4.0 OVERARCHING STATEMENTS

Date of release: September 5, 2019, Revised October 29, 2021

Note: At the time of the publication of the modified Delphi report in CMAJ Open[1] the FIBRES trial[2] was not published (randomized control trial (RCT) of cryoprecipitate vs. fibrinogen concentrate for bleeding after cardiac surgery). The FIBRES trial confirmed the hemostatic and safety equivalence of fibrinogen concentrate with cryoprecipitate. 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.

A definitive randomized controlled trial involving over 12,000 patients with gastrointestinal hemorrhage found that tranexamic acid does not reduce death from gastrointestinal bleeding and increases the risk of thromboembolic complications[4].

References

1. Callum JL, Yeh CH, Petrosoniak A, et al. A regional massive hemorrhage protocol developed through a modified Delphi technique. CMAJO 2019 Sep 3;7(3):E546-E561. (Note: A comprehensive list of references for the below overarching statements can be found within this paper)
2. Callum J, Farkouh ME, Scales DC, et al. Effect of Fibrinogen Concentrate vs Cryoprecipitate on Blood Component Transfusion After Cardiac Surgery: The FIBRES Randomized Clinical Trial. JAMA. 2019;322(20):1966–1976. doi:10.1001/jama.2019.17312
3. Rowell SE, et al. Effect of Out-of-Hospital Tranexamic Acid vs Placebo on 6-Month Functional Neurologic Outcomes in Patients With Moderate or Severe Traumatic Brain Injury. JAMA. 2020 Sep 8;324(10):961-974. doi: 10.1001/jama.2020.8958. Erratum in: JAMA. 2020 Oct 27;324(16):1683. PMID: 32897344; PMCID: PMC7489866.
4. HALT-IT Trial Collaborators. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. Lancet. 2020 Jun 20;395(10241):1927-1936. doi: 10.1016/S0140-6736(20)30848-5. PMID: 32563378; PMCID: PMC7306161.

Statement	Description
1	**All hospitals shall have a 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 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 a policy for rapid transport of patients with massive hemorrhage to a facility with an MHP would be required at such a facility.
2	**The protocol shall be developed by a multidisciplinary team and approved by the Hospital Transfusion Committee (or other relevant multidisciplinary committee).** The MHP requires support from multiple hospital services including, but not limited to: emergency, trauma, surgery, anesthesiology, critical care, blood transport personnel, communication services, and laboratory personnel.[10] The protocol should be reviewed and approved by the Hospital Transfusion Committee (or other relevant hospital committee) and the Medical Advisory Committee.
3	**The protocol shall incorporate the principles of damage control resuscitation, specifically giving highest priority to treating the source of hemorrhage.** Damage control resuscitation principles in traumatic injury include abbreviated surgical and/or endovascular interventions for hemorrhage 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 hemostatic control have been achieved.[19] 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.[14,20,21] Ongoing hemorrhage leads to worsening coagulopathy and other physiologic derangements.[22] Although the role of damage control resuscitation outside of traumatic injury is unknown, prompt hemorrhage control is likely to be an important component of care.[23,24]

4	**The protocol shall consider the available resources at the institution.** The hospital must consider the available resources of the institution when developing the local protocol. Centres caring for pediatric patients should ensure personnel are prepared for weight-based dosing and the use of size specific equipment (e.g., warming devices, intravenous infusion equipment). Smaller and more remote hospitals located at a distance from the blood supplier will need to make adjustments 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 hemorrhage. 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. 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 an infusion; (4) administration of Prothrombin Complex Concentrates (PCC) and fibrinogen concentrate instead of plasma and cryoprecipitate; (5) use of point of care technology for laboratory testing; and (6) cross-training hospital personnel from other patient care areas.
5	**A single protocol for all patients is preferred in order to ensure compliance; there should be specific guidance provided for select patient populations (e.g., obstetrical patients should receive early fibrinogen replacement).** A survey from academic hospitals found that 60% of respondents have a single protocol for all patients.[25] Compliance with a single MHP is poor in published studies,[11,15,26] raising the concern that consistent care would be further compromised by multiple protocols for different bleeding scenarios. The panel recommended a single, standardized protocol in response to the massively bleeding patient with options to tailor the protocol for specific patient populations. Examples: In massive obstetrical hemorrhage, consideration should be given to measuring fibrinogen levels early and repeatedly, administering fibrinogen replacement if the level falls below 2.0 g/L,[27] and use of an intrauterine balloon device as a bridge to definitive bleeding control.[28] In gastrointestinal hemorrhage, consideration should be given for prompt endoscopic therapy for hemorrhage control.[29,30] In post-cardiac surgery hemorrhage, there is evidence to support the use of viscoelastic testing (as compared to standard laboratory tests) in reducing the risk of major bleeding.[31] Pediatric patients require weight-based dosing of blood components and hemostatic adjuncts, consideration for potentially higher transfusion triggers depending on co-morbidities and age, and provider awareness of increased risk for hyperkalemia and hypothermia.[32-35]
6	**The protocol should be reviewed at a minimum of every three years.** The science and clinical trial activity in the area of massive hemorrhage, coagulopathy, and MHPs is rapidly evolving. Each institutional MHP should be reviewed at a minimum of every three years to ensure alignment with the 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 and the Medical Advisory Committee.

7	**The protocol shall be called "The Massive Hemorrhage Protocol", and if activated as an overhead announcement, referred to as "Code Transfusion".** The existence of several different terms for the protocol across Ontario has created confusion and delays to 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 to activate the "massive transfusion protocol"). The panel, after much deliberation, has chosen the protocol name of the **"Massive Hemorrhage 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 hemorrhage 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 clearly defined in the protocol, but that if a hospital-wide overhead announcement was implemented, a standard term should be used at 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 under acute pressure (and to refrain from calling for non-emergency blood products and non-urgent test results).
8	**Participating team members should have access to formal training and drills to increase awareness, adherence, and effective delivery of the MHP.** 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 hemorrhage scenarios. Simulations have been successfully employed for training in obstetrical hemorrhage,[36] pediatric hemorrhage,[37] and trauma.[38] A systematic review of 33 studies involving 1,203 resident and medical student participants found simulation was associated with improved provider behavior and patient outcomes.[39] In a systematic review of 13 studies of trauma team training, both non-technical skills and team-based performance improved.[40] Importantly, these improvements extend to patient outcomes as simulation-based training is associated with improved outcomes in trauma and cardiac arrest care.[41,42]
9	**The written 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 circumstances.
10	**The transport service(s) should be promptly notified if the decision is made to transfer the patient to another hospital for definitive hemorrhage control. If required, the patient should be transferred as soon as and as safely as possible by appropriate staff and transport resources, to an institution where definitive hemorrhage control can be performed.** There are 150 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 stocks of blood components available at all hospitals without very high levels of wastage. Timely evacuation of massively bleeding patients from smaller centres to larger centres capable of definitive hemorrhage control is needed for two reasons: (1) small blood stocks held in remote hospitals (typically small number of RBCs, no platelet pools, and limited stocks of frozen plasma); and, (2) lack of access to definitive surgical or radiologic intervention to allow for hemorrhage control. There is little published 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.[43] Clinicians working with limited capacity to achieve surgical hemostasis should aim to transfer as soon and as safely as possible.

11	**The protocol shall have activation criteria.** Under-activation (i.e. delayed or no activation of MHP for patients who require hemorrhage control and blood components) could be catastrophic as it may result in 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).[44] 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 human resources away from competing needs. Despite concern that appropriate and timely activation are 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 this setting are the Shock Index (heart rate divided by blood pressure or modified pediatric shock index[45]) and the ABC score (one point each for penetrating injury, blood pressure $\leq$90 mmHg, heart rate $\geq$120 and positive FAST (Focused Assessment with Sonography for Trauma on ultrasound), with the shock index performing slightly better in traumatic injury.[46] New data suggest that resuscitation intensity ($\geq$4 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.[47] In pediatric patients, a retrospective study of combat injured children defined massive transfusion as requirement for ≥ 40 mL/kg of blood components transfused within 24 hours.[48] 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.
12	**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 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.[49] 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.
13	**The protocol shall specify the team members required to respond when the protocol is activated.** Executing all of 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 hemorrhage, the location of the patient, the type of hemorrhage, and the institution's available resources. For example, the neonatal team will be required to attend postpartum hemorrhages to provide immediate care for the neonate, while in trauma MHPs managed in the trauma room where nursing to patient ratios are already high, 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.

14	**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, a 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.[50] Simulation training for clinicians leading trauma resuscitation improves confidence and reduces anxiety.[51] Formal feedback of trauma team leaders in training by faculty is associated with improvement in leadership skills over time.[52]
15	**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 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.[53] 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 transfusion medicine laboratory.
16	**The transfusion medicine laboratory and the core laboratory shall be notified of all MHP activations.** Early and prompt notification of the transfusion medicine laboratory 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 so as 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.
17	**All critical laboratory results and important coagulation parameters (hemoglobin, platelet count, INR, and fibrinogen) shall be communicated verbally 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 coagulation results (hemoglobin, platelet count, INR, and fibrinogen) 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.[54] 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 rapid movement of the clinical team from one hospital location to another.
18	**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.

19	**Patients and/or their Substitute Decision Maker for whom the massive hemorrhage protocol was activated should be informed. Actual (e.g., transfusion-associated circulatory overload, hyperkalemia, etc.) and potential adverse effects should be disclosed. Furthermore, women of childbearing potential should be informed of the risk of red blood cell alloimmunization.** 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 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 risks[55] 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/or 6 months post-transfusion (many antibodies are evanescent and there is a brief window for detection).[56]
20	**The collection and testing of the group and screen sample shall be prioritized in the protocol to mitigate the impact on group O red blood cells and AB plasma stocks.** 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 blood stocks.[57] The vast majority of AB plasma units are transfused to non-AB recipients.[58] Given the pressure on AB plasma stocks, it has not been possible to provide male-only AB plasma for all recipients with resultant cases of transfusion-related acute lung injury from female AB plasma.[59] Hence, the draw of the group and screen sample, rapid transport of the sample to the laboratory, and testing of the sample should be prioritized.
21	**Laboratory testing should be done at baseline and at a minimum hourly until the protocol is terminated**. See rationale below for statement 22.
22	**The recommended minimum laboratory testing (where the test is available) at each blood draw should be: CBC, INR, activated partial thromboplastin time (aPTT; baseline only), fibrinogen, electrolytes, calcium (ionized), 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 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 hemostatic resuscitation is required at least hourly. Current guidelines recommend early and repeated measures of hematology and coagulation parameters.[21] 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 correlated 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 hemorrhage is associated with worse outcomes; however, there is considerable overlap and minimal difference between outcome groups to be clinically useful.[27] 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.[31] Biochemical tests (e.g., potassium, calcium, and pH) may indicate potential complications from massive transfusion or inadequate resuscitation of hemorrhagic 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]

23	**The protocol should state the minimum laboratory protocol resuscitation targets for transfusion: (1) hemoglobin>80 g/L (RBC); (2) INR<1.8 (plasma or prothrombin complex concentrates); (3) Fibrinogen>1.5 g/L (cryoprecipitate or fibrinogen concentrates); (4) platelets > 50 x10^9/L; (5) ionized calcium >1.15 mmol/L. Relevant transfusion targets can also be used if viscoelastic testing is performed.** As there are no prospective studies evaluating laboratory 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.[21,63] 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). Certain pediatric 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.[33-35]
24	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 26.
25	**All patients should receive interventions to prevent hypothermia and achieve normothermia (≥36°C).** See rationale below for statement 26.
26	**All patients should receive warmed intravenous fluids, red blood cells and plasma to avoid hypothermia.** In both traumatic injury and postpartum hemorrhage, temperature monitoring is infrequently performed and when measured, hypothermia is common.[64,65] Hypothermia in traumatic injury is associated with worse outcomes,[66,67] although prospective trials have not confirmed whether aggressive warming protocols would alter outcomes.[68] Mild hypothermia is associated with a 22% increase in the risk of transfusion.[69] 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.[70]
27	**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.[71,72] At large academic centres with frequent MHP activation, all components should be transported in validated containers to mitigate component wastage.
28	**The MHP protocol should ensure there are processes in place to ensure an uninterrupted supply of blood components 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 hemorrhage, 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.

29	**If the blood group is unknown, O Rh D-negative red blood cells should only be used for female patients of childbearing potential (age<45).** O Rh D-negative stocks are insufficient to allow all patients of unknown blood group to be supported with O Rh D-negative RBCs until the blood group is resulted in the laboratory information system. 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%.[73,74] Immunization to the D-antigen is only relevant for females who wish to have future pregnancies. Over 99% of births occur in women under the age of 45 years,[75] and hospital MHPs should restrict the use of O Rh D-negative RBCs for women under this age. For conscious women, efforts should be made to determine their age early in the course of care so that the transfusion medicine service can be instructed to supply the optimal Rh D-type of blood. The risk of immunization from Rh D-positive platelets is 1% and therefore Rh-immunoglobulin should only be provided to Rh D-negative women under the age of 45 (after transfer to the intensive care unit but within 72 hours of the Rh D-incompatible platelet transfusion).[76]
30	**Uncrossmatched red blood cells shall be available at the bedside within 10 minutes of MHP activation.** See rationale below for statement 31.
31	**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).[44] 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 and severe injury, it is appropriate to order RBCs to the emergency department in advance of patient arrival.
32	**There is no threshold of units of group O red blood cells 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.
33	**The protocol shall state the reversal strategy for commonly used 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.

34

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. Two prospective randomized trials have failed to confirm a survival benefit of a RBC: plasma ratio of 1:1 (compared to 2:1).[77,78] 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 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, platelets and/or cryoprecipitate (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. Pediatric institutions should develop age and weight based MHP component protocols to ensure that blood components and fractionated coagulation factors are delivered in appropriate ratios. In institutions that care for pediatric patients, the transfusion boxes must come with clear instructions for the clinical team to mitigate the risk of over- or under-transfusion.

Standard approach	Simplified options for smaller organizations
Box 1 should contain 4 RBC.	No modification required.
Box 2 should contain 4 RBC, 4 plasma.	Box 2 (where plasma **not** stocked in hospital transfusion laboratory) should contain 4 RBC, 2000 IU PCC, and 4 grams Fibrinogen Concentrate. Efforts should be made to transfer the bleeding patient to a centre capable of definitive hemorrhage control.
Box 3* should contain 4 RBC, 2 plasma, and fibrinogen replacement (10 units Cryoprecipitate or 4 grams Fibrinogen concentrate).	As above.
Platelets, when stocked in the hospital transfusion laboratory, should be transfused based on the platelet count.	Platelets, when **not** stocked in the hospital transfusion laboratory, should be ordered in for transfusion (if patient cannot be promptly transferred out). If patient is transferred before platelets transfused, this should be communicated to the receiving hospital.

* Few patients will require more than 12 RBCs due to an acute hemorrhage. By 12 units of RBCs, transfusion decisions for plasma and fibrinogen replacement should be made based on the hourly measurement of the INR and the fibrinogen levels and orders communicated promptly to the blood bank.

35

Recombinant factor VIIa (rVIIa) should only be considered when massive hemorrhage is refractory to surgical hemostasis, medical optimization of coagulation parameters, acidosis, and hypocalcemia, and used in consultation with an expert in the management of coagulopathy in the massively bleeding patient. Recombinant activated factor VIIa (rVIIa) has not been shown to improve mortality in prospective, randomized controlled trials. [81,82] In contrast, rVIIa is associated with an increase in thromboembolic complications.[82] Given the concerns regarding lack of efficacy and potential risks, all other lower risk hemostatic therapies should be exhausted and it should only be used in consultation with an expert in the management of coagulopathy of the massively bleeding patient.

36	**Fibrinogen concentrate 4 grams (equivalent to approximately 10 U of cryoprecipitate) can be used as a reasonable alternative to cryoprecipitate for fibrinogen replacement.** 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 transported frozen at all times. Once thawed and pooled it expires after 4 hours. Given the time intensive preparation requirements and limited shelf-life, it is reasonable for some hospitals to transition to pathogen-reduced fibrinogen concentrates. There are no large randomized controlled trials of cryoprecipitate and fibrinogen concentrates to determine equivalence, although a large trial in cardiac surgery related hemorrhage is ongoing (FIBRES Study, NCT03037424).[83] For pediatric patients a dose of approximately 50 mg/kg of fibrinogen concentrate up to a maximum of 4 grams is suggested.[84]
37	**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 ≥1.5g/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 trauma, usually guided by viscoelastic point-of-care testing.[85] 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 pediatric patients a dose of 25 IU/kg of PCCs (rounded to the closest 500 IU) up to a maximum of 2000 units is suggested.[86,87]
38	**Patient and product identification pre-transfusion bedside check shall be performed prior to transfusion of any component to avoid mistransfusion.** Transfusion-related errors remain common in the emergency department.[88,89] 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.
39	**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 admitted during major hemorrhage or after traumatic injury are frequently registered with a temporary name and number (e.g., Unidentified, Andrew) or with an incomplete registration (e.g., no date of birth). Modifications to key identifiers 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 transfusion medicine laboratory to ensure no gaps in release of laboratory test results or transfusion support.

40	**Tranexamic acid should be administered as soon as intravenous or intraosseous access is achieved but within 3-hours from time of injury or within 3-hours from MHP activation in all other patients.** Tranexamic acid improves mortality in the setting of trauma[90] and postpartum hemorrhage.[91] 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.[92] There is no increased risk of venous or arterial thromboembolic complications.[93] Dosages and infusion rates vary depending on the study protocol (1 gram bolus plus 1 gram infusion over 8 hours,[90] 1 gram bolus and 1 gram bolus repeated at 1 hour,[94] 1 gram bolus and repeated if ongoing bleeding at 30 minutes or greater[91], 2 gram bolus at the scene of the injury [Rowell SE, et al, 2020]). 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 pediatric trauma, but it is accepted practice for use in pediatric trauma patients requiring transfusion within the same time parameters as adults. For pediatric patients the initial bolus of tranexamic acid can be dosed at 15 mg/kg up to a maximum of 1 gram and additional doses/infusion based on local policy.[95,96] The role of tranexamic acid in gastrointestinal bleeding has not been confirmed; a large multicenter trial is underway (HALT-IT Trial Collaborators, 2020) to determine if tranexamic acid assists with hemostasis and reduces transfusion or mortality rates.[97] Tranexamic acid should be readily available in clinical areas where massive hemorrhage is common to prevent delays in administration.
41	**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.[11,15] 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 42 should be tracked on consecutive MHP activations by a multidisciplinary team with feedback to the frontline staff at regular intervals.
42	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:

	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 (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 pediatric 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 arrival/onset of hemorrhage.	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 pediatric patients) or before this level in patients dying due to hemorrhage 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	

Reference list for Delphi Statements can be found at the end of the toolkit.