Patient Blood Management Guidelines: Module 1

Critical Bleeding Massive Transfusion

Patient Blood Management Guidelines:
Module 1 – Critical Bleeding / Massive Transfusion

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

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)

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:

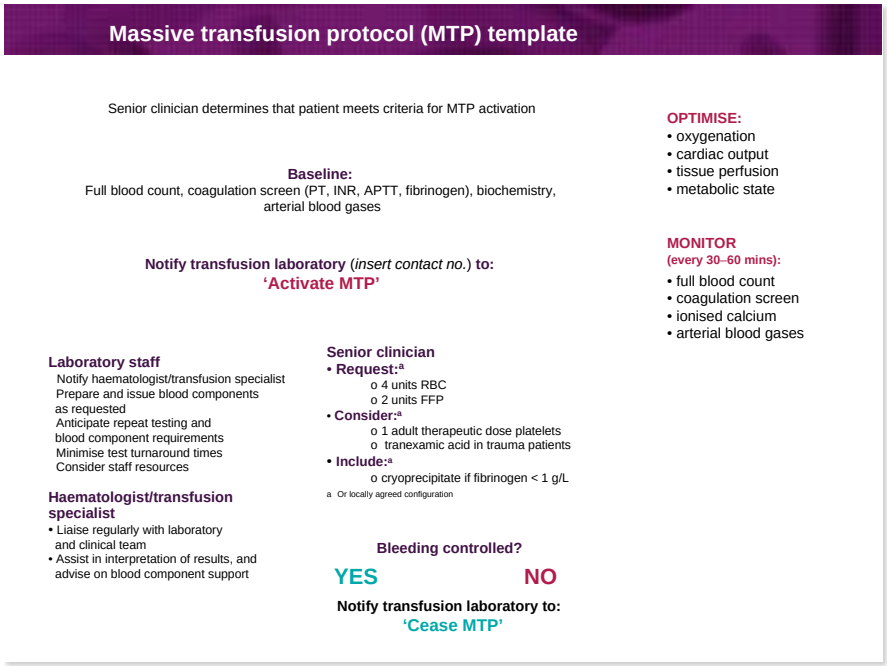
- Grade A – Body of evidence can be trusted to guide practice
- Grade B – Body of evidence can be trusted to guide practice in most situations
- Grade C – Body of evidence provides some support for recommendation(s) but care should be taken in its application
- Grade D – Body of evidence is weak and 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).	4.2
R2	B	C The routine use of rFVIIa in trauma patients with critical bleeding	

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).



. 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 guidelines[1] was needed because of:

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

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).

. 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.

. 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:

. 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

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 practice*[2]

  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 – Appendixes*[3]

  This volume contains appendixes that document the literature searches, study quality appraisal, NHMRC evidence statement forms and evidence summaries for the individual studies.

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: • 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: • recommendations • practice points	Questions listed in Box 2.1 and discussed in Chapter 4
Background specific to this module	Background material	Used to: • 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]

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.[9]

Box 2.1 Systematic review questions

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?**

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 2009[10]

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 2009[10]

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 aetiologic review, and by clinical experience.

. Background

3. 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).

4. 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.

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

. 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.

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 extremities[40] 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.

. Blood

Massive Transfusion

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 hours[54] 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.

. Clinical practice guidance based on evidence or consensus

This chapter provides clinical guidance in the form of

Question (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]

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

Question (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 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.)					
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.)					
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.)					
FFP, fresh frozen plasma; RBC, red blood cell = A = B = C = D (See table 2.2)					

Practice points

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.

In patients with critical bleeding requiring massive transfusion, insufficient

. Effect of anaemia on outcomes

Question (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 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

PP **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

. Effect of red cell transfusion on outcomes

Question (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.

. Effect of recombinant activated factor VII on outcomes

Question (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.[93] 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.[94] 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	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) and variable effect on morbidity (Grade C).–

(See table 2.3 for definitions of NHMRC grades for recommendations)

Practice points

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).

When rFVIIa is administered to patients with critical bleeding requiring massive transfusion, an initial dose of 90 µg / kg is reasonable.

See

. Effect of blood components on outcomes

Question (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 ≤ 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
In trauma patients with critical bleeding requiring massive transfusion, an RBC:FFP ratio of ≤ 2:1 is associated with reduced mortality.[61, 75] (See evidence matrix 10 in Appendix E.)	X	✓✓	✓	✓	✓

FFP, fresh frozen plasma; RBC, red blood cell

✓✓✓ = A ✓✓ = B ✓ = C X = D (See table 2.2)

. Triggers for blood component transfusion

Question (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.

. 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. Evidence gaps and areas of future research

5.1.1 Effect of physiological parameters on outcomes

Question (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 (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, 90] 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 (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 (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.

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 (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?

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 components.[98] 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.

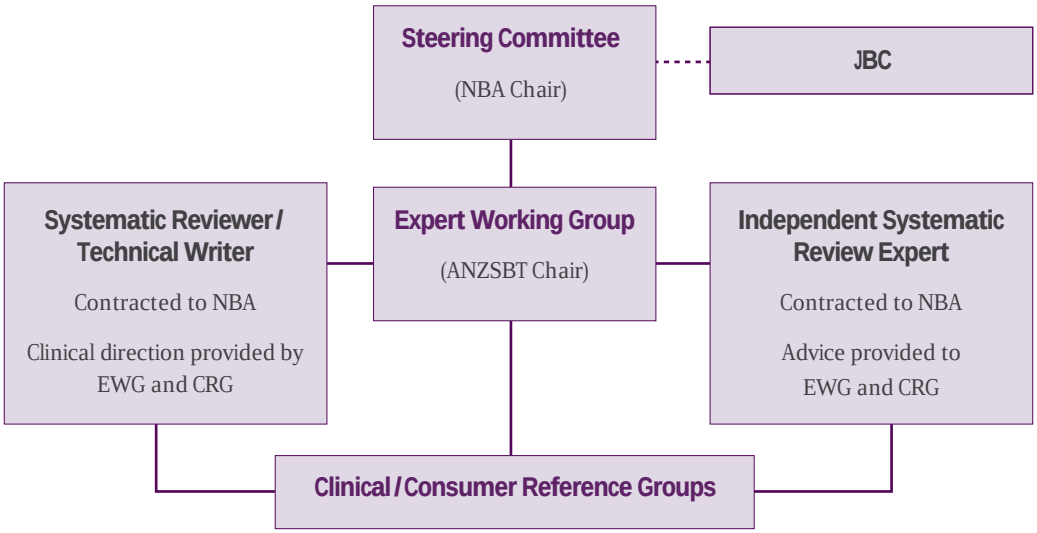
The results of the evaluation will be used to inform future review of the guidelines. Economic issues were considered when formulating the evidence-based

Appendix A
Governance

A 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

A Terms of reference

Systematic reviewers and technical writers

The NBA contracted systematic reviewers and technical writers to conduct systematic reviews of

A 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

National Health and Medical Research Council appointed Guidelines Assessment Register consultants

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

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

Appendix C
Blood sectors

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**

Appendix D
Process report

D 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,2ne.dvctic,2neopmeoeerine froGARe,

D 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.

D 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

Clinical question

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.
	tisfactory (C). health-care settings.

dos

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e? Part 2 – Algorith

patients with critical bleedi

red blood cells:fresh frozen pl

y.[5,70,71] However, due to the poss

mend a target ratio of RBC:FFP:pla

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.

Appendix F
Product information

Component	Content and characteristics	Volume per bag[a]	Typical adult dose (~ 70 kg)	Number of bags to provide typical dose
FFP	• 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	• A pool of platelets derived			

Component	Content and characteristics	Volume per bag[a]	Typical adult dose (~ 70 kg)	Number of bags to provide typical dose
FFP	• 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	• A pool of platelets derived from the buffy coat of four whole blood donations • Leucodepleted	200–350 mL	NA	1
Platelet apheresis	• A suspension of platelets prepared from a single apheresis donor • Leucodepleted	180–400 mL	NA	1
Cryo-precipipmÍ A pool a3624.98962d.R22586.45 A 8 T7( )ŢJ withA pfibrinogen level586.45786 bags to whole blood donations				

Appendix G
Massive transfusion protocol template

Massive transfusion protocol (MTP) template

Senior clinician determines that patient meets criteria for MTP activation

Baseline:
Full blood count, coagulation screen (PT, INR, APTT, fibrinogen), biochemistry, arterial blood gases

Notify transfusion laboratory (

Senior clinician

- **Request:**[a]
  - 4 units RBC
  - 2 units FFP
- **Consider:**[a]
  - 1 adult therapeutic dose platelets
  - tranexamic acid in trauma patients
- **Include:**[a]
  - cryoprecipitate if fibrinogen < 1 g/L

a Or locally agreed configuration

The use of rFVIIa in trauma patients is not recommended due to its lack of effect on mortality (Grade B) and variable effect on morbidity

References

14 Stainsby D, MacLennan S, Thomas D, Isaac J and Hamilton PJ (2006). Guidelines on the management of massive blood loss. *British Journal of Haematology* 135(5):634–641. http://www.ncbi.nlm.nih.gov/pubmed/17107347 (Accessed February 2011)

15 Mitra B, Mori A, Cameron PA, Fitzgerald M, Street A and Bailey M (2007). Massive blood transfusion and trauma resuscitation. *Injury* 38(9):1023–1029. http://www.ncbi.nlm.nih.gov/pubmed/17572415 (Accessed February 2011)

16 Mitra B, Mori A, Cameron PA, Fitzgerald M, Paul E and Street A (2010). Fresh frozen plasma (FFP)

30 Bickell WH, Wall MJ, Jr., Pepe PE, Martin RR, Ginger VF, Allen MK and Mattox KL (1994). Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *New England Journal of Medicine* 331(17):1105–1109. http://www.ncbi.nlm.nih.gov/pubmed/7935634 (Accessed February 2011)

31 Sampalis JS, Tamim H, Denis R, Boukas S, Ruest SA, Nikolis A, Lavoie A, Fleiszer D, Brown R, Mulder D and Williams JI (1997). Ineffectiveness of on-site intravenous lines: is prehospital time the culprit? *Journal of Trauma* 43(4):608–615. http://www.ncbi.nlm.nih.gov/pubmed/9356056 (Accessed February 2011)

32 Crawford ES (1991). Ruptured abdominal aortic aneurysm. *Journal of Vascular Surgery* 13(2):348–350. http://www.ncbi.nlm.nih.gov/pubmed/1990175 (Accessed February 2011)

33 Hardman DT, Fisher CM, Patel MI, Neale M, Chambers J, Lane R and Appleberg M (1996). Ruptured abdominal aortic aneurysms: who should be offered surgery? *Journal of Vascular Surgery* 23(1):123–129. http://www.ncbi.nlm.nih.gov/pubmed/8558727 (Accessed February 2011)

34 Stahel PF, Smith WR and Moore EE (2008). Hypoxia and hypotension, the "lethal duo" in traumatic brain injury: implications for prehospital care. *Intensive Care Medicine* 34(3):402–404. http://www.ncbi.nlm.nih.gov/pubmed/17938886 (Accessed February 2011)

35 Moore EE, Burch JM, Franciose RJ, Offner PJ and Biffl WL (1998). Staged physiologic restoration and damage control surgery. *World Journal of Surgery* 22(12):1184–1190. http://www.ncbi.nlm.nih.gov/pubmed/9841741 (Accessed February 2011)

36 Moore FA and Moore EE (1995). Evolving concepts in the pathogenesis of postinjury multiple organ failure. *The Surgical Clinics of North America* 75(2):257–277. http://www.ncbi.nlm.nih.gov/pubmed/7899997 (Accessed February 2011)

37 Rosenfeld JV (2004). Damage control neurosurgery. *Injury* 35(7):655–660. http://www.ncbi.nlm.nih.gov/pubmed/15203305 (Accessed February 2011)

38 Kossmann T, Trease L, Freedman I and Malham G (2004). Damage control surgery for spine trauma. *Injury* 35(7):661–670. http://www.ncbi.nlm.nih.gov/pubmed/15203306 (Accessed February 2011)

39 Giannoudis PV and Pape HC (2004). Damage control orthopaedics in unstable pelvic ring injuries. *Injury* 35(7):671–677. http://www.ncbi.nlm.nih.gov/pubmed/15203307 (Accessed February 2011)

40 Hildebrand F, Giannoudis P, Kretteck C and Pape HC (2004). Damage control: extremities. *Injury* 35(7):678–689. http://www.ncbi.nlm.nih.gov/pubmed/15203308 (Accessed February 2011)

41 Shapiro MB, Jenkins DH, Schwab CW and Rotondo MF (2000). Damage control: collective review. *Journal of Trauma* 49(5):969–978. http://www.ncbi.nlm.nih.gov/pubmed/11086798 (Accessed February 2011)

42 Walsh TS, McArdle F, McLellan SA, Maciver C, Maginnis M, Prescott RJ and McClelland DB (2004). Does the storage time of transfused red blood cells influence regional or global indexes of tissue oxygenation in anemic critically ill patients? *Critical Care Medicine* 32(2):364–371. http://www.ncbi.nlm.nih.gov/pubmed/14758149 (Accessed February 2011)

43 Kiraly LN, Underwood S, Differding JA and Schreiber MA (2009). Transfusion of aged packed red blood cells results in decreased tissue oxygenation in critically injured trauma patients. *Journal of Trauma* 67(1):29–32. http://www.ncbi.nlm.nih.gov/pubmed/19590304 (Accessed February 2011)

44 Leal-Noval SR, Munoz-Gomez M, Arellano-Orden V, Marin-Caballos A, Amaya-Villar R, Marin A, Puppo-Moreno A, Ferrandiz-Millon C, Flores-Cordero JM and Murillo-Cabezas F (2008). Impact of age of transfused blood on cerebral oxygenation in male patients with severe traumatic brain injury. *Critical Care Medicine* 36(4):1290–1296.
http://www.ncbi.nlm.nih.gov/pubmed/18379257 (Accessed February 2011)

45 Andriessen P, Kollee LA and van Dijk BA (1993). [Effect of age of erythrocyte concentration administered to premature infants: a retrospective study]. *Tijdschr Kindergeneeskd* 61(3):82–87.
http://www.ncbi.nlm.nih.gov/pubmed/8211940 (Accessed February 2011)

46 Weiskopf RB, Feiner J, Hopf H, Lieberman J, Finlay HE, Quah C, Kramer JH, Bostrom A and Toy P (2006). Fresh blood and aged stored blood are equally efficacious in immediately reversing anemia-induced brain oxygenation deficits in humans. *Anesthesiology* 104(5):911–920.
http://www.ncbi.nlm.nih.gov/pubmed/16645441 (Accessed February 2011)

47 Spinella PC, Carroll CL, Staff I, Gross R, Mc Quay J, Keibel L, Wade CE and Holcomb JB (2009). Duration of red blood cell storage is associated with increased incidence of deep vein thrombosis and in hospital mortality in patients with traumatic injuries. *Critical Care* 13(5):R151.
http://www.ncbi.nlm.nih.gov/pubmed/19772604 (Accessed February 2011)

48 Vamvakas EC and Carven JH (1999). Transfusion and postoperative pneumonia in coronary artery bypass graft surgery: effect of the length of storage of transfused red cells. *Transfusion* 39(7): 701–710.
http://www.ncbi.nlm.nih.gov/pubmed/10413277 (Accessed February 2011)

49 Offner PJ, Moore EE, Biffl WL, Johnson JL and Silliman CC (2002). Increased rate of infection associated with transfusion of old blood after severe injury. *Archives of Surgery* 137(6):711–716.
http://www.ncbi.nlm.nih.gov/pubmed/12049543 (Accessed February 2011)

50 Zallen G, Offner PJ, Moore EE, Blackwell J, Ciesla DJ, Gabriel J, Denny C and Silliman CC (1999). Age of transfused blood is an independent risk factor for postinjury multiple organ failure. *American Journal of Surgery* 178(6):570–572.
http://www.ncbi.nlm.nih.gov/pubmed/10670874 (Accessed February 2011)

51 Purdy FR, Tweeddale MG and Merrick PM (1997). Association of mortality with age of blood transfused in septic ICU patients. *Canadian Journal of Anaesthesia* 44(12):1256–1261.
http://www.ncbi.nlm.nih.gov/pubmed/9429042 (Accessed February 2011)

52 Basran S, Frumento RJ, Cohen A, Lee S, Du Y, Nishanian E, Kaplan HS, Stafford-Smith M and Bennett-Guerrero E (2006). The association between duration of storage of transfused red blood cells and morbidity and mortality after reoperative cardiac surgery. *Anesthesia and Analgesia* 103(1):15–20.
http://www.ncbi.nlm.nih.gov/pubmed/16790618 (Accessed February 2011)

53 Hillman K and Bishop G (2004). *Clinical Intensive Care and Acute Medicine*, Cambridge University Press, Cambridge.

54 Spinella PC (2008). Warm fresh whole blood transfusion for severe hemorrhage: U.S. military and potential civilian applications. *Critical Care Medicine* 36(7 Suppl):S340–345.
http://www.ncbi.nlm.nih.gov/pubmed/18594261 (Accessed February 2011)

55 Hughes JD, Macdonald VW and Hess JR (2007). Warm storage of whole blood for 72 hours. *Transfusion* 47(11):2050–2056.
http://www.ncbi.nlm.nih.gov/pubmed/17958534 (Accessed February 2011)

56 Repine TB, Perkins JG, Kauvar DS and Blackborne L (2006). The use of fresh whole blood in massive transfusion. *Journal of Trauma* 60(6 Suppl):S59–69.
http://www.ncbi.nlm.nih.gov/pubmed/16763483 (Accessed February 2011)

57 Kauvar DS, Holcomb JB, Norris GC and Hess JR (2006). Fresh whole blood transfusion: a controversial military practice. *Journal of Trauma* 61(1):181–184.
http://www.ncbi.nlm.nih.gov/pubmed/16832268 (Accessed February 2011)

58 Gruenwald CE, McCrindle BW, Crawford-Lean L, Holtby H, Parshuram C, Massicotte P and Van Arsdell G (2008). Reconstituted fresh whole blood improves clinical outcomes compared with stored component blood therapy for neonates undergoing cardiopulmonary bypass for cardiac surgery: a randomized controlled trial. *Journal of Thoracic and Cardiovascular Surgery* 136(6):1442–1449.
http://www.ncbi.nlm.nih.gov/pubmed/19114187 (Accessed February 2011)

59 Mou SS, Giroir BP, Molitor-Kirsch EA, Leonard SR, Nikaidoh H, Nizzi F, Town DA, Roy LC, Scott W and Stromberg D (2004). Fresh whole blood versus reconstituted blood for pump priming in heart surgery in infants. *New England Journal of Medicine* 351(16):1635–1644.
http://www.ncbi.nlm.nih.gov/pubmed/15483282 (Accessed February 2011)

60 Manno CS, Hedberg KW, Kim HC, Bunin GR, Nicolson S, Jobes D, Schwartz E and Norwood WI (1991). Comparison of the hemostatic effects of fresh whole blood, stored whole blood, and components after open heart surgery in children. *Blood* 77(5):930–936.
http://www.ncbi.nlm.nih.gov/pubmed/1995100 (Accessed February 2011)

61 Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, Sebesta J, Jenkins D, Wade CE and Holcomb JB (2007). The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *Journal of Trauma* 63(4):805–813.
http://www.ncbi.nlm.nih.gov/pubmed/18090009 (Accessed February 2011)

62 Cosgriff N, Moore EE, Sauaia A, Kenny-Moynihan M, Burch JM and Galloway B (1997). Predicting life-threatening coagulopathy in the massively transfused trauma patient: hypothermia and acidoses revisited. *Journal of Trauma* 42(5):857–861.
http://www.ncbi.nlm.nih.gov/pubmed/9191667 (Accessed February 2011)

63 Ferrara A, MacArthur JD, Wright HK, Modlin IM and McMillen MA (1990). Hypothermia and acidosis worsen coagulopathy in the patient requiring massive transfusion. *American Journal of Surgery* 160(5):515–518.
http://www.ncbi.nlm.nih.gov/pubmed/2240386 (Accessed February 2011)

64 Gonzalez EA, Moore FA, Holcomb JB, Miller CC, Kozar RA, Todd SR, Cocanour CS, Balldin BC and McKinley BA (2007). Fresh frozen plasma should be given earlier to patients requiring massive transfusion. *Journal of Trauma* 62(1):112–119.
http://www.ncbi.nlm.nih.gov/pubmed/17215741 (Accessed February 2011)

65 Stinger HK, Spinella PC, Perkins JG, Grathwohl KW, Salinas J, Martini WZ, Hess JR, Dubick MA, Simon CD, Beekley AC, Wolf SE, Wade CE and Holcomb JB (2008). The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. *Journal of Trauma* 64(2 Suppl):S79–85.
http://www.ncbi.nlm.nih.gov/pubmed/18376176 (Accessed February 2011)

66 Vaslef SN, Knudsen NW, Neligan PJ and Sebastian MW (2002). Massive transfusion exceeding 50 units of blood products in trauma patients. *Journal of Trauma* 53(2):291–295.
http://www.ncbi.nlm.nih.gov/pubmed/12169936 (Accessed February 2011)

67 Wilson RF, Binkley LE, Sabo FM, Jr., Wilson JA, Munkarah MM, Dulchavsky SA and Diebel LN (1992).

Electrolyte and acid-base changesolsf Ti WkP11.01 214.es revisited.

69 Vivien B, Langeron O, Morell E, Devilliers C, Carli PA, Coriat P and Riou B (2005). Early hypocalcemia in severe trauma. *Critical Care Medicine* 33(9):1946–1952. http://www.ncbi.nlm.nih.gov/pubmed/16148464 (Accessed February 2011)

70 Cinat ME, Wallace WC, Nastanski F, West J, Sloan S, Ocariz J and Wilson SE (1999). Improved survival following massive transfusion in patients who have undergone trauma. *Archives of Surgery* 134(9):964–968. http://www.ncbi.nlm.nih.gov/pubmed/10487591 (Accessed February 2011)

71 Gunter OL, Jr., Au BK, Isbell JM, Mowery NT, Young PP and Cotton BA (2008). Optimizing outcomes in damage control resuscitation: identifying blood product ratios associated with improved survival. *Journal of Trauma* 65(3):527–534. http://www.ncbi.nlm.nih.gov/pubmed/18784564 (Accessed February 2011)

72 McLaughlin DF, Niles SE, Salinas J, Perkins JG, Cox ED, Wade CE and Holcomb JB (2008). A predictive model for massive transfusion in combat casualty patients. *Journal of Trauma* 64(2 Suppl):S57–63. http://www.ncbi.nlm.nih.gov/pubmed/18376173 (Accessed February 2011)

73 Schreiber MA, Perkins J, Kiraly L, Underwood S, Wade C and Holcomb JB (2007). Early predictors of massive transfusion in combat casualties. *Journal of the American College of Surgeons* 205(4):541–545. http://www.ncbi.nlm.nih.gov/pubmed/17903727 (Accessed February 2011)

74 Dann EJ, Michaelson M, Barzelay M, Hoffman R and Bonstein L (2008). Transfusion medicine during the summer of 2006: lessons learned in northern Israel. *Transfusion Medicine Reviews* 22(1):70–76. http://www.ncbi.nlm.nih.gov/pubmed/18063193 (Accessed February 2011)

75 Duchesne JC, Hunt JP, Wahl G, Marr AB, Wang YZ, Weintraub SE, Wright MJ and McSwain NE, Jr. (2008). Review of current blood transfusions strategies in a mature level I trauma center: were we wrong for the last 60 years? *Journal of Trauma* 65(2):272–276. http://www.ncbi.nlm.nih.gov/pubmed/18695461 (Accessed February 2011)

93 Dutton R, Hauser C, Boffard K, Dimsitts J, Bernard G, Holcomb J, Leppaniemi A, Tortella B and Bouillon B (2009). Scientific and logistical challenges in designing the CONTROL trial: recombinant factor VIIa in severe trauma patients with refractory bleeding. *Clinical Trials* 6(5):467–479. http://www.ncbi.nlm.nih.gov/pubmed/19737846 (Accessed February 2011)

94 Isbister J, Phillips L, Dunkley S, Jankelowitz G, McNeil J and Cameron P (2008). Recombinant activated factor VII in critical bleeding: experience from the Australian and New Zealand Haemostasis Register. *Internal Medicine Journal* 38(3):156–165. http://www.ncbi.nlm.nih.gov/pubmed/17916172 (Accessed February 2011)

95 Bochicchio GV, Napolitano L, Joshi M, Bochicchio K, Meyer W and Scalea TM (2008). Outcome analysis of blood product transfusion in trauma patients: a prospective, risk-adjusted study. *World Journal of Surgery* 32(10):2185–2189. http://www.ncbi.nlm.nih.gov/pubmed/18575931 (Accessed February 2011)

96 Cameron P, Phillips L, Balogh Z, Joseph A, Pearce A, Parr M and Jankelowitz G (2007). The use of recombinant activated factor VII in trauma patients: Experience from the Australian and New Zealand haemostasis registry. *Injury* 38(9):1030-1038. http://www.ncbi.nlm.nih.gov/pubmed/17706654 (Accessed February 2011)

97 Dunkley S, Phillips L, McCall P, Brereton J, Lindeman R, Jankelowitz G and Cameron P (2008). Recombinant activated factor VII in cardiac surgery: experience from the Australian and New Zealand Haemostasis Registry. *Ann Thorac Surg* 85(3):836-844. http://www.ncbi.nlm.nih.gov/pubmed/18291152 (Accessed February 2011)

98 Snyder-Ramos SA, Mohnle P, Weng YS, Bottiger BW, Kulier A, Levin J and Mangano DT (2008). The ongoing variability in blood transfusion practices in cardiac surgery. *Transfusion* 48(7):1284–1299. http://www.ncbi.nlm.nih.gov/pubmed/18422857 (Accessed February 2011)

99 Calman K (1996). The Health of the Nation. *British Journal of Hospital Medicine* 56(4):125-126. http://www.ncbi.nlm.nih.gov/pubmed/8872334 (Accessed February 2011)

100 National Health and Medical Research Council (NHMRC) (2000). *How to use the evidence: assessment and application of scientific evidence.* NHMRC handbook series, NHMRC, Canberra, Australia http://www.nhmrc.gov.au/publications/synopses/cp69syn.htm (Accessed February 2011)

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