

# Research questions for the update of PBM Guidelines: Module 1 – Critical Bleeding/Massive Transfusion

(Systematic review underway)

## Question 1

**In patients with critical bleeding, which physiologic, biochemical and metabolic (including temperature) parameters should be measured early and frequently, and what values of these parameters are indicative of critical physiologic derangement?**

<i>Question type</i>	<i>Population</i>	<i>Predictor</i>	<i>Outcome</i>	<i>Importance of outcome<sup>a</sup></i>
Main question (Prognostic)	Patients with critical bleeding  Stratify by: - age <sup>b</sup> - setting <sup>c</sup>	Temperature Acid-base status Ionised calcium Haemoglobin Platelet count PT/INR APTT Fibrinogen level	<ul style="list-style-type: none"> <li>Mortality</li> <li>Transfusion volumes (RBCs, FFP, CRYO, PLT, fibrinogen concentrate)</li> </ul>	<ul style="list-style-type: none"> <li>Critical</li> <li>Resource use</li> </ul>
<i>Additional information</i>				
Data to extract	Age Setting Exclude neonates <sup>d</sup> and individuals with hereditary bleeding disorders		Reported as per included studies <u>Mortality</u> - all-cause at 24 h and/or at the latest timepoint collected <u>Transfusion volumes</u> - any blood component (except albumin) at 24 h and/or at the latest timepoint	Included in previous module <sup>e</sup> .

APTT, activated partial thromboplastin time; CRYO, cryoprecipitate; FFP, fresh frozen plasma; INR, international normalised ratio; PLT, platelets; PT, prothrombin time; RBC, red blood cell

<sup>a</sup> Critical, important or resource use.

<sup>b</sup> Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).

<sup>c</sup> E.g., trauma, obstetric, perioperative (cardiothoracic, general surgery, gastrointestinal, liver transplant), paediatric, other.

<sup>d</sup> Newborns up to 28 days following birth.

<sup>e</sup> Two Practice Points were made: (PP1) parameters should be measured early and frequently and (PP2) stated values considered to be indicative of critical physiologic derangement. The CRG noted that scoring systems are too difficult to implement in practice, and that any guidance should be limited to readily available measures. The CRG also noted the uptake in practice of the use of viscoelastic parameters to guide the use of massive transfusion, and that this aspect of care is being addressed via new question (Q8).

## Question 2

In patients with critical bleeding, what is the effectiveness of major haemorrhage protocols?					
Question type	Population	Intervention	Comparator	Outcome	Importance of outcome <sup>a</sup>
Main question (Interventional)	Patients with critical bleeding  Stratify by: - age <sup>b</sup> - setting <sup>c</sup>	Defined major haemorrhage protocol (MHP)	No defined MHP	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Transfusion volumes (RBCs, FFP, PLT, CRYO, fibrinogen concentrate)</li> <li>• Wastage of blood products</li> <li>• Time to delivery of blood products</li> </ul>	<ul style="list-style-type: none"> <li>• Critical</li> <li>• Critical, Resource use</li> <li>• Resource use</li> <li>• Resource use</li> </ul>
<i>Additional information</i>					
Data to extract	Age Setting Exclude neonates <sup>d</sup> and individuals with hereditary bleeding disorders	Details of the MHP not required		Reported as per included studies <u>Mortality</u> - all-cause at 24 h and/or the latest timepoint collected <u>Transfusion volumes</u> - any blood component (except albumin) at 24 h and/or at the latest timepoint	An important aspect of this new question is to highlight the system level implications of implementing an MHP (i.e., time to delivery of blood products, product wastage etc.)

CRYO, cryoprecipitate; FFP, fresh frozen plasma; MHP, major haemorrhage protocol; PLT, platelets; RBC, red blood cell

<sup>a</sup> Critical, important or resource use.

<sup>b</sup> Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).

<sup>c</sup> E.g., trauma, obstetric, perioperative (cardiothoracic, general surgery, gastrointestinal, liver transplant), paediatric, other.

<sup>d</sup> Newborns up to 28 days following birth.

### Question 3

In patients with critical bleeding, what is the optimal dose, timing and ratio (algorithm) of RBCs to blood component therapy (FFP, platelets, cryoprecipitate or fibrinogen concentrate) to reduce morbidity, mortality and transfusion?					
Question type	Population	Intervention <sup>a</sup>	Comparator	Outcome	Importance of outcome <sup>b</sup>
Main question (Interventional)	Patients with critical bleeding receiving major transfusion  Stratify by: - age <sup>c</sup> - setting <sup>d</sup>	1. MHP 2. RBC:FFP ratio 3. RBC:PLT ratio 4. RBC:CRYO ratio	1. No MHP 2. Different RBC:FFP ratio 3. Different RBC:PLT ratio 4. Different RBC:CRYO ratio	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Morbidity</li> <li>• Transfusion volume (RBCs, FFP, PLT, CRYO, fibrinogen concentrate)</li> </ul>	<ul style="list-style-type: none"> <li>• Critical</li> <li>• Important</li> <li>• Resource use</li> </ul>
<i>Additional information</i>					
Data to extract	Age Setting Exclude neonates <sup>e</sup> and individuals with hereditary bleeding disorders	Details of the predefined MHP (dose, timing, ratio) Details of the RBC: blood component ratio	Details of the predefined MHP (dose, timing, ratio) Details of the RBC: blood component ratio	Reported as per included studies <u>Mortality</u> – all-cause at 24 h and/or at the latest timepoint collected <u>Morbidity</u> – any prespecified adverse outcome including ARDS, sepsis, TE, multiorgan failure <u>Transfusion volumes</u> – any blood component (except albumin) at 24 h and/or at the latest timepoint	

ARDS, acute respiratory distress syndrome; CRYO, cryoprecipitate; FFP, fresh frozen plasma; MHP, major haemorrhage protocol; PLT, platelets; RBC, red blood cell, TE, thromboembolism

<sup>a</sup> 1 vs 1, 2 vs 2, etc.

<sup>b</sup> Critical, important or resource use.

<sup>c</sup> Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).

<sup>d</sup> E.g., trauma / nontrauma (obstetric, perioperative [cardiothoracic, general surgery, gastrointestinal, liver transplant], paediatric, other.

<sup>e</sup> Newborns up to 28 days following birth

## Question 4

In patients at risk of critical bleeding, is the transfusion of increased volumes of RBCs associated with an increased risk of mortality or adverse effects?				
Question type	Population	Prognostic factor	Outcome	Importance of outcome <sup>a</sup>
Main question (Prognostic)	Patients at risk of critical bleeding <sup>b</sup>  Stratify by: - age <sup>c</sup> - setting <sup>d</sup>	Volume of RBC transfused	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Morbidity</li> <li>• Time on mechanical ventilator</li> </ul>	<ul style="list-style-type: none"> <li>• Critical</li> <li>• Critical</li> <li>• Resource use</li> </ul>
<i>Additional information</i>				
Data to extract	Age Setting Exclude neonates <sup>e</sup> and individuals with hereditary bleeding disorders	Definition of 'increased volumes' based on definition used by authors Record volumes of RBCs Record volumes/ratio of FFP and PLT if available	Reported as per included studies <u>Mortality</u> – all-cause at 24 h and at the latest timepoint collected <u>Morbidity</u> - any prespecified adverse outcome including ARDS, sepsis, TE, multiorgan failure <u>Time on mechanical ventilator</u>	Considered as an interventional question in the previous module. <sup>f</sup>

ARDS, acute respiratory distress syndrome; FFP, fresh frozen plasma; PLT, platelet; RBC, red blood cell ; TE, thromboembolism

<sup>a</sup> Critical, important or resource use.

<sup>b</sup> Patients at risk of critical bleeding' includes patients with penetration injuries who may not otherwise develop critical bleeding but if over-transfused before haemorrhage control may go on to do so.

<sup>c</sup> Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).

<sup>d</sup> E.g., trauma, obstetric, perioperative (cardiothoracic, general surgery, gastrointestinal, liver transplant), paediatric, other.

<sup>e</sup> Newborns up to 28 days following birth

<sup>f</sup> Relevant existing guidance is PP6 (risks associated with high volumes of RBC transfusion) and PP7 (reduced risk of mortality and ARDS with an MTP). No studies were found of transfusion versus no transfusion. Two prospective cohort studies were included (Chaiwat, 2009; Silverboard 2005) but they did not address restrictive or liberal strategies. These studies were subject to survival bias and volume effect (bias from injury load as more severe injuries are managed with a higher volume of RBC).

## Question 5

In patients with critical bleeding, what is the effect of rFVIIa treatment on morbidity, mortality and transfusion rate?					
Question type	Population	Intervention	Comparator	Outcome	Importance of outcome <sup>a</sup>
Main question (Interventional)	Patients with critical bleeding, specifically those with ongoing, bleeding who fail to achieve adequate haemostasis despite surgical management and appropriate blood component therapy <sup>b</sup>  Stratify by: - age <sup>c</sup> - setting <sup>d</sup>	Use of rFVIIa as treatment <sup>e</sup>	Standard best practice care without rFVIIa	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Morbidity</li> <li>• Transfusion volume (RBCs, FFP, PLT, CRYO, fibrinogen concentrate)</li> </ul>	<ul style="list-style-type: none"> <li>• Critical</li> <li>• Critical</li> <li>• Resource use</li> </ul>
<b>Additional information</b>					
Data to extract	Age Setting Exclude neonates <sup>f</sup> and individuals with hereditary bleeding disorders	Exclude rFVIIa as prophylaxis in patients who are already critically bleeding	As described	Reported as per included studies <u>Mortality</u> – all-cause and/or at the latest timepoint collected <u>Morbidity</u> - any prespecified adverse outcome including ARDS, sepsis, TE, multiorgan failure <u>Transfusion volume</u> – any blood product at 24h and/or at the latest timepoint reported	Included in previous module <sup>g</sup> Much of the off-label use of rFVIIa is for patients with critical bleeding unresponsive to conventional haemostasis measures (surgical and blood component therapy) and should be the focus of this question.

ARDS, acute respiratory distress syndrome; CRYO, cryoprecipitate; FFP, fresh frozen plasma; MTP, major transfusion protocol; PLT, platelets; RBC, red blood cell ; TE, thromboembolism

<sup>a</sup> Critical, important or resource use.

<sup>b</sup> A blood transfusion (which includes FFP, platelets, cryoprecipitate and any other blood-derived product) that is deemed appropriate when used in an evidence-based fashion and where the effects of the transfusion are felt to outweigh any potential risks and complications that may arise from the transfusion.

<sup>c</sup> Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).

<sup>d</sup> Surgical (cardiothoracic, vascular, liver transplant) / nonsurgical (including obstetric haemorrhage, pulmonary haemorrhage, gastrointestinal bleeding, paediatric, other).

<sup>e</sup> In Australia and NZ rFVIIa is approved for the control of bleeding and prophylaxis for surgery in patients with specific clotting disorders. Use outside these indications (including critical bleeding following trauma) is considered 'off-label'.

<sup>f</sup> Newborns up to 28 days following birth

<sup>g</sup> Recommendation 2 – 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).

## Question 6

In patients with critical bleeding, what is the effect of FFP, cryoprecipitate, fibrinogen concentrate, prothrombin complex concentrate and/or platelet transfusion on RBC transfusion and patient outcomes?					
Question type	Population	Intervention <sup>a</sup>	Comparator	Outcome	Importance of outcome <sup>b</sup>
Main question (Interventional)	Patients with critical bleeding  Stratify by: - age <sup>c</sup> - setting <sup>d</sup>	1. FFP 2. Cryoprecipitate 3. Platelet  4. Fibrinogen concentrate 5. PCC	1. No FFP (or varying administration of) 2. No CRYO (or varying administration of) 3. No Platelets (or varying administration of) 4. No Fibrinogen concentrate (or varying administration) 5. No PCC (or varying administration of)	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Morbidity</li> <li>• Transfusion volumes (RBCs, FFP, PLT, CRYO, fibrinogen concentrate)</li> <li>• Hospital LOS</li> <li>• ICU LOS</li> </ul>	<ul style="list-style-type: none"> <li>• Critical</li> <li>• Critical</li> <li>• Critical, Resource use</li> <li>• Resource use</li> <li>• Resource use</li> </ul>
<i>Additional information</i>					
Data to extract	Age Setting Exclude neonates <sup>e</sup> and individuals with hereditary bleeding disorders	PCC – not limited, but note product type		Reported as per included studies <u>Mortality</u> – all-cause at 24 hand/or at the latest timepoint collected <u>Morbidity</u> - any prespecified adverse outcome including ARDS, sepsis, TE, multiorgan failure <u>Transfusion volumes</u> – any blood_product at 24h and/or at the latest timepoint reported <u>LOS</u> – only if prespecified	Included in previous module <sup>f</sup> Human PCC (Prothrombinex) added to the question. A three-factor preparation is used in Australia and New Zealand, so care will need to be taken when applying findings from Europe to the local settings for this intervention. Evidence related to fibrinogen has been published since the previous NBA systematic review.

ARDS, acute respiratory distress syndrome ; CRYO, cryoprecipitate; FFP, fresh frozen plasma; MTP, major transfusion protocol; NBA, National Blood Authority; PCC, prothrombin complex concentrate; PLT, platelets; PP, practice point; RBC, red blood cell; TE, thromboembolism

<sup>a</sup> 1 vs 1; 2 vs 2 etc.

<sup>b</sup> Critical, important or resource use.

<sup>c</sup> Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).

<sup>d</sup> E.g., trauma, obstetric, perioperative (cardiothoracic, general surgery, gastrointestinal, liver transplant), paediatric, other.

<sup>e</sup> Newborns up to 28 days following birth

<sup>f</sup> No Recommendations or PPs were made. The SR identified four level III studies that assessed the effect of FFP or platelet transfusion on mortality or morbidity. Outcomes were confounded by survivor bias. No studies examined fibrinogen or cryoprecipitate.

## Question 7

In patients with critical bleeding, what is the effect of antifibrinolytics on blood loss, RBC transfusion and patient outcomes?					
Question type	Population	Intervention	Comparator	Outcome	Importance of outcome <sup>g</sup>
Main question (Interventional)	Patients with critical bleeding <i>Stratify by:</i> - age <sup>h</sup> - setting <sup>i</sup>  Subgroup: • Patients who have received major transfusion	TXA	No TXA	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Morbidity</li> <li>• Blood loss</li> <li>• RBC transfusion volume</li> </ul>	<ul style="list-style-type: none"> <li>• Critical</li> <li>• Important</li> <li>• Important</li> <li>• Resource use</li> </ul>
<i>Additional information</i>					
Data to extract	Age Setting Exclude neonates <sup>j</sup> and individuals with hereditary bleeding disorders	Differentiate between all product (TXA, aprotinin, EACA) Include IV only (exclude oral) Timing should be from onset of bleeding/trauma	Describe SoC	Reported as per included studies <u>Mortality</u> – all-cause and death due to bleeding at 24 h and/or at the latest timepoint collected <u>Morbidity</u> - any prespecified adverse outcome including ARDS, sepsis, TE, multiorgan failure <u>Blood loss</u> – prespecified volume reported as continuous or dichotomous outcome <u>Transfusion volumes</u> – only RBC volume at 24 h and/or at the latest timepoint reported	Not included in previous module <sup>k</sup>

RBC, red blood cell; TE, thromboembolism

<sup>g</sup> Critical, important or resource use.

<sup>h</sup> Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).

<sup>i</sup> E.g., trauma, obstetric, perioperative (cardiothoracic, general surgery, gastrointestinal, liver transplant), paediatric, other.

<sup>j</sup> Newborns up to 28 days following birth

<sup>k</sup> Reference was made to the CRASH II study in the body of the Guidelines (published after the literature search date), and guidance provided regarding consideration of use of TXA (not a Recommendation or a PP). The CRASH II study population does not fully align with the population of interest for the Guidelines.

## Question 8

In patients with critical bleeding does the use of viscoelastic testing change patient outcomes?					
Subquestions (in full)	Nil				
Question type	Population	Intervention	Comparator	Outcome	Importance of outcome <sup>39</sup>
Main question (Interventional)	Patients with critical bleeding  Stratify by: - age <sup>40</sup> - setting <sup>41</sup>	Viscoelastic haemostatic assays to guide transfusion of blood component therapy (TEG or ROTEM)	Blood component therapy guided by MTP protocol and/or Standard Laboratory Tests such as prothrombin time ratio and/or INR	<ul style="list-style-type: none"> <li>• Mortality</li> <li>• Morbidity</li> <li>• Transfusion volume (RBC, FFP, PLT, CRYO, fibrinogen concentrate)</li> <li>• Time to transfusion</li> <li>• Dose/type of transfusion</li> </ul>	<ul style="list-style-type: none"> <li>• Critical</li> <li>• Important</li> <li>• Resource use</li> <li>• Resource use</li> <li>• Resource use</li> </ul>
<i>Additional information</i>					
Data to extract	Age Setting Exclude neonates <sup>42</sup> and individuals with hereditary bleeding disorders	Exclude Sonoclot Note details of algorithm used	Note details of SoC	Reported as per included studies <u>Mortality</u> – all-cause at 24 h and/or at the latest timepoint collected <u>Morbidity</u> - any prespecified adverse outcome including ARDS, sepsis, TE, multiorgan failure <u>Transfusion volumes</u> – any blood product at 24 h and/or at the latest timepoint reported	Not included in previous module <sup>43</sup>

Source: Module 1 GRADE templates [version 7 July 2017]

INR, international normalised ratio; MTP, major transfusion protocol; RBC, red blood cell; ROTEM, thromboelastometry; TEG, thromboelastography

<sup>39</sup> Critical, important or resource use.

<sup>40</sup> Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).

<sup>41</sup> E.g., trauma, obstetric, perioperative (cardiothoracic, general surgery, gastrointestinal, liver transplant), paediatric, other.

<sup>42</sup> Newborns up to 28 days following birth

<sup>43</sup> The CRG is aware of the publication of new evidence regarding the use of TEG/ROTEM since the previous Guidelines.



## Question 9

In patients with critical bleeding what is the effect of cell salvage on patient outcomes?					
Question type	Population	Intervention	Comparator	Outcome	Importance of outcome <sup>44</sup>
Main question (Interventional)	Patients with critical bleeding  Stratify by: - age <sup>45</sup> - setting <sup>46</sup>	Cell salvage	No cell salvage	<ul style="list-style-type: none"> <li>Mortality</li> <li>Morbidity</li> <li>Overall financial cost</li> <li>Transfusion volume (RBC, FFP, PLT, CRYO, fibrinogen concentrate)</li> </ul>	<ul style="list-style-type: none"> <li>Critical</li> <li>Critical</li> <li>Critical, Resource use</li> <li>Resource use</li> </ul>
<i>Additional information</i>					
Data to extract	Age Setting Exclude neonates <sup>47</sup> and individuals with hereditary bleeding disorders Exclude use of cell salvage in the elective setting			<p>Reported as per included studies</p> <p><u>Mortality</u> - all-cause at 24 h and/or at the latest timepoint collected</p> <p><u>Morbidity</u> - any prespecified adverse outcome including ARDS, sepsis, TE, multiorgan failure, or markers of coagulopathy (INR, APTT, TEG)</p> <p><u>Transfusion volumes</u> – any blood product at 24 h and/or at the latest timepoint reported</p> <p><u>Financial cost</u> – if available.</p>	<p>Not included in previous module<sup>48</sup></p> <p>A SR for intraoperative cell salvage was prepared within Module 2 of the PBM Guidelines<sup>49</sup></p> <p>While there is not full alignment of the indication/population, it is expected that many of the studies in the Module 2 SR will be relevant to Q9 of Module 1.</p>

APTT, activated partial thromboplastin time; INR, international normalised ratio; MTP, major transfusion protocol; RBC, red blood cell; TEG, thromboelastography

<sup>44</sup> Critical, important or resource use.

<sup>45</sup> Adult (aged over 18 years), child (aged 2 to 12 years), adolescent (aged 13 to 18 years), infants (aged 1 to 23 months).

<sup>46</sup> E.g., trauma, obstetric, perioperative (cardiothoracic, general surgery, gastrointestinal, liver transplant), paediatric, other.

<sup>47</sup> Newborns up to 28 days following birth

<sup>48</sup> The CRG is aware of the publication of new evidence regarding the use of cell salvage in an emergency/trauma setting (as opposed to the typical setting of elective surgery).

<sup>49</sup> Module 2, Technical Report Volume 1b, Section 3.2.1. (see Recommendation 15 and Practice Point 13 in that module).