Patient Blood Management Guidelines: Module 5

Obstetrics and Maternity

Patient Blood Management Guidelines Module – 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

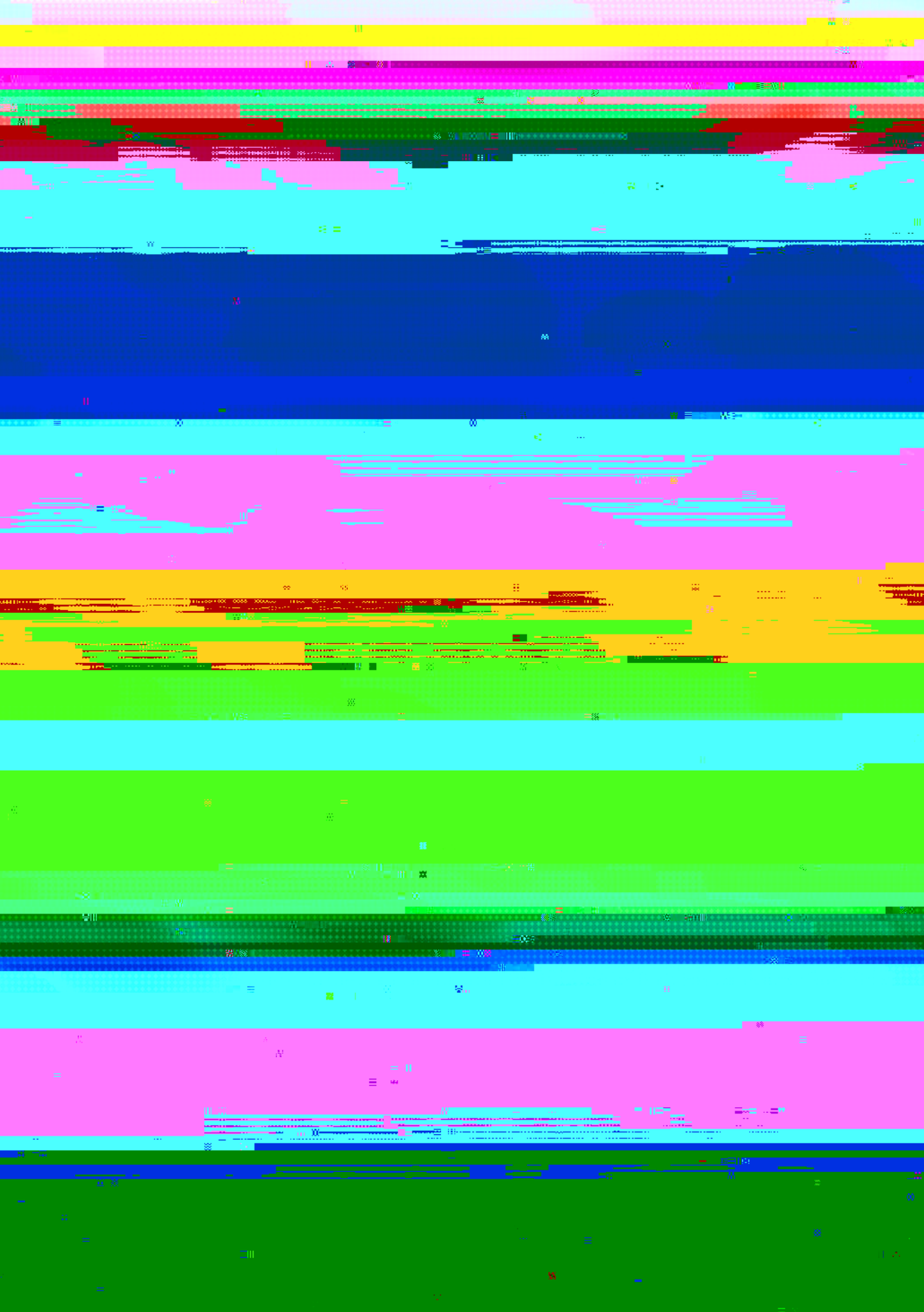
Australasian Society of Haemostasis and Thrombosis

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



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

Tables

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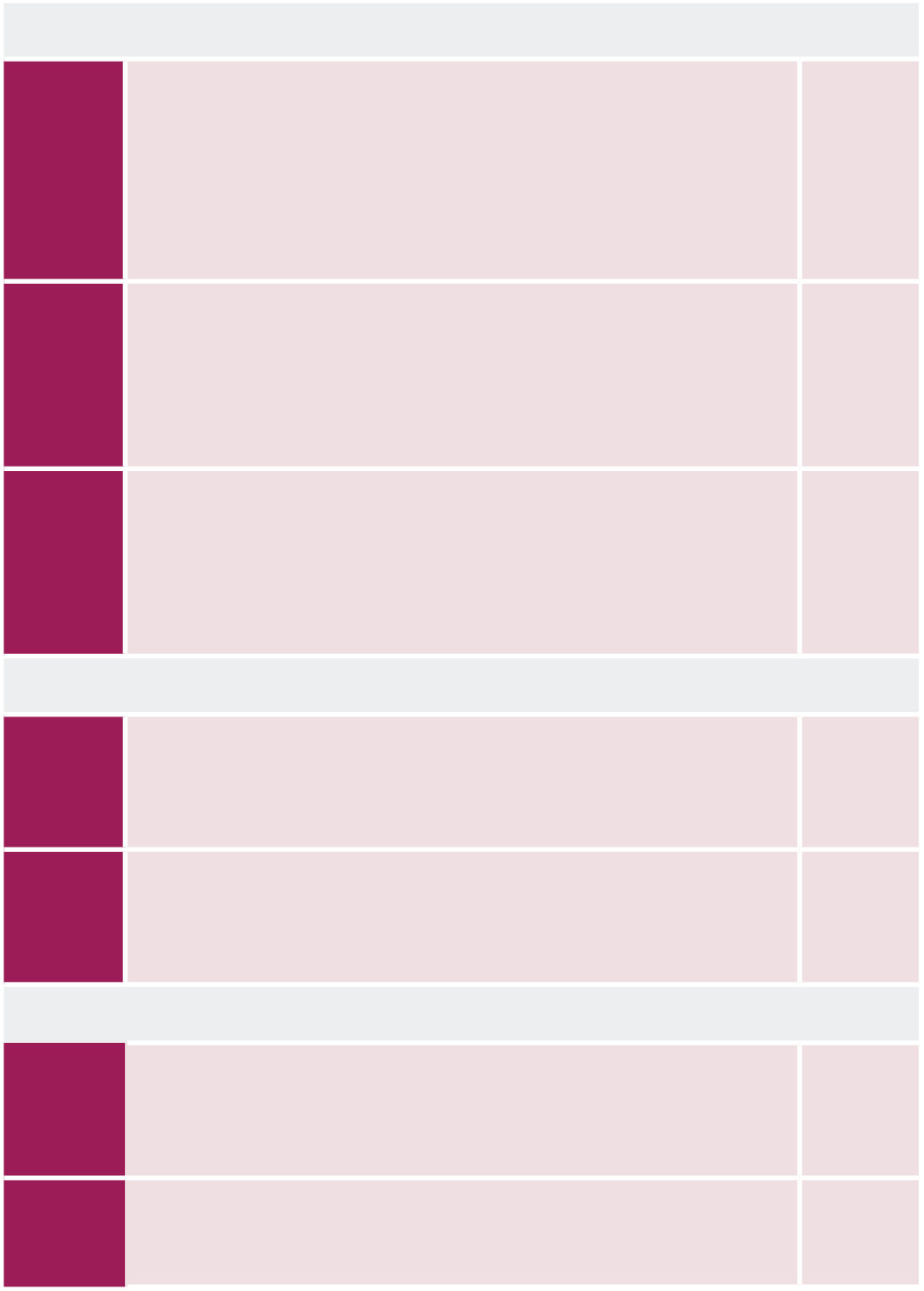
Plain English summary

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

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:

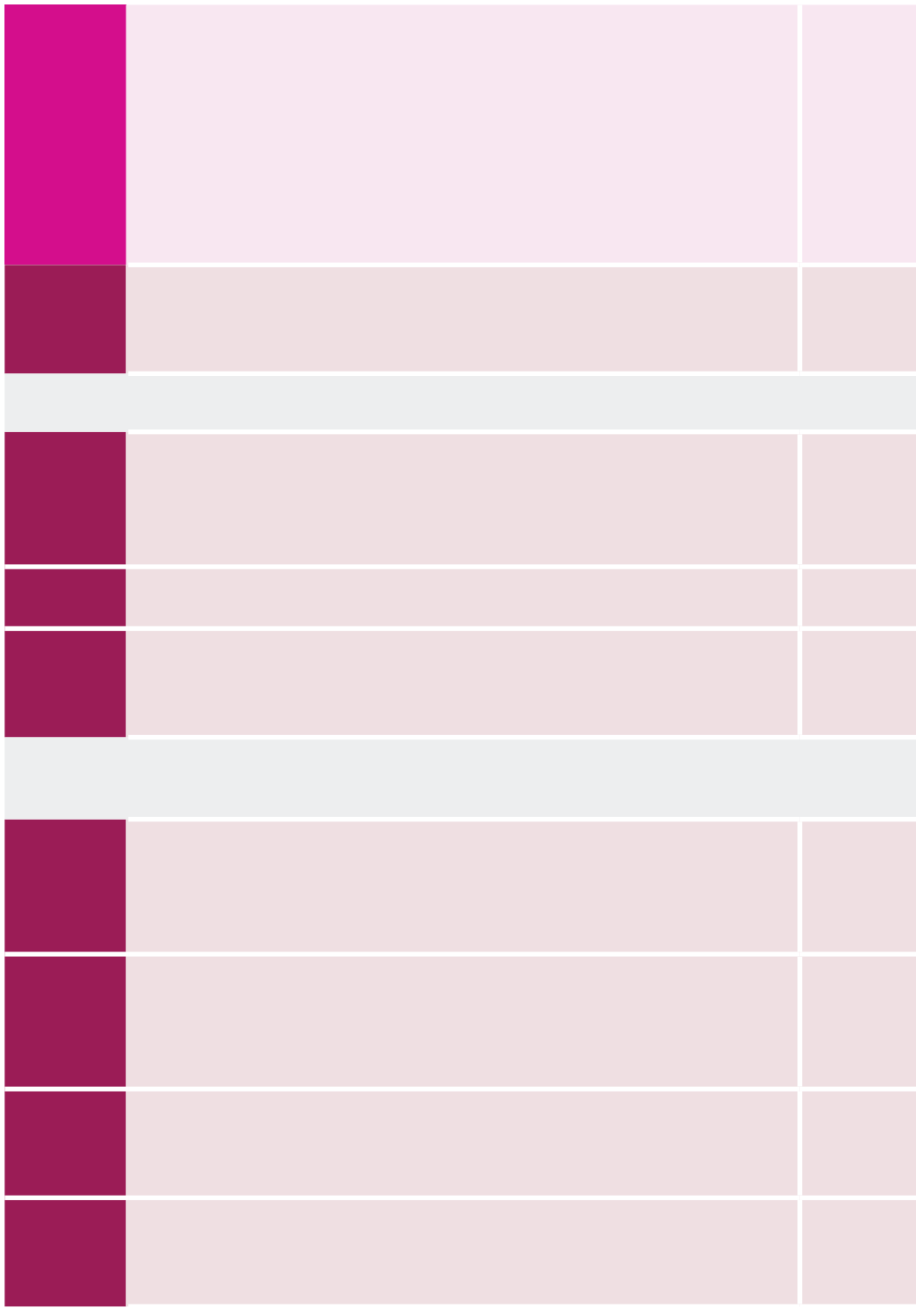
Identifier and grade	Guidance recommendations practice points and expert opinion points	Relevant section of document
ORAL AND OR PARENTERAL IRON		
R1	The routine administration of iron supplementation to all pregnant women is not recommended[a] [a] In accordance with *Clinical practice guidelines Antenatal care Module* [2]	
R2	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	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	



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.	.
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.	. .
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 R and R and practice points PP PP	. .
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 al ▪ Hb concentration . g L RBC transfusion is usually inappropriate. ▪ Hb concentration of . 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 < 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.	. .

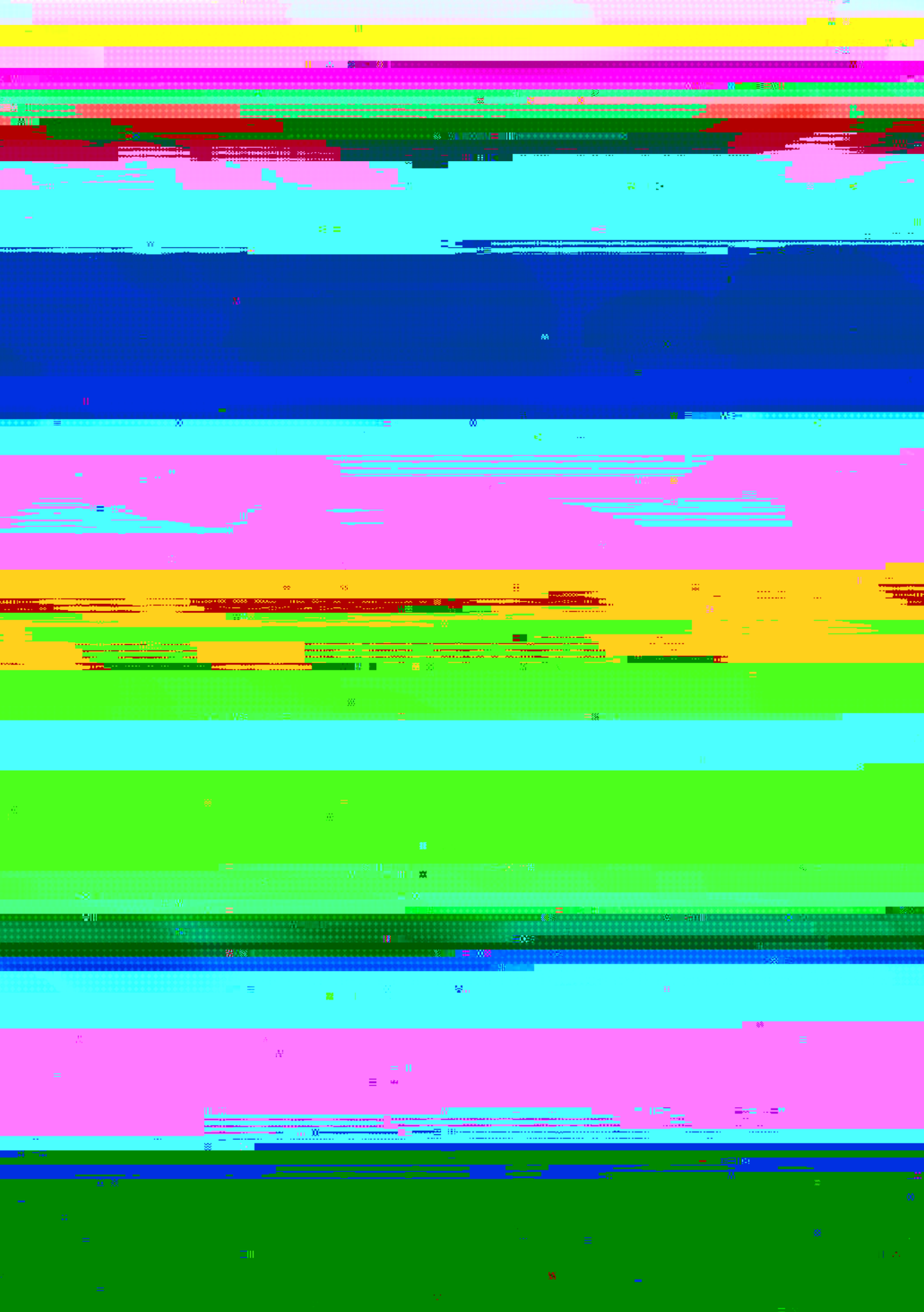
Identifier and grade	Guidance recommendations practice points and expert opinion points	Relevant section of document
BLOCK COMPONENT TRANSFUSION MODIFIED BLOOD COMPONENTS CMV SERONEGATIVE AND PHENOTYPED		
EOP12	CMV safe blood products should be offered to all pregnant women regardless of CMV status when 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.*	.
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.	.
COAGULOPATHIC PATIENTS AT RISK OF BLEEDING		
PP19	In general a platelet count . 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		

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.	
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.	
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 < C ▪ pH < base excess worse than lactate mmol L ▪ ionised calcium < mmol L ▪ platelet count < L ▪ PT normal ▪ INR ▪ APTT normal ▪ fibrinogen level < g L.	



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 PP7 PP. in *Patient Blood Management Guidelines: Module Critical Bleeding Massive Transfusion* and PP in *Patient Blood Management Guidelines: Module Perioperative* 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 . g kg is suggested.	
TRANEXAMIC ACID		
PP32	In maternity patients with significant blood loss the early use within 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.	
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*.	
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.	

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 g sa muldal b 7av Tdt u	docum setoive matiohaer



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.

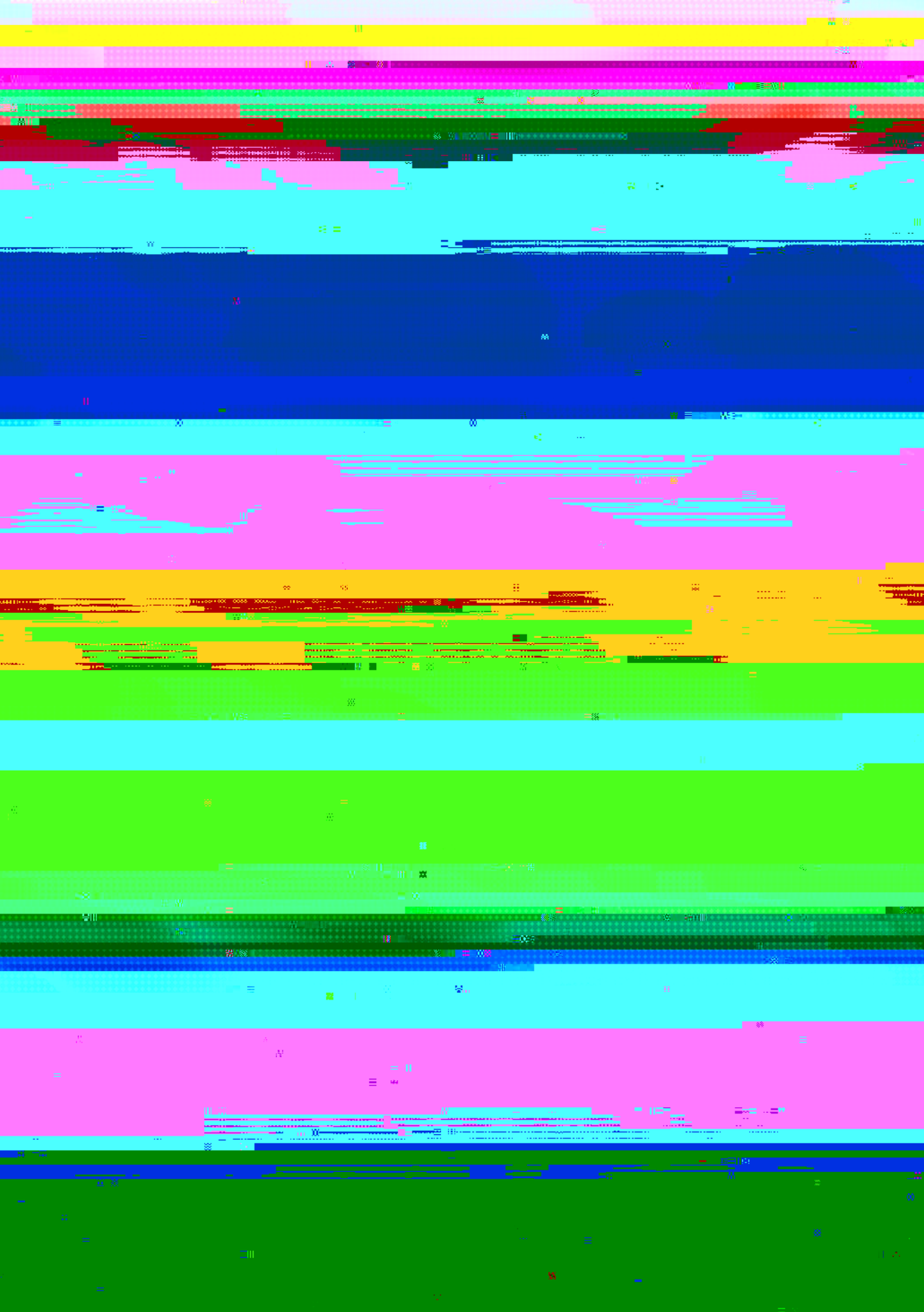
Patient blood management (PBM) improves patient outcomes by ensuring that the focus of the patient's medical and surgical management is on improving and conserving the patient's own blood. As a consequence of the better management patients usually require fewer transfusions of donated blood components, 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.

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



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[1]. The methods used in applying this

. Clinical research questions

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 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 **– In maternity patients, what is the effect of RBC transfusion on patient outcomes? (Interventional question)**
- Question **– 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 **– In maternity patients, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and / or platelet transfusion on patient outcomes? (Interventional question)**
- Question **– 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

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 1 Background research questions

- Background Question **– 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

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.

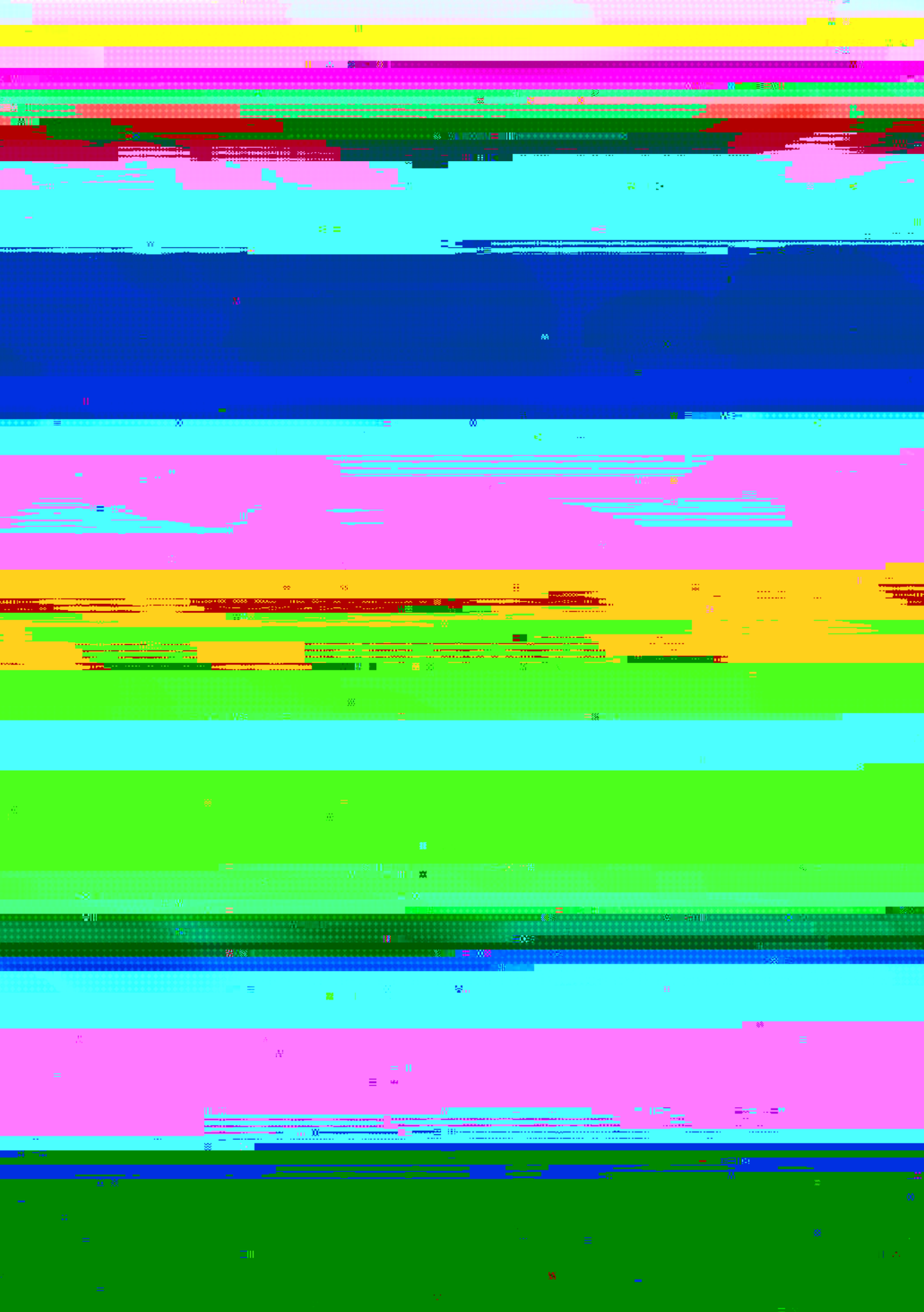
Evidence statements were only transformed into 'action-oriented' recommendations where:

- 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 1 Body of evidence matrix



Clinical guidance

Introduction

Purpose and audience

This document is intended to assist and guide health-care professionals in making clinical decisions

Table ,+ Description of interventions

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)**	✓				

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 R and R , and practice points PP PP
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 æl ▪ Hb concentration . g L RBC transfusion is usually inappropriate. ▪ Hb concentration of . 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 < 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

Effect of non-transfusion interventions to increase haemoglobin concentration

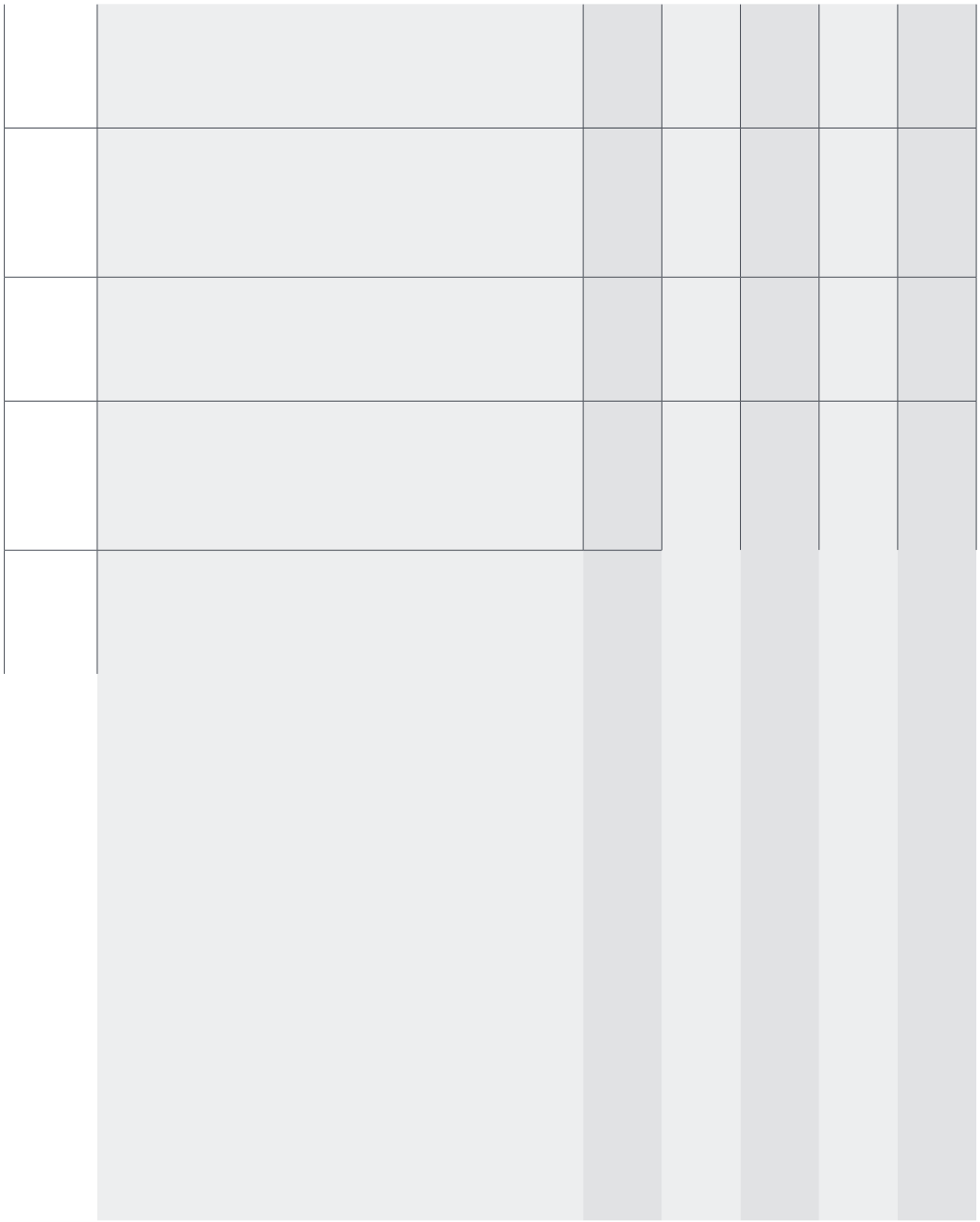
Question (Interventional question)

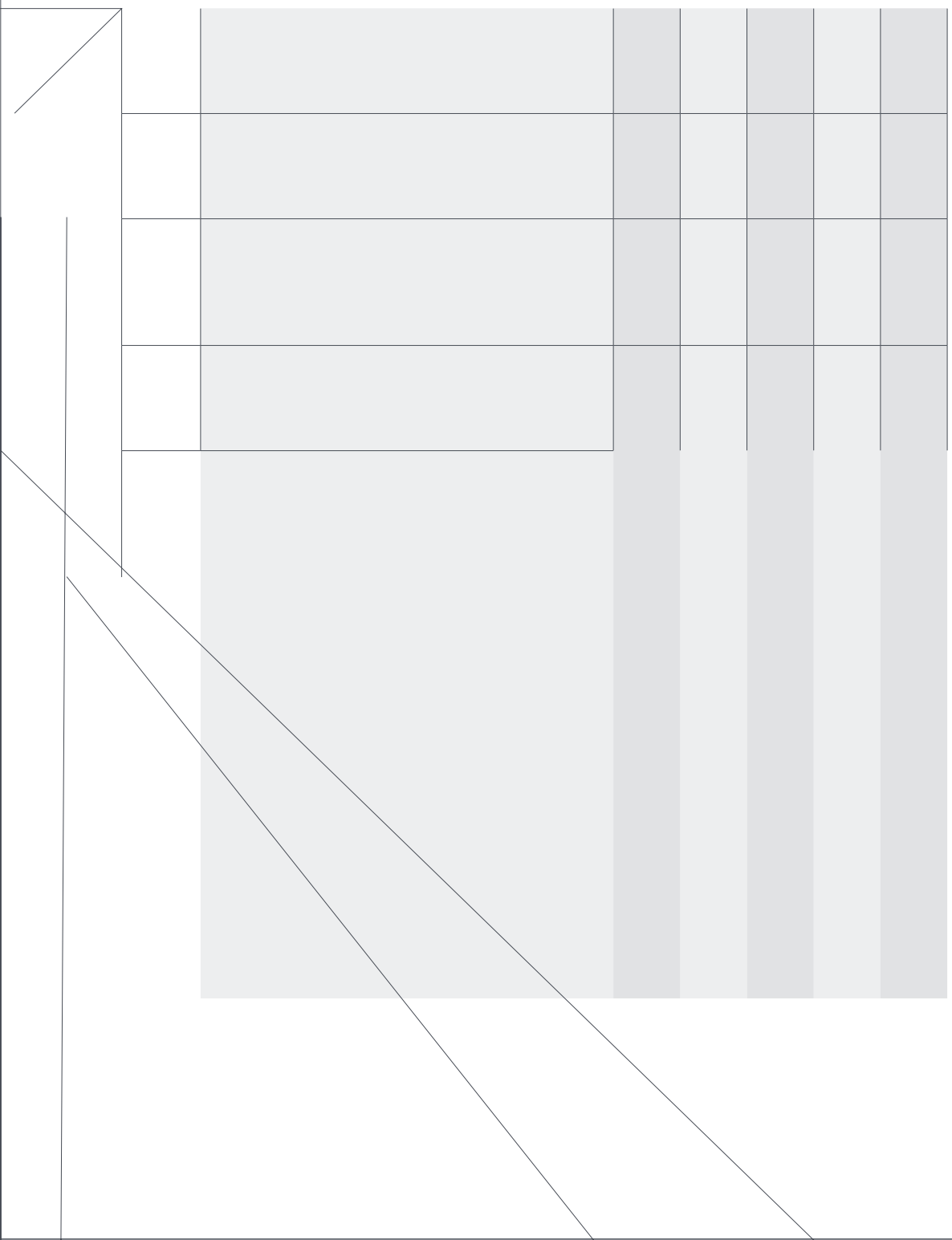
In maternity patients what is the effect of non transfusion interventions to increase haemoglobin concentration on morbidity mortality and need for RBC blood transfusion(

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





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

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

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.

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)**	✓				

RECOMMENDATION erythropoiesis stimulating agents	
R4	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

Effect of blood components on outcomes

Question (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,

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

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

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 < C ▪ pH < base excess worse than lactate mmol L ▪ ionised calcium < mmol L ▪ platelet count < L ▪ PT normal ▪ INR ▪ APTT normal ▪ fibrinogen level < g L.
PP18	In women with major obstetric haemorrhage requiring massive transfusion suggested doses of blood components are[a] ▪ FFP mL kg ▪ platelets adult therapeutic dose ▪ cryoprecipitate g. [a] Or as directed by the haematologist transfusion specialist. See Appendix E for dose equivalents

. Use of blood conservation strategies

Question (Interventional)

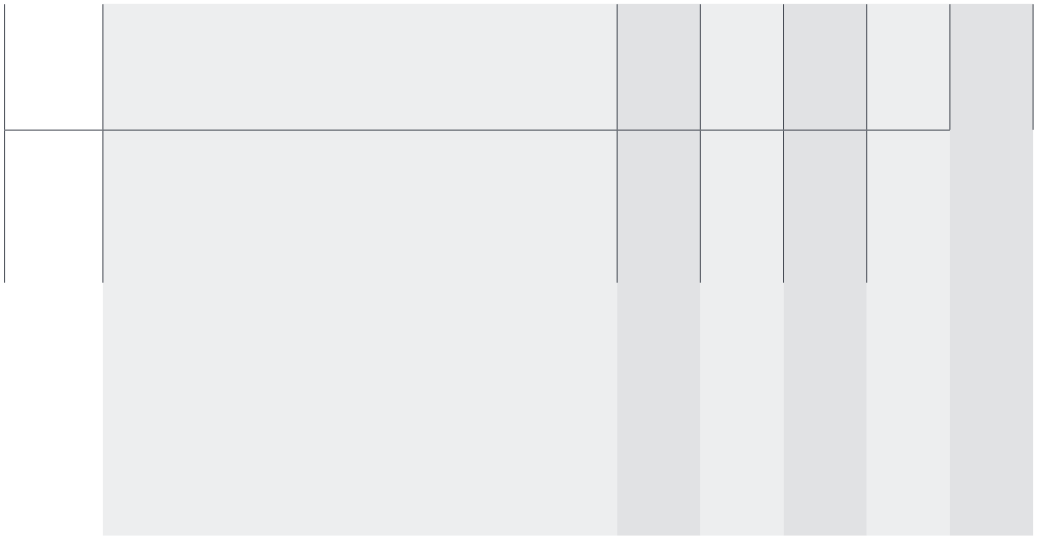
In maternity patients what is the effect of non obstetric strategies that aim to minimise maternal blood loss in the peripartum period on transfusion and clinical outcomes(

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.

Point of care testing



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.

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.

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*.

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

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		

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.

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)**	✓✓	✓			

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 , hours of the

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.

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 B or hookworm should be screened for in selected women.

FBC, full blood count

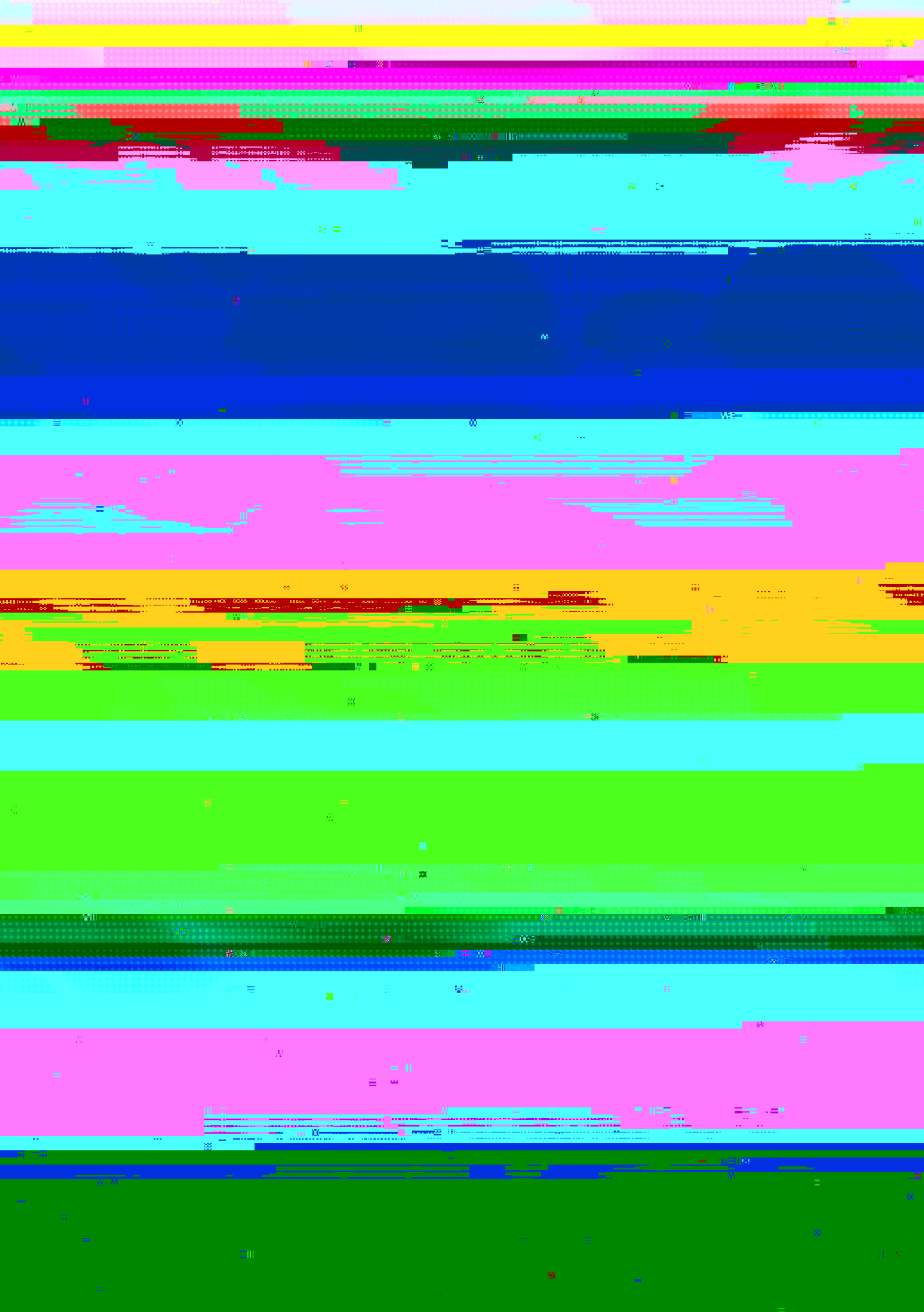
EOP2	Women should be provided with information and advice in relation to minimising anaemia for example by adequate spacing of pregnancies consumption of a healthy diet and optimal management of any medical comorbidities.

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



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 — 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 to .

. Anaemia as a risk factor

Background question

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 B 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

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 Haemoglobin levels in pregnancy United States population

GESTATION WEEKS							
12	**16**	**20**	**24**	**28**	**32**	**36**	**40**
HAEMOGLOBIN g L MEAN 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 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.

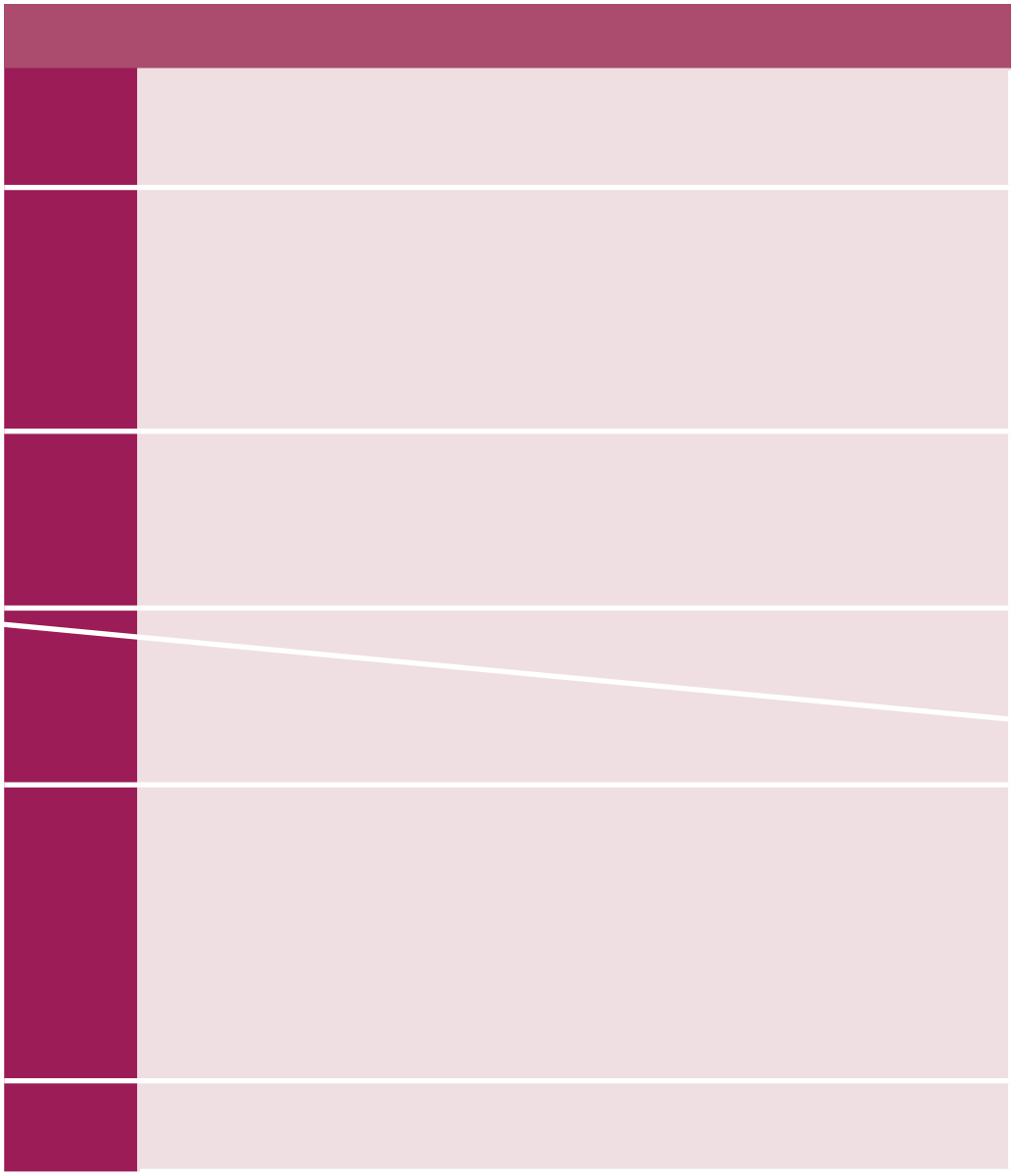
. Transfusion support for maternity services

Background question

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.



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.

High risk populations

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

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.

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

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

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]

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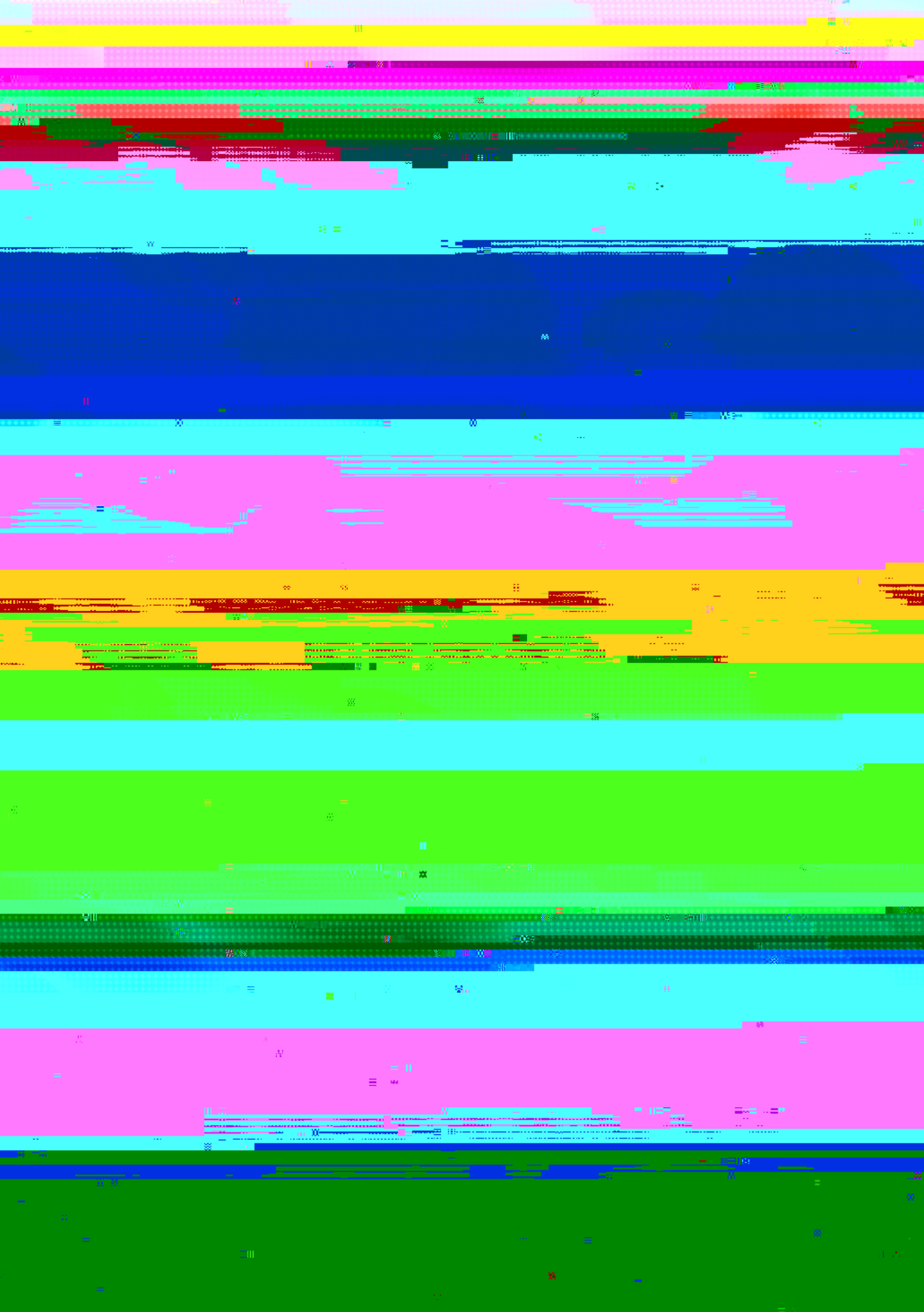
. Care of patients in whom transfusion is not an option

Background question

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

- **Prescribe antenatal iron therapy for women in whom substantial blood loss is expected and who**



Future directions

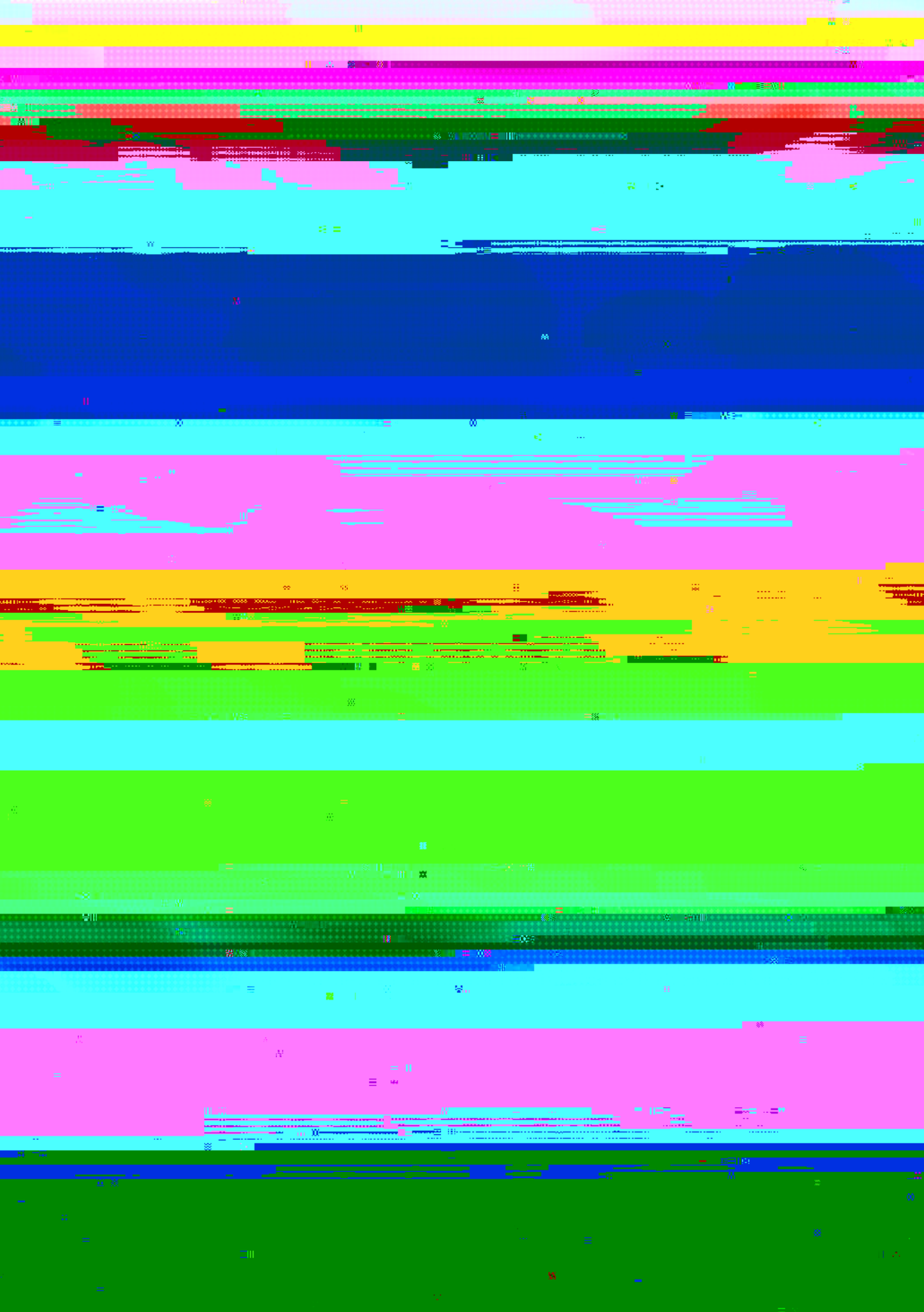
The systematic review for this module found sufficient evidence to make recommendations on the use of iron and ESA therapy in the maternity patient.

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.

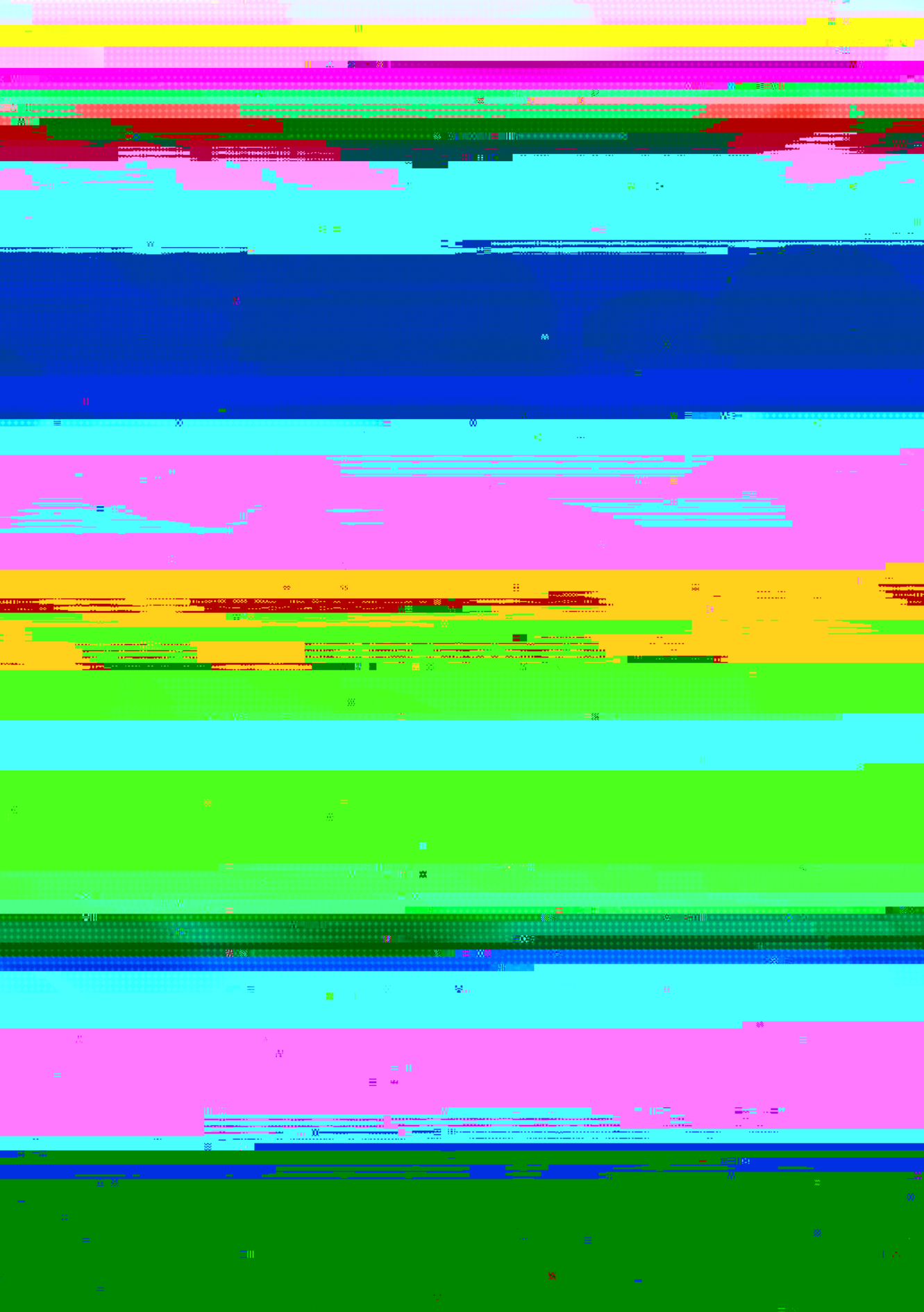
Evidence gaps and areas of future research

- 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

- **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.**



Implementing, evaluating and maintaining the guidelines



Appendix A
Governance

A 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:

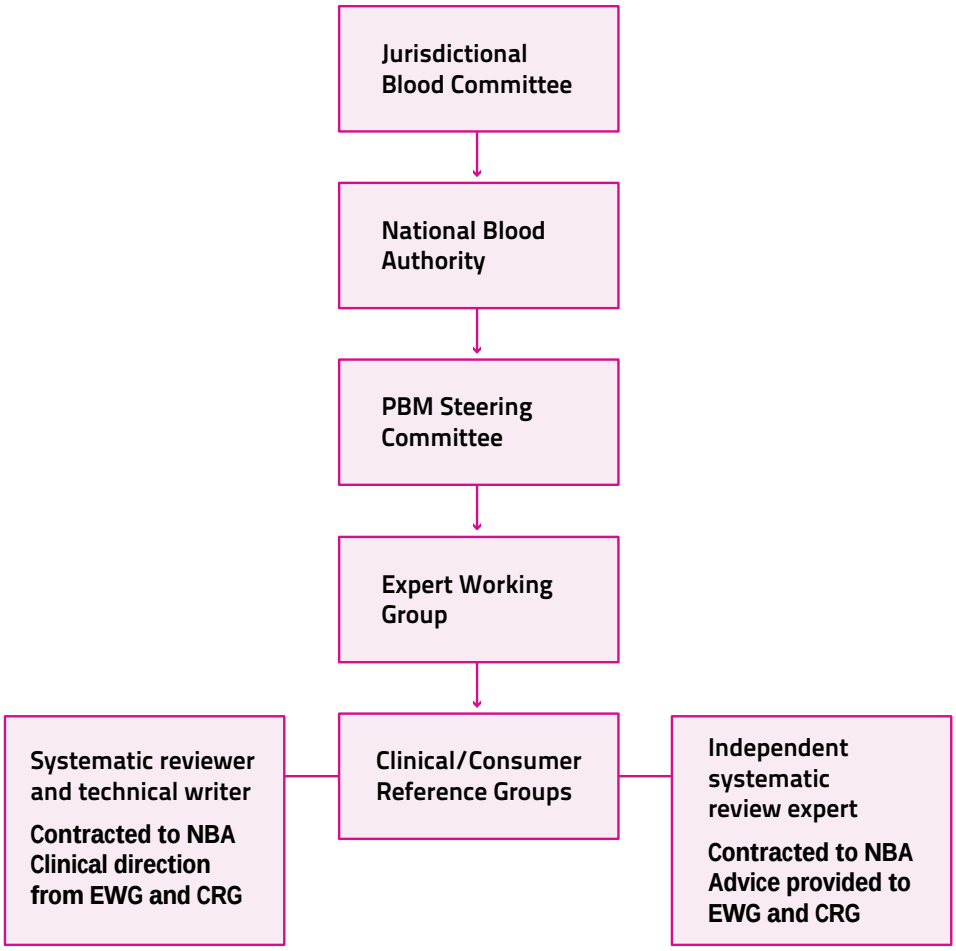
- **a Steering Committee, which was responsible for the initial development and governance of the entire project; this has now become the PBM Steering Committee, which oversees the implementation strategy for the PBM Guidelines**
- **an Expert Working Group (EWG), responsible for providing advice on 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.

A 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 A Management framework for development of the guidelines



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

A 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**

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)**

A 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)

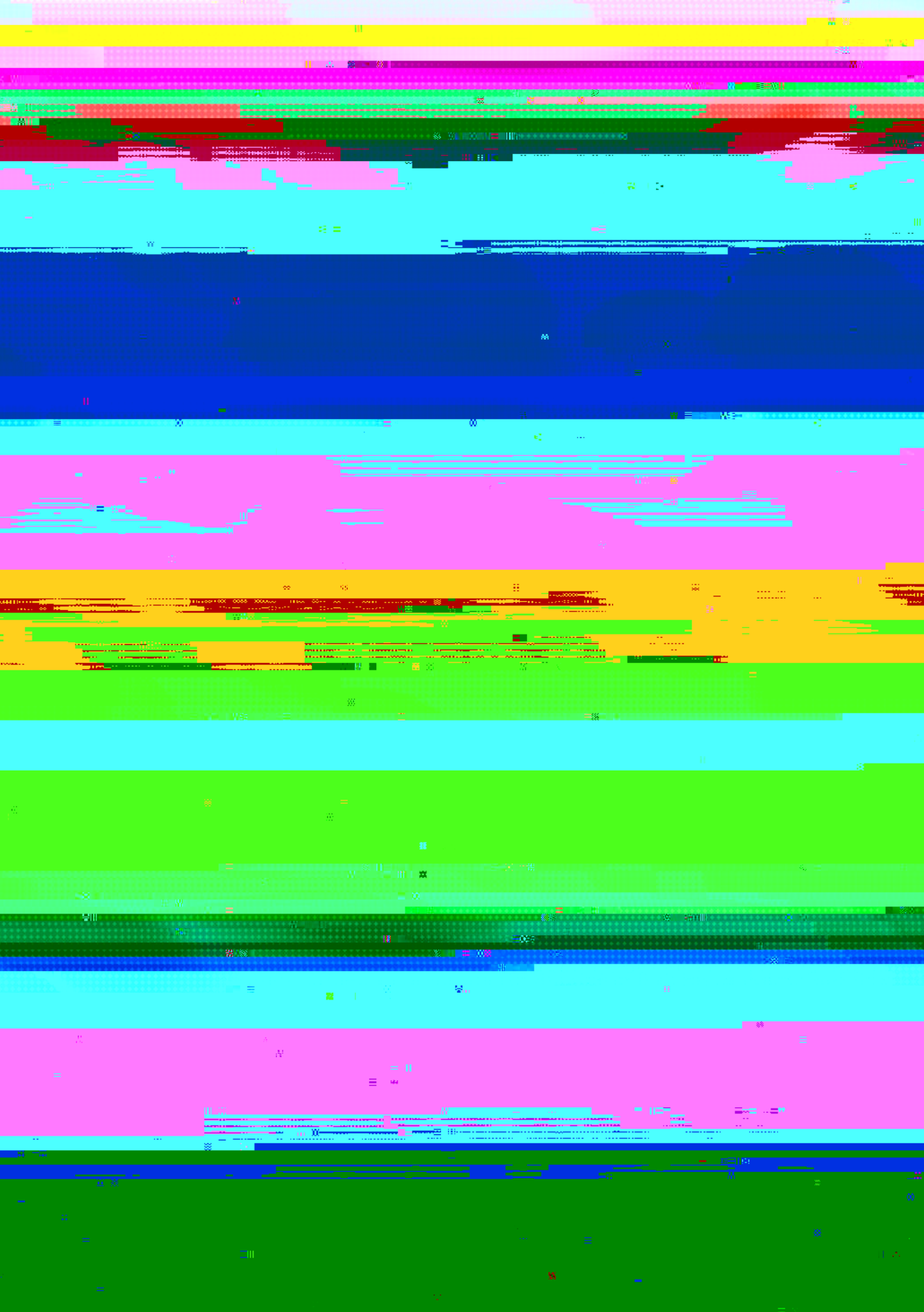
Independent systematic review expert

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



Appendix B
Process report

B Development process and methodology

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

B 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.

B Methodology

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

B 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.**

B 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)**

B Finalising the guidelines

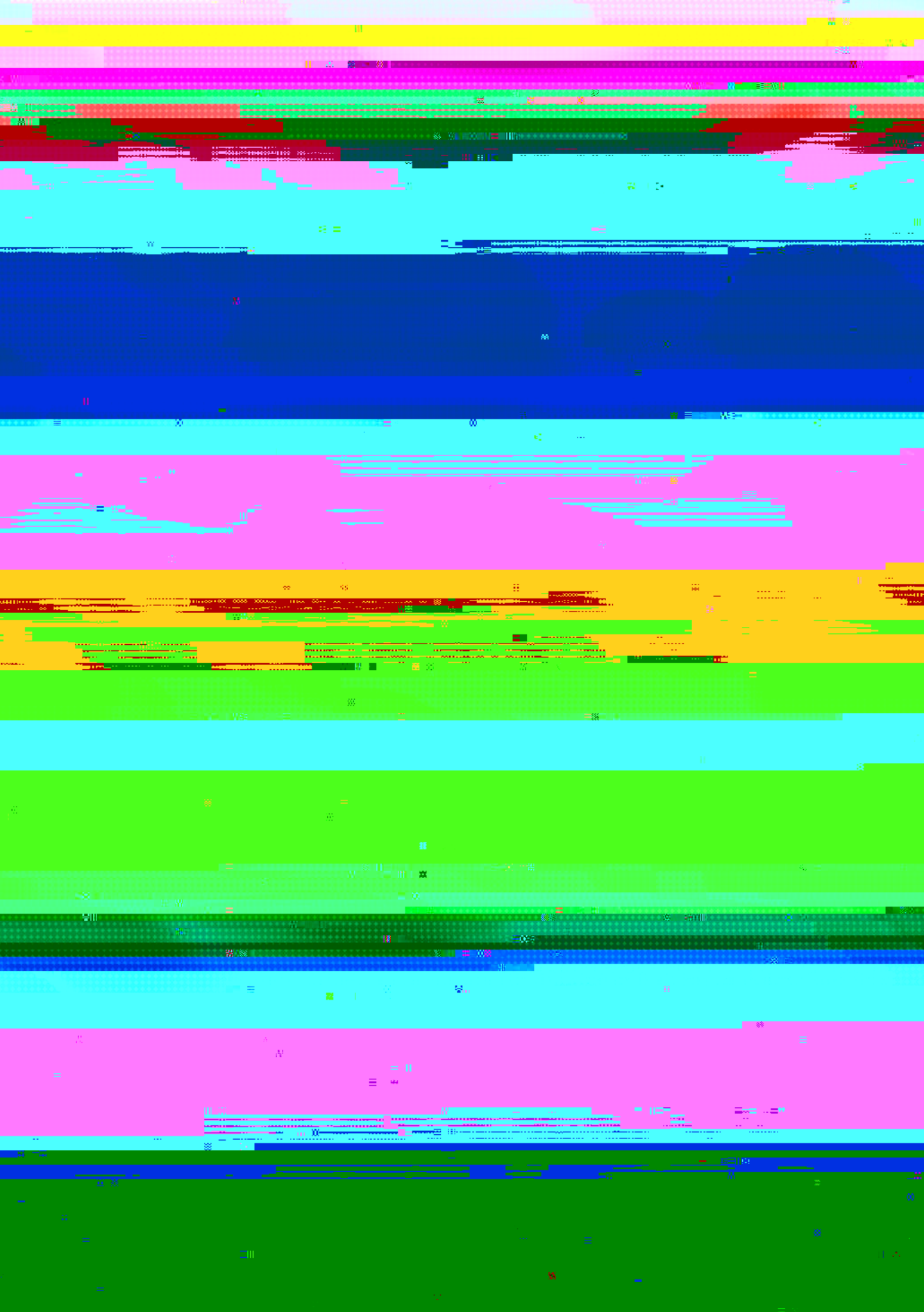
AGREE II assessment

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



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]
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]

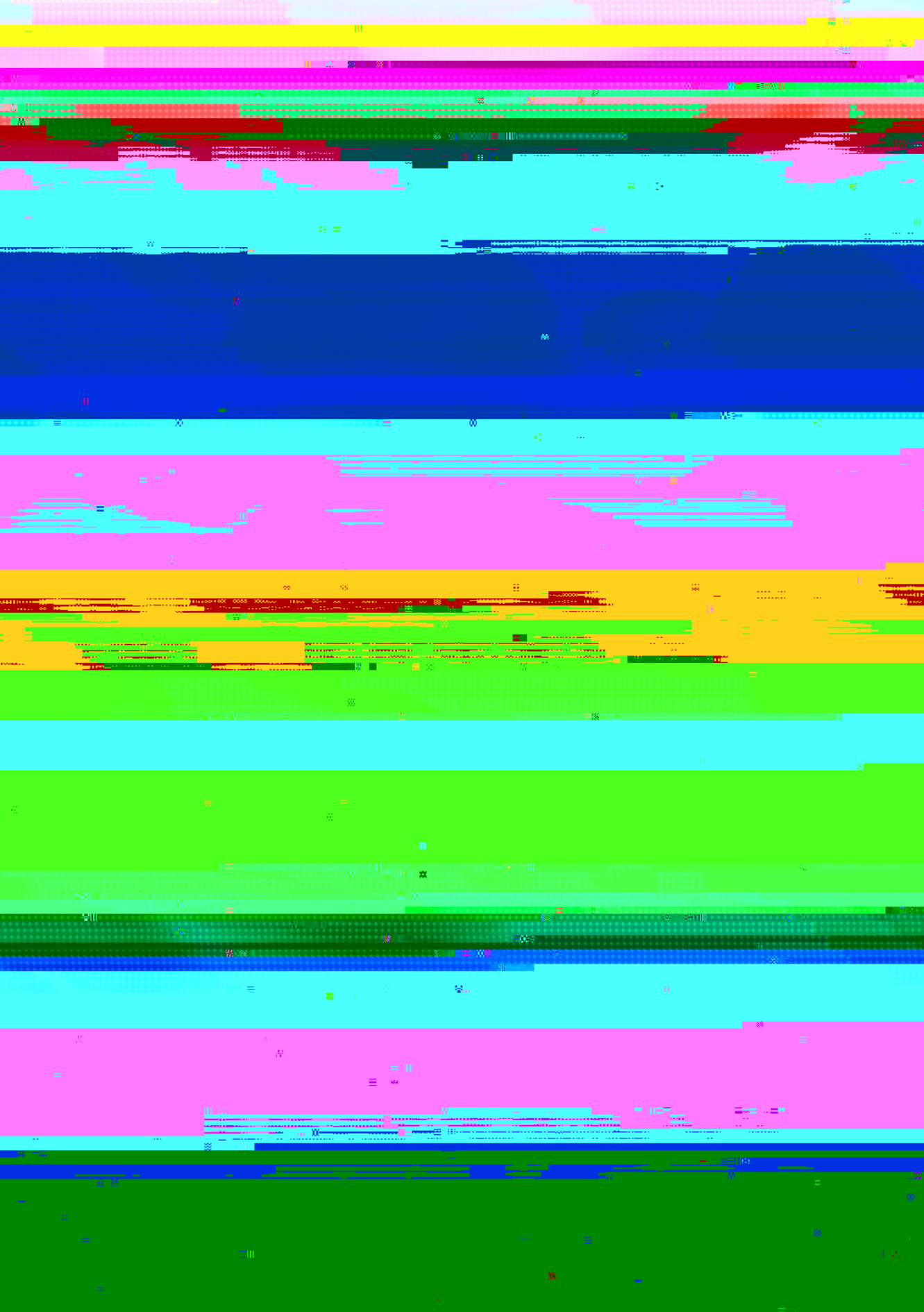
Source: Australian Red Cross Blood Service website (www.transfusion.com.au, accessed 28 July 2014)

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 C4 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

D 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**

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.

D 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.**

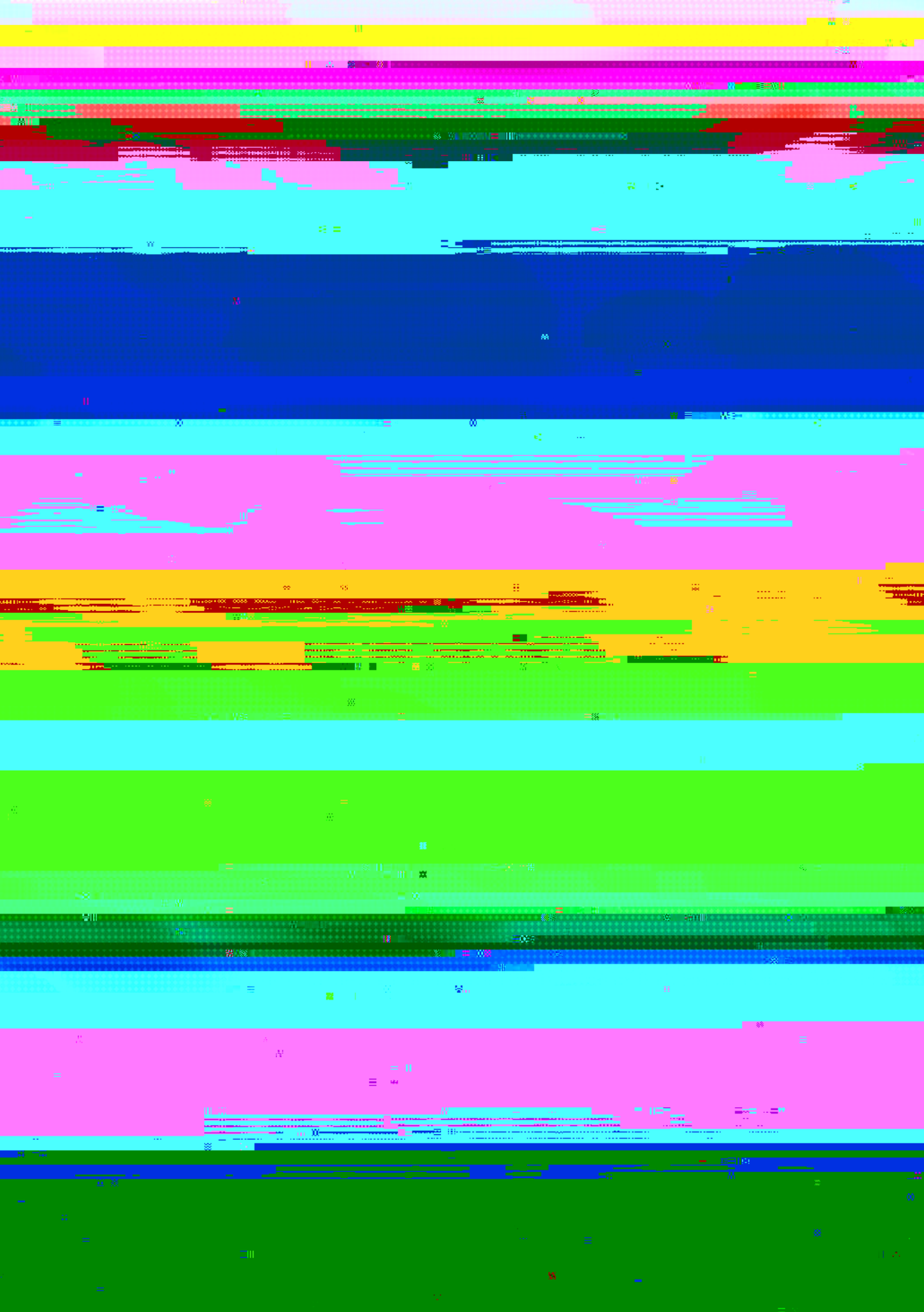
New Zealand Blood Service

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.

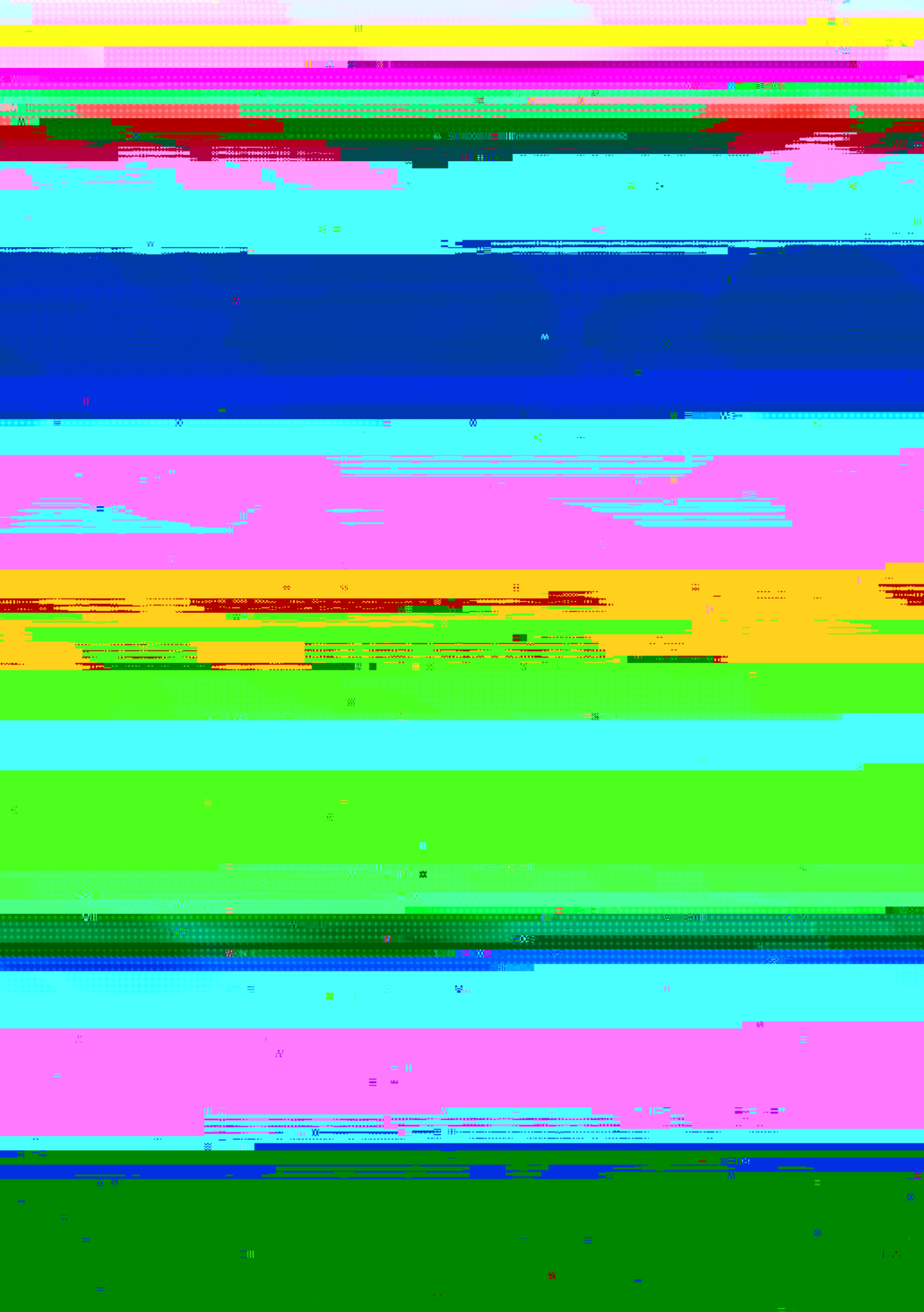
In addition to its role in collecting, processing and distribution of blood and blood products, the NZBS is actively involved in the provision of blood banking and clinical services within New Zealand's major hospitals.



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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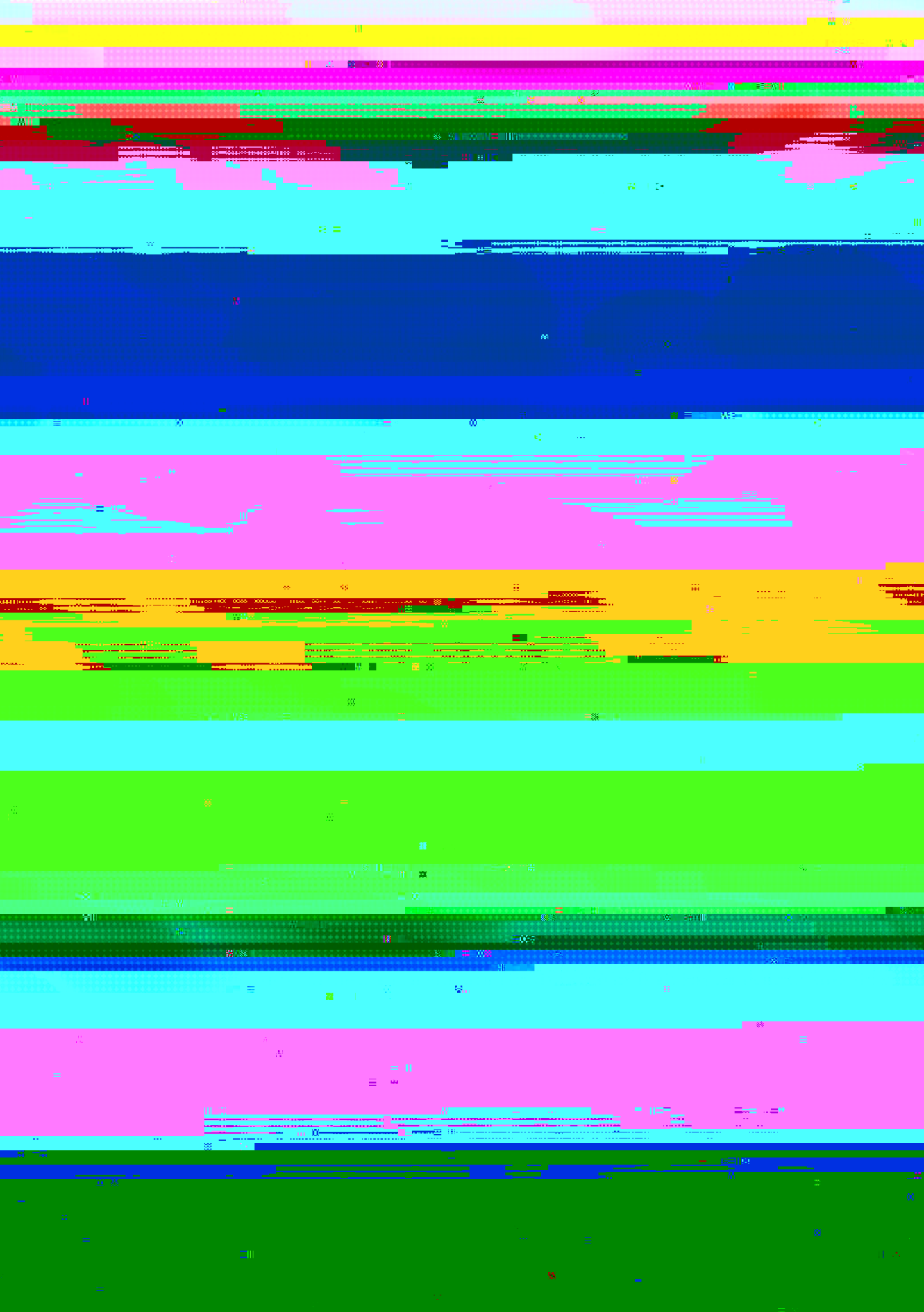

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