



MASSIVE HAEMORRHAGE PROTOCOL (MHP) 2.0

Recommendation Statements

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Key publications since release of version 1.0:

- 1. Fibrinogen concentrates vs. Cryoprecipitate:** At the time of the publication of the modified Delphi report in CMAJ Open¹ the FIBRES trial² was not yet published (randomized controlled trial (RCT) of cryoprecipitate vs. fibrinogen concentrate for management of bleeding after cardiac surgery in patients with hypofibrinogenemia). The FIBRES trial confirmed the hemostatic and safety equivalence of fibrinogen concentrate to cryoprecipitate. Two small paediatric RCTs demonstrated similar hemostatic equivalence of fibrinogen to cryoprecipitate to manage bleeding in infants after cardiac surgery^{3,4} and demonstrated similar perioperative ex vivo clot degradation with less post-CPB blood transfusions, and no increased bleeding or thrombotic complications.⁵ Given that fibrinogen concentrate is safer (pathogen reduced) and logistically less complex for hospitals to administer (no ABO group, not frozen, room temperature storage), cryoprecipitate has been removed from the toolkit and replaced with fibrinogen concentrate.^{6,7}
- 2. Tranexamic acid in major gastrointestinal haemorrhage:** An RCT involving over 12,000 patients with gastrointestinal haemorrhage found that tranexamic acid does not reduce death from gastrointestinal bleeding and increases the risk of thromboembolic complications.⁸ The inclusion criteria leave room for clinician interpretation as enrollment occurred “if the clinician was substantially uncertain whether to use TXA”. Tranexamic acid is therefore no longer routinely recommended for management of gastrointestinal haemorrhage however, there may be certain circumstances where it is used.
- 3. Empiric fibrinogen replacement before laboratory documentation of hypofibrinogenemia:** Two randomized trials (one in traumatic injury⁹ and one in post-partum haemorrhage¹⁰) found no improvement in patient outcomes with early, empiric fibrinogen replacement. Hence, empiric fibrinogen replacement is no longer recommended in the centres where fibrinogen can be measured and goal-directed treatment is possible.
- 4. Whole Blood:** At the time of this publication, there is no randomized controlled trial (RCT) evidence demonstrating the superiority of whole blood. In Canada, whole blood is currently used exclusively within the context of clinical studies. If a patient enrolled in the Study of Whole Blood in Frontline Trauma (SWIFT trial) has received whole blood, the MHP should be continued as outlined in the study protocol.^{99,100}

OVERARCHING STATEMENTS

Statement	Description
1	All hospitals that may need to treat major haemorrhage (adults and/or children) shall have an age-appropriate protocol to guide the management of a massively bleeding patient. The panel concluded that an MHP is required to standardize the approach to the massively bleeding patient for all hospitals. For the purposes of the MHP, a hospital is defined as any organization that either maintains a red blood cell inventory or staffs an emergency department, urgent care centre, critical care unit, labour and delivery, or operating room. The panel recognized there are small clinic facilities where a bleeding patient may be encountered but where transfusion is currently not available and an MHP would not be appropriate. The panel concluded that such facilities would instead require a policy for rapid transport of patients with massive haemorrhage to a facility where MHP could be administered.
2	The protocol shall be developed by a multidisciplinary team and approved by the Hospital Transfusion Committee (or another relevant multidisciplinary committee). The MHP requires support from multiple hospital services including, but not limited to: emergency, trauma, surgery, anaesthesiology, critical care, blood transport personnel, communication services, and laboratory personnel. ¹¹ The protocol should be reviewed and approved by the Hospital Transfusion Committee (or other relevant multi-disciplinary hospital committee) and the Medical Advisory Committee.

3	<p>The protocol should include prioritizing control of haemorrhage (i.e., damage control surgery and/or embolization) and haemostatic resuscitation to limit further blood loss. Damage control resuscitation principles in traumatic injury include abbreviated surgical and/or endovascular interventions for haemorrhage control and management of intra-abdominal contamination, critical care support to correct deranged physiologic measures (hypothermia, acidosis, coagulopathy); with definitive surgical repair delayed until stabilization and haemostatic control have been achieved.¹² In the severely injured trauma population, damage control resuscitation is associated with reduced mortality, although the approach has never been tested in a randomized controlled trial.^{13,14,15} Ongoing haemorrhage leads to worsening coagulopathy and other physiologic derangements.¹⁶ Although the role of damage control resuscitation outside of traumatic injury is unknown, prompt haemorrhage control is likely to be a critically important component of care.^{17,18}</p>
4	<p>The protocol shall consider the available resources and expertise at the institution. The hospital must consider the available resources of the institution when developing the local protocol. Centres caring for paediatric patients should ensure personnel are prepared for weight-based dosing and the use of size appropriate equipment (e.g., warming devices, intravenous infusion equipment). Smaller and more remote hospitals located at a distance from the blood supplier will need to streamline their MHP to compensate for the limited number of team members, blood component inventory and laboratory testing menus, and ability to provide definitive surgical or endovascular control of haemorrhage. The MHP will need to specify, if required, which and how patients should be transferred in a timely manner to other facilities for definitive treatment.</p> <p>Examples for simplification for smaller/remote sites include: (1) pre-labelled uncrossmatched red blood cell (RBC) units ready for immediate transfusion; (2) pre-prepared laboratory sample collection kits; (3) administration of a single bolus of tranexamic acid rather than as a bolus followed by an infusion; (4) administration of Prothrombin Complex Concentrates (PCC) and fibrinogen concentrate instead of plasma; (5) use of point of care technology for laboratory testing; and (6) cross-training hospital personnel from other patient care areas.</p>
5	<p>A single protocol for all patients (trauma and non-trauma) is preferred to ensure high levels of protocol adherence.</p> <p>*Hospitals that even occasionally look after children must include paediatric considerations in their MHP.</p> <p>A previous survey from academic hospitals found that 60% of respondents have a single protocol for all patients.¹⁹ Compliance with a single MHP is poor in published studies,^{20,21,22} raising the concern that consistent care could be hindered by multiple protocols for different bleeding scenarios. The panel recommended a single, standardized protocol for all massively bleeding patients, with options to tailor the protocol for specific patient populations. Examples: In massive obstetrical haemorrhage, consideration should be given to measuring fibrinogen levels early and repeatedly, administering fibrinogen replacement if the level falls below 2.0 g/L,²³ and use of an intrauterine balloon device as a bridge to definitive bleeding control.²⁴ In gastrointestinal haemorrhage, consideration should be given for prompt endoscopic therapy for haemorrhage control whereas tranexamic acid is not routinely indicated.^{8,25,26} In post-cardiac surgery haemorrhage, there is evidence to support the use of viscoelastic testing (as compared to standard laboratory tests) to guide transfusion therapy and prothrombin complex concentrates over plasma for management of coagulation deficiencies.^{27,28} Paediatric patients require weight-based dosing of blood components and haemostatic adjuncts, consideration for potentially higher transfusion thresholds depending on co-morbidities and age, and provider awareness of increased risk of hyperkalemia and hypothermia.²⁹⁻³²</p>
6	<p>The institutional protocol should be reviewed at a minimum of every three years. The science and clinical trial activity around massive haemorrhage, coagulopathy, and MHPs is rapidly evolving. Each institutional MHP should be reviewed at a minimum of every three years to ensure alignment with the most up-to-date scientific evidence and the Provincial MHP. The protocol revision should be conducted by a multidisciplinary team as detailed in Statement 2 and approved by the Hospital Transfusion Committee (or similar hospital committee) and the Medical Advisory Committee.</p>

7	<p>The protocol shall be called “The Massive Haemorrhage Protocol (MHP)”, and if announced overhead, referred to as “Code Transfusion”. The existence of several different terms for the protocol across Ontario has created confusion and delays in activation (e.g., a trainee calling communications to activate the Code Omega protocol at a hospital that activates the protocol by calling the Transfusion Medicine Laboratory (TML) and refers to the protocol as “massive transfusion protocol”). The panel, after deliberation and voting, has chosen the protocol name of the “Massive Haemorrhage Protocol” for the following reasons: (1) Massive transfusion is most commonly defined in adults as a transfusion of 10 or more units of RBCs in a 24 hour period - however, some patients will not survive to receive 10 units and many patients between 4 and 10 units need additional therapies contained in an MHP; (2) The name highlights the importance of definitive haemorrhage control; and (3) An MHP is more than just a transfusion protocol and includes non-transfusion interventions (e.g., maintenance of normothermia, use of antifibrinolytics). The panel agreed that the method for MHP activation should be site-specific and should be clearly defined in the protocol; if a hospital-wide overhead announcement is implemented, a standard term should be used by all institutions. The consensus term chosen by the panel is “Code Transfusion” due to its clarity, ease of pronunciation, and lack of overlap phonetically with other “colour” codes (e.g., Code Bleed or Code Blood with Code Blue). The value of an overhead announcement is that it provides redundancy if the paging system fails and notifies all hospital employees that the laboratory is dealing with an emergency (i.e. calls about non-emergency blood product issues and/or non-urgent test results should be postponed).</p>
8	<p>Participating team members shall have access to formal training and recurring drills to increase MHP adherence, and effective delivery. To achieve high levels of team performance and protocol adherence, team members require access to formal training material and exposure to multidisciplinary drills or simulations. This is particularly important for high-stress and rarely encountered massive haemorrhage scenarios. Simulations have been successfully employed for training in obstetrical haemorrhage,³³ paediatric haemorrhage,³⁴ and trauma.³⁵ A systematic review of 33 studies involving 1,203 resident and medical student participants found simulation was associated with improved provider behaviour and patient outcomes.³⁶ In a systematic review of 13 studies of trauma team training, both non-technical skills and team-based performance improved.³⁷ Importantly, these improvements extend to patient outcomes as simulation-based training is associated with improved outcomes in trauma and cardiac arrest care.^{38,39}</p>
9	<p>The MHP should be readily accessible as a reference tool for all team members. To achieve high levels of protocol compliance among staff, ready access to the MHP is required. The local institution should develop resources (either in electronic or paper format) to assist clinicians with MHP compliance. The format and medium should be dictated by the local hospital policies and procedures.</p>
10	<p>a) If the decision is made to transfer the patient to another hospital for definitive hemorrhage control, there should be prompt notification to the transport service(s) and a method to communicate that the patient has a life-threatening hemorrhage.</p> <p>b) If a patient requires interfacility transfer to an institution where definitive hemorrhage control can be performed, if available, blood components/products should be transported with the patient. There are 158 hospitals in Ontario that have access to transfusion support. Due to Ontario’s large geographic size and numerous remote regions, it would not be possible to have large inventory of blood components available at all hospitals without high levels of wastage. Timely transfer of massively bleeding patients from smaller centres to larger centres capable of definitive haemorrhage control is needed for two reasons: (1) limited inventory of blood components in small/remote hospitals (typically small number of RBCs, no platelets, and limited number/no frozen plasma units); (2) limited access to laboratory testing (e.g., fibrinogen levels or viscoelastic testing) to allow for transition to goal-directed personalized haemostatic support; (3) lack of access to definitive surgical or radiologic intervention to allow for haemorrhage control. There is little published evidence on evacuation time targets within civilian settings. Rapid evacuation (<60 minutes) among military trauma patients with non-compressible torso injury and amputation injury is associated with reduced mortality.⁴⁰ Clinicians working with limited capacity to achieve surgical haemostasis should aim to transfer as soon and as safely as possible.</p>

11	<p>Among patients who receive pre-hospital blood components/products, a structured handover process should be used between pre-hospital teams and in-hospital teams that accurately track blood products administered during the pre-hospital or transfer process. MHP and blood transfusions are a high-risk intervention whereby errors in blood product administration can have severe, even fatal, consequences. A structured handover process ensures seamless communication between pre-hospital and in-hospital teams, enhancing patient safety and continuity of care. Accurate tracking of blood products administered in the field is critical to avoid duplication, ensure appropriate monitoring for transfusion reactions, and inform ongoing management decisions. Studies indicate that communication breakdowns during transitions of care are a significant source of errors, underscoring the importance of standardized handover protocols for effective teamwork and better clinical outcomes.^{41,42}</p> <p>Standardized handover tools for Adult and Paediatrics for “Definitive Care” and “Non-definitive Care” can be found on the ORBCoN website www.transfusionontario.org or by clicking on this link</p>
12	<p>a) The protocol shall have activation criteria.</p> <p>b) A two-step approach to MHP activation is preferred in most cases, balancing the need for timely access to blood products against wastage. This is operationalized with step 1 (administration of 4 units of uncrossmatched RBCs or 20-40cc/kg for paediatric patients) and if additional products are required, then step 2 (activation of MHP). In centres with limited resources (e.g. only RBCs available) step 2 may not be feasible. The priority will be administration of adjunct haemostatic products and transfer to a centre for definitive care. Under certain circumstances, the clinician may activate MHP prior to any blood product administration. In these instances, the use of a validated tool is strongly recommended to guide decision-making (ABC, RABT, Shock Index or Shock Index Paediatric Adjusted [SIPA]).</p> <p>Under-activation (i.e. delayed or no activation of MHP for patients who require haemorrhage control and blood components) could be catastrophic as it may result in an otherwise preventable exsanguination. Retrospective studies suggest that delays in initial blood component administration is associated with worse outcomes (each 1-minute delay to the arrival of the first pack of blood components is associated with a 5% increase in the risk of death).⁴³ In contrast, over-activation (i.e., MHP activation that is ultimately not required) may lead to unnecessary transfusion, wastage of blood components, and diversion of resources away from competing needs. Despite concern that appropriate and timely activation is critical, there are no criteria with both high sensitivity and specificity for predicting the need for massive transfusion. The two most commonly used scores validated in adults in this setting are the Shock Index of >1.0-1.4 (heart rate divided by blood pressure or modified paediatric shock index⁴⁴) and an ABC score of 2 or greater (one point each for penetrating injury, blood pressure \leq90 mmHg, heart rate \geq120 and positive FAST (Focused Assessment with Sonography for Trauma on ultrasound), with the shock index performing slightly better in traumatic injury.⁴⁵ New data suggest that resuscitation intensity (\geq4 units of fluid in first 30 minutes with “1 unit” defined as any of 1 U RBC, 1 U plasma, 500 mL colloid, or 1L crystalloid) may represent an important alternative metric to identify patients who require MHP activation.⁴⁶ In paediatric patients, a retrospective study of combat injured children defined massive transfusion as requirement for \geq 40 mL/kg of blood components transfused within 24 hours.⁴⁷ A recent retrospective review of 287 paediatric trauma cases identified transfusion of > 20 ml/kg of blood components within 1-hr as an optimal threshold for activating an MHP, as it effectively predicted mortality risk, need for urgent haemorrhage control procedure and second bleeding episodes.⁴⁸ A systematic review and meta-analysis evaluating tools to predict transfusion needs in children with major trauma recommended using the shock index paediatric adjusted [SIPA] where shock index=HR/sBP with age-adjusted normal values as follows: 0-6 yrs \leq 1.2; 7-12 yrs \leq1.0 and 13-17 yr \leq 0.9.⁴⁹ Given the current lack of evidence to support one set of activation criteria over another, the activation criteria should be set by the hospital to meet the needs of the local patient population.</p>

13	<p>The protocol shall have termination criteria. Termination of the protocol allows personnel to return unused blood components to regular inventory, cease ordering blood components from the blood supplier, cease thawing and preparation of frozen components, and divert resources to competing needs. In contrast, premature termination may lead to a reduction in the number of team members at the bedside, in the frequency of laboratory testing, and in the availability of blood components. Termination should be considered when bleeding source control has been attained, hemodynamic stability has been achieved, vasopressor requirements have diminished, and the transfusion rate has slowed such that additional transport personnel are no longer required. Typically, when these features are present, transfusion decisions can be guided by laboratory test results.⁵⁰ Alternatively, it is appropriate to terminate MHP when the goals of care change or patient is moribund. As no explicit criteria have been validated, termination criteria should be determined at the local hospital level. The method to communicate the termination of the MHP should be specified in the local hospital protocol. In MHP reactivation, resume with the last sequenced transfusion box.</p>
14	<p>The protocol shall specify the team members required to respond when the protocol is activated. Executing all the necessary tasks specified in an MHP, in addition to all the other clinical tasks required to achieve surgical control of blood loss, will require mobilization of an interdisciplinary team. The precise composition of the clinical team can be modified by the acuity of the haemorrhage, the location of the patient, the type of haemorrhage, and the institution’s available resources. For example, the neonatal team will be required to attend postpartum haemorrhages to provide immediate care for the neonate, while in trauma MHPs are managed in the trauma room where nursing to patient ratios are already high and additional nursing staff may not be required. Given the association between survival and the time arrival of the first cooler of blood components, a dedicated transport team for both blood samples and components is critical.</p>
15	<p>The protocol should specify how the lead clinician at the bedside is designated. How the lead clinician for the MHP is assigned should be specified in the local hospital protocol as it will be highly variable depending on the patient population served and the institutional resources. A broad range of physicians could serve as the team leader. In addition, in smaller organizations without on-site physicians, an appropriately trained nurse practitioner or midwife may be the most appropriate team leader. There may be a transition in leadership as the patient moves from one location to another. The process of handover from one leader to the next should be explicitly stated in the protocol. There must be training in non-technical skills for the team leads to promote high performance for communication, situational awareness, and decision-making skills. In simulation training, higher performance on non-technical skills by the team lead (situational awareness and decision making) correlates with critical task completion and improved team performance.⁵¹ Simulation training for clinicians leading trauma resuscitation improves confidence and reduces anxiety.⁵² Formal feedback of trauma team leaders in training by faculty is associated with improvement in leadership skills over time.⁵³</p>
16	<p>The protocol shall specify the team member(s) designated to be responsible for blood component and sample transport. The protocol shall specify the team members designated to be responsible for both the transportation of blood components and patient blood samples for laboratory testing. Although the protocol specifies the initial use of a ratio-based resuscitation (standardized RBCs to plasma) to mitigate the risk of coagulopathy, this does not prevent over-transfusion or provide assurance that coagulation competence will be maintained.⁵⁴ Early and repeated laboratory testing (with rapid transportation of the samples to the laboratory) to confirm adequacy of transfusion resuscitation is required. It is also critical that blood components are rapidly supplied to the bedside and that empty coolers are returned to the TML.</p>
17	<p>The Transfusion Medicine Laboratory and the Core Laboratory shall be notified of all MHP activations. Early and prompt notification of the TML will assist with timely blood component delivery, rapid transition to group specific blood, and designation of the transfusion medicine technologist team leader. A single individual on the clinical side should be the sole source of contact between the clinical team and the transfusion medicine technologist leader to reduce the risk of duplicate transfusion orders. Activation of the core laboratory technologists will ensure designation of the laboratory technologist team leader, rapid identification of MHP samples, prioritization of the testing, complete testing of all required tests for the MHP, and immediate communication of test results to the clinical team.</p>

18	<p>All critical and important laboratory results that guide resuscitation (e.g., haemoglobin, platelet count, INR, fibrinogen, calcium, potassium and lactate/base deficit) shall be communicated directly to the clinical team as soon as they are available. During MHP activation, the clinical team may not have ready access to the electronic health record due to patient acuity and clinical area layout. It is therefore required that all critical results (preliminary or complete, and as defined by the local laboratory) and important laboratory results be verbally communicated to the clinical team as soon as the results are available. This may mitigate the risks of under-transfusion or over-transfusion and improve time to correction of other biochemical derangements (hyperkalemia, hypocalcemia, acidosis). The “push of information” is thought to be an important tool to improve team performance.⁵⁵ Consideration should be given to having dedicated mobile phones to mitigate the risk of communication failure between the laboratory and the clinical team due to movement of the clinical team from one hospital location to another (eg. trauma bay to OR to ICU).</p>
19	<p>The timing of protocol activation and termination shall be recorded in the patient’s chart. Documentation of the activation and termination times must be recorded in the patient chart in the format specified by the local institutional policy. This could be documented by hand or electronically in the nursing or physician notes or in the electronic computerized physician ordering system. These times are necessary during the review of the patient chart for the purposes of quality improvement.</p>
20	<p>The healthcare team should discuss potential long-term effects of massive transfusion with surviving patients (and/or their substitute decision maker) at some point during hospitalization. Specifically, individuals of childbearing potential should be informed of the risk of red blood cell alloimmunization. Post-discharge follow-up and counseling should be considered for all surviving patients. At the earliest possible opportunity, the most responsible physician (or delegate) must have a conversation with the patient and/or their substitute decision maker regarding why the MHP was activated, the number and types of components and products transfused, the transfusion complications observed, and the potential long-term consequences of transfusion. Informed consent for transfusion should be obtained as per local hospital policy. Patients have variable perceptions related to transfusion risks⁵⁶ and accurate communication of the potential risks is important to achieve patient-centered care. Individuals of childbearing potential should be informed of the risk of red cell alloimmunization that may result in hemolytic disease of the fetus and newborn and should be counseled to undergo red blood cell antibody screening at 6 weeks and 6 months post-transfusion (many antibodies are evanescent and there is a brief window for detection).⁵⁷</p>
21	<p>The collection and testing of the group and screen sample shall be prioritized in the protocol to mitigate the impact on group O Rh negative red blood cells and AB plasma. Both group O RBCs and AB plasma are in chronic short supply in Canada. The proportion of group O RBCs transfused to non-group O recipients is increasing, with trauma accounting for 10% of this pressure on group O RBC inventory.⁵⁸ The vast majority of AB plasma units are transfused to non-AB recipients.⁵⁹</p>
22	<p>Laboratory testing should be done at baseline and at a minimum hourly until the protocol is terminated. See rationale below for statement 23.</p>

23	<p>The recommended minimum laboratory testing (where the test is available) at each hourly blood draw should be: CBC, coagulation testing (PT/INR, activated partial thromboplastin time [aPTT; baseline only], fibrinogen (OR viscoelastic testing), electrolytes, calcium (ionized), arterial or venous blood gas (pH and base excess) and lactate. Baseline laboratory testing is prognostic,⁶⁰ identifies patients on oral anticoagulant medications in need of reversal, and directs immediate need for components and products in excess of the base ratio of RBCs to plasma. Although the proposed MHP includes the use of early ratio-based resuscitation for plasma prior to availability of laboratory test results of coagulation, this does not guarantee that coagulopathy will be prevented and raises the risk of over-transfusion of unnecessary blood components. Laboratory confirmation of adequate haemostatic resuscitation is required at least hourly. Current guidelines recommend early and repeated measures of haematology and coagulation parameters.¹⁵ The measurement of the aPTT is only recommended at baseline to detect anticoagulant effect of certain anticoagulants (e.g., dabigatran) and preexisting bleeding disorders (e.g., hemophilia). If the baseline INR and aPTT are concordant then further aPTT measures are not indicated and may in fact delay release of the other coagulation test results.⁶¹ The magnitude of the elevation of the PTT in postpartum haemorrhage is associated with worse outcomes; however, there is considerable overlap and minimal difference between outcome groups to be clinically useful.²³ Transitioning from blind ratio based component therapy to one based on either conventional laboratory testing or point of care viscoelastic testing has the potential to minimize unnecessary transfusions and allow for targeted component therapy.²⁷ Rapid identification and correction of haemostatic abnormalities is critical to achieving haemostasis and foregoing laboratory testing is never appropriate. Biochemical tests (e.g., potassium, calcium, and pH) may indicate potential complications from massive transfusion or inadequate resuscitation of haemorrhagic shock. Lactate measurements are also predictive of mortality, although the role of serial measurements in improving patient outcomes has not been confirmed in clinical trials.⁶²</p>
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24	<p>The protocol should state the minimum laboratory protocol resuscitation targets for transfusion: (1) hemoglobin >70-90 g/L (RBC); (2) INR <1.8 (plasma or prothrombin complex concentrates); (3) Fibrinogen >1.5-2.0 g/L (fibrinogen concentrates); (4) platelets > 50 x10⁹/L or >100 in case of CNS bleeding or injury (platelet concentrates); (5) ionized calcium >1.15 mmol/L (calcium chloride or gluconate). Relevant transfusion targets can also be used if viscoelastic testing is performed. As there are no prospective studies evaluating laboratory haemostatic resuscitation targets in the setting of massive bleeding, the suggested laboratory targets are based on the consensus opinion of the panelists and are concordant with the published literature.^{15, 63} These are minimum targets to be maintained throughout the resuscitation and are not meant to be overly prescriptive (i.e., restricting blood component issue based on the above values). A cluster trial of 70-90 g/L vs. 100-120 g/L in traumatic injury was conducted and found similar outcomes between the two groups.⁶⁴ Certain paediatric populations, such as neonates, patients with congenital heart disease, receiving extracorporeal life support, or in severe respiratory distress may require higher thresholds for RBC transfusion during an MHP.³⁰⁻³²</p>
25	<p>Ionized calcium (iCa²⁺) is preferred over total calcium (Total Ca²⁺) testing and should occur at baseline and thereafter at least hourly or after each MHP pack transfused, with a target iCa²⁺ range of 1.15-1.3 mmol/L (Total Ca²⁺ 2.25-2.50 mmol/L). Consider empiric calcium dosing when the patient is symptomatic and/or calcium laboratory results are unavailable.</p> <p>Ionized calcium is the biologically active form of calcium in blood, directly involved in critical physiological functions, including cardiac contractility, coagulation and neuromuscular function. Total calcium levels may not accurately reflect active calcium status, particularly in critically ill patients with fluctuations in protein levels or acid-base disturbances. In a 2021 meta-analysis¹⁰¹, 56% of critically injured patients were hypocalcemic upon hospital arrival highlighting this is a frequent metabolic disturbance even before blood products are administered. The citrate contained in blood products may further worsen this hypocalcemia by binding calcium (citrate toxicity), reducing circulating iCa levels, an effect more pronounced during large volume transfusions or reduced citrate metabolism (from pre-existing liver failure, hypoperfusion or reduced capacity at the extremes of age), making real-time monitoring crucial. Multiple studies demonstrate that low iCa is associated with increased mortality in trauma patients underscoring the importance of monitoring and correcting these levels. Severe hypocalcemia is defined as iCa²⁺ <0.9 mmol/L and levels <0.65-0.8 mmol/L are associated with cardiac arrhythmias, hypotension, decreased cardiac output and coagulopathy. Empiric administration of calcium among patients receiving MHP lacks RCT level evidence demonstrating benefit. However, in hospitals without the ability to measure calcium levels in a timely manner there is sufficient observational evidence to suggest empiric calcium administration to protect against hypocalcemia especially among patients with life-threatening bleeding who are receiving large volume transfusions. Intravenous administration of calcium chloride may be preferred over calcium gluconate, provided there is adequate sized vascular access (≥ 20 gauge), as it contains a 3-fold greater amount of elemental calcium (270 vs 90 mg) and doesn't require hepatic metabolism to release the calcium ion moiety. Concomitant hypomagnesemia may be responsible for hypocalcemia refractory cardiac arrhythmias in children and magnesium replacement often corrects the hypocalcemia.⁶⁵</p>
26	<p>All massively bleeding patients should have a temperature measured within 15 minutes of arrival or protocol activation and then at a minimum of every 30 minutes (or continuously where available) until the protocol is terminated. See rationale below for statement 28.</p>
27	<p>Patients should receive interventions to prevent hypothermia and achieve normothermia (≥36°C). See rationale below for statement 28.</p>
28	<p>All fluids and applicable blood components/products should be warmed. In both traumatic injury and postpartum haemorrhage, temperature monitoring is infrequently performed and when measured, hypothermia is common.^{66,67} Hypothermia in traumatic injury is associated with worse outcomes,^{68,69} although prospective trials have not confirmed whether aggressive warming protocols would alter outcomes.⁷⁰ Mild hypothermia is associated with a 22% increase in the risk of transfusion.⁷¹ Warming of patients improves their comfort and therefore even in the absence of a confirmed survival benefit it should be a core part of every MHP.⁷²</p>

29	<p>Red blood cells should be delivered in a validated container to prevent wastage. RBCs are a valuable resource requiring strategies to reduce wastage during transport to and storage at the patient bedside. Numerous investigators have validated that wastage can be mitigated with appropriate temperature-controlled devices with resultant substantial cost savings.^{73,74} At large academic centres with frequent MHP activation; all components should be transported in validated containers to mitigate component wastage.</p>
30	<p>The MHP should ensure that there are processes in place to facilitate continued supply of blood components or products to the bedside. The local MHP should include processes to ensure an uninterrupted supply of blood components to the bedside until termination. Specifically, the next cooler should be brought to the patient location before the previous cooler is empty. This will minimize the risk of lacking necessary blood components during the resuscitation. The person assigned to maintain the uninterrupted supply of blood components should be specified in the protocol. The procedure for requesting the next set of blood components should be stated in the protocol, easy to perform in the setting of massive haemorrhage, and designed with the intention of preventing wrong patient transfusion errors. The delivery of blood components to the bedside should not be equated with an order for transfusion.</p>
31	<p>If the blood group is unknown, limit use of O Rh D-negative red blood cells to patients of child-bearing potential (age less than 45 years). O Rh D-negative RBC inventory is insufficient to support with transfusions all patients whose blood group has not been determined. The risk of alloimmunization in an Rh D-negative patient after exposure to Rh D-positive RBCs in the setting of major bleeding is 20%.^{75,76} Immunization to the D-antigen is only relevant for patients who have child bearing potential and may wish to have future pregnancies. Over 99% of births occur in individuals under the age of 45 years⁷⁷ and hospital MHPs should restrict the use of O Rh D-negative RBCs for individuals of child-bearing potential and under this age. For conscious individuals, efforts should be made to determine their age early during their care so that the transfusion medicine service can be instructed to supply the optimal Rh D-type of RBC. If O Rh negative RBC are not available, use O Rh positive RBC until blood group is determined and monitor for anti-D alloimmunization.</p>
32	<p>Red blood cells shall be available at the bedside within 10 minutes of MHP activation. If crossmatched units are not available within 10 minutes, issue uncrossmatched RBC. See rationale below for statement 33.</p>
33	<p>In bleeding patients in need of red blood cell transfusion, uncrossmatched red blood cells should be transfused until crossmatch compatible red blood cells are available. In retrospective analyses in trauma resuscitation, faster time to delivery of the first pack of RBCs is associated with superior survival (every 1 minute delay to the first pack was associated with a 5% increase in the odds of mortality).⁴³ Collection of the group and screen sample, transport of the sample to the laboratory, centrifugation of the sample, testing and result release into the laboratory information system require approximately 70-90 minutes. Therefore, following MHP activation, it is not appropriate to wait for crossmatch-compatible RBCs. The transfusion laboratory must have a protocol and process for the immediate release of uncrossmatched RBCs. In severe traumatic injury, where communication from the pre-hospital emergency services suggests the patient will need immediate transfusion due to hemodynamic instability, it is appropriate to order RBCs to the emergency department in advance of patient arrival.</p>
34	<p>There is no threshold of number of group O red blood cell units above which a switch to group specific red blood cells is prohibited. The switch to group specific red blood cells and plasma should be done as soon as possible. Each unit of RBCs in Canada is produced with a minimal amount of residual plasma (less than 30 mL per unit) and therefore even after 10 to 20 units of group O RBCs the amount of incompatible plasma is trivial and does not preclude a transition to group specific RBCs. To avoid situations where a blood group can no longer be determined due to sheer volume of universal donor products transfused, group and screen specimens should be prioritized. This will allow for an expedient switch to group specific components and preserve the limited inventory of O RBC and AB plasma.</p>
35	<p>The protocol shall include the reversal strategies for oral anticoagulants. The MHP protocol shall include a table with all approved anticoagulant therapies and their appropriate reversal strategy, including the dosage(s) of the therapies to be administered.</p>

36	<p>The initial management of the rapidly bleeding patient that precludes the use of laboratory-guided transfusion should begin with immediate red blood cell (RBC) transfusion and then transfusions at a RBC:plasma ratio of 2:1 followed by lab-guided transfusions when practicable.</p> <p>Standard approach, Adults: 1. MHP Pack 1 should contain 4 RBC units (may be issued before trauma patient arrival or before Code Transfusion activation). 2. MHP Pack 2 should contain 4 RBC and 4 plasma units. 3. Subsequent MHP Packs should contain 4 RBC and 2 plasma units. 4. Platelets and fibrinogen concentrate should be transfused based on hourly laboratory test results.</p> <p>Simplified options for smaller organizations without the ability to provide plasma (due to lack of plasma inventory, inability to thaw plasma rapidly, or lack of laboratory personnel): 1. As per standard approach, Adult. 2. MHP Pack 2 and 3 should contain 4 RBC units, 2000 IU of PCC and 4 g of fibrinogen concentrate. 3. Efforts should be made to transfer the bleeding patient to a centre capable of definitive haemorrhage control. 4. Platelets, when not stocked in the hospital transfusion laboratory, should be ordered in for transfusion (if patient cannot be promptly transferred out). If the patient is transferred before platelets are transfused and the patient is thrombocytopenic, this should be communicated to the receiving hospital. One prospective randomized trial failed to confirm a survival benefit of a RBC: plasma ratio of 1:1 (compared to 2:1).⁷⁸ There are no related paediatric RCTs. A large retrospective review of experience before and after implementation of 1:1 resuscitation failed to find a mortality benefit.⁷⁹ The Canadian consensus conference on massive transfusion recommended a ratio of 2:1 (RBC:plasma) followed by transition to laboratory-guided blood component administration as soon as possible.⁸⁰ The standard approach outlined below, and based on expert consensus, is applicable to most large adult hospitals. No blood components or products should be transfused without a clear order and specified infusion rate from the team leader or delegate. Simplified options are provided for institutions that do not stock plasma and/or platelets (or are unable to provide the components in a rapid manner due to limited numbers of personnel or lack of thawing devices), or that cannot provide definitive surgical or radiological care, and the goal is to stabilize in preparation for transport out by land or air ambulance. Paediatric institutions should develop age and weight based MHP component protocols to ensure that blood components and products are delivered in appropriate ratios. In institutions that care for paediatric patients, the transfusion boxes must come with clear instructions for the clinical team to mitigate the risk of over- or under-transfusion.</p> <p>*If the patient has received pre-activation RBCs and MHP is subsequently activated with pack 1 containing only RBCs then endeavor to achieve a 2:1 ratio as soon as practically possible.</p> <p>** Few patients will require more than 12 RBCs due to an acute haemorrhage. By 12 units of RBCs or 60-90 minutes, transfusion decisions for plasma, platelet and fibrinogen replacement should be made based on the hourly measurement of the INR, platelet count, and the fibrinogen levels and orders communicated promptly to the TML (alternatively, transfusion thresholds based on viscoelastic testing should be used) Ratio based resuscitation is never appropriate outside of an MHP (e.g., GI bleed).</p> <p>For guidance on paediatric dosing refer to standardized packs and weight-based dosing table available on the ORBCoN website at www.transfusionontario.org or by clicking on this link</p>
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37	<p>Empiric administration of fibrinogen replacement is not recommended based on RCT evidence among traumatically-injured and obstetrical patients and observational evidence among other patients. The administration of fibrinogen replacement should occur with evidence of hypofibrinogenemia (laboratory levels or viscoelastic testing). At centres without available fibrinogen testing, the clinician may administer fibrinogen replacement based on clinical evidence of microvascular coagulopathy (e.g. oozing from IV sites) or profound hemodynamic instability where hypofibrinogenemia is predicted. Two randomized controlled trials (CRYOSTAT-2 conducted in patients with trauma and who required MHP activation and FIDEL conducted in patients with persistent PPH after vaginal delivery) have shown that early, empiric fibrinogen replacement does NOT improve patient outcomes. Cryoprecipitate in Canada is provided as individual units that must be thawed, reconstituted with saline and then pooled. This takes approximately 30-45 minutes of technologist's time and may compete with their ability to perform laboratory testing or prepare other components. The product can only be kept for one year after donation. It must be always transported frozen. Once thawed and pooled it expires after 4 hours. Given the lack of pathogen-reduction, large number of donor exposures, time intensive preparation requirements and limited shelf-life, hospitals should transition to pathogen-reduced fibrinogen concentrates. A large randomized controlled trial of cryoprecipitate and fibrinogen concentrates for bleeding patients after cardiac surgery and hypofibrinogenemia found equivalent efficacy and safety.² For paediatric patients a dose of approximately 50 mg/kg of fibrinogen concentrate up to a maximum of 4 grams is suggested.⁸¹</p>
38	<p>At institutions lacking sufficient resources to issue plasma (e.g., no thawing device or no plasma stocked in inventory), Prothrombin Complex Concentrates (PCC) 2000 IU can be substituted for coagulation factor replacement. Fibrinogen replacement should be given concurrently with PCCs unless the fibrinogen level is known to be $\geq 1.5\text{g/L}$. Similar to the challenges with cryoprecipitate, some smaller organizations may have challenges in providing plasma during an MHP (no thawing device or not stocked in the laboratory due to rarity of use). In these situations, a reasonable option is to transfuse PCCs and fibrinogen concentrates. This is a common strategy employed in many European countries and outcomes appear to be similar to a plasma resuscitation strategy in traumatic injury, usually guided by viscoelastic point-of-care testing.⁸² A randomized trial of plasma and PCC-FC in traumatic injury found equivalent efficacy and safety.^{6, 7} This strategy should be seen as a bridge prior to transport to an institution capable of definitive surgical management and more complete transfusion support. For paediatric patients a dose up to 25 IU/kg of PCCs (rounded to the closest 500 IU) to a maximum of 2000 units is suggested.^{83,84}</p>
39	<p>Patient and product identification pre-transfusion bedside check shall be performed prior to transfusion of any component and/or product to avoid mistransfusion. Transfusion-related errors remain common in the emergency department.^{85,86} Under no circumstances can the patient and product identification pre-transfusion bedside check be aborted, especially in mass casualty scenarios where there may be multiple patients receiving blood components simultaneously. A patient identification band must be affixed to the patient for the entirety of the resuscitation and be utilized for positive patient identification for collection of laboratory tests and administration of blood components/products.</p>

40	<p>Patient demographics shall not be updated/changed until after termination of the protocol. Once MHP is terminated, patient demographics should be updated as soon as possible. Patients who cannot be appropriately identified on admission are assigned temporary demographics to allow for identification. Modifications to key identifiers (eg. Name or DOB) during active resuscitation may delay the issue of blood components from the transfusion service or may result in an erroneous incompatibility detected at the pre-transfusion bedside check. The update of the patient identification should be delayed until the patient has stabilized and with coordination between the nursing team and the TML to ensure no gaps in release of laboratory test results or transfusion support.</p>
41	<p>In the acute resuscitation phase of major haemorrhage without brain injury, use of a restrictive volume replacement strategy is preferred, but remains at physicians' discretion. A low systolic blood pressure of 80-90 mmHg (or MAP 50-60 mmHg) may be permitted as long as adequate clinical perfusion. If fluid resuscitation with transfusion alone is unable to achieve hemodynamic/perfusion targets, use of vasopressor agents can be considered.</p> <p>Permissive hypotension is a term that emerged from studies of penetrating trauma patients demonstrating improved mortality among those with lower BP targets and delayed fluid resuscitation. Intuitively this reduces bleeding by promoting clot formation and haemostasis allowing for a greater chance to survive to definitive haemorrhage control.⁸⁷ In blunt trauma patients, the evidence is less clear perhaps as there is a greater chance of multiple sources of haemorrhage combined with significant coagulopathy. There lacks high-quality evidence among non-trauma massively bleeding patients. A controlled or restrictive resuscitation strategy must be balanced with the need to promote brain perfusion, further complicated by head/spinal cord injury in many trauma patients. The optimal blood pressure (MAP or systolic) in severely bleeding patients is not clearly defined and likely dependent on multiple factors including source of haemorrhage, presence/absence of brain injury, baseline blood pressure, phase of resuscitation, need for prolonged transfer etc.⁸⁸ Based on expert opinion and physiological principles, a systolic blood pressure (SBP) of 80–90 mmHg (MAP 50–60 mmHg) is reasonable for bleeding patients. These goals should be considered dynamic as interventions (i.e. intubation) may warrant transiently higher targets. In cases of significant head or spinal cord injury, these targets may need adjustment to maintain cerebral perfusion pressure (CPP) ≥ 60 mmHg in adults, where CPP = MAP – intracranial pressure (ICP) or central venous pressure (CVP) (whichever is higher). For infants and children, an adequate CPP ranges from 40–60 mmHg. Hypotensive resuscitation is relatively contraindicated in paediatric trauma due to the higher incidence of traumatic brain injury (TBI) and a more robust cardiovascular response than adults, which can mask Class III hemorrhagic shock. Interventions such as intubation that may decrease blood pressure may also warrant higher targets transiently, highlighting the importance of physician discretion. In non-trauma massively bleeding patients, these targets are also reasonable yet remains a domain relatively absent of any high quality evidence.</p> <p>Finally, the role of vasopressors to augment blood pressure in the massively bleeding patient has long been controversial. There is weak evidence in the trauma literature for the use of vasopressors. There is a long-held belief that hypotensive bleeding patients require blood products. This is likely true, however in situations whereby a patient remains haemodynamically stable despite large volume transfusion, vasopressors should be considered as an important adjunctive therapy.^{89, 90} The physical exam is important as it is postulated that patients with peripherally cool extremities may not experience as much benefit to vasopressors given already significant vasoconstriction while those with warm extremities and peripheral vasodilation may benefit. There remains insufficient evidence to guide the use of vasopressors in trauma resuscitation (and by extension, non-trauma bleeding patients) however they may reduce the quantity of blood products required and should be considered on a case by case basis.</p>

42	<p>Tranexamic acid (TXA) should be administered as soon as possible, but within 3-hours from time of injury or within 3-hours from MHP activation. Clinical circumstances (e.g. GI bleeding) may warrant case specific considerations for TXA administration. Tranexamic acid improves mortality in the setting of trauma⁹¹ and postpartum haemorrhage.⁹² It is most effective when given immediately, with the survival benefit decreasing by 10% for every 15 minute delay in administration and with no benefit after 3 hours from injury/onset of bleeding.⁹³ There is no increased risk of venous or arterial thromboembolic complications.⁹⁴ Dosages and infusion rates vary depending on the study protocol (1 gram bolus plus 1 gram infusion over 8 hours,⁹¹ 1 gram bolus and 1 gram bolus repeated at 1 hour,⁹⁵ 1 gram bolus and repeated if ongoing bleeding at 30 minutes or greater⁹², 2 gram bolus at the scene of the injury).⁹⁶ Dosage and infusion rate should be determined by the local institution. Simplification may be needed in more resource-challenged locations and a single 2-gram bolus may be preferred. Evidence for tranexamic acid is currently limited in paediatric trauma, but it is accepted practice for use in paediatric trauma patients requiring transfusion within the same time parameters as adults. For paediatric patients the initial bolus of tranexamic acid can be dosed at 15-30 mg/kg up to a maximum of 2 gram and additional doses/infusion based on local policy (e.g. infusion rates of 5-15 mg/kg/hr).^{97,98} A definitive trial of empiric high-dose tranexamic acid in gastrointestinal bleeding found that tranexamic acid did not improve patient outcomes and was associated with an increased risk of thrombosis, suggesting its use in gastrointestinal bleeding is likely limited.⁸ Tranexamic acid should be readily available in clinical areas where massive haemorrhage is common to prevent delays in administration.</p>																																				
43	<p>MHP activations should be reviewed by a multidisciplinary committee for quality assurance. Compliance with MHPs is poor during the resuscitation of a critically ill patient who has multiple competing priorities.^{20,21} Implementation of an MHP is just the first step to improving the care of massively bleeding patients; training, simulations, check-lists, audit and feedback are needed to achieve high levels of performance. At a minimum, the quality metrics listed in statement 44 should be tracked on consecutive MHP activations by a multidisciplinary team with feedback to the frontline staff at regular intervals.</p>																																				
44	<p>The following quality metrics should be tracked on all activations of the protocol and the data reviewed quarterly at the hospital transfusion committee and the Medical Advisory Committee:</p> <table border="1" data-bbox="248 1087 1520 1858"> <thead> <tr> <th></th> <th>Quality metric</th> <th>Local Reporting</th> <th>Provincial Reporting</th> </tr> </thead> <tbody> <tr> <td>Q1</td> <td>The proportion of patients receiving tranexamic acid within 1 hour of protocol activation.</td> <td>X</td> <td>X</td> </tr> <tr> <td>Q2</td> <td>The proportion of patients in whom RBC transfusion is initiated within 15 minutes of protocol activation.</td> <td>X</td> <td>X</td> </tr> <tr> <td>Q3</td> <td>The proportion of patients (requiring transfer for definitive care) with initiation of call for transfer within 60 minutes of protocol activation.</td> <td>X</td> <td></td> </tr> <tr> <td>Q4</td> <td>The proportion of patients achieving a temperature >35°C at termination of the protocol.</td> <td>X</td> <td></td> </tr> <tr> <td>Q5</td> <td>The proportion of patients with hemoglobin levels maintained between 60-110 g/L during protocol activation, excluding certain paediatric populations (e.g., neonates) that may require higher hemoglobin values.</td> <td>X</td> <td></td> </tr> <tr> <td>Q6</td> <td>The proportion of patients transitioned to group specific RBCs and plasma within 90 minutes of haemorrhage protocol activation.</td> <td>X</td> <td>X</td> </tr> <tr> <td>Q7</td> <td>The proportion of patients with appropriate activation (>6 RBC units in first 24 hours; >40 ml/kg/24 hours of RBCs in paediatric patients) or death due to haemorrhage within 24 hours.</td> <td>X</td> <td></td> </tr> <tr> <td>Q8</td> <td>The proportion of patients without any blood component wastage (including plasma that is thawed and not used within the 5 day limit on another patient).</td> <td>X</td> <td></td> </tr> </tbody> </table>		Quality metric	Local Reporting	Provincial Reporting	Q1	The proportion of patients receiving tranexamic acid within 1 hour of protocol activation.	X	X	Q2	The proportion of patients in whom RBC transfusion is initiated within 15 minutes of protocol activation.	X	X	Q3	The proportion of patients (requiring transfer for definitive care) with initiation of call for transfer within 60 minutes of protocol activation.	X		Q4	The proportion of patients achieving a temperature >35°C at termination of the protocol.	X		Q5	The proportion of patients with hemoglobin levels maintained between 60-110 g/L during protocol activation, excluding certain paediatric populations (e.g., neonates) that may require higher hemoglobin values.	X		Q6	The proportion of patients transitioned to group specific RBCs and plasma within 90 minutes of haemorrhage protocol activation.	X	X	Q7	The proportion of patients with appropriate activation (>6 RBC units in first 24 hours; >40 ml/kg/24 hours of RBCs in paediatric patients) or death due to haemorrhage within 24 hours.	X		Q8	The proportion of patients without any blood component wastage (including plasma that is thawed and not used within the 5 day limit on another patient).	X	
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Massive Haemorrhage Protocol (MHP) 2.0

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