

Patient Blood Management Guidelines: Module 1

Critical Bleeding Massive Transfusion

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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 Friday 12th November 2010, 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 in that they are based on the systematic identification and synthesis of the best available scientific evidence and make clear recommendations for health professionals practising in an Australian health care setting. The NHMRC expects that all guidelines will be reviewed no less than once every five years.

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

Patient Blood Management Guidelines:

Module 1 – Critical Bleeding / Massive Transfusion

Development of this module was achieved through clinical input and expertise of representatives from the Colleges and Societies listed below and an independent consumer advocate (see [Appendix A](#)). The National Blood Authority gratefully acknowledges these contributions.

Australasian College for Emergency Medicine

Australian and New Zealand College of Anaesthetists

Australian and New Zealand Intensive Care Society

Australian and New Zealand Society of Blood Transfusion

Australian Orthopaedic Association

Australian Red Cross Blood Service

College of Intensive Care Medicine of Australia and New Zealand

Haematology Society of Australia and New Zealand

Royal Australian and New Zealand College of Obstetricians and Gynaecologists

Royal Australasian College of Physicians

Royal Australasian College of Surgeons

Royal College of Nursing Australia

Royal College of Pathologists of Australasia

Thalassaemia Australia

College and Society endorsement of this Module can be found at www.nba.gov.au

Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the circumstances, clinician's judgement and patient's preferences in each individual case. It is designed to provide information to assist decision making. Recommendations contained herein are based on the best available evidence published up to July 2009. The relevance and appropriateness of the information and recommendations in this document depend on the individual circumstances. Moreover, the recommendations and guidelines are subject to change over time.

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

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Abbreviations and acronyms

ACS	American College of Surgeons
AHMAC	Australian Health Ministers' Advisory Council
AHMC	Australian Health Ministers' Conference
ANZSBT	Australian & New Zealand Society of Blood Transfusion
APTT	activated partial thromboplastin time
ARCBS	Australian Red Cross Blood Service
ARDS	acute respiratory distress syndrome
ASBT	Australasian Society of Blood Transfusion
CI	confidence interval
CRG	Clinical/Consumer Reference Group
CTEPC	Clinical, Technical and Ethical Principal Committee
DIC	disseminated intravascular coagulation
ESA	erythropoiesis stimulating agent
EWG	Expert Working Group
FFP	fresh frozen plasma
FUWB	fresh (or ultra-fresh) unrefrigerated whole blood
GAR	Guidelines Assessment Register
INR	international normalised ratio
JBC	Jurisdictional Blood Committee
MTP	massive transfusion protocol
NBA	National Blood Authority
NHMRC	National Health and Medical Research Council
NZBS	New Zealand Blood Service
OR	odds ratio
PICO	population, intervention, comparator and outcome
PP	practice point
PPO	population, predictor and outcome
PRO	population, risk factor and outcome
PT	prothrombin time
R	recommendation
RBC	red blood cell
RCT	randomised controlled trial
rFVIIa	recombinant activated factor VII
TGA	Therapeutic Goods Administration

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Executive summary

This document, *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/ Massive Transfusion*, is the first in a series of six modules that focus on evidence-based patient blood management. The other five modules are perioperative, medical, critical care, obstetrics and paediatrics (including neonates). Together, the six modules replace the 2001 National Health and Medical Research Council/Australasian Society of Blood Transfusion (NHMRC/ASBT) *Clinical practice guidelines on the use of blood components*.¹

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

This Executive summary includes:

- a summary of the *recommendations* that were developed by the CRG, based on evidence from a systematic review
- a summary of the *practice points* that were developed by the CRG through consensus decision-making
- a template for a *massive transfusion protocol* (MTP)^a, which can be adapted to meet local needs.

Details of the systematic review used in the development of this module are given in the two-volume technical report that accompanies this document.^{2,3}

Materials relevant to clinicians who manage patients with critical bleeding requiring massive transfusion will be developed to accompany this module; these materials will be available online and in print.

^aThe use of the word 'protocol' in 'massive transfusion protocol' throughout this report is not strictly prescriptive.

Summary of recommendations

The CRG developed recommendations (given below) 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, which were set by the NHMRC:

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

No.	Grade	Recommendation	Relevant section of document
R1	C	It is recommended that institutions develop an MTP that includes the dose, timing and ratio of blood component therapy for use in trauma patients with, or at risk of, critical bleeding requiring massive transfusion (Grade C).⁴⁻⁵	4.2
R2	B	C The routine use of rFVIIa in trauma patients with critical bleeding requiring massive transfusion is not recommended because of its lack of effect on mortality (Grade B)⁶ and variable effect on morbidity (Grade C).⁶	4.6

MTP, massive transfusion protocol; rFVIIa, recombinant activated factor VII

Summary of practice points

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

No.	Practice point	Relevant section of document
PP1	<p>In patients with critical bleeding requiring massive transfusion, the following parameters should be measured early and frequently:</p> <ul style="list-style-type: none"> ▪ temperature ▪ acid–base status ▪ ionised calcium ▪ haemoglobin ▪ platelet count ▪ PT/INR ▪ APTT ▪ fibrinogen level. <p>With successful treatment, values should trend towards normal.</p>	4.1
PP2	<p>Values indicative of critical physiologic derangement include:</p> <ul style="list-style-type: none"> ▪ temperature < 35°C ▪ pH < 7.2, base excess > –6, lactate > 4 mmol/L ▪ ionised calcium < 1.1 mmol/L ▪ platelet count < 50 × 10⁹/L ▪ PT > 1.5 × normal ▪ INR > 1.5 ▪ APTT > 1.5 × normal ▪ fibrinogen level < 1.0 g/L. 	4.1
PP3	<p>In critically bleeding patients requiring, or anticipated to require, massive transfusion, an MTP^a should be used. A template MTP is provided within this module.^b</p> <p>^aThe use of the word ‘protocol’ in ‘massive transfusion protocol’ throughout this report is not strictly prescriptive.</p> <p>^bThe template MTP is intended for local adaptation.</p>	4.2
PP4	<p>In patients with critical bleeding requiring massive transfusion, insufficient evidence was identified to support or refute the use of <i>specific</i> ratios of RBCs to blood components.</p>	4.2
PP5	<p>In patients with critical bleeding requiring massive transfusion, haemoglobin concentration should be interpreted in the context of haemodynamic status, organ perfusion and tissue oxygenation.</p>	4.3

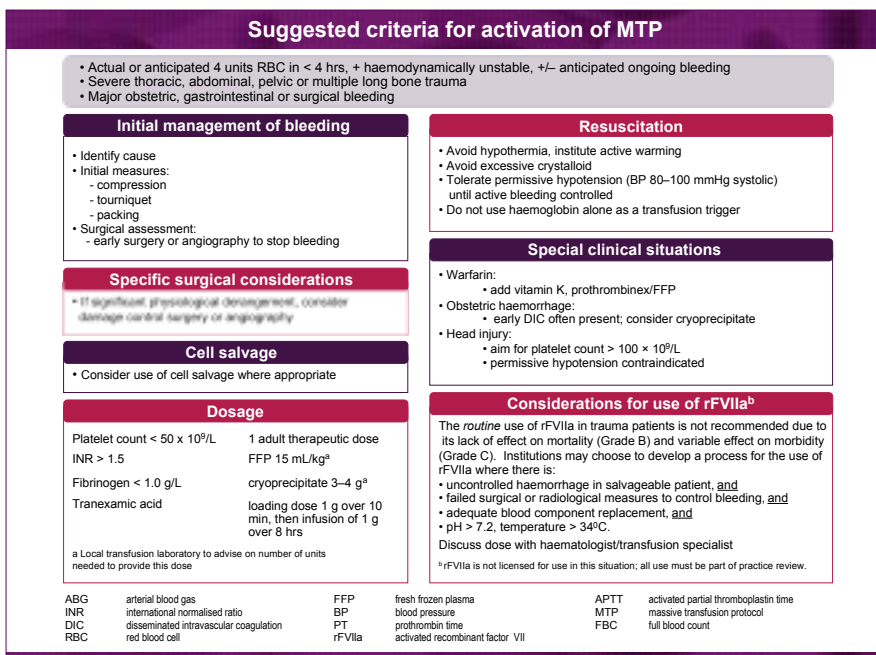
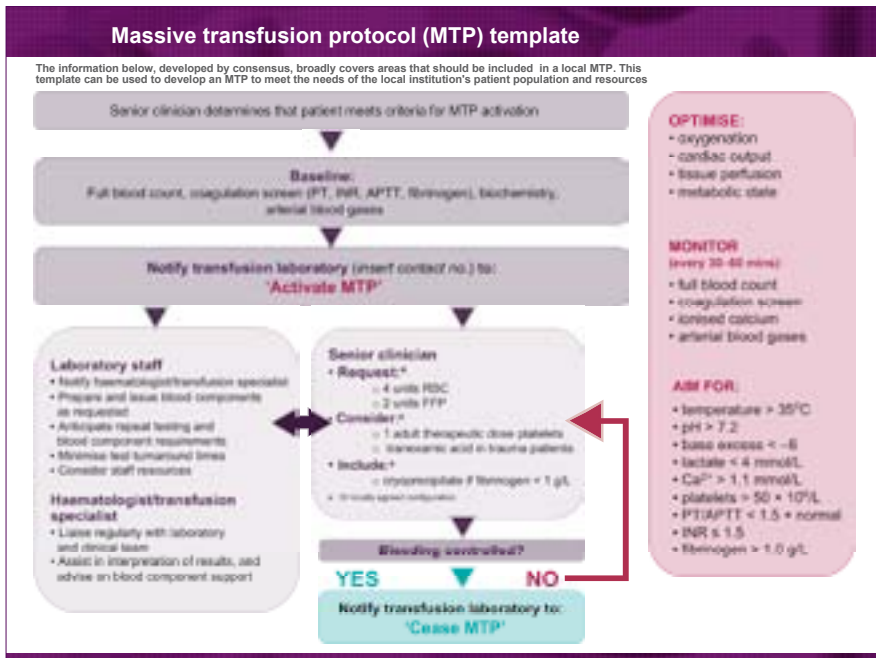
No.	Practice point	Relevant section of document
PP6	In patients with critical bleeding requiring massive transfusion, the use of RBC and other blood components may be life saving. However, transfusion of increased volumes of RBC and other blood components may be independently associated with increased mortality and ARDS.	4.4
PP7	In patients with critical bleeding requiring massive transfusion, the use of an MTP to facilitate timely and appropriate use of RBC and other blood components may reduce the risk of mortality and ARDS.	4.4
PP8	An MTP should include advice on the administration of rFVIIa when conventional measures – including surgical haemostasis and component therapy – have failed to control critical bleeding. NB: rFVIIa is not licensed for this use. Its use should only be considered in exceptional circumstances where survival is considered a credible outcome (see Template MTP example).	4.6
PP9	When rFVIIa is administered to patients with critical bleeding requiring massive transfusion, an initial dose of 90 µg/kg is reasonable.	4.6
PP 10	In patients with critical bleeding requiring massive transfusion, suggested doses of blood components are: ^a <ul style="list-style-type: none"> ▪ FFP: 15 mL/kg ▪ platelets: 1 adult therapeutic dose ▪ cryoprecipitate: 3–4 g. <p>^a Or as directed by the haematologist/transfusion specialist in specific clinical situations, such as obstetrics.</p>	4.8
APTT, activated partial thromboplastin time; ARDS, acute respiratory distress syndrome; FFP, fresh frozen plasma; INR, international normalised ratio; MTP, massive transfusion protocol; PT, prothrombin time; RBC, red blood cell; rFVIIa, recombinant activated factor VII		

CRASH 2 ²		
	In trauma patients with or at risk of significant haemorrhage, tranexamic acid (loading dose 1 g over 10 minutes, followed by infusion of 1 g over 8 hours) should be considered. The CRASH 2 trial was published on 14 June 2010 after the cut-off date of the systematic review. ² No systematic review was conducted on tranexamic acid in critical bleeding/massive transfusion. The study population was not restricted to critical bleeding requiring massive transfusion.	4.9

Massive transfusion protocol template

An editable electronic template MTP is available on the NBA's website www.nba.gov.au

The MTP template is also shown in [Appendix G, Chapter 4](#) discusses local adaptation of the template MTP (4.10.1) and the development of guidelines on activation and cessation of the MTP (4.10.2).



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.

These principles apply in the management of any haematological disorder. Patient blood management optimises the use of donor blood and reduces transfusion-associated risk.

If blood components are likely to be indicated, transfusion should not be a default decision. Instead, the decision on whether to transfuse should be carefully considered, taking into account the full range of available therapies, and balancing the evidence for efficacy and improved clinical outcome against the potential risks.

This document, *Patient Blood Management Guidelines: Module 1 – Critical Bleeding/Massive Transfusion*, is the first in a series of six modules that focus on evidence-based patient blood management. The other five modules are listed in Table 1.1, below. Together, the six modules will replace the 2001 National Health and Medical Research Council/Australasian Society of Blood Transfusion (NHMRC/ASBT) *Clinical practice guidelines on the use of blood components*.¹

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

Revision of the 2001 guidelines¹ was needed because of:

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

Definitions (see Chapter 3.1)

'Critical bleeding' may be defined as major haemorrhage that is life threatening and likely to result in the need for massive transfusion.

'Massive transfusion' may be defined:

- in adults, as a transfusion of half of one blood volume in 4 hours, or more than one blood volume in 24 hours (adult blood volume is approximately 70 mL/kg)
- in children, as a transfusion of more than 40 mL blood/kg (blood volume of children older than neonates is approximately 80 mL/kg).

1.1 Development of the guidelines

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

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

Table 1.1 Phases of development of guideline modules

Phase	Modules
I	Critical bleeding/massive transfusion Perioperative
II	Medical Critical care
III	Obstetrics Paediatric/neonatal

1.2 Governance structure

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

- a Steering Committee, responsible for the overall development and governance of the entire project
- an Expert Working Group (EWG), responsible for clinical oversight and integration of the six modules
- Clinical/Consumer Reference Groups (CRGs – one for each of the six modules), with membership including representation from relevant colleges, societies and consumer groups, to provide expert knowledge and input
- systematic reviewers and a technical writer, contracted by the NBA to review the literature and develop a draft of each module
- Guidelines Assessment Register (GAR) consultants, to provide advice and mentoring to the systematic reviewers, technical writer, EWG 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. The NBA website includes a list of colleges and societies that have endorsed these guidelines.^c [Appendix A](#) lists the membership of the bodies involved in governance of the guidelines. Details of how the guidelines will be implemented and updated are provided in [Chapter 6](#).

^bThe structure of the Australian blood sector is outlined in Appendix C
^c<http://www.nba.gov.au/>

1.3 Structure of the document and related materials

1.3.1 The document

This module includes:

- *recommendations* – based on evidence from the systematic review
- *practice points* – based on consensus decision-making, where the systematic review found insufficient high-quality data to produce evidence-based recommendations, but clinicians require guidance to ensure good clinical practice
- a template for a massive transfusion protocol (MTP) – summarising the guidance given in this document, and drafted using expert opinion. ^{d,e}

The recommendations and practice points are summarised in the Executive summary, which also includes a copy of the MTP template.

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](#))
- background material on clinical issues not covered by the systematic review ([Chapter 3](#))
- clinical practice guidance, setting out the main findings of the systematic review and other considerations documented by the CRG; recommendations and practice points, as appropriate; and discussion of the process for developing and implementing an MTP ([Chapter 4](#))
- recommendations for further research ([Chapter 5](#))
- information on implementing, evaluating and maintaining the guidelines ([Chapter 6](#)).

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

^dThe use of the word 'protocol' in 'massive transfusion protocol' throughout this report is not strictly prescriptive.

^e The template MTP is intended for local adaptation.

1.3.2 Related materials

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

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

- *Technical report on patient blood management in critical bleeding/massive transfusion: Volume 1 – Review of the evidence and evidence-based recommendations for clinical practice²*

This volume includes background information and the results of the systematic review pertaining to the clinical questions posed within this guideline.

- *Technical report on patient blood management in critical bleeding/massive transfusion: Volume 2 – Appendixes³*

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.⁸ The methods used in applying this process to the development of this module are outlined below, and are given in full in the accompanying two-volume technical report.^{2,3} A summary of the overall process for development of this module is given in [Appendix D](#).

2.1 Clinical research questions – development and details

Between July and November 2008, the relevant clinical research questions for this module were developed, prioritised, combined and refined by the EWG, the NHMRC GAR consultants and the CRG ([Appendix A](#)). The process resulted in different types of questions, as shown in Table 2.1.

Table 2.1 Details of question types

Question type	Answered based on	Uses	Location in document
Specific to this module	Systematic review	Used to develop: <ul style="list-style-type: none"> ▪ recommendations ▪ practice points 	Questions listed in Box 2.1 and discussed in Chapter 4
Generic (i.e. relevant to all six modules in the series)	Systematic review	Used to develop: <ul style="list-style-type: none"> ▪ recommendations ▪ practice points 	Questions listed in Box 2.1 and discussed in Chapter 4
Background specific to this module	Background material	Used to: <ul style="list-style-type: none"> ▪ capture information considered as being outside the scope of the systematic review questions ▪ provide general information for the guidelines. 	Questions listed in Box 2.2 and discussed in Chapter 3

The specific, generic and background questions were crafted in such a way that they attempted to provide answers in clinically relevant areas of uncertainty; however, it was recognised that in some areas there would be little or no high-quality published evidence. The questions were further refined through consultation among the systematic reviewer, CRG, NBA and NHMRC GAR consultants. Details of research question criteria are presented in Volume 1 of the technical report.²

2.2 Review and research

2.2.1 Systematic review process

Systematic reviews were undertaken to attempt to answer the questions specific to critical bleeding or massive transfusion, and the generic questions relevant to all six modules. 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.³ Searches were conducted in relevant electronic databases, bibliographies of studies identified as relevant, and literature recommended by expert members of the CRG.

The systematic review included only data from studies that met the relevant inclusion criteria, were of adequate quality and were published before July 2009.² Identification of relevant evidence and assessment of evidence was conducted in accordance with NHMRC standards and procedures for externally developed guidelines.²

Box 2.1 Systematic review questions

Questions 1 and 2 are specific to critical bleeding or massive transfusion (i.e. to this module); questions 3–8 are relevant to all six modules of these guidelines.

- **Question 1** – In patients with critical bleeding requiring massive transfusion, what is the effect of variation of physiologic, biochemical and metabolic (including temperature) parameters on morbidity, mortality and transfusion rate? (Prognostic question)
- **Question 2** – In patients with critical bleeding requiring massive transfusion, does the dose, timing and ratio (algorithm) of RBCs to blood component therapy (FFP, platelets, cryoprecipitate or fibrinogen concentrate) influence morbidity, mortality and transfusion rate? (Interventional question)
- **Question 3** – In patients with critical bleeding requiring massive transfusion, is anaemia an independent risk factor for adverse outcomes? (Aetiological question)
- **Question 4** – In patients with critical bleeding requiring massive transfusion, what is the effect of RBC transfusion on patient outcomes? (Interventional question)
- **Question 5** – In patients with critical bleeding requiring massive transfusion, what is the effect of non-transfusion interventions to increase haemoglobin concentration on morbidity, mortality and need for RBC blood transfusion? (Interventional question)
- **Question 6** – In patients with critical bleeding requiring massive transfusion, what is the effect of rFVIIa (prophylaxis or treatment) on morbidity, mortality and transfusion rate? (Interventional question)
- **Question 7** – In patients with critical bleeding requiring massive transfusion, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes? (Interventional question)
- **Question 8** – In patients with critical bleeding requiring massive transfusion, what INR (PT/APTT) for FFP, fibrinogen level for cryoprecipitate and platelet count for platelets concentrates should patients be transfused to avoid risks of significant adverse events? (Prognostic question)

APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalised ratio; PT, prothrombin time; RBC, red blood cell; rFVIIa, recombinant activated factor VII

2.2.2 Background material

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

Box 2.2 Background research questions

- **Background question 1** – What is critical bleeding?
- **Background question 2** – What is the definition of massive transfusion? What is an agreed (suitable) definition of massive transfusion?
- **Background question 3** – In the management of critical bleeding, are (a) permissive hypotension, also called minimal volume hypotensive resuscitation, and (b) damage control surgery associated with improved patient outcomes?
- **Background question 4** – Does the use of fresh (stored unrefrigerated for < 48 hours) or ultra-fresh (stored for < 4 hours) whole blood influence patients' morbidity and mortality?
- **Background question 5** – What effect does the age of red blood cells used in transfusions have on patients' morbidity and mortality?

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 2.2, 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 was done to minimise 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.

Table 2.2 Body of evidence matrix

Component	A - Excellent	B - Good	C - Satisfactory	D - Poor
Evidence base	Several Level I or II studies with low risk of bias	One or two Level II studies with low risk of bias or a systematic review, or multiple Level III studies with low risk of bias	Level III studies with low risk of bias, or Level I or II studies with moderate risk of bias	Level IV studies, or Level I–III studies with high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency can be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted

Component	A - Excellent	B - Good	C - Satisfactory	D - Poor
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 2009¹⁰

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 2.3)
- 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.

Table 2.3 Definitions of NHMRC grades for recommendations

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

Source: NHMRC 2009¹⁰

Where there was insufficient quality or quantity of evidence, it was not possible to develop evidence-based recommendations. In this situation, the CRG developed practice points through a consensus-based process, to guide clinical practice.

For prognostic and aetiological questions, the evidence base provided only an indication of the risk associated with a particular factor; thus, it was not possible to make an evidence-based recommendation for a change in practice. Instead, the CRG's consensus-based process, used to develop practice points to guide practice, was informed by the prognostic and aetiological review, and by clinical experience.

3. Background

3.1 Definitions

There are no universally accepted definitions of critical bleeding or massive transfusion.

3.1.1 Critical bleeding

Critical bleeding is a term used to describe a range of clinical scenarios where bleeding may result in significant patient morbidity or mortality. Broadly, critical bleeding falls into one of two categories (which may overlap):

- major haemorrhage that is life threatening and is likely to result in the need for massive transfusion
- haemorrhage of a smaller volume in a critical area or organ (e.g. intracranial, intraspinal or intraocular), resulting in patient morbidity or mortality.

For the purpose of this document, critical bleeding will refer only to the first category.

'Critical bleeding' may be defined as major haemorrhage that is life threatening and likely to result in the need for massive transfusion.

3.1.2 Massive transfusion

Massive transfusion has been defined based on the volume of blood loss or on the volume transfused. The most widely used definition proposes the loss or transfusion of one blood volume (about 7% of body weight in adults) over 24 hours;¹¹⁻¹⁴ or approximately 10 units of red blood cells (RBCs). Alternative, 'real time' definitions include replacement of half a blood volume within 4 hours,^{15,16} or blood loss of more than 150 mL per minute.¹³

The different definitions reflect the diverse clinical scenarios in which critical bleeding occurs. Ultimately, the importance of defining critical bleeding or massive transfusion is to facilitate early recognition of this condition, or its potential, so that appropriate management can be instituted.

In adults, 'massive transfusion' may be defined as a transfusion of half of one blood volume in 4 hours, or more than one blood volume in 24 hours (adult blood volume is approximately 70 mL/kg).

3.2 Pregnancy and children

3.2.1 Critical bleeding in pregnancy

Obstetric haemorrhage, including postpartum haemorrhage, can rapidly become life threatening and require massive transfusion. There is potential for concealed haemorrhage and early development of disseminated intravascular coagulation (DIC) in these patients. A module dedicated to obstetrics will be available in Phase III of the patient blood management guidelines.

3.2.2 Critical bleeding in children

There are important differences between children and adults, including blood volume, ability to tolerate blood loss, and age-appropriate haemoglobin and haematocrit levels.¹⁷

For practical purposes, massive transfusion in children may be defined as transfusion of > 40 mL blood/kg. A module dedicated to paediatrics (including neonates) will be available in Phase III of the patient blood management guidelines.

In children, 'massive transfusion' may be defined as a transfusion of more than 40 mL blood/kg. (The normal blood volume of a child is approximately 80 mL/kg.)

3.3 Early clinical assessment

Common causes of critical bleeding include trauma, gastrointestinal bleeding, ruptured aortic aneurysm, obstetric haemorrhage and surgical procedures.¹⁸ It can be difficult to recognise the early signs of blood loss. However, significant blood loss from any cause results in a sequence of physiological responses that help to maintain cardiac output and preserve blood flow to vital organs. Thus, changes in physiological and biochemical parameters can be used to recognise a critical haemorrhage.¹⁹ Reliance on systolic blood pressure alone may delay recognition of haemorrhagic shock.

The physiological response to haemorrhage may also vary with underlying conditions (e.g. cardiovascular disease), the presence of certain medications or drugs, the patient's age and the presence of hypothermia.²⁰

A useful classification of blood loss that may assist with the clinical assessment of the bleeding adult patient has been described by the American College of Surgeons (ACS) in their advanced trauma life support education program; this classification is shown in [Table 3.1](#).

Management of critical bleeding should focus on early recognition of blood loss, rapid control of the source of bleeding and restoration of circulating blood volume.

Initial assessment of the bleeding patient should include evaluation of:

- history
- systolic blood pressure
- heart rate
- pulse pressure
- peripheral perfusion
- mental status
- respiratory rate
- urine output
- haemoglobin and haematocrit
- coagulation status
- acid–base status
- temperature

Table 3.1 Estimated blood loss based on patient’s initial presentation

Class of haemorrhagic shock				
	I	II	III	IV
Blood loss (mL)	Up to 750	750–1500	1500–2000	> 2000
Blood loss (% blood volume)	Up to 15	15–30	30–40	> 40
Pulse rate (per minute)	< 100	100–120	120–140	> 140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mm Hg)	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate (per minute)	14–20	20–30	30–40	> 35
Urine output (mL/hour)	> 30	20–30	5–15	Negligible
Central nervous system/ mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic

Source: Adapted from American College of Surgeons (ACS) Committee on Trauma (2008)¹⁹
 Reproduced with permission from ACS

Note: Values are estimated for a 70 kg male

3.4 Permissive hypotension and minimal volume resuscitation

Historically, the management of haemorrhagic shock has emphasised fluid resuscitation with crystalloid solution, to achieve and maintain a normal blood pressure.^{21,22} However, aggressive volume resuscitation can cause serious problems, including:

- oedema, compartment syndrome²³ and acute lung injury
- exacerbation of anaemia, thrombocytopenia and coagulopathy due to haemodilution²⁴⁻²⁶
- exacerbation of bleeding due to possible clot disruption.^{24,27}

In contrast, permissive hypotension and minimal volume resuscitation are strategies in which systolic blood pressures of 80–100 mm Hg are tolerated while bleeding is controlled.²⁸ These concepts are not new (they date back to World War I²⁹) and several studies have shown survival benefit.^{30,31} Permissive hypotension is widely practised for ruptured abdominal aortic aneurysms.^{32,33}

Permissive hypotension is contraindicated in patients with traumatic brain injury, because reduced perfusion pressure and oxygenation can lead to secondary brain injury.³⁴

Permissive hypotension and minimal volume resuscitation are generally preferable to aggressive volume resuscitation while active bleeding is being controlled.

Permissive hypotension is contraindicated in patients with possible traumatic brain injury.

The safe low threshold for systolic blood pressure is unknown, and elderly patients require specific consideration.

The maximum safe duration for permissive hypotension is unknown.

3.5 Early surgical management

It is essential to stop bleeding as soon as possible. This can be achieved using compression, tourniquet, packing, surgical control, embolisation or topical haemostatic agents, or a combination of these approaches.

Damage control surgery refers to the timely use of a staged approach in the treatment of the actively bleeding shocked patient. This approach emphasises control of bleeding and prevention of further contamination, to allow the correction of hypothermia, coagulopathy and acidosis before definitive surgery is undertaken.³⁵

There are five critical decision-making stages in damage control surgery:³⁶

- Stage 1: Early patient selection
- Stage 2: Abbreviated life-saving surgery
- Stage 3: Secondary resuscitation
- Stage 4: Deferred definitive surgery
- Stage 5: Reconstructive surgery, if required

Damage control principles have been applied in abdominal trauma, neurosurgery,³⁴ chest trauma,³⁷ spinal trauma,³⁸ pelvic fractures,³⁹ injuries to the extremities⁴⁰ and physiologically compromised non-trauma patients.⁴¹

Damage control surgery may be indicated for patients with severe haemorrhagic shock. The decision to switch over to damage control mode should be made early.

3.6 Blood

3.6.1 Age of transfused red blood cells

Storage of whole blood and blood components leads to numerous changes, often referred to as the 'storage lesion'. The changes to RBCs include:

- reduced levels of 2,3 diphosphoglycerate
- increased oxygen affinity
- shape change
- reduced deformability
- decreased viability

The result is reduced tissue oxygenation and obstruction of the microcirculation, which may contribute to organ failure in critically ill patients. With increasing storage time, there is also generation of inflammatory mediators, cytokines and lipids; these have been implicated in immunomodulation, transfusion-related acute lung injury, febrile transfusion reactions and cellular injury.

The shelf-life of stored RBCs is currently up to 42 days, depending on the additive solution used. Additives used to buffer pH, prevent coagulation, delay the biochemical, metabolic and molecular changes, and preserve oxygen-carrying capacity include CPDA-1 (citrate, phosphate, dextrose and adenine) and SAG-M (sodium chloride, adenine, glucose and mannitol). The introduction of universal prestorage leukodepletion of RBCs may reduce storage lesion and its sequelae.

A key question is whether time-dependent changes have any measurable effect on patient outcomes. Studies of the effect on tissue oxygenation,⁴²⁻⁴⁴ blood chemistry,⁴⁵ cognitive function and neurological recovery⁴⁶ have reached different conclusions. Some studies have claimed an association between older blood and increased incidence of venous thromboembolism,⁴⁷ severe infections,^{48,49} multiorgan failure⁵⁰ and mortality.^{47,51,52}

Limitations of existing studies include variability in study populations, study size, confounding effects of transfusion volume, varying definitions of 'young' and 'old' blood, and changes in production processes; for example, the introduction of leukodepletion. Most studies are analyses of registry-based data, and the observational design cannot address all important outcomes or account for all confounders. A randomised controlled trial (RCT) failed to find an effect of age of blood on tissue oxygenation in critically ill patients, or on cognitive performance in anaemic but otherwise healthy adults.⁴² Well-designed prospective studies are needed to determine whether storage time of RBCs affects clinical outcomes.

Currently, there is insufficient evidence to support restricting RBCs transfused to critically ill patients to blood stored for only a short period of time (e.g. < 14 days).

3.6.2 Fresh whole blood

Fresh unrefrigerated whole blood (FUWB) has been variously defined as blood collected at less than 4 hours (ultra-fresh)⁵³ 24 hours⁵⁴ and 72 hours.⁵⁵ Most published data concern FUWB stored at room temperature for less than 24 or 48 hours, but not less than 4 hours.⁵⁴

FUWB may have a role in massive transfusion, without the potential for clinical sequelae from storage lesion. However, few well-conducted studies have investigated the efficacy or risks of using FUWB, and reports of its benefits have been largely anecdotal.

The use of FUWB has been advocated in cardiac surgery, burns and massive transfusion, particularly in the military setting.^{54,56,57} The potential role of FUWB in civilian settings has been extrapolated from the military experience.

A recent study of neonates undergoing cardiopulmonary bypass surgery reported improved clinical outcomes with reconstituted FUWB compared with stored blood components.⁵⁸ However, other studies have reported conflicting results.^{59,60}

The use of FUWB that has not been screened at the time of donation carries an increased risk of transmission of infectious agents. Additional potential risks of FUWB include ABO haemolysis and (if the product has not been irradiated) transfusion-associated graft-versus-host disease.

The use of FUWB is best limited to clinical trials and situations where there is life-threatening bleeding, and blood component therapy is unavailable.

4. Clinical practice guidance based on evidence or consensus

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 eight questions that formed the basis of the systematic review. Full details of the findings of the systematic review are given in the accompanying technical report. ^{2,3}

This chapter also provides guidance on adapting the MTP template ([Appendix G](#)) to suit the local patient population and health care resources.

4.1 Effect of physiological parameters on outcomes

Question 1 (prognostic)

In patients with critical bleeding requiring massive transfusion, what is the effect of variation of physiologic, biochemical and metabolic (including temperature) parameters on morbidity, mortality and transfusion rate?

The evidence was obtained from 10 studies, comprising 8 retrospective^{15 61-67} and 2 prospective^{68,69} analyses of registry data, medical records or charts.

Most of the studies of critically bleeding and transfused patients found that reduced core body temperature,^{14 60-62} lower pH or higher base deficit,^{14 61,62,65-68} coagulopathy^{14 62,68}, and thrombocytopenia^{14 68} were associated with increased mortality. However, two studies did not find an association with reduced body temperature^{63,67} and one study found no association with higher base deficit.⁶³

Five studies calculated the odds of predicting mortality (or survival) among patients with critical bleeding requiring massive transfusion.^{15 61,64,65,68} Although not strictly a study of massive transfusion (because patients included received ≥ 5 units RBCs within 24 hours of admission), Mitra found that a number of factors were independent predictors of mortality:¹⁵

- hypothermia (odds ratio [OR] = 0.72; 95%CI: 0.56, 0.92; p = 0.01)
- thrombocytopenia (OR = 0.99; 95%CI: 0.98, 1; p < 0.01)
- increased international normalised ratio (INR) (OR = 1.62; 95%CI: 1.18, 2.24; p < 0.01)
- prolonged partial thromboplastin time (OR = 1.01; 95%CI: 1.01, 1.02; p < 0.01)
- low fibrinogen level (OR = 0.52; 95%CI: 0.28, 0.99; p = 0.05)
- low pH (OR = 0.01; 95%CI: 0, 0.29; p = 0.01)
- low bicarbonate levels (OR = 0.86; 95%CI: 0.77, 0.96; p = 0.01).

Insufficient studies were found to provide an evidence statement on the effects of hypothermia, metabolic acidosis, thrombocytopenia and coagulopathy on morbidity or transfusion rate.

Mortality was found to be highest where acidosis and hypothermia occurred with coagulopathy.¹⁵ This combination has become known as the 'lethal triad' or 'bloody vicious cycle'. To improve patient survival and outcomes, management strategies should be directed to avoiding or reducing the extent of these complications.

Evidence statement

Evidence statement	Evidence	Consistency	Clinical Impact	Generalisability	Applicability
<p>Hypothermia, metabolic acidosis, thrombocytopenia and coagulopathy may be independently associated with increased mortality.^{15 61 63-68}</p> <p>(See evidence matrix 1 in Appendix E.)</p>	X	✓	✓	✓✓	✓✓
<p>✓✓✓ = A ✓✓ = B ✓ = C X = D (See table 2.2)</p>					

Practice points

PP1

In patients with critical bleeding requiring massive transfusion, 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.

PP2

Values indicative of critical physiologic derangement include:

- temperature < 35°C
- pH < 7.2, base excess > –6, lactate > 4 mmol/L
- ionised calcium < 1.1 mmol/L
- platelet count < 50 × 10⁹/L
- PT > 1.5 × normal
- INR > 1.5
- APTT > 1.5 × normal
- fibrinogen level < 1.0 g/L

APTT, activated partial thromboplastin time; INR, international normalised ratio; PP, practice point; PT, prothrombin time

4.2 Effect of dose, timing and ratio of component therapy on outcomes

Question 2 (interventional)

In patients with critical bleeding requiring massive transfusion, does the dose, timing and ratio (algorithm) of RBCs to blood component therapy (FFP, platelets, cryoprecipitate or fibrinogen concentrate) influence morbidity, mortality and transfusion rate?

FFP, fresh frozen plasma; RBC, red blood cell

The literature review identified 28 studies as being relevant. Of these, six were Level III studies^{4,5,70-73} and the remainder were Level IV.^{54,61,62,64-66,74-89} Some studies^{71,72} involved a military population and should therefore be interpreted with caution because of baseline differences between military and civilian populations (e.g. higher incidence of severe, penetrating trauma).

A survival advantage is associated with decreasing the ratio of RBCs to fresh frozen plasma (FFP), platelets or cryoprecipitate/fibrinogen administered to patients undergoing massive transfusion.^{65,76,78,89} The decrease in mortality associated with administering low versus high ratios of RBCs to blood components was associated with a significant decrease in deaths from exsanguination. This decrease was attributed to administration of lower ratios of RBCs to FFP, platelets, apheresis platelets and fibrinogen.^{61,65,76,79}

More deaths were reported in patients receiving high ratios of RBCs to blood components compared with low-ratio recipients. However, these results should be interpreted carefully, because of the potential for survival bias (that is, patients who die early are more likely to have received a higher RBC:component ratio).⁸⁴

The types and content of the studies varied in terms of blood components and the ratios given; therefore, the optimum target ratio is difficult to determine. In trauma patients, a ratio of RBC:FFP:platelets of $\leq 2:1:1$ was associated with improved survival.^{5,70,71} A number of these studies used a ratio of, or near to, 1:1.^{4,5,70,71,76,78,79,85,89} Other studies used a ratio of $< 2:1:1$.^{5,70,71} However, based on analysis of the available studies and the possibility of survival bias, it is not possible to recommend a target ratio of RBC:FFP:platelets.

In non-trauma patients, there were insufficient data to support or refute the use of a defined ratio of blood component replacement. Although these patients do not have the initial coagulopathy commonly seen in trauma, critical bleeding may still result in development of hypothermia, acidosis and coagulopathy. Coordination of the management of these patients through use of an MTP is recommended. Blood component replacement should be guided by clinical assessment and results of coagulation tests.

Fibrinogen is an essential component of the coagulation system, due to its role in initial platelet aggregation and formation of a stable fibrin clot. Current critical bleeding guidelines recommend keeping the fibrinogen level above 1.0 g/L.^{14,90} If fibrinogen levels are not maintained using FFP, replacement using cryoprecipitate or fibrinogen concentrate is indicated. However, in the setting of major obstetric haemorrhage, early administration of cryoprecipitate or fibrinogen concentrate may be necessary.

Optimum management requires prompt action, as well as good communication and coordination between treating clinicians, diagnostic laboratories and the transfusion service provider. This is best facilitated by the development and deployment of an MTP that clearly outlines responsibilities and requirements. A [template MTP](#) was developed by the CRG (see [Section 4.10](#)). Local adaptation of such a protocol – taking into account blood component availability and other resources – fosters a coordinated multidisciplinary approach.

Evidence statements

	Evidence	Consistency	Clinical Impact	Generalisability	Applicability
In trauma patients with critical bleeding requiring massive transfusion, the use of a protocol that includes the dose, timing and ratio of blood component therapy is associated with reduced mortality. ^{4,5} (See evidence matrix 2 in Appendix E .)	X	✓✓	✓✓	✓✓	✓
In trauma patients with critical bleeding requiring massive transfusion, a ratio of ≤ 2:1:1 of RBCs:FFP:platelets is associated with reduced mortality. ^{5,70,71} However, due to the possibility of survivor bias, it is not possible to recommend a target ratio of RBC:FFP:platelets. (See evidence matrix 3 in Appendix E .)	X	✓✓✓	✓	✓	✓
In trauma patients with critical bleeding requiring massive transfusion, early transfusion of FFP and platelets is associated with reduced mortality and subsequent RBC requirements. ^{85,89} (See evidence matrix 4 in Appendix E .)	X	✓✓✓	✓	✓✓	✓
FFP, fresh frozen plasma; RBC, red blood cell ✓✓✓ = A ✓✓ = B ✓ = C X = D (See table 2.2)					

Recommendation

R1

C

It is recommended that institutions develop an MTP that includes the dose, timing and ratio of blood component therapy for use in trauma patients with, or at risk of, critical bleeding requiring massive transfusion (Grade C).^{4,5}

(See [table 2.3](#) for definitions of NHMRC grades for recommendations)

Practice points

PP3

In critically bleeding patients requiring, or anticipated to require, massive transfusion, an MTP^a should be used. A template MTP is provided within this module.^b

a The use of the word 'protocol' in 'massive transfusion protocol' throughout this report is not strictly prescriptive.
b The template MTP is intended for local adaptation.

PP4

In patients with critical bleeding requiring massive transfusion, insufficient evidence was identified to support or refute the use of *specific* ratios of RBCs to blood components.

MTP, massive transfusion protocol; PP, practice point; R, recommendation; RBC, red blood cell

4.3 Effect of anaemia on outcomes

Question 3 (aetiological)

In patients with critical bleeding requiring massive transfusion, is anaemia an independent risk factor for adverse outcomes?

Anaemia has been defined by the World Health Organization as a haemoglobin level < 130 g/L in males and < 120 g/L in females. In critically ill patients in intensive care, anaemia is commonly present, and a number of studies have assessed the association of anaemia with adverse outcomes. However, no studies were identified that assessed the association between anaemia and adverse outcomes in patients with critical bleeding requiring massive transfusion. It is unlikely that the effects of anaemia will be able to be independently assessed in this group of patients.

Evidence statement	Evidence	Consistency	Clinical Impact	Generalisability	Applicability
No studies were identified that assessed the association of anaemia with adverse outcomes that confined their analysis to patients with critical bleeding requiring massive transfusion.	NA	NA	NA	NA	NA

Practice point

PP5

In patients with critical bleeding requiring massive transfusion, haemoglobin concentration should be interpreted in the context of haemodynamic status, organ perfusion and tissue oxygenation.

PP, practice point

4.4 Effect of red cell transfusion on outcomes

Question 4 (interventional)

In patients with critical bleeding requiring massive transfusion, what is the effect of RBC transfusion on patient outcomes?

RBC, red blood cell

A limited number of studies are available on the effect of transfusion on critically bleeding patients. Because it is unethical to conduct RCTs of transfusion versus no transfusion for critically bleeding patients, no Level I or II studies were found. Two prospective cohort (Level III) studies were identified.^{91,92} Both assessed the impact of RBC transfusion on in-hospital mortality and acute respiratory distress syndrome (ARDS). One found no difference in risk of in-hospital mortality,⁹¹ whereas the other found a higher risk in patients transfused with more than 10 units.⁹² Because the studies could not control who did or did not receive transfusion, it was not possible to determine whether the risk of death associated with RBC transfusion resulted from the transfusion itself or whether transfusion occurred more often among severely injured patients, whose risk of death was consequently higher. However, multivariate logistic regression analysis to adjust for potential confounders (age, gender, injury type and severity) demonstrated a 4% increased risk of in-hospital mortality per unit of blood transfused in the first 24 hours.⁹² Both studies found an increased risk of ARDS in patients who had received more than 10 units of RBCs. Multivariate logistic regression analysis demonstrated a 4% increased risk of ARDS per unit of blood transfused in the first 24 hours.

Although RBC transfusion can be life saving in critically bleeding patients, the transfusion of RBCs and blood components is associated with potential risks, including infection, acute lung injury, multiorgan failure, systemic inflammatory response syndrome and mortality. As far as possible, exposure to components should be minimised. Use of an MTP is recommended, to coordinate management and guide replacement therapy to minimise transfusion.

Evidence statements	Evidence	Consistency	Clinical Impact	Generalisability	Applicability
In trauma patients with critical bleeding requiring massive transfusion, an increased volume of transfused red cells may be independently associated with increased mortality. ^{91,92} (See evidence matrix 5 in Appendix E .)	✓	✓✓	✗	✓	✓
In trauma patients with critical bleeding requiring massive transfusion, an increased volume of transfused red cells is independently associated with ARDS. ^{91,92} (See evidence matrix 6 in Appendix E .)	✓	✓✓	✓	✓	✓
✓✓✓ = A ✓✓ = B ✓ = C ✗ = D (See table 2.2)					

Practice points

PP6 In patients with critical bleeding requiring massive transfusion, the use of RBC and other blood components may be life saving. However, transfusion of increased volumes of RBC and other blood components may be independently associated with increased mortality and ARDS.

PP7 In patients with critical bleeding requiring massive transfusion, the use of an MTP to facilitate timely and appropriate use of RBC and other blood components may reduce the risk of mortality and ARDS.

ARDS, acute respiratory distress syndrome; MTP, massive transfusion protocol; PP, practice point; RBC, red blood cell

4.5 Effect of non-transfusion interventions to increase haemoglobin concentration

Question 5 (interventional)

In patients with critical bleeding requiring massive transfusion, what is the effect of non-transfusion interventions to increase haemoglobin concentration on morbidity, mortality and need for RBC transfusion?

RBC, red blood cell

Non-transfusion interventions to increase haemoglobin concentration (e.g. iron and erythropoiesis-stimulating agents, ESAs) are not applicable in the setting of critical bleeding requiring massive transfusion. The review did not include a search for synthetic oxygen-carrying solutions or cell salvage techniques.

A systematic review of cell salvage techniques is included in other modules of these guidelines.

Evidence statement	Evidence	Consistency	Clinical Impact	Generalisability	Applicability
In critically bleeding patients requiring massive transfusion, no evidence could be found regarding non-transfusion interventions to increase haemoglobin concentration.	NA	NA	NA	NA	NA

4.6 Effect of recombinant activated factor VII on outcomes

Question 6 (interventional)

In patients with critical bleeding requiring massive transfusion, what is the effect of rFVIIa (prophylaxis or treatment) on morbidity, mortality and transfusion rate?

Currently, recombinant activated factor VII (rFVIIa) is approved in Australia and New Zealand 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 (with glycoproteinIIb-IIIa, and/or antibodies to human leukocyte antigen plus refractoriness to platelet infusion). Any use outside of these indications is considered 'off-licence'.

Although the literature review for this question identified nine systematic reviews, only one trial met the inclusion criteria (i.e. critical bleeding requiring massive transfusion).⁶ This study reported no statistically significant differences in 48-hour or 30-day mortality between patients receiving rFVIIa and those receiving placebo, in either the blunt or penetrating trauma patient groups. In the patients with blunt trauma, there was a significant reduction in the volume of RBC transfusion and the incidence of massive transfusion and ARDS. The number of thromboembolic events was too small to determine any significant difference between the treatment and placebo groups.

A further international placebo-controlled double-blind RCT — CONTROL — was intended to assess the efficacy and safety of rFVIIa in exsanguinating trauma patients.²² The trial began active recruitment in October 2005, but was halted on 11 June 2008 because the observed mortality in the 576 enrolled patients was so far below expectations that, with the planned number of subjects, the study would have lacked the statistical power to demonstrate a benefit. As of April 2010, the effect of rFVIIa on the study outcomes has not been published.

Much of the current use of rFVIIa is for patients with critical bleeding unresponsive to conventional measures of surgical haemostasis and adequate component therapy. This use remains controversial, particularly because of concerns about the risk of potential thrombotic complications.

When rFVIIa is used in off-licence situations, the dose of rFVIIa is also under debate. Doses of 100–200 µg/kg in critical bleeding due to trauma have been reported.⁶ Due to logistics and ethical considerations, studies to determine efficacy and dose are unlikely to be performed; therefore, cumulative registry data may assist in providing guidance. The Haemostasis Registry was established to provide a database of off-licence use in hospitals throughout Australia and New Zealand. Registry data published in 2007 reported a median dose of rFVIIa of approximately 90 µg/kg.²⁴ Up to mid-2009, more than 2800 cases had been entered.

Evidence statements

	Evidence	Consistency	Clinical Impact	Generalisability	Applicability
In trauma patients with critical bleeding requiring massive transfusion, administration of rFVIIa has no effect on 48-hour or 30-day mortality. ⁶ (See evidence matrix 7 in Appendix E .)	✓✓	NA	X	✓	✓✓
In patients with critical bleeding requiring massive transfusion, there is insufficient evidence to determine any association between rFVIIa and thromboembolism. ⁶ (See evidence matrix 8 in Appendix E .)	✓✓	NA	X	✓	✓✓
In patients with blunt trauma and critical bleeding requiring massive transfusion, administration of rFVIIa is associated with reduced RBC transfusion requirements and incidence of ARDS. ⁶ In patients with penetrating trauma and critical bleeding requiring massive transfusion, administration of rFVIIa has no effect on morbidity. ⁶ (See evidence matrix 9 in Appendix E .)	✓✓	NA	✓	✓	✓✓
✓✓✓ = A ✓✓ = B ✓ = C X = D NA = not applicable (one study only) (See table 2.2)					

Recommendation

R2	B	C	<p>The routine use of rFVIIa in trauma patients with critical bleeding requiring massive transfusion is not recommended because of its lack of effect on mortality (Grade B)⁶ and variable effect on morbidity (Grade C).⁶</p>
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(See [table 2.3](#) for definitions of NHMRC grades for recommendations)

Practice points

- PP8** An MTP should include advice on the administration of rFVIIa when conventional measures – including surgical haemostasis and component therapy – have failed to control critical bleeding.
- NB: rFVIIa is not licensed for this use. Its use should only be considered in exceptional circumstances where survival is considered a credible outcome (see [Template MTP](#) example).
- PP9** When rFVIIa is administered to patients with critical bleeding requiring massive transfusion, an initial dose of 90 µg/kg is reasonable.
- MTP, massive transfusion protocol; PP, practice point; R, recommendation; rFVIIa, recombinant activated factor VII

4.7 Effect of blood components on outcomes

Question 7 (interventional)

In patients with critical bleeding requiring massive transfusion, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes?

FFP, fresh frozen plasma

Four Level III studies examined the effect of FFP or platelet transfusion on mortality or morbidity.^{5, 61, 75, 95} An RBC:FFP ratio of $\leq 2:1$ was reported to be associated with reduced mortality.^{61, 75} However, this outcome is potentially confounded by survivor bias. No studies investigated the use of fibrinogen or cryoprecipitate as an intervention.

Evidence statement

Evidence statement	Evidence	Consistency	Clinical Impact	Generalisability	Applicability
<p>In trauma patients with critical bleeding requiring massive transfusion, an RBC:FFP ratio of $\leq 2:1$ is associated with reduced mortality.^{61, 75}</p> <p>(See evidence matrix 10 in Appendix E.)</p>	X	✓ ✓	✓	✓	✓
<p>FFP, fresh frozen plasma; RBC, red blood cell</p> <p>✓✓✓ = A ✓✓ = B ✓ = C X = D (See table 2.2)</p>					

4.8 Triggers for blood component transfusion

Question 8 (prognostic)

In patients with critical bleeding requiring massive transfusion, at what INR (or PT/APTT) for FFP, fibrinogen level for cryoprecipitate and platelet count for platelets concentrates should patients be transfused to avoid risks of significant adverse events?

APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalised ratio; PT, prothrombin time

The systematic review found no studies relevant to the identification of an INR (or prothrombin time [PT]/activated partial thromboplastin time [APTT]), fibrinogen level, or platelet count to trigger a blood component transfusion in patients with critical bleeding requiring massive transfusion.

There are no published data on the trigger levels for blood components. Therefore, the CRG developed practice points that integrate information from other sources, including previously published guidelines and consensus recommendations.

Most important in the management of these patients is regular assessment of the efficacy of replacement therapy using clinical assessment of microvascular bleeding and ongoing monitoring of coagulation parameters. Because there is an unavoidable delay in provision of laboratory results, the use of point-of-care testing, including thromboelastography, is increasing. The review did not include point-of-care testing.

Evidence statement	Evidence	Consistency	Clinical Impact	Generalisability	Applicability
In critically bleeding patients requiring massive transfusion, there was insufficient evidence to identify an INR (or PT/APTT), fibrinogen level, or platelet count to trigger a blood component transfusion.	NA	NA	NA	NA	NA

Practice point

PP
10

In patients with critical bleeding 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 in specific clinical situations, such as obstetrics.

APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalised ratio; MTP, massive transfusion protocol; PP, practice point; PT, prothrombin time

4.9 Effect of tranexamic acid

The systematic review did not assess the effect of antifibrinolytic therapy in critically bleeding patients requiring massive transfusion. However, a recently published RCT has demonstrated improved survival in trauma patients who received tranexamic acid.² (See Appendix 5 of Volume 1 of the technical report.²) In this international, multicentre RCT of more than 20 000 patients, tranexamic acid (loading dose 1 g over 10 minutes, followed by infusion of 1 g over 8 hours) demonstrated a significant reduction in:

- all-cause mortality at 4 weeks after injury (14.5% vs. 16.0%; relative risk [RR] = 0.91, 95%CI: 0.85, 0.97; p = 0.0035)
- risk of death from bleeding (4.9% vs. 5.7%, RR = 0.85; 95%CI: 0.76, 0.96; p = 0.0077).

The study population was beyond the scope of this module (i.e. it was not restricted to those with critical bleeding requiring massive transfusion), and the study was published after the deadline for this review. Nevertheless, the CRG considers the results to be noteworthy and suggests that tranexamic acid should be considered in trauma patients with, or at risk of, significant haemorrhage. Tranexamic acid should be considered as an adjunct in these patients, not as a 'magic bullet'. It should be administered as part of a locally adapted MTP in the setting of overall patient management, including strict attention to the control of bleeding, physiological and metabolic parameters, coagulation status and temperature maintenance.

The effect of antifibrinolytic therapy will be covered in other modules of these guidelines.

CRASH 2²

In trauma patients with, or at risk of, significant haemorrhage, tranexamic acid (loading dose 1 g over 10 minutes, followed by infusion of 1 g over 8 hours) should be considered.

The CRASH 2 trial² was published on 14 June 2010 after the cut-off date of the systematic review. No systematic review was conducted on tranexamic acid in critical bleeding/massive transfusion. The study population was not restricted to critical bleeding requiring massive transfusion.

4.10 Development of a massive transfusion protocol

A template MTP is provided in [Appendix G](#). This section discusses local adaptation of the template MTP, and development of guidelines on activation and cessation of the MTP.

4.10.1 Local adaptation

A multidisciplinary team should adapt the template MTP to:

- incorporate the recommendations and practice points provided in this module
- take into account local resources (e.g. access to blood components)
- provide details of how components will be delivered to the correct patient and location
- include supporting information that explains how the clinical, laboratory and support staff will communicate
- highlight the need for early communication with a haematologist or transfusion specialist.

The template MTP can also be modified for specific populations such as obstetric patients, given the potential for concealed haemorrhage and early development of DIC.

The local facility should also develop materials to accompany the MTP, clarifying the roles and responsibilities of the team members (e.g. task cards).

4.10.2 Activation and cessation

The multidisciplinary team should also develop guidelines for the activation and cessation of the MTP. This will help to ensure that the MTP is used appropriately, and wastage of blood components is minimised.

Activation of the MTP should take into account:

- cause and rate of the haemorrhage
- mechanism of injury (if present)
- current physiological state
- likely requirement for ongoing blood component support.

The template MTP given in [Appendix G](#) includes suggestions on when to activate an MTP. The guidelines on activation and cessation of the MTP should be clearly communicated to all relevant staff.

Use of the MTP should be audited.

5. Future directions

The systematic review for this module highlighted a lack of high-quality evidence. Further research is needed to provide a stronger evidence base.

This chapter:

- describes the evidence gaps identified for each review question and suggests areas of future research
- identifies topics that were not included in the systematic review, but may be considered in revisions of this module.

5.1 Evidence gaps and areas of future research

5.1.1 Effect of physiological parameters on outcomes

Question 1 (prognostic)

In patients with critical bleeding requiring massive transfusion, what is the effect of variation of physiologic, biochemical and metabolic (including temperature) parameters on morbidity, mortality and transfusion rate?

In patients with critical bleeding requiring massive transfusion, accepted clinical practice is to strive to maintain normal physiologic, biochemical and metabolic parameters. It is therefore not practical to undertake RCTs in this area. Nevertheless, the review identified sufficient evidence to support the currently accepted clinical practice, and this is addressed in practice points 1 and 2. It is debatable whether or not this is an evidence gap, but further research is recommended.

5.1.2 Effect of dose, timing and ratio of component therapy on outcomes

Question 2 (interventional)

In patients with critical bleeding requiring massive transfusion, does the dose, timing and ratio (algorithm) of RBCs to blood component therapy (FFP, platelets, cryoprecipitate or fibrinogen concentrate) influence morbidity, mortality and transfusion rate?

FFP, fresh frozen plasma; RBC, red blood cell

In the complex setting of critical bleeding requiring massive transfusion, there are many constraints to the design of clinical trials of blood replacement strategies. A major historical problem has been the inability to control for the transfusion decision, which includes not only the defined threshold for red cell administration, but also the indication for component therapy (i.e. FFP, platelets and cryoprecipitate).

The best evidence examining the use of specific ratios of RBC:FFP:platelets came from studies of trauma patients with critical bleeding requiring massive transfusion in the military setting; however, there are few studies in other clinical settings. Also, the studies did not account for the possibility of survivor bias (e.g. patients who die early may receive less FFP than those who survive, so mortality may be lower in patients transfused with more FFP). Thus, it was not possible to recommend a specific ratio.

The strength of evidence related to this intervention would be increased if the design of clinical trials were to include the need to prospectively control for the use of predetermined defined ratios (algorithm based) compared to goal-directed component therapy. The effect of each intervention would also need to be assessed by its effect on the changes in the relevant coagulation measurement (platelet count for platelets, INR or PT for FFP, and fibrinogen for cryoprecipitate or fibrinogen concentrate) as well as the effect on morbidity, mortality and transfusion rate.

Current published critical bleeding guidelines recommend keeping the fibrinogen level above 1.0 g/L.^{14, 20} In the setting of major obstetric haemorrhage, early administration of cryoprecipitate or fibrinogen concentrate may be necessary.

Further research is needed to:

- compare goal-directed therapy to the use of specific ratios of RBCs to blood components in all patients with critical bleeding requiring massive transfusion (including time of administration of component therapy)
- determine the optimum level of fibrinogen and the role of fibrinogen concentrate in critically bleeding patients requiring massive transfusion
- evaluate the role of MTPs.

5.1.3 Effect of anaemia on outcomes

Question 3 (aetiological)

In patients with critical bleeding requiring massive transfusion, is anaemia an independent risk factor for adverse outcomes?

It is unlikely that anaemia can be assessed as an independent risk factor in critically bleeding patients requiring massive transfusion.

5.1.4 Effect of red cell transfusion on outcomes

Question 4 (interventional)

In patients with critical bleeding requiring massive transfusion, what is the effect of RBC transfusion on patient outcomes?

RBC, red blood cell

This question is controversial, given the paradox that, although there is increasing evidence of the hazards of receiving allogeneic blood, RBC transfusion may be life saving in the setting of critical bleeding requiring massive transfusion.

The review identified studies that demonstrated an independent association between the amount of RBC transfusion, and mortality and the development of ARDS. However, in the absence of religious or other personal objections to transfusion, it is unacceptable to withhold RBC transfusion due to these risks if doing so is likely to result in death from exsanguination or tissue hypoxia.

Further research is needed to independently evaluate the risks of RBC and component therapy, even in the complex clinical setting of critical bleeding requiring massive transfusion.

5.1.5 Effect of non-transfusion interventions to increase haemoglobin concentration

Question 5 (interventional)

In patients with critical bleeding requiring massive transfusion, what is the effect of non-transfusion interventions to increase haemoglobin concentration on morbidity, mortality and the need for RBC blood transfusion?

RBC, red blood cell

It is unlikely that non-transfusion interventions (e.g. haematinics and ESAs) to increase haemoglobin concentration will be able to be assessed for their effect on morbidity, mortality and the need for RBC transfusion in critically bleeding patients requiring massive transfusion.

5.1.6 Effect of recombinant activated factor VII on outcomes

Question 6 (interventional)

In patients with critical bleeding requiring massive transfusion, what is the effect of rFVIIa (prophylaxis or treatment) on morbidity, mortality and transfusion rate?

rFVIIa, recombinant activated factor VII

From the available Australian and New Zealand data, the median dose of rFVIIa used off license in critically bleeding patients is approximately 90µg/kg,^{94,96,97} however, lower doses (i.e. 45–60 µg/kg) have been used.

Further research is needed to determine, in patients with critical bleeding requiring massive transfusion, the efficacy, safety and dose of rFVIIa, through studies that:

- clearly define the indication or trigger for the administration of the drug
- include a placebo arm
- take into account the indication for administration of component therapy, particularly platelets and cryoprecipitate (or fibrinogen concentrate), because the efficacy of rFVIIa depends on the availability of substrate fibrinogen and platelets.

5.1.7 Effect of blood components on outcomes

Question 7 (interventional)

In patients with critical bleeding requiring massive transfusion, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes?

FFP, fresh frozen plasma

This question clearly overlaps with question 2, which relates to the administration of RBC and component therapy according to ratios.

Some studies have demonstrated beneficial effects of the early use of component therapy in trauma patients. If early component therapy does help to control bleeding, the total RBC transfusion requirement would be reduced.

Further research is needed to investigate the effects of early use of component therapy in critically bleeding patients, through controlled studies that clearly define the indication or trigger for the administration of a particular component.

A challenge for studies in this clinical setting is the relative inability to control for the many variables that may contribute to ongoing bleeding. For example, early administration of component therapy may be futile if there has been no progress in the surgical control of bleeding. Conversely, in many situations it is almost impossible to differentiate between bleeding due to surgery and to haemostatic failure.

5.1.8 Triggers for blood component transfusion

Question 8 (prognostic)

In patients with critical bleeding requiring massive transfusion, at what INR (or PT/APTT) for FFP, fibrinogen level for cryoprecipitate and platelet count for platelets concentrates should patients be transfused to avoid risks of significant adverse events?

APTT, activated partial thromboplastin time; FFP, fresh frozen plasma; INR, international normalised ratio; MTP, massive transfusion protocol; PT, prothrombin time

This question overlaps with questions 2 and 7. In the setting of critically bleeding patients requiring massive transfusion, the systematic review found no studies of transfusion triggers for FFP, platelets, cryoprecipitate or fibrinogen concentrate.

Further research is needed into transfusion triggers for FFP, platelets, cryoprecipitate or fibrinogen concentrate.

5.2 Topics for future consideration

The following topics were not included in the systematic review, but may be considered in revisions of this module:

- antifibrinolytic therapy
- oxygen therapeutics (e.g. synthetic haemoglobins)
- cell salvage techniques
- point-of-care testing (e.g. thromboelastography and thromboelastometry).

6 Implementing, evaluating and maintaining the guidelines

The NBA, in collaboration with the Steering Committee and EWG members, developed a plan to guide appropriate communication on the implementation of this module. The plan identifies target audiences for the module, strategies and 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 components⁹⁸. A plan was designed to evaluate implementation of the six modules of the guidelines and to determine:

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

The results of the evaluation will be used to inform future review of the guidelines. Economic issues were considered when formulating the evidence-based recommendations, and the recommendations appear unlikely to have major cost implications. Thus, cost will not be a barrier to implementation of the recommendations.

This module will be reviewed and amended in five years unless an issue arises (e.g. new clinical evidence relevant to practice) that triggers a need to review the document earlier.

The Principal Medical Officer of the NBA will convene the group of experts to undertake the review, and will be the person who can be contacted on major issues, events or practice changes.

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

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

Your correspondence will be forwarded to the Principal Medical Officer for consideration in the next scheduled review.

A list of colleges and societies that have endorsed this module will be available on the NBA website. <http://www.nba.gov.au/>

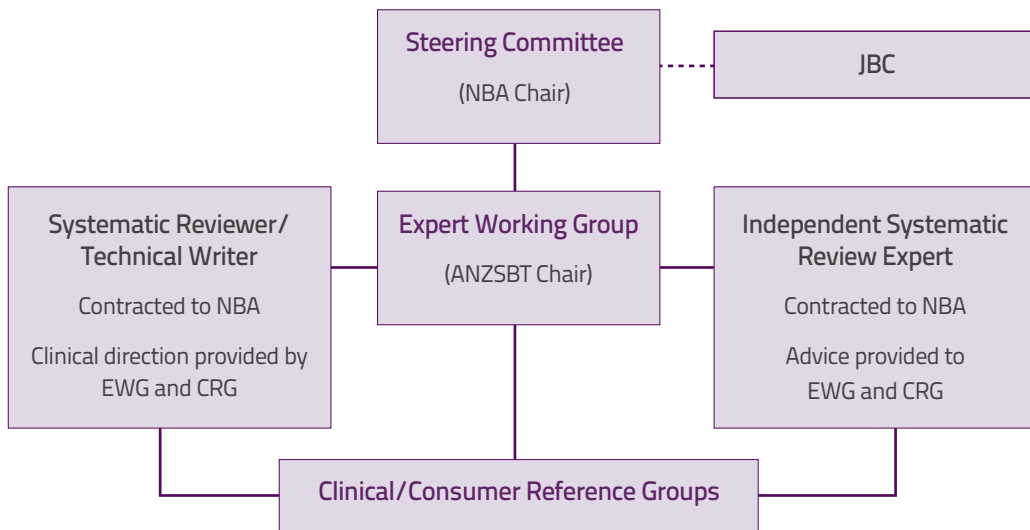
Appendix A

Governance

A1 Management framework for guideline development

Figure A1 illustrates the management framework used to manage the development of the six modules of the guidelines.

Figure A1 Management framework for development of the guidelines



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

A2 Terms of reference

Steering Committee

The overarching Steering Committee was established to provide coordination and direction for development of the guidelines. It was chaired by the NBA, with representation from the ANZSBT, the NHMRC (including a member from the National Institute of Clinical Studies), a state expert and an expert from the Australian Government Department of Health and Ageing. The role of the Steering Committee was to:

- develop and oversee the project plan for the revision of the guidelines
- recommend the membership of the EWG to the NBA Chief Executive Officer, who will appoint the recommended members
- endorse the scope of the project as proposed by the EWG, and the process by which it will be undertaken
- ensure that there is effective communication and consultation with all relevant stakeholders for the duration of the project, including the development of a communications and engagement strategy that meets NHMRC requirements
- provide information through the NBA to the Jurisdictional Blood Committee (JBC) on the project
- review resources that are dedicated to the project, to ensure that they are sufficient for the project to meet its deadlines
- review and approve revisions to the project plan and terms of reference
- address other matters as raised by members of the Steering Committee or EWG.

Expert Working Group

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

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

A2 Terms of reference

Systematic reviewers and technical writers

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

Clinical/Consumer Reference Groups

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

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

Guidelines Assessment Register expert

Two GAR experts were appointed by the NHMRC to provide advice and mentoring to the EWG and CRG, and to ensure that the new guidelines and the development process implemented by each reference group complied with NHMRC requirements.

A3 Membership of bodies involved in governance of the guidelines

Steering Committee

Dr Alison Turner (Chair)	National Blood Authority
Dr Heather Buchan	National Institute of Clinical Studies
Ms Cathy Clutton	National Health and Medical Research Council
Ms Vesna Cvjeticanin	National Health and Medical Research Council
Mr Ken Davis	Australian & New Zealand Society of Blood Transfusion
Prof Henry Ekert	Australian Government Department of Health & Ageing
Ms Susan Ireland	Jurisdictional Blood Committee
Dr Amanda Thomson	Australian & New Zealand Society of Blood Transfusion

Expert Working Group

Dr Craig French (Co-chair)	College of Intensive Care Medicine of Australia and New Zealand and Australian & New Zealand Intensive Care Society
Dr Amanda Thomson (Co-chair)	Australian & New Zealand Society of Blood Transfusion
A/Prof Donald Bowden	Thalassaemia Australia
A/Prof Mark Dean	Haematology Society of Australia and New Zealand and Royal Australasian College of Physicians
Mr Shannon Farmer	Independent consumer advocate
Dr Chris Hogan	National Blood Authority
Ms Janine Learmont	Royal College of Nursing, Australia
Dr Helen Liley	Royal Australasian College of Physicians, Paediatric & Child Health Division
Dr Robert Lindeman	Royal College of Pathologists of Australasia
A/Prof Larry McNicol	Australian & New Zealand College of Anaesthetists
Prof John Olynyk	University of Western Australia Department of Medicine, Fremantle Hospital
Prof Michael Permezel	Royal Australian & New Zealand College of Obstetricians and Gynaecologists
Dr Kathryn Robinson	Australian Red Cross Blood Service
Dr Helen Savoia	Royal College of Pathologists of Australasia
Dr Richard Seigne	Australian & New Zealand Society of Blood Transfusion
Dr Philip Truskett	Royal Australasian College of Surgeons
Dr John Vinen	Australasian College for Emergency Medicine

Clinical/Consumer Reference Group for Critical Bleeding/Massive Transfusion

A/Prof Larry McNicol (Chair)	Anaesthetist	Australian & New Zealand College of Anaesthetists
Prof Zsolt Balogh	Trauma surgeon	Royal Australasian College of Surgeons
Mr Shannon Farmer	Consumer	Independent consumer advocate
Dr Craig French	Intensive care physician	College of Intensive Care Medicine of Australia and New Zealand and Australian & New Zealand Intensive Care Society
Prof Russell Gruen	Trauma Surgeon	Royal Australasian College of Surgeons
Dr Chris Hogan	Haematologist	National Blood Authority
Dr Richard Seigne	Anaesthetist	Australian & New Zealand Society of Blood Transfusion
Mr Daryl Teague	Orthopaedic surgeon	Australian Orthopaedic Association
Dr Amanda Thomson	Haematologist	Australian & New Zealand Society of Blood Transfusion
Dr Philip Truskett	Surgeon	Royal Australasian College of Surgeons
Dr John Vinen	Emergency care physician	Australasian College for Emergency Medicine

Background research

Dr George Grigoriadis	Haematology/Transfusion Registrar, The Alfred Hospital/ Australian Red Cross Blood Service – Supervisor A/Prof Erica Wood
Dr Andrew Martin	Research Fellow Trauma Surgery, John Hunter Hospital – Supervisor Prof Zsolt Balogh
Dr Zoe McQuilten	Clinical Research Fellow, Australian Red Cross Blood Service – Supervisor A/Prof Erica Wood
Dr Sant-Rayn Pasricha	Haematology/Transfusion Registrar, Royal Melbourne Hospital/ Australian Red Cross Blood Service – Co-supervisors, Dr Chris Hogan and A/Prof Erica Wood
Dr Loyal Pattuwage	Project Officer, National Trauma Research Institute – Supervisor Prof Russell Gruen; review and support Dr Chris Hogan
Dr Andrea Warwick	Surgical Registrar, Alfred Trauma Service – Supervisor Prof Russell Gruen; review and support Dr Chris Hogan
Dr Dejan Krstik	Assistant Director, National Blood Authority – Supervisor Prof Russell Gruen; review and support Dr Chris Hogan
Ms Jennifer Roberts	Director, National Blood Authority – Supervisor Prof Russell Gruen; review and support Dr Chris Hogan

National Health and Medical Research Council appointed Guidelines Assessment Register consultants

Ms Tracy Merlin	Adelaide Health Technology Assessment (AHTA), University of Adelaide
Ms Skye Newton	Adelaide Health Technology Assessment (AHTA), University of Adelaide

Project Management and Committee Secretariat – provided by the NBA

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

Systematic review team for critical bleeding/massive transfusion

Dr Jane Adams	IMS Health Australia (Engagement Manager, Health Outcomes)
Ms Miranda Bailey	IMS Health Australia (Senior Consultant, Health Outcomes)
Mr Laurence Fong	IMS Health Australia (Principal, Pricing and Market Access)
Dr John Gillespie	IMS Health Australia (Engagement Manager, Health Outcomes)
Mr Alasdair Godfrey	IMS Health Australia (Engagement Manager,, Health Outcomes)
Ms Ann Jones	IMS Health Australia (Senior Medical Editor, Health Outcomes)
Dr Jodie Wilson	Independent contractor to IMS Health Australia
Ms Teresa Wozniak	IMS Health Australia (Consultant, Health Outcomes)

Medical writing (Guideline only) and technical editing – Health Technology Analysts

Dr Suzanne Campbell	Health Technology Analysts (Health Outcomes Manager)
Dr Adele Weston	Health Technology Analysts (Director)
Dr Hilary Cadman	Cadman Editing Services (independent contractor to Health Technology Analysts)

A4 Conflict of interest

All members of the Steering Committee, CRG and EWG declared any conflicts of interest before starting work on the guidelines. Conflicts of interest were reviewed at intervals during the development of the guidelines and required to be declared at the commencement of each meeting.

A5 Acknowledgements

The CRG thanks the following facilities, whose MTPs were considered in developing the template MTP:

- Australia
 - Northern Sydney Central Coast Area Health Service
 - Queensland Blood Products Advisory Committee
 - Royal Perth Hospital, Western Australia
 - Royal Adelaide Hospital, South Australia
 - Sydney South West Area Health Service
 - The Alfred, Victoria
- New Zealand
 - Auckland District Health Board
 - Canterbury District Health Board

The CRG thanks the Haemostasis Registry, Department of Epidemiology and Preventive Medicine, Monash University for providing access to their data on rFVIIa.

Appendix B

Transfusion risks in the context of patient blood management

Traditionally, it has been assumed that blood transfusion benefits patients; however, a benefit has not been demonstrable in many clinical scenarios. In addition, evidence is accumulating that transfusion-related acute lung injury is more common than previously thought, and that more recently identified conditions – including transfusion-related immunomodulation – may cause patients harm.

The risk of transmission of infectious diseases has reduced significantly in recent years through improved manufacturing and laboratory processes. Nevertheless, there is still a small 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.

Of the recognised adverse events associated with transfusion, the most common is transfusion-associated circulatory overload, which is reported in up to 1% of patients receiving transfusions.

The clinical decision to undertake transfusion therapy should only be made after full consideration of the risks and benefits. Table B.1 summarises the risks and benefits; [Table B.2](#) puts the risks into perspective; and Table B.3 presents the Calman chart, which may be useful to clinicians for explaining risks to patients.⁹²

Table B.1 Transfusion risks and benefits

Therapy	Risks	Benefits
Blood transfusion, including RBCs, platelets, FFP and cryoprecipitate	<ul style="list-style-type: none"> ▪ Administrative error leading to transfusion of incorrect blood component, with potential for severe transfusion reaction (haemolytic) due to blood group (ABO) incompatibility ▪ Transfusion transmitted infections (extremely rare) ▪ Transfusion-related acute lung injury ▪ Other transfusion reactions (mild febrile to severe anaphylaxis) ▪ Bacterial infection from contaminated blood or platelets ▪ Transfusion-associated circulatory overload (usually iatrogenic) ▪ Transfusion-related immunomodulation 	<ul style="list-style-type: none"> ▪ RBC to prevent critical lack of oxygen to the body tissues ▪ Platelets to treat or prevent bleeding ▪ FFP to treat or prevent bleeding ▪ Cryoprecipitate to treat or prevent bleeding

FFP, fresh frozen plasma; RBC, red blood cell

Table B.2 Transfusion risks in perspective

Transfusion risk	Estimated rate ^a (highest to lowest risk)	Calman rating ^b
Transfusion-associated circulatory overload (iatrogenic)	Up to 1 in 100 transfusions	High
Haemolytic reactions	Delayed: 1 in 4,000–9,000 Acute: 1 in 12,000–77,000	Low Very low
Anaphylaxis (IgA deficiency)	1 in 20,000–50,000	Very low
Bacterial sepsis: platelets	1 in 75,000	Very low
Bacterial sepsis: RBCs	1 in 500,000	Minimal
Transfusion-related acute lung injury	1 in 5,000–190,000	Low to minimal
Hepatitis B	1 in 739,000	Minimal
HIV	1 in 5.4 million	Negligible
Hepatitis C	1 in 2.7 million	Negligible
Malaria	1 in 4.9 million – 10.2 million	Negligible
Variant CJD (not tested)	Never reported in Australia	Negligible
Transfusion-associated graft-versus-host disease	Rare	Negligible
Transfusion-related immunomodulation	Not quantified	Unknown

CJD, Creutzfeldt-Jakob disease; IgA, immunoglobulin A; RBC, red blood cell
^a Risk per unit transfused unless otherwise specified
^b See Calman 1996 ⁹⁹

Source: Australian Red Cross Blood Service website (www.transfusion.com.au), accessed 9 December, 2009

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

Table B.3 Calman Chart a (UK risk per one year)

Rating	Rate	Example
Negligible	< 1 in 1,000,000	Death from lightning strike
Minimal	1 in 100,000–1,000,000	Death from train accident
Very low	1 in 10,000–100,000	Death from an accident at work
Low	1 in 1,000–10,000	Death from a road accident
High	> 1 in 1,000	Transmission of chicken pox to susceptible household contacts

^a See Calman 1996 ⁹⁹

Patient blood management involves a precautionary approach to the administration of blood components, particularly red cells. Discussion of alternative strategies is relevant for all patients, not just those who choose not to accept a transfusion.

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.

In the process of obtaining 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.

Appendix C

Blood sectors

C1 Australian blood sector

Australian Health Ministers' Conference and Australian Health Ministers' Advisory Council

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

Clinical, Technical and Ethical Principal Committee

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

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

Jurisdictional Blood Committee

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

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

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

National Blood Authority

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

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

Therapeutic Goods Administration

The 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 of 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 (ARCBS) 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 ARCBS 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 ARCBS also has significant transfusion medicine expertise and clinical involvement.

C2 New Zealand blood sector

Ministry of Health

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

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

Medsafe

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

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

New Zealand Blood Service

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

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

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

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

Appendix D

Process report

D1 Development process

A review by the NBA of the 2001 *Clinical practice guidelines on the use of blood components*¹ led to a decision by the NHMRC, ANZSBT and NBA to develop a series of six guidelines on patient blood management, of which this document is the first. The guidelines development process was initiated by a Steering Committee chaired by the NBA. In 2008, an EWG was formed to oversee development of the series of guidelines.

A CRG, with membership including an independent consumer advocate and representation from relevant colleges and societies, was established to develop the critical bleeding/massive transfusion module, with assistance from systematic reviewers and a technical writer, and advice and mentoring from GAR consultants initially contracted by the NHMRC. Further details of the governance framework are provided in [Section 1.2](#) and [Appendix A](#).

D2 Research phase

Relevant clinical research questions were developed, prioritised, combined and refined by the EWG and the CRG for this guideline, and further refined through consultation among the systematic reviewer, CRG, NBA and NHMRC GAR consultants. A two-volume technical report, *Patient blood management in critical bleeding/massive transfusion*, was circulated to the EWG in 2009.^{2,3}

D3 Methodology

Methods are outlined in Chapter 2, with greater detail given in Volume 1 of the accompanying technical report.² Briefly, the clinical research questions for systematic review were structured according to PICO ('population, intervention, comparator and outcome' for intervention questions), PPO ('population, predictor and outcome' for prognostic questions) or PRO ('population, risk factor and outcome' for aetiology questions) 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 of Cumulative Index to Nursing and Allied Health Literature and Australasian Medical Index. The electronic searches included articles published between 1966 and April–June 2009.

Inclusion criteria were determined from the PICO, PPO or PRO criteria that formed the basis of the systematically reviewed research questions. Non-English publications were excluded. Studies that were eligible for inclusion were evaluated according to NHMRC levels of evidence hierarchy, dimensions of evidence, and quality assessment criteria.^{10,100} An NHMRC evidence statement form was completed for each systematically reviewed research question. Where there was sufficient evidence to formulate a recommendation, NHMRC grading criteria were applied to indicate the strength of the body of evidence underpinning the recommendation.¹⁰ Where it was not possible to develop evidence-based recommendations because no evidence was identified, or where additional information was required to supplement recommendations and guide clinical practice, the CRG developed practice points through a consensus-based process (Volume 1 of the technical report, Appendix 4).²

D4 Public consultation

Public consultation was conducted from Monday 12 April to Friday 14 May 2010, during which time the draft module was available on the NBA website. 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.

Twenty-seven formal submissions were received, including one very detailed submission from an independent international reviewer from Canada. The CRG met in on 19 and 20 May 2010 to consider all responses to the public consultation submission and, where necessary, revise this module in accordance with the submissions.

One of the recurrent themes in the submissions was that access to health-care resources (products, specialist advice and equipment) varies between geographical and health-care settings, creating a need for general guidance on how to develop an MTP for a local setting, rather than a prescriptive MTP. The MTP in the public consultation draft was intended as an example; however, in response to the submissions, the template MTP has been modified, and further advice has been provided on how the template can be adapted to suit the local patient population and health-care resources.

Another recurrent theme was that ratios provided in the public consultation draft were based on data that could be subject to survivor bias, because outcomes were based on subgroup analyses. In response, the document has been modified to provide a stronger emphasis on goal directed—rather than ratio-driven protocols in the management of the critically bleeding patient requiring massive transfusion, and a clear statement that evidence was not found to support or refute specific ratios.

Many other changes to the module were made to address comments and concerns raised in submissions, and to improve clarity.

D5 Finalising the module

The final draft of the Module and technical reports were reviewed by a guidelines development expert (formerly a GAR) to assess compliance with NHMRC requirements for externally developed guidelines. The Module was then reviewed by an AGREE II expert to assess the Module against international quality standards. The Module and accompanying documents were then sent to the NHMRC for methodological and independent peer review on 6 August 2010.

The module was further refined in response to the reviewer's recommendations.

Approval from the NHMRC was received on 12 November, 2010.

Appendix E

Evidence matrixes

Evidence matrix 1

Clinical question	In patients with critical bleeding requiring massive transfusion, what is the effect of variation of physiologic, biochemical and metabolic (including temperature) parameters on morbidity, mortality and transfusion rate?
Evidence statement	Hypothermia, metabolic acidosis, thrombocytopenia and coagulopathy may be independently associated with increased mortality. ^{15, 61, 63-68}
Evidence base	Poor (D): Eight Level IV studies with high risk of bias. ^{15, 61, 63-68}
Consistency	<p>Satisfactory (C): Some inconsistency reflecting genuine uncertainty around clinical question. Studies investigating:</p> <p><i>Hypothermia:</i> Consistency in definition of outcome. Similar direction of effect (i.e. hypothermia associated with poor survival), although some inconsistency in statistical significance, with three studies showing similar results and two studies in which temperature was not a significant predictor of mortality.</p> <p><i>pH:</i> All five studies were consistent with regard to low pH/acidosis being significantly associated with poorer survival. The definition of the outcome and the threshold parameters for pH values were also consistent.</p> <p><i>Base deficit:</i> Consistency in outcome definition. There was some inconsistency in direction of effect – three studies indicated an association between increased base deficit and poor survival, and two indicated that base deficit was not a significant predictor of mortality.</p> <p><i>INR:</i> All four studies were consistent with regard to a higher international normalised ratio (INR) being associated with poor survival. The definition of the outcome and the threshold parameters for INR values were also consistent.</p> <p><i>Prothrombin time:</i> N/A. One study included for this outcome.</p> <p><i>Partial thromboplastin time:</i> Two studies identified were inconsistent with regard to the association between PTT and mortality.</p> <p><i>Platelet count:</i> Three studies were inconsistent with regard to the association between low platelet count and mortality, primarily because different definitions were used.</p>
Clinical impact	<p>Satisfactory (C): Moderate clinical impact. Studies investigating:</p> <p><i>Hypothermia:</i> Sample size was sufficiently large (ranged from n = 45 to n = 246). Three studies showed that reduced core body temperature was associated with increased mortality in patients who had critical bleeding and those who were transfused. Gonzalez et al (2007)⁶⁴ and Moore et al (2008)⁶⁸ showed that reduced body temperature was not significantly associated with mortality in patients who experienced shock resuscitation or haemorrhagic shock.</p> <p><i>pH:</i> All five studies showed that reduced pH was associated with increased mortality in patients with critical bleeding and those who were transfused.</p> <p><i>Base deficit:</i> Sample size was sufficiently large (ranged from n = 45 to n = 252). Three studies showed that an increase in base deficit was associated with an increased mortality in critically bleeding and transfused patients. Two studies showed base deficit was not significantly associated with mortality in patients who experience shock resuscitation or have haemorrhagic shock.</p>

<p>Clinical impact</p>	<p><i>INR:</i> Sample size was sufficiently large (ranged from n = 97 to n = 247). All studies showed that an increase in INR was associated with increased mortality in critically bleeding and transfused patients.^{15, 61, 64, 68} Gonzalez and colleagues stratified analysis by admission to emergency department and admission to an intensive care unit.⁶⁴</p> <p><i>Prothrombin time:</i> Small sample size (n = 45).</p> <p><i>Partial thromboplastin time:</i> Two studies included are of limited clinical impact, each demonstrating different activated partial prothrombin time (APTT) parameters and statistical significance. Sample size is sufficient (n = 45 to n = 119).</p> <p><i>Platelet count:</i> Three studies included; the largest study reporting on this outcome found that non-survivors had lower platelet counts. Sample size is sufficient with the included studies (n = 45 to n = 174).</p> <p>In all studies, consideration of adverse events was not applicable to this recommendation as the outcome is mortality.</p>
<p>Generalisability</p>	<p>Good (B): Studies investigating:</p> <p><i>Hypothermia:</i> All participants in three studies were trauma patients and one study analysed shock resuscitation patients. All patients were critically bleeding.</p> <p><i>pH:</i> Participants in four studies were trauma patients; one study analysed patients with haemorrhagic shock.</p> <p><i>Base deficit:</i> Participants in three studies were trauma patients,^{61, 65, 66} one study was on haemorrhagic shock patients⁶⁸ and one study on shock resuscitation patients.⁶⁴ All patients were critically bleeding.</p> <p><i>INR:</i> Participants in two studies were trauma patients,^{15, 61} one haemorrhagic shock⁶⁸ and one study shock resuscitation patients.⁶⁴</p> <p><i>Prothrombin time:</i> One study included.</p> <p><i>Partial thromboplastin time:</i> Small sample size and contradictory results for the two studies included.</p> <p><i>Platelet count:</i> Contradictory results for all three studies included.</p> <p>There were no study design restrictions as all studies were case series; hence, patients were in natural environments when the outcome was measured.</p>
<p>Applicability</p>	<p>Good (B): Studies investigating:</p> <p><i>Hypothermia:</i> Three United States based studies and one Australian based study.</p> <p><i>pH:</i> Four United States based studies and one Australian based study.</p> <p><i>Base deficit:</i> Five United States based studies.</p> <p><i>INR:</i> Three United States based studies and one Australian based study.</p> <p><i>Prothrombin time:</i> One United States based study.</p> <p><i>Partial thromboplastin time:</i> One United States based and one Australian based study.</p> <p><i>Platelet count:</i> Two United States based studies and one Australian based study.</p> <p>This evidence base is applicable to the Australian setting and there are no organisational or cultural barriers.</p>

Evidence matrix 2

Clinical question	In patients with critical bleeding requiring massive transfusion, does the dose, timing and ratio (algorithm) of RBCs to blood component therapy (FFP, platelets, cryoprecipitate or fibrinogen concentrate) influence morbidity, mortality and transfusion rate? Part 1 – Algorithm
Evidence statement	In trauma patients with critical bleeding requiring massive transfusion, the use of a protocol that includes the dose, timing and ratio of blood component therapy is associated with reduced mortality. ^{4,5}
Evidence base	Poor (D). One Level III study with a high risk of bias; ⁴ one Level III study with a moderate risk of bias. ⁵
Consistency	Good (B): The studies were mostly consistent in their findings and inconsistency may be explained.
Clinical impact	Good (B). Substantial clinical impact. Studies included predominantly small sample sizes for an assessment of mortality differences, but the clinical impact was significant, with an absolute difference in mortality of approximately 10%.
Generalisability	Good (B). Both studies included patients with critical bleeding requiring massive transfusion.
Applicability	Satisfactory (C). Both studies were conducted in United States health-care settings.

Evidence matrix 3

Clinical question	In patients with critical bleeding requiring massive transfusion, does the dose, timing and ratio (algorithm) of RBCs to blood component therapy (FFP, platelets, cryoprecipitate or fibrinogen concentrate) influence morbidity, mortality and transfusion rate? Part 2 – Algorithm
Evidence statement	In trauma patients with critical bleeding requiring massive transfusion, a ratio of $\leq 2:1:1$ of red blood cells: fresh frozen plasma: platelets is associated with reduced mortality. ^{5, 20, 21} However, due to the possibility of survivor bias, it is not possible to recommend a target ratio of RBC: FFP: platelets.
Evidence base	Poor (D). Two Level III studies with a high risk of bias; ^{20, 21} one Level III study with a moderate risk of bias. ⁵ Survivor bias is likely to have affected results.
Consistency	Excellent (A). All studies were consistent in their findings.
Clinical impact	Satisfactory (C). Moderate clinical impact. Studies included predominantly small sample sizes.
Generalisability	Satisfactory (C). All studies included patients with critical bleeding requiring massive transfusion; however, the definition of massive transfusion in Cinat et al (1999) ²⁰ was ≥ 50 units of RBC or whole blood in 48 hours.
Applicability	Satisfactory (C). All studies were conducted in United States health-care settings.

Evidence matrix 4

Clinical question	In patients with critical bleeding requiring massive transfusion, does the dose, timing and ratio (algorithm) of RBCs to blood component therapy (FFP, platelets, cryoprecipitate or fibrinogen concentrate) influence morbidity, mortality and transfusion rate? Part 2 – Timing.
Evidence statement	In trauma patients with critical bleeding requiring massive transfusion, early transfusion of fresh frozen plasma and platelets is associated with reduced mortality and subsequent red blood cell requirements. ^{85,89}
Evidence base	Poor (D). Two Level IV studies with a high risk of bias. ^{85,89}
Consistency	Excellent (A). The studies were consistent in their findings.
Clinical impact	Satisfactory (C). More than 400 patients were reviewed in each study.
Generalisability	Good (B). Both studies included patients with critical bleeding requiring massive transfusion and the populations were civilian.
Applicability	Satisfactory (C). Both studies were conducted in United States health-care setting.

Evidence matrix 5

Clinical question	In patients with critical bleeding requiring massive transfusion, what is the effect of RBC transfusion on patient outcomes?
Evidence statement	In trauma patients with critical bleeding requiring massive transfusion, an increased volume of transfused red cells may be independently associated with increased mortality. ^{91,92}
Evidence base	Satisfactory (C): Two Level III studies with a moderate risk of bias. ^{91,92}
Consistency	Good (B): Results of the two studies were consistent, although the different reference group in the studies make comparisons not completely clear.
Clinical impact	Poor (D): The studies are underpowered, with confidence interval values that cross 1.0 (odds ratio); thus, the likely clinical impact is unclear.
Generalisability	Satisfactory (C): Some generalisability to the target population.
Applicability	Satisfactory (C): Both studies were completed in the United States.

Evidence matrix 6

Clinical question	In patients with critical bleeding requiring massive transfusion, what is the effect of RBC transfusion on patient outcomes?
Evidence statement	In trauma patients with critical bleeding requiring massive transfusion, an increased volume of transfused red cells is independently associated with acute respiratory distress syndrome. ⁹¹⁻⁹²
Evidence base	Satisfactory (C): Two Level III studies with a moderate risk of bias. ^{91,92}
Consistency	Good (B): Results of the two studies were consistent, although the different reference group in the studies make comparisons not completely clear.
Clinical impact	Satisfactory (C): The studies report a moderate clinical impact.
Generalisability	Satisfactory (C): Some generalisability to the target population.
Applicability	Satisfactory (C): Both studies were completed in the United States.

Evidence matrix 7

Clinical question	In patients with critical bleeding requiring massive transfusion, what is the effect of recombinant activated factor VII (rFVIIa) (prophylaxis or treatment) on morbidity, mortality and transfusion rate?
Evidence statement	In trauma patients with critical bleeding requiring massive transfusion, administration of rFVIIa has no effect on 48-hour or 30-day mortality. ⁶
Evidence base	Good (B): One good quality Level II study. ⁶
Consistency	Not applicable (NA): Only one study.
Clinical impact	Poor (D): There is no clinical impact from rFVIIa.
Generalisability	Satisfactory (C): The studies seem to be generalisable to critical bleeding patients resulting from blunt or penetrating trauma; however, the additional exclusion criteria need to be taken in to consideration before considering the results generalisable to all critically bleeding patients.
Applicability	Good (B): Study samples from 32 hospitals throughout Australia, Canada, France, Germany, Israel, Singapore, South Africa and the United Kingdom. Although only one hospital was in Australia the Canadian and United Kingdom settings are comparable to Australia.

Evidence matrix 8

Clinical question	In patients with critical bleeding requiring massive transfusion, what is the effect of recombinant activated factor VII (rFVIIa) (prophylaxis or treatment) on morbidity, mortality and transfusion rate?
Evidence statement	In patients with critical bleeding requiring massive transfusion, there is insufficient evidence to determine any association between rFVIIa and thromboembolism. ⁶
Evidence base	Good (B): One good quality Level II study. ⁶
Consistency	Not applicable (NA). Only one study.
Clinical impact	Poor (D): The low incidence of the thromboembolic events and consequent lack of statistical power mean that the data are insufficient to draw any conclusions.
Generalisability	Satisfactory (C): The studies seem to be generalisable to a critically bleeding population resulting from blunt or penetrating trauma; however, the additional exclusion criteria need to be taken into account before considering the results generalisable to all critically bleeding patients.
Applicability	Good (B): Study samples from 32 hospitals throughout Australia, Canada, France, Germany, Israel, Singapore, South Africa and the United Kingdom. Although only one hospital was in Australia, the Canadian and United Kingdom settings are comparable to Australia.

Evidence matrix 9

Clinical question	In patients with critical bleeding requiring massive transfusion, what is the effect of recombinant activated factor VII (rFVIIa) (prophylaxis or treatment) on morbidity, mortality and transfusion rate?
Evidence statement	In patients with blunt trauma and critical bleeding requiring massive transfusion, administration of recombinant activated factor VII (rFVIIa) is associated with reduced red blood cell (RBC) transfusion requirements and the incidence of acute respiratory distress syndrome (ARDS). ⁶ In patients with penetrating trauma and critical bleeding requiring massive transfusion, administration of rFVIIa has no effect on morbidity. ⁶
Evidence base	Good (B): One good quality Level II study. ⁶
Consistency	Not applicable (NA). Only one study.
Clinical impact	Satisfactory (C): Moderate clinical impact. In blunt trauma patients administration of rFVIIa is associated with reduced RBC transfusion requirements and the incidence of ARDS. In patients with penetrating trauma administration of rFVIIa has no effect on morbidity.
Generalisability	Satisfactory (C): The studies seem to be generalisable to a critical bleed population resulting from blunt or penetrating trauma; however, the additional exclusion criteria need to be taken in to consideration before considering the results generalisable to all critically bleeding patients.
Applicability	Good (B): Study samples from 32 hospitals throughout Australia, Canada, France, Germany, Israel, Singapore, South Africa and the United Kingdom. Although only one hospital was in Australia the Canadian and United Kingdom settings are comparable to Australia.

Evidence matrix 10

Clinical question	In patients with critical bleeding requiring massive transfusion, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, and/or platelet transfusion on patient outcomes?
Evidence statement	In trauma patients with critical bleeding requiring massive transfusion, a red blood cell (RBC):FFP ratio of $\leq 2:1$ is associated with reduced mortality. ^{61, 75}
Evidence base	Poor (D): Two Level III studies with a high risk of bias. ^{61, 75}
Consistency	Good (B). Both studies looked at several different outcomes. Where similar outcomes were reported findings were generally consistent.
Clinical impact	Satisfactory (C). Moderate clinical impact. One study has $n = 246$, ⁶¹ the other has $n = 135$. ⁷⁵ A RBC:FFP ratio of $\leq 2:1$ was reported to be associated with reduced mortality, but there is uncertainty about whether this is related to survivor bias or the effect of the intervention.
Generalisability	Satisfactory (C). Both studies included patients with critical bleeding who required massive transfusion. One study was conducted in a military war zone setting which is not directly generalisable to a civilian setting. ⁶¹
Applicability	Satisfactory (C). One study was in a United States military hospital and the other ⁷⁵ was in the United States health-care setting. ⁶¹

Appendix F

Product information

Table F.1 Blood component product information and dosage – Australia

Component	Content and characteristics	Volume per bag ^a	Typical adult dose (~ 70 kg)	Number of bags to provide typical dose
FFP	<ul style="list-style-type: none"> ▪ Plasma recovered from a whole blood donation or apheresis collection ▪ Contains all coagulation factors 	250–334 mL	10–15 mL/kg	3–4
Platelets: pooled	<ul style="list-style-type: none"> ▪ A pool of platelets derived from the buffy coat of four whole blood donations ▪ Leucodepleted 	>160 mL	1 bag	1
Platelets: apheresis	<ul style="list-style-type: none"> ▪ A suspension of platelets prepared from a single apheresis donor ▪ Leucodepleted 	100–400 mL	1 bag	1
Cryo-precipitate	<ul style="list-style-type: none"> ▪ Prepared from a single donated whole blood unit ▪ Contains an average of > 0.35 g/bag ▪ Contains high levels of fibrinogen, factor VIII, von Willebrand factor, factor XIII, fibronectin 	30–40 mL	3–4 g fibrinogen	8–10
Cryo-precipitate: apheresis	<ul style="list-style-type: none"> ▪ Prepared from FFP obtained from a plasmapheresis donor ▪ Contains an average of > 0.8 g/bag 	60 mL (± 10%)	3–4 g fibrinogen	4–5

FFP, fresh frozen plasma

^aActual volume indicated on label

Table F.2 Blood component product information and dosage – New Zealand

Component	Content and characteristics	Volume per bag ^a	Typical adult dose (~ 70 kg)	Number of bags to provide typical dose
FFP	<ul style="list-style-type: none"> ▪ Plasma recovered from a whole blood donation or apheresis collection ▪ Contains all coagulation factors ▪ Leucodepleted 	180–300 mL	10–15 mL/kg	3–4
Platelet pooled	<ul style="list-style-type: none"> ▪ A pool of platelets derived from the buffy coat of four whole blood donations ▪ Leucodepleted 	200–350 mL	NA	1
Platelet apheresis	<ul style="list-style-type: none"> ▪ A suspension of platelets prepared from a single apheresis donor ▪ Leucodepleted 	180–400 mL	NA	1
Cryo-precipitate	<ul style="list-style-type: none"> ▪ Prepared from FFP obtained from a plasmapheresis donor with a fibrinogen level > 2.4 g/L ▪ Contains an average of 1.4 g/bag ▪ Contains high levels of factor VIII, von Willebrand factor, factor XIII, fibronectin. ▪ Leucodepleted 	80–120 mL	3–4 g	2–3

FFP, fresh frozen plasma; NA, not applicable

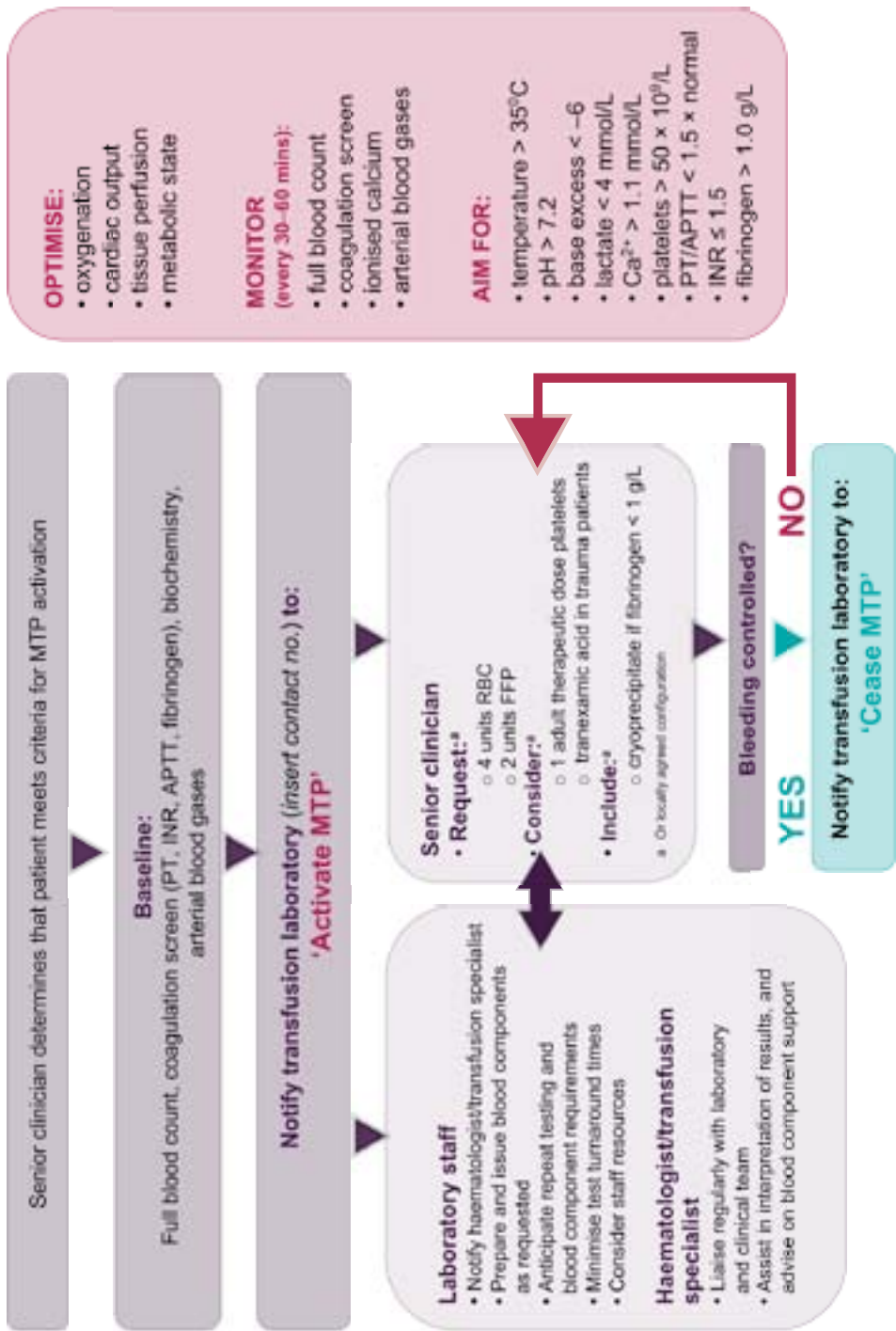
^a Actual volume indicated on label

Appendix G

Massive transfusion protocol template

Massive transfusion protocol (MTP) template

The information below, developed by consensus, broadly covers areas that should be included in a local MTP. This template can be used to develop an MTP to meet the needs of the local institution's patient population and resources



Suggested criteria for activation of MTP

- Actual or anticipated 4 units RBC in < 4 hrs, + haemodynamically unstable, +/- anticipated ongoing bleeding
- Severe thoracic, abdominal, pelvic or multiple long bone trauma
- Major obstetric, gastrointestinal or surgical bleeding

Initial management of bleeding

- Identify cause
- Initial measures:
 - compression
 - tourniquet
 - packing
- Surgical assessment:
 - early surgery or angiography to stop bleeding

Specific surgical considerations

- If significant physiological derangement, consider damage control surgery or angiography
- Consider use of cell salvage where appropriate

Dosage

Platelet count < 50 x 10⁹/L 1 adult therapeutic dose
 INR > 1.5 FFP 15 mL/kg^a
 Fibrinogen < 1.0 g/L cryoprecipitate 3–4 g^a
 Tranexamic acid loading dose 1 g over 10 min, then infusion of 1 g over 8 hrs

^a Local transfusion laboratory to advise on number of units needed to provide this dose

ABG	arterial blood gas	FFP	fresh frozen plasma
INR	international normalised ratio	BP	blood pressure
DIC	disseminated intravascular coagulation	PT	prothrombin time
RBC	red blood cell	rFVIIa	activated recombinant factor VII

Resuscitation

- Avoid hypothermia, institute active warming
- Avoid excessive crystalloid
- Tolerate permissive hypotension (BP 80–100 mmHg systolic) until active bleeding controlled
- Do not use haemoglobin alone as a transfusion trigger

Special clinical situations

- Warfarin:
 - add vitamin K, prothrombinex/FFP
- Obstetric haemorrhage:
 - early DIC often present; consider cryoprecipitate
- Head injury:
 - aim for platelet count > 100 x 10⁹/L
 - permissive hypotension contraindicated

Considerations for use of rFVIIa^b

The routine use of rFVIIa in trauma patients is not recommended due to its lack of effect on mortality (Grade B) and variable effect on morbidity (Grade C). Institutions may choose to develop a process for the use of rFVIIa where there is:

- uncontrolled haemorrhage in salvageable patient, and
- failed surgical or radiological measures to control bleeding, and
- adequate blood component replacement, and
- pH > 7.2, temperature > 34°C.

Discuss dose with haematologist/transfusion specialist

^brFVIIa is not licensed for use in this situation; all use must be part of practice review.

activated partial thromboplastin time	APTT
massive transfusion protocol	MTP
full blood count	FBC

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