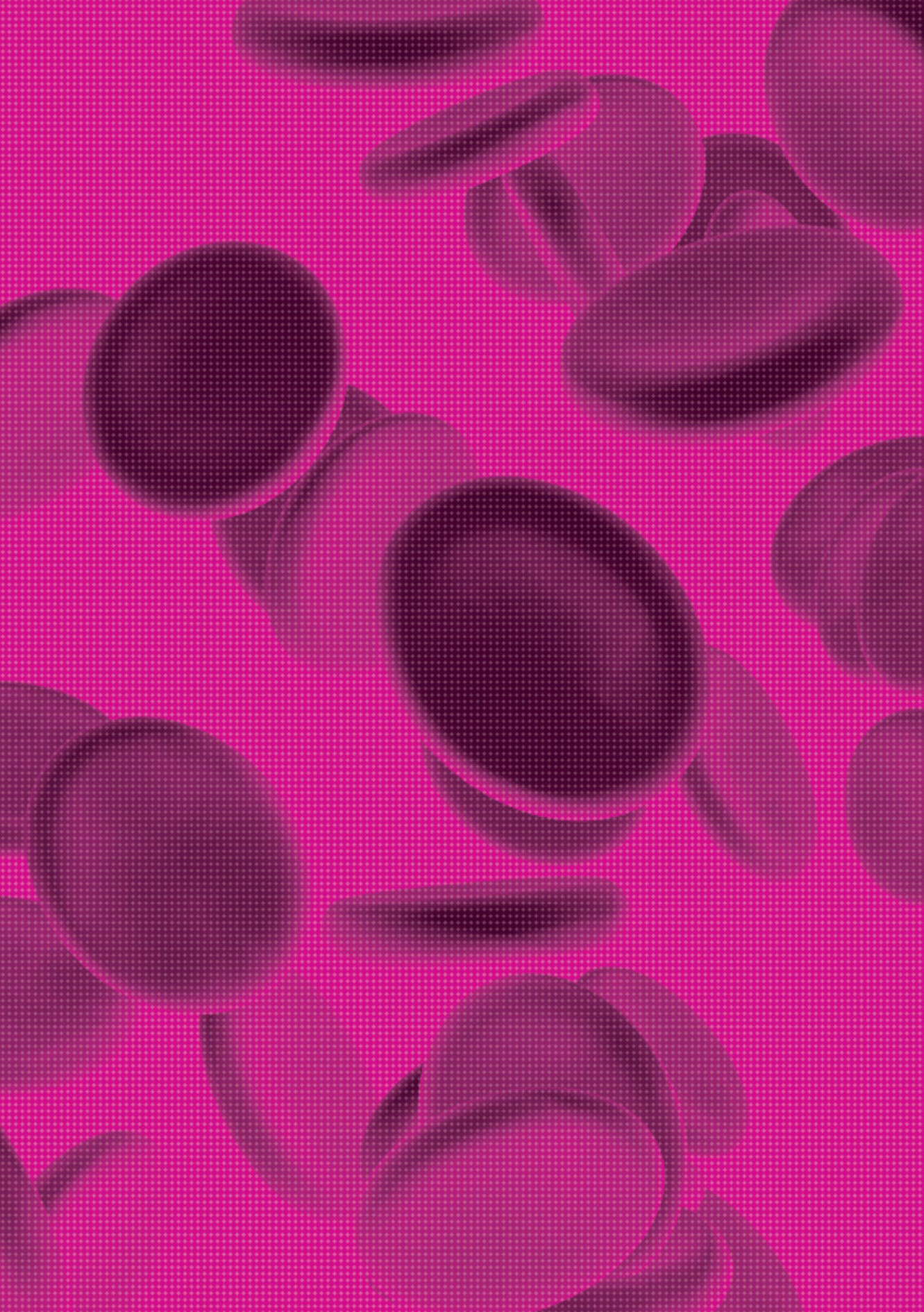

Index

A

abbreviations, *front section*
Aboriginal and Torres Strait Islander populations, 27, 58–9, 64
access to transfusion support, 65–6
acronyms, *front section*
AGREE II assessment, 96
alloantibodies in maternity patients, 4
anaemia
  advice on minimising, 59
  as a risk factor, 62–4
  causes of, 63–4
  definition, 31, 62
  ESA therapy and, 42
  future research goals, 74
  patients for whom transfusion is not an option, 71
  screening for, 59
  treatment of, 32
antenatal care, patients for whom transfusion is not an option, 70–1
antibody screening, *see* blood grouping and screening
antifibrolytic therapy (tranexamic acid), 9, 55–8, 69
Australian and New Zealand Society of Blood Transfusion, 14, 67
Australian blood sector, 104–5
Australian Commission on Safety and Quality in Health Care, 78
Australian Health Ministers' Advisory Council, 104
Australian Red Cross Blood Service, 105, 109

B

background research questions, 20–1, 61–71, 88
birth weights, *see* fetal outcome
bleeding maternity patients, *see* maternity patients; obstetric haemorrhage
blood component transfusions, 6, 44
blood conservation strategies, 49–58
blood grouping and screening
  before birth, 67
  during pregnancy, 4
blood sectors, 103–6
Blood Transfusion in Obstetrics, 31
BloodSafe eLearning Australia Program, 78
body of evidence matrix, 23

C

caesarian deliveries, 55–6, 67
Calman Chart, 101
cell salvage, 9–10
clinical commentary
  intraoperative cell salvage, 51
  interventional radiology, 53
  point-of-care testing, 50
  RBC transfusions, 31
  recombinant activated factor VII, 55
  tranexamic acid, 58
Clinical/Consumer Reference Groups
  document developed by, 1–2
  in governance structure, 82
  in terms of reference, 85
  membership of, 87–8
clinical guidance, 25–59
Clinical Practice Guidelines on the Use of Blood Components, 1, 14
clinical research questions, development of, 20–1
CMV seronegative blood products, 6
coagulopathic patients
  at risk of bleeding, 6
  blood component transfusions and, 46
  FFP and, 45
  practice points, 48
combination or fixed ratio therapy, evidence statements, 46
conflict of interest declarations, 93–5
consensus process, 92
consumer selection process, 86
Council of Australian Governments Health Council, 104
critical bleeding, 6–8, 26
critical physiologic derangement, 7, 47
cryoprecipitate, 45–6, 69
cytomegalovirus-safe blood products, 65, 67–8

D

databases searched, 20

Denmark studies, haemoglobin levels in pregnancy, 63

development process and methodology, 92

disseminated intravascular coagulation, 27

E

endorsement of guidelines, 78

erythropoiesis-stimulating agent therapy, 3, 41–2

ethical issues, patients for whom transfusion is not an option, 71

evaluating guidelines, 77–9

evidence gaps, 74–5

evidence statements

- combination or fixed ratio therapy, 46
- cryoprecipitate, 45–6
- development of, 22–3
- erythropoiesis-stimulating agent therapy, 42
- fibrinogen concentrate, 45–6
- formation of, 27–8
- fresh frozen plasma, 44–5
- intraoperative cell salvage, 50
- interventional radiology, 52
- oral and/or parenteral iron, 34–8
- platelet transfusions, 45–6
- point-of-care testing, 49
- recombinant activated factor VII, 54
- tranexamic acid, 55–6

exclusion criteria, research reports, 21

expert opinion points

- adapting massive transfusion protocol to obstetrics, 68
- anaemia, 59, 62
- basis for, 15
- maternity services, 64–5
- patients for whom transfusion is not an option, 62
- summary of, 2

Expert Working Group, 82, 84–5, 87

F

ferritin testing, 4, 62

fetal outcome

- erythropoiesis-stimulating agent therapy and, 43
- iron therapy and, 37, 41

fibrinogen concentrate, 45–6, 48, 69

fibrinogen levels, 68

finalising guidelines, 96

folic acid, 35–40

fresh frozen plasma, 44–5, 69

future directions, 73–5

future research goals, 78

G

gastrointestinal side-effects of iron, 33

governance structure, 81–9

grading scheme, definitions, 2, 23

guidelines

- development of, 14–16, 82–3
- finalising, 96
- implementing, evaluating and maintaining, 77–9
- review and update, 79

H

haemoglobin levels in pregnancy, *see also* anaemia

- interventions to increase, 32
- optimal range, 63
- RBC transfusions and, 30

haemorrhage management, *see also* obstetric haemorrhage; postpartum haemorrhage

- patients for whom transfusion is not an option, 71

high-risk populations, 66

Hospitals Principal Committee, 104

hysterectomy for patients for whom transfusion is not an option, 70

I

implementing guidelines, 77–9
inclusion criteria, 21
independent systematic review expert, 88
Indigenous Australians, 27, 58–9, 64
intraoperative cell salvage, 50–1
interventional radiology, 10, 51–3
intramuscular (IM) iron, 3, 36–8, 40–1
intravenous (IV) iron, 3, 36–8, 40–1
iron therapy, *see* oral and/or parenteral iron

J

Jurisdictional Blood Committee, 104

K

K negative RBC products, 6, 65, 68
Kell antigen system, 68

L

labour management, patients for whom transfusion is not an option, 71
legal issues, patients for whom transfusion is not an option, 71
leucodepleted (CMV-safe) blood products, 65, 67
literature search dates, 21

M

maintaining guidelines, 77–9
management framework for guideline development, 82–3
massive transfusion protocols, 8–9, 54, 68
maternal anaemia, *see* anaemia
maternity patients, *see also* obstetric haemorrhage; postpartum haemorrhage
  blood grouping and screening, 4
  definition, 26
  ESA therapy, 3
  future research goals, 74
  iron therapy for, 3
  not actively bleeding, 5
  number given transfusions, 26
  RBC transfusions and, 31
  transfusion support for, 64–8
medical writing staff, 89
Medsafe (NZ), 105
methods, 16–23, 92
Ministry of Health (NZ), 105
morbidly adherent placenta, 52
mortality
  erythropoiesis-stimulating agent therapy and, 43
  iron therapy and, 38, 41
  tranexamic acid and, 57

N

National Blood Agreement, 104–5
National Blood Authority
  guidelines developed by, 14
  Project Management and Committee Secretariat, 89
  role of, 105
National Maternity Services Capability Framework, 65
National Patient Blood Management Guidelines Implementation Strategy, 78
National Safety and Quality Health Service Standards, 78
New Zealand blood sector, 105–6
New Zealand Blood Service, 105–6, 109
NHMRC approval of guidelines, 96
non-transfusion interventions, 32
NZBS Collection and Manufacturing Standards, 105

O

obstetric haemorrhage, *see also* postpartum haemorrhage
  future research goals, 74
  high-risk populations, 66
  increasing incidence of, 26
  management of, 26–7, 47
  practice points, 6–8
Optum systematic review team, 89
oral and/or parenteral iron
  effectiveness of, 32–41
  for Aboriginal and Torres Strait Island populations, 59
  future research goals, 74
  summary of recommendations, 3

P

parenteral iron, *see* oral and/or parenteral iron
patient blood management, 13, 99–101
patient population and setting, 26–7
patients for whom transfusion is not an option, 4–5, 70–1
PBM Steering Committee, 82, 84
permissive hypotension, 69
physiologic derangement, critical, 7, 47
placenta previa, 50
plain English summary of recommendations, 1–10
plasma. fresh frozen, 44–5, 69
platelet counts, acceptable levels, 6
platelet transfusions, 45–6, 69
point-of-care testing, 49–50
postpartum anaemia, *see* anaemia
postpartum haemorrhage, *see also* haemorrhage management; obstetric haemorrhage
  blood component transfusions and, 45
  coronial inquiry into death from, 67
  management of, 26–7, 31
  recombinant activated factor VII, 54
  tranexamic acid and, 55–6
practice points
  basis for, 15
  coagulopathic patients, 48
  erythropoiesis-stimulating agent therapy and, 43
  intraoperative cell salvage, 51
  interventional radiology, 53
  obstetric haemorrhage, 47
  oral and/or parenteral iron, 39
  RBC transfusion, 30
  summary of, 2
  tranexamic acid, 57
pregnancy, *see also* maternity patients
  definition of, 26
pretransfusion laboratory testing guidelines, 66–7
preventative radiology, *see* interventional radiology
process report, 91–6
product information, 109
Project Management and Committee Secretariat, 89
public consultation, 95

R

rare red cell phenotypes, 66
recombinant activated factor VII, 9, 53–5, 69
recommendations
  basis for, 15
  erythropoiesis-stimulating agent therapy, 43
  oral and/or parenteral iron, 39
  summary of, 2
red blood cell transfusions
  effect on outcomes, 28–31
  for anaemia treatment, 5
  for critical bleeding, 7
  for maternity patients, 68
red cell alloantibodies, 66
red cell selection, 67–8
references, 111–22
related materials, 16
research phase, 92
review and research, 21
review of guidelines, 79
Rh D negative maternity patients, 10, 51
risk assessment chart, 101
Royal Australian and New Zealand College of Obstetricians and Gynaecologists management of postpartum haemorrhage, 31

S

screening, *see* blood grouping and screening
sickle cell disease, RBC transfusions and, 31
Steering Committee, *see also* PBM Steering Committee
  guidelines developed by, 78
  in terms of reference, 84
  membership of, 87
structure of the document, 15
summary of recommendations, 2
systematic review process, 20–1, 86
systematic review team, 88–9

T

technical writers, 86
terms of reference, 84–6
Therapeutic Goods Administration, 105

therapeutic radiology, *see* interventional radiology
thromboembolic events
erythropoiesis-stimulating agent therapy and, 43
management of, 27
tranexamic acid and, 58
Torres Strait Islanders, 27, 58–9, 64
tranexamic acid, 9, 55–8, 69
transfusions, *see also* massive transfusion protocols; red blood cell transfusions
alternatives when not an option, 4–5, 70–1
for maternity patients, 5
incidence of and iron therapy, 40
incidence of in NSW, 26
risk assessment, 99–101
support for in maternity services, 64–8
TXA use and incidence and volume of, 57

U

UAB catheterisation, 53
update of guidelines, 79
US studies, haemoglobin levels in pregnancy, 62

V

vaginal birth, blood group screening prior to, 67

W

World Health Organization anaemia guidelines, 63