The transfusion of blood components such as red blood cells (RBCs) and plasma is increasingly common in prehospital and transport medicine. In addition, the potential benefits of out-of-hospital administration of whole blood or blood products such as fibrinogen and prothrombin complex concentrate in selected patients are being investigated. In this report, we use the umbrella term “out-of-hospital transfusion” (OHT) to refer to the transfusion of whole blood, blood components such as RBCs and plasma, or blood products such as fibrinogen and prothrombin complex concentrate. Although the increasing practice of OHT suggests general consensus on a likely clinical benefit, evidence regarding the effect of OHT on morbidity and mortality is limited and conflicting. The generalizability of the limited evidence is further complicated in that the feasibility and potential benefit of OHT are dependent on multiple regional factors such as geography, patient factors and health care configuration. For example, 2 secondary analyses of the data sets from the Prehospital Air Medical Plasma (PAMPer) and the Control of Major Bleeding After Trauma (COMBAT) clinical trials suggested that OHT was beneficial if transport times were greater than 20 minutes and that a benefit present in blunt trauma does not translate to a benefit in penetrating trauma. In addition, out-of-hospital management of acute hemorrhage...
extends beyond OHT and includes factors such as administration of tranexamic acid, avoidance of hypothermia and physical means of hemorrhage control where possible.9,10 Efficient and effective implementation of OHT requires a combination of medical and logistic considerations that span multiple specialties. This is particularly relevant in countries like Canada, with long transport times to tertiary care centres, and remote communities that have limited or no access to physicians or blood components and products at their local health care facilities.11

We invited an expert panel to provide expert opinions on out-of-hospital hemorrhage management and, in particular, OHT to develop national consensus recommendations to guide OHT practice and to begin to optimize the effectiveness and safety of OHT.

Methods

We used a modified RAND Delphi process to create an expert consensus document on the development of OHT protocols by Canadian critical care transport organizations (CCTOs). The study period was July 2021 to June 2022.

Study design

We used a modified RAND Delphi process to establish recommendations for the development of local or regional OHT protocols. The Delphi technique is deemed a relevant source of evidence in health care research and is particularly important if randomized controlled trials are unavailable to set health care policies.12 It is a systematic, interactive method that relies on a panel of experts to converge on consensus statements after a series of iterative written surveys.13 Based on the study team’s experience with a recent Delphi study on in-hospital massive hemorrhage protocols,14 we modified the original technique by adding a panel discussion to the written survey rounds. This was to allow an exchange of information and opinions between participants of different backgrounds and levels of expertise. We also chose the RAND/UCLA Appropriateness Method,15 in which the participants were encouraged to edit the list of recommendations during the written survey rounds, as well as add further recommendations or comments in free-text fields.

We did not specify the number of written survey rounds a priori. Based on previous similar research,14 we estimated that 2–4 written survey rounds would be required to achieve satisfaction for feedback and stagnation for consensus. The study team reviewed all feedback and progress toward consensus after the second written survey round to decide whether further written rounds would be of benefit. Given the considerable geographic distance between participants, we used an online survey tool (JotForm, https://www.jotform.com/) for the written survey rounds of the Delphi study and an online meeting platform for the panel discussion.

Data source

At the start of the process, the study team created a list of 41 statements relating to OHT, covering the following domains:

- General oversight and clinical governance
- Storage and transport of blood components and products
- Initiation of OHT
- Types of blood components and products
- Delivery and monitoring of OHT
- Indications for and use of transfusion adjuncts
- Resuscitation targets to guide transfusion.

The lead author (J.V.-F.) drafted the initial statements and domains based on clinical experience using OHT in CCTOs in the United Kingdom and Canada, after which B.N., J.L. and S.M. each provided written comments and revisions, resulting in a second draft. The third and final draft was agreed on during a meeting of the entire study team (B.N., J.V.-F., J.L., S.M.).

Participants

The study team created a list of subject experts for study participation from personal contacts, with the following inclusion criteria: senior clinician in a CCTO, or in-hospital trauma care with an interest in transfusion or in a transfusion service involved in OHT, and current clinical practice in Canada. In addition, potential participants on this list were given the option to nominate further experts for potential participation in the study. During this selection process of potential study participants, we use purposive sampling based on professional background, clinical specialty, and location of practice. Given the relatively small pool of eligible experts in Canada, we sought a sample size of 15–20 participants to achieve good representation.15 Potential participants were contacted via email, with 2 further follow-up emails in 2-week intervals. The recruitment email contained a short summary of the study objective and design (Appendix 1, available at www.cmajopen.ca/content/11/3/E546/suppl/DC1), and participants completed a written consent form for participation. There was no financial remuneration. The study team did not participate in the written survey rounds; B.N. and J.V.-F. moderated the panel discussion but did not express opinions on statements discussed.

Delphi process and statistical analysis

In each written survey round, participants were asked to score each of the recommendation statements on a Likert scale ranging from 1 (“Definitely should not include”) to 7 (“Definitely should include”). Participants were also asked to propose wording changes to existing statements, add comments or add additional statements they considered important. Participants were blinded to the other participants’ identities and responses during the written survey rounds. Once all participants had submitted their ratings and comments, the research team calculated median Likert scores for each statement and reviewed all comments. The research team was blinded to the identity of the participants during this phase of the Delphi process. The following outcomes were possible after each written survey round:

- Median score 6–7: consensus achieved. Statement included as written, or with minor adjustments based on participants’ comments if these changes did not alter the meaning of the statement. These statements were excluded from further rounds.
Research Ethics Office, Unity Health Toronto (REB 21-155).

Results

We invited 29 subject experts, of whom 17 (7 females [41%] and 10 males [59%]) agreed to participate in the study. All participants held senior positions within their respective organizations. Table 1 provides an overview of the participants’ backgrounds.

Of the 12 subject experts who did not participate, 1 declined and 11 did not respond. As part of the purposive sampling strategy, the study team attempted to recruit additional participants from provinces that were underrepresented, but these efforts were ultimately unsuccessful. Overall, the study team identified 21 subject experts, and a further 8 were nominated by potential participants.

After reviewing the results of the written survey rounds 1 and 2, the study team concluded that no further progress on consensus could be achieved through further written rounds, and we proceeded to the online panel discussion. The final modified RAND Delphi structure used in this study therefore consisted of 3 rounds: 2 written surveys of recommendation statements, followed by a panel discussion. All participants completed rounds 1 and 2 of the modified Delphi process, and 13 participants (76%) attended the virtual panel meeting (round 3). All participants who were unable or wished not to attend the virtual meeting reviewed the recording or transcription, or both, and provided further commentary if required. All 17 participants reviewed the final list of statements. Table 2 shows the progression toward consensus for all the statements.

<table>
<thead>
<tr>
<th>Table 1: Characteristics of study participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
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<tr>
<td>----------------</td>
</tr>
<tr>
<td>Profession</td>
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<tr>
<td>Physician</td>
</tr>
<tr>
<td>Critical care paramedic</td>
</tr>
<tr>
<td>Registered nurse</td>
</tr>
<tr>
<td>Specialty</td>
</tr>
<tr>
<td>Transfusion medicine</td>
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<tr>
<td>Emergency medicine</td>
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<tr>
<td>Trauma surgery</td>
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<tr>
<td>Prehospital/transport</td>
</tr>
<tr>
<td>Province</td>
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<tr>
<td>Ontario</td>
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<tr>
<td>British Columbia</td>
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<td>Alberta</td>
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<tr>
<td>Saskatchewan</td>
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<tr>
<td>Quebec</td>
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</tbody>
</table>

Presentation of results

The final agreed-on statements were included in a table with domains and order of statements updated based on participants’ feedback. In addition, the study team drafted a rationale for each statement, based on current literature and participants’ comments during the Delphi rounds. All participants were given the opportunity to review the recommendation statements and the corresponding rationales in their final form before completion of the study.

Authorship

After reviewing the participants’ contributions to the research project, the study team decided to offer coauthorship to all participants during the final Delphi round. All participants consented to authorship and reviewed the final manuscript.
Table 2 (part 1 of 2): Statements and progress over the 3 Delphi rounds toward consensus on out-of-hospital transfusion protocols

<table>
<thead>
<tr>
<th>Domain; statement</th>
<th>Median score* (range) (abstaining vote if applicable)</th>
<th>Round 1</th>
<th>Round 2</th>
<th>Round 3†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. General oversight and clinical governance</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1</td>
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<td>1.2</td>
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<td>1.4</td>
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<td>1.5</td>
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<td></td>
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<tr>
<td>1.7</td>
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<tr>
<td>1.8</td>
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<td>2.4</td>
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<tr>
<td>3. Initiation of out-of-hospital transfusion</td>
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<td>3.7</td>
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Table 2 (part 2 of 2): Statements and progress over the 3 Delphi rounds toward consensus on out-of-hospital transfusion protocols

<table>
<thead>
<tr>
<th>Domain; statement</th>
<th>Median score* (range) (abstaining vote if applicable)</th>
<th>Round 1</th>
<th>Round 2</th>
<th>Round 3†</th>
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<tr>
<td>4. Types of blood components and products</td>
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<td>4.7</td>
<td>6 (2–7)</td>
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<td></td>
<td>Merged with other statement</td>
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<tr>
<td>5. Delivery and monitoring of out-of-hospital transfusion</td>
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<tr>
<td>5.7</td>
<td>7 (2–7)</td>
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<td></td>
<td>Merged with other statement</td>
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<tr>
<td>6. Indications for and use of transfusion adjuncts</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>7. Resuscitation targets to guide transfusion</td>
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<td>7.1</td>
<td>6 (4–7)</td>
<td></td>
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<td>7.2</td>
<td>6 (4–7)</td>
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<td>Accept revised version</td>
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</tr>
<tr>
<td>7.3</td>
<td>New statement</td>
<td>5 (2–7; 1)</td>
<td>Round 2 (score)</td>
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</tr>
</tbody>
</table>

*On a Likert scale ranging from 1 (“Definitely should not include”) to 7 (“Definitely should include”).
†Panel discussion results.
Table 3 (part 1 of 5): Consensus statements on the development of out-of-hospital transfusion protocols

<table>
<thead>
<tr>
<th>Domain; statement</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. General oversight and clinical governance</strong></td>
<td></td>
</tr>
<tr>
<td>1.1 All CCTOs shall have a protocol to guide OHT.</td>
<td>The panel agreed on the importance of standardization of OHT within CCTOs. For the purpose of this document, CCTOs should be viewed as organizations that provide a critical-care level of stabilization and transport of severely ill or injured patients, whether by ground or air ambulance. This includes scene calls and interfacility transfers. Most Canadian local and regional emergency medical services ground ambulances will probably not be dispatched to sufficient numbers of critically ill patients to warrant the addition of OHT to such services. However, some emergency medical services might create smaller units for second-tier dispatch to selected patient groups (for example, major trauma), and such units should be considered CCTOs in the context of this document.</td>
</tr>
<tr>
<td>1.2 The protocol shall be developed by a multidisciplinary team, be approved by the participating transfusion service, and comply with best practices and local and national transfusion guidelines.</td>
<td>An OHT protocol requires support from multiple organizations and individuals. This includes, but is not limited to, prehospital providers, aviation safety experts (in some cases), blood transport personnel, communication services and laboratory personnel. The protocol should be reviewed and approved by the hospital transfusion committee and the CCTO’s medical advisory committee.</td>
</tr>
<tr>
<td>1.3 The protocol shall incorporate principles of damage-control resuscitation, including appropriate treatment of ongoing hemorrhage and careful selection of a receiving hospital that can provide appropriate definitive hemorrhage control.</td>
<td>Damage-control resuscitation principles in prehospital trauma care include control of external hemorrhage; application of pelvic binders (if indicated); correction of deranged physiologic measures, with particular focus on avoiding hypothermia and acidosis; and the administration of TXA. Extensive crystalloid administration should be avoided if possible. New technologies such as partial resuscitative endovascular balloon occlusion of the aorta (P-REBOA) might play a role in internal hemorrhage control in the future. Many damage-control resuscitation principles can be applied to nontraumatic causes of hemorrhagic shock, but the panel acknowledges the lack of clear evidence. Notwithstanding the increasing number of therapeutic options outlined above, timely transfer to a receiving hospital with the resources required for definitive hemorrhage control remains a key component of care for patients experiencing hemorrhagic shock.</td>
</tr>
<tr>
<td>1.4 The protocol shall reflect the types and amounts of blood components and products that can be stored and transported by the CCTO, as well as additional components and products that might be available from sending facilities.</td>
<td>The panel anticipated that the quantity and variety of blood components and products that CCTOs will be able to access is likely going to evolve with the publication of numerous prehospital trials currently underway. Optimal care for patients with major hemorrhage might require a combination of the CCTO’s stock and further blood components and products that might be available from sending facilities, and protocols should provide guidance for such situations.</td>
</tr>
<tr>
<td>1.5 The protocol should be reviewed at specified regular intervals, when the CCTO adopts new relevant products or procedures, or if new, practice-changing evidence emerges.</td>
<td>The panel acknowledges the pace of ongoing research in this area, with a number of relevant randomized controlled trials expected over the coming years. In addition, changes in blood transfusion services might make new products available in the near future based on needs and logistics, for example, lyophilized plasma or whole blood.</td>
</tr>
<tr>
<td>1.6 A single protocol for all patients is preferred in order to ensure compliance; there should be specific guidance provided for selected patient populations.</td>
<td>Previous research has demonstrated poor compliance with major hemorrhage protocols during in-hospital transfusions and a potential detrimental effect on patient outcomes. To optimize compliance with OHT protocols, the panel recommended a single protocol for patients with active, major bleeding. This single protocol should include or reference considerations for specific situations such as trauma, obstetric hemorrhage, gastrointestinal bleeding, acquired coagulopathy or pediatric hemorrhage.</td>
</tr>
<tr>
<td>1.7 Each CCTO shall have named lead(s) and contact person(s) for any issues related to OHT.</td>
<td>Owing to the inherently unpredictable nature of the critical care transport environment, situations will arise that are not directly addressed by protocols already in place. It is imperative that CCTOs have a responsive and accountable system to deal with any queries and issues in a safe and timely fashion.</td>
</tr>
<tr>
<td>1.8 All OHT procedures should be reviewed by a designated individual (for example, the named lead for OHT [see statement 1.9]) or committee for quality assurance.</td>
<td>Adherence to major hemorrhage protocols in regard to safety measures, indication for transfusion and damage-control resuscitation is a critical aspect of assuring patient benefit and efficient use of blood products during in-hospital care. Although no direct evidence exists for protocols guiding transfusion in prehospital and retrieval settings, it is likely that the in-hospital evidence is transferrable, and many CCTOs routinely review all cases involving OHT. CCTOs should have a mechanism to review all cases of OHT, including feedback to care providers and shared learning across the CCTO.</td>
</tr>
</tbody>
</table>
1.9 In addition to the minimal regional and national training requirements for competence in blood product transfusion, prehospital care providers shall have formal training specific to blood transfusion in the prehospital or transport medicine setting.

1.10 Any clinical or administrative adverse events, errors or near-misses shall be documented and reported through the CCTO’s incident report system. This shall trigger a notification of the named lead(s) of the CCTO and the participating transfusion service.

1.11 The quality metrics in Box 1 should be tracked on all OHTs and the data reviewed quarterly at the CCTO’s medical advisory committee, with representation from the participating transfusion service.

1.12 If the patient (or a substitute decision-maker) is unable to consent to OHT, this should be documented in the CCTO’s patient records. If consent can be obtained, documentation of consent should include an explanation of the risks and alternatives to OHT.

1.13 CCTOs shall comply with all Health Canada Blood Regulations, and applicable Canadian Standards Association and provincial standards that govern OHT.

### Table 3 (part 2 of 5): Consensus statements on the development of out-of-hospital transfusion protocols

<table>
<thead>
<tr>
<th>Domain: statement</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Storage and transport of blood components and products</td>
<td></td>
</tr>
<tr>
<td>2.1 Blood components and products shall be stored in validated storage containers in accordance with national and regional accreditation standards of the participating transfusion service.</td>
<td>One of the main logistical challenges of OHT is the storage of blood components and products outside of blood transfusion services’ laboratories. As per many transfusion standards, the use of validated containers is required to reduce the risk of transfusion complications and wastage.</td>
</tr>
<tr>
<td>2.2 Containers shall be closely inspected/monitored for any compromise or defects at defined times (i.e., start and end of shift, before initiation of OHT, on return to participating transfusion service).</td>
<td>Containers will be frequently moved between different storage areas at CCTO bases, aircraft and vehicles, and will also be transported to the patient’s side at scene or sending facility. The frequent movement and storage in compartments shared with other equipment in aircrafts or vehicles introduces a risk of damage to containers, with the subsequent risk of wastage of blood components and products if not recognized and mitigated.</td>
</tr>
<tr>
<td>2.3 If a temperature-monitoring device is included in the storage container, it shall be inspected for temperature range violations before initiation of OHT.</td>
<td>Depending on local practices, such as choice of storage containers and frequency of exchange of blood components and products, temperature-monitoring devices will be included in the storage containers. Identifying any temperature violations before initiation of OHT is a critical step in avoiding transfusion complications.</td>
</tr>
</tbody>
</table>
Table 3 (part 3 of 5): Consensus statements on the development of out-of-hospital transfusion protocols

<table>
<thead>
<tr>
<th>Domain; statement</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>2.4 Prehospital providers handling blood components and products should receive training regarding the safe storage and handling of the containers, and as well as the procedures for receiving blood components and products from the transfusion service, and returning blood components and products to the transfusion service.</td>
<td>Training in the clinical aspects of OHT is addressed in statement 1.12. However, the panel agreed that specific training and instructions regarding the storage, handling and exchange procedures for blood products and components were important to reduce the risk of wastage.</td>
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3. Initiation of out-of-hospital transfusion

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<tr>
<th>Domain; statement</th>
<th>Rationale</th>
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<tbody>
<tr>
<td>3.1 The indication for OHT is confirmed or suspected hemorrhagic shock secondary to traumatic or nontraumatic hemorrhage AND 2 or more of: • SBP &lt; 90 mm Hg • Heart rate &gt; 110 beats/min • Clinical signs of end-organ dysfunction • Lactate level &gt; 4 mmol/L • Hemoglobin level &lt; 90 g/L • Base excess &lt; –6</td>
<td>Although the panel expected that trauma would be the main cause for OHT, it is important to also consider OHT in nontraumatic causes of hemorrhagic shock such as obstetric, gastrointestinal, peri- or postoperative, or aneurysmal hemorrhage. Previous research in patients with trauma has shown that clinician gestalt alone is a poor predictor of the need for massive transfusion, which suggests the need for standardized transfusion protocol triggers. The combination of clinical and laboratory parameters to trigger OHT in this statement aims to provide guidance but also some flexibility to the health care provider. For patients whose condition is unstable in need of urgent transfusion (at least 2 of hypotension, tachycardia, or end-organ dysfunction), OHT can be commenced without the need for laboratory testing. In patients with none or only 1 of these clinical signs of hemorrhagic shock, OHT might still be beneficial, and the decision can be augmented by obtaining point-of-care laboratory values, if possible. In patients with trauma, additional factors such as injury patterns (amputation, pelvic fracture, penetrating trauma) or positive findings of Focused Assessment with Sonography in Trauma (FAST) scanning can be used to determine the indication for transfusion.</td>
</tr>
<tr>
<td>3.2 In addition to acute hemorrhagic shock, OHT may be initiated in other cases in which a transport physician considers the benefits to outweigh the risks.</td>
<td>Although statement 3.1 aims to provide a comprehensive trigger for OHT, there might be situations that do not fulfill the above criteria in which OHT might be considered. As these cases are likely to have a less time-sensitive nature and more marginal benefit–risk ratios, the panel agreed that this decision should be made by a CCTO transport physician.</td>
</tr>
<tr>
<td>3.3 OHT may be commenced without physician authorization within the boundaries of a clearly defined medical directive, or if the anticipated delay would result in major harm to the patient (e.g., severe hemodynamic compromise).</td>
<td>Transfusion of blood products typically requires physician orders. However, the panel agreed that critically ill or injured patients might come to harm if initiation of OHT is delayed owing to the need to obtain remote physician authorization. Protocols should therefore include mechanisms for autonomous initiation of OHT within clearly defined boundaries (see statement 3.2, for example).</td>
</tr>
<tr>
<td>3.4 The indication for commencing OHT should be clearly documented in the patient’s records.</td>
<td>Blood components and products are scarce resources. In addition, the risk–benefit ratio of OHT needs to be carefully considered for individual patients. Documentation of indications for OHT is necessary to demonstrate the consideration of risk to benefit and for auditing protocol adherence.</td>
</tr>
<tr>
<td>3.5 If feasible, a pretransfusion blood sample should be obtained by the prehospital provider to be used by the hospital transfusion service for ABO and Rh investigations.</td>
<td>Pretransfusion samples, although not immediately beneficial in the context of OHT, can be valuable for blood transfusion services when further transfusions are required, reduce downstream use of group O RBC and support eligibility for organ donation if indicated. The panel had concerns regarding the increased workload for prehospital providers and accurate sample labelling. Nevertheless, a number of CCTOs currently obtain pretransfusion samples when feasible, and this option should be considered in the development of OHT protocols.</td>
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4. Types of blood components and products

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<tbody>
<tr>
<td>4.1 At a minimum, OHT stocks of CCTOs shall include 2 units of O Rh(D)-negative RBCs.</td>
<td>The panel agreed that, pending availability of whole blood and further evidence for other blood components and products, RBCs are the central component of OHT. The panel considered that a large number of patients could safely receive O Rh(D)-positive RBCs. However, for patients truly requiring O Rh(D)-negative RBCs, the CCTO’s stock of RBCs might be the only blood component or product available, and, as such, CCTOs should stock O Rh(D)-negative RBCs whenever possible. In addition, logistical considerations favour CCTOs carrying 1 type of RBC consistently rather than a mix of RBC Rh types. Finally, administration of Rh(D)-positive blood without a pretransfusion sample can delay Rh-group determination considerably after OHT.</td>
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Table 3 (part 4 of 5): Consensus statements on the development of out-of-hospital transfusion protocols

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<td>4.2 If blood group is unknown, O Rh(D)-negative RBCs shall be the preferred RBC for patients of child-bearing potential. CCTOs may consider the use of O Rh(D)-positive RBCs for all other patients.</td>
<td>In addition to the CCTO’s O Rh(D)-negative RBCs (statement 4.1), further blood products might be available through the CCTO or sending health care facility. The Ontario Massive Hemorrhage Protocol guideline suggests the use of O Rh(D)-positive RBCs for all patients with the exception of patients of child-bearing potential, in order to maintain sufficient O Rh(D)-negative stocks. Group O Rh(D)-positive RBCs should be used in these circumstances, if this is possible without delay.</td>
</tr>
<tr>
<td>4.3 Depending on local availability, feasibility and clinical requirements, CCTOs may consider including plasma in addition to RBCs.</td>
<td>Correction or prevention of coagulopathy is an important aspect of damage-control resuscitation for hemorrhagic shock. Many CCTOs internationally stock plasma in addition to or instead of RBCs. The Ontario Massive Hemorrhage Protocol guidelines suggest a ratio of RBCs to plasma of 2:1 in massive transfusion, and there is evidence that prehospital administration of plasma might improve survival in patients with trauma with longer transfer times. Although availability of group AB plasma is limited in Canada, CCTOs should consider including plasma if availability and logistics allow this.</td>
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<tr>
<td>4.4 CCTOs may consider storing and transporting 2000 IU of PCC and 4 g of fibrinogen concentrate as an alternative to thawed plasma.</td>
<td>The Ontario Massive Hemorrhage Protocol guidelines recommend PCC and fibrinogen as an alternative to plasma for health care facilities where plasma is not immediately available for logistic reasons. CCTOs are similar to such facilities in their limited storage capabilities of blood components and products, and therefore could consider the addition of PCC and fibrinogen to their OHT stocks as an alternative to plasma.</td>
</tr>
<tr>
<td>4.5 Additional blood components and products, such as larger volumes of RBCs or thawed plasma, platelets or specific clotting factor concentrates may be requested from the sending health care facility as required. The benefits of obtaining these additional products need to be balanced against the risks of delaying transfer of the patient.</td>
<td>Frequently in hemorrhagic shock, and particularly with longer transport times to definitive care, the CCTO’s stock of blood components and products will be insufficient to meet the patient’s needs. The option of obtaining further blood products from a sending health care facility or a health care facility on route to definitive care should be explored. The potential benefits of releasing these limited stocks from the sending facility need to be weighed against the risk of depleting local resources, to the potential detriment of other patients requiring care at the sending facility. Importantly, this process should occur with no or minimal delay in transport to definitive care, and thus should be initiated early on, if appropriate.</td>
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5. Delivery and monitoring of out-of-hospital transfusion

5.1 Prehospital providers should have access to a standard operating procedure that includes the indication for and administration and monitoring of OHT, and the management of adverse reactions. | OHT might be an infrequent event for prehospital providers working in Canadian CCTOs. Access to relevant standard operating procedures, electronically or in print, is essential to ensure protocol adherence, and their use has been shown to improve quality of care in other aspects of prehospital or retrieval medicine. |

5.2 RBCs and plasma shall be given through a commercial, portable and approved warming device. | Avoidance of hypothermia is an important aspect of damage-control resuscitation. Blood components and products that are stored at low temperatures (RBCs and plasma) should therefore be given through a warming device. Multiple portable devices for use in the critical care transport environment are commercially available. |

5.3 All patients receiving OHT should have their temperature measured within 30 minutes of provider assessment, and then at a minimum of every 30 minutes (or continuously where available) until arrival at the receiving hospital. | In both traumatic injury and postpartum hemorrhage, temperature monitoring is infrequently performed, and, when the temperature is measured, hypothermia is common. Hypothermia in traumatic injury is associated with worse outcomes, although prospective trials have not confirmed whether aggressive warming protocols would alter outcomes. 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 OHT. |

5.4 All patients should receive interventions to prevent hypothermia and achieve normothermia (≥ 36°C) | See rationale for statement 5.3. |

5.5 Point-of-care hemoglobin level, lactate level and/or base excess may be used to guide OHT (see statements 3.1 and 7.2) but should not delay initiation of transfusion in critically ill or injured patients. | During in-hospital massive hemorrhage protocols, regular laboratory testing is used to direct management. A number of commercially available point-of-care testing devices are now small and light enough that they have been successfully incorporated into the critical care transport environment. The panel encourages the use of point-of-care testing, with the caveat that it should not impede or delay OHT in critically ill or injured patients. |
Table 3 (part 5 of 5): Consensus statements on the development of out-of-hospital transfusion protocols

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<td>5.6 Monitoring for and clinical management of transfusion reactions should follow the same standards as for in-hospital blood transfusions.</td>
<td>Transfusion reactions range from relatively common and benign febrile nonhemolytic reactions to rare and severe hemolytic transfusion reactions. The monitoring for and management of such transfusion reactions should be clearly outlined in standard operation procedures and should closely mirror established protocols of in-hospital practice. Since the vast majority of RBCs administered during OHT will be uncrossmatched, patients should be closely monitored for signs and symptoms of delayed hemolytic transfusion reactions.</td>
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<tr>
<td>6. Indications for and use of transfusion adjuncts</td>
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<tr>
<td>6.1 TXA should be given as soon as possible with any OHT for hemorrhagic shock due to trauma within the previous 3 hours.</td>
<td>Early administration of TXA has been shown to reduce mortality from traumatic hemorrhage, with the effect gradually decreasing over time. Administration of TXA later than 3 hours after the initial injury is associated with increased mortality. Current recommendations include a 1-g bolus followed by either a further 1 g of TXA as bolus or infusion, or a single 2-g bolus.</td>
</tr>
<tr>
<td>6.2 TXA should be given as soon as possible with any OHT for hypovolemic shock due to postpartum hemorrhage.</td>
<td>Early administration of TXA has been shown to reduce mortality from postpartum hemorrhage, with earlier administration more beneficial than later administration.</td>
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<td>6.3 Consideration of calcium gluconate or calcium chloride administration should be prompted by OHT protocols at defined intervals (e.g., after 2 units and after every 4 units thereafter).</td>
<td>Hypocalcemia is common in patients with trauma and is associated with increased mortality. RBCs are preserved with citrate, which could cause or exacerbate hypocalcemia, particularly during OHT with large volumes of RBCs. Calcium plays an important role in the clotting cascade and as an inotrope. The panel considers there to be insufficient evidence for routine calcium administration during OHT; however, a prompt to consider empirical administration or point-of-care testing (if feasible) is considered beneficial.</td>
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<tr>
<td>6.4 PCC, 2000 IU, should be given empirically for adult patients requiring OHT because of hemorrhage and taking warfarin or a direct factor Xa inhibitor (e.g., rivaroxaban, apixaban, edoxaban).</td>
<td>The Canadian National Advisory Committee on Blood and Blood Products recommends the empirical administration of 2000 IU of PCC in patients taking warfarin with major bleeding and an unknown International Normalized Ratio. The same dosage is recommended for the management of severe bleeding in patients taking a direct factor Xa inhibitor.</td>
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<tr>
<td>7. Resuscitation targets to halt ongoing transfusion</td>
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<td>7.1 OHT should be re-evaluated if the following SBP has been achieved in acute traumatic hemorrhagic shock: • ≥ 90 mm Hg if blunt trauma • ≥ 110 mm Hg if suspected or confirmed traumatic brain injury • ≥ 80 mm Hg if penetrating trauma</td>
<td>Permissive hypotension has become an established concept in early damage-control resuscitation for trauma. However, much uncertainty remains as to what the ideal blood pressure targets are and after what time more aggressive restoration of perfusion might be beneficial. This statement reflects commonly used SBP targets. These values should be seen as a trigger to review the current situation and OHT, rather than an automatic stop of an ongoing transfusion. The factors outlined in statement 7.2 can be used to supplement decision-making.</td>
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<tr>
<td>7.2 For longer transfers, particularly interfacility transfers, or in patients in whom active bleeding has stopped, the following factors, in addition to SBP, can be used to guide the amount and speed of OHT: • Heart rate • Lactate level • Hemoglobin level • Base excess • Signs of organ dysfunction (urine output, signs of cardiac ischemia, level of consciousness).</td>
<td>There is considerable uncertainty regarding when to stop or reduce an ongoing OHT. The decision should be supported by multiple data points, in addition to factors such as the volume of remaining blood components and products and length of transport to definite care. See also rationale for statement 7.1.</td>
</tr>
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Note: CCTP = critical care transport organization, OHT = out-of-hospital transfusion, PCC = prothrombin complex concentrate, RBC = red blood cell, SBP = systolic blood pressure, TXA = tranexamic acid.
Of the 41 initial statements, 21 were accepted with no or only minor changes after round 1, and 5 were merged with others. The remaining 15 statements were modified according to participants’ comments and included in round 2, together with 7 additional new statements suggested by participants. In round 2, a further 9 statements were accepted, and 2 statements were merged with another. No statements received median scores of 1 or 2 in either of the first 2 rounds. The remaining 11 statements were discussed in the virtual panel meeting. During the panel meeting (including feedback from participants who were unable to attend), consensus was achieved on all but 2 statements. Table 3 contains a comprehensive list of the 39 final consensus statements and their rationales, Box 1 lists the 9 quality metrics, and Table 4 shows the 2 statements for which no consensus was achieved.

### Interpretation

Through a modified RAND Delphi process, we developed 39 expert consensus statements and 9 quality metrics on the transfusion of blood components and products in the prehospital and retrieval setting. This guidance document specifically addresses OHT and the CCTOs responsible for implementing and assuring the quality of OHT. Although some of the guidance in this document is specific to the Canadian setting, to the best of our knowledge, this is one of the very few documents providing guidance on OHT internationally.66 We hope it will prove useful to CCTOs in Canada and other countries around the world. The consensus statements cover various aspects of OHT, from logistics to clinical aspects and quality-assurance measures. As such, we consider the multidisciplinary makeup of the expert panel participating in the study to be an important strength of this research.

The 2 domains for which gaining consensus was more challenging were domains 3 (initiation of OHT) and 4 (types of blood components or products). This slower, and, in the case of 2 statements, failed progress toward consensus in these domains likely reflects the lack of clear evidence and considerable variation in practice in these areas.67 From our experience during this modified RAND Delphi process, we stress the benefit of an exchange of information among the subject

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**Box 1: Suggested quality metrics for quarterly review by the critical care transport organization’s medical advisory committee**

- **Strongly recommended**
  - Number of wasted blood components and products (absolute number and proportion of total blood components and products)
  - Transfusion-related errors (i.e., ABO/Rh incompatibility, compromised blood products)
  - Independent double checks of blood components and products
  - Proportion of patients receiving OHT who met protocol indications
  - Proportion of blood components and products successfully traced to final disposition (i.e., transfused, returned to transfusion services, wasted)

- **Recommended**
  - Proportion of patients with OHT where receiving facilities were notified of need for further in-hospital transfusion, before arrival (pre-alert).
  - Proportion of patients who received tranexamic acid within 1 h of first contact with CCTO (if within 3 h of injury or acute postpartum hemorrhage)
  - Proportion of patients who had temperature of > 35°C by time of arrival at receiving hospital
  - Proportion of patients of child-bearing potential who received O Rh(D)-negative RBCs

Note: CCTO = critical care transport organization, OHT = out-of-hospital transfusion, RBC = red blood cell.

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**Table 4: Statements for which consensus was not achieved**

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<tr>
<td>4.6 In suspected or confirmed hemorrhagic shock secondary to trauma, balanced transfusion with plasma, RBCs and platelets in a ratio of 1:1:1–1:1:2 is ideal. As hospital major hemorrhage protocols usually lead with RBCs, prehospital providers should consider prioritizing plasma transfusion, as well as communicating the need for early transfusion of plasma and platelets to the receiving hospital, to achieve a balanced transfusion over the patient’s journey.</td>
<td>The panel considered there to be insufficient evidence to make strong recommendations on balanced transfusion and the use of plasma in the prehospital and retrieval setting. Although there was general agreement that a balanced transfusion approach, as outlined in the Ontario consensus document on in-hospital major hemorrhage protocols,14 is likely beneficial, the panel agreed that an attempt to standardize such an approach in the prehospital and retrieval setting was beyond the scope of this document. The panel considered the results of the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial65 to show no difference in outcomes between a ratio of RBCs to plasma of 1:1 and 2:1.</td>
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<tr>
<td>7.3 Crystalloids and vasopressor/inotrope infusions should be used to treat hemorrhagic shock only if there is diagnosed or suspected concurrent cardiac impairment or neurogenic shock, or in a peri-arrest situation, or where blood components and products are not available or have been depleted.</td>
<td>Similar to the rationale for statement 4.6, the panel largely agreed with the clinical arguments supporting this statement65 but considered it to be beyond the scope of this document.</td>
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Note: RBC = red blood cell.
experts, particularly between patient-facing clinicians and transfusion specialists, as well as the importance of striking a balance between specific and flexible guidance statements.

The importance of dialogue among subject experts is reflected in several statements that found consensus only after the panel discussion. In particular, statements in domain 4 did not achieve consensus (or, in 1 case, rejection) until round 3. Transfusion medicine experts were able to outline the current estimates of the risk of Rh(D) sensitization, which was considerably lower than many patient-facing clinicians had assumed. On the other hand, logistical considerations, the higher proportion of patients of child-bearing potential receiving OHT in some participants’ CCTOs, and the higher risk of errors in the critical care transport setting compared to in-hospital practice resulted in agreement to primarily recommend O Rh(D) negative RBCs for CCTOs. Other important discussion points during the panel meeting were the limited availability of plasma — which contrasted with a desire by many patient-facing clinicians to stock blood components and products that could provide clotting factors and volume — and the consideration of alternatives to plasma, such as prothrombin complex concentrate and fibrinogen.

Statement 3.1, regarding the indication to commence OHT, can be seen as an example of the panel’s attempt to balance specific guidance with flexibility. Although there are multiple scores and algorithms to predict the requirement for massive transfusion for patients with trauma in the emergency department, none of the current methods to decide on which patients benefit from early transfusion in trauma achieve particularly high specificity or sensitivity. In addition, most of these scores have not been validated in the prehospital setting or in nontraumatic causes of major hemorrhage. The authors of a recent systematic review on the topic concluded that the process to trigger major hemorrhage protocols should be “individualized to hospital resources and skill set to aid clinical judgment.” This conclusion holds particular truth in the context of OHT in the setting of the unique geographic challenges faced by CCTOs in Canada. The patient population requiring OHT might be as diverse as a patient with trauma transported via a 30-minute flight from the scene of an accident to the nearest trauma centre, a patient with a perioperative major hemorrhage in a smaller hospital requiring a 90-minute interfacility transfer to the nearest tertiary care centre, or a patient with postpartum hemorrhage in a remote nursing station with no access to blood products or laboratory testing, and transport time exceeding 2 hours. We believe that this expert consensus document can help to overcome such challenges through a nationwide approach to OHT protocols that provides specific guidance while taking into account the variability in geography, patient factors, in-hospital and prehospital blood product availability, and other available resources.

Regarding the statements of domain 4 (types of blood components and products), currently there is a lack of solid evidence to support strong recommendations. However, research in this field is developing at a steady pace. Although we attempted to incorporate a level of flexibility to accommodate this limitation, this guidance document will need to be reviewed and updated in the future, in keeping with statement 1.5. For example, the Prehospital Lyophilized Plasma (PREHOP-PLYO) trial, comparing OHT of lyophilized plasma to normal saline in patients with trauma, was published shortly after we completed our Delphi rounds. However, given the small sample (150 patients) and the current unavailability of lyophilized plasma in Canada, the results of that trial have no immediate impact on this guidance document. Appendix 2 (available at www.cmajopen.ca/content/11/3/E546/suppl/DC1) provides an overview of ongoing trials that will provide relevant results over the coming years.

Importantly, we consider this document a starting point rather than an end product in the process of ensuring consistent and equitable access to blood components and products for all patients, irrespective of geographic location. Although outside the scope of this project, we have created a national collaboration and OHT working group with all Canadian CCTOs to assure that processes are aligned as much as possible across the Canadian provinces, that emerging evidence and new technology are reviewed in a timely and efficient manner, and that quality-improvement measures are shared across organizations. This collaboration will also ideally include a pan-Canadian OHT registry with consistent data entry from all participating CCTOs for quality assurance and future research projects. This registry will allow us to measure adherence to these recommendations by Canadian CCTOs over the coming years.

Limitations

Our modified RAND Delphi study achieved representation from major relevant clinical specialties and a wide geographic distribution. However, we were not able to recruit clinicians from every Canadian province, and there was a lack of representation from obstetricians and patient representatives. As with any self-selecting group of experts, there is the risk of recruiting only participants with similar opinions. Based on participants’ comments during the survey rounds and panel discussion, the study team was reassured that a wide range of opinion was captured during the study process. Although direct participation of patient representatives would have been challenging given the very specific focus of the study, we could have involved patient and public representatives in the planning stages of the research. Finally, no pediatric specialists participated in this research, and we did not provide any specific guidance on the pediatric population. Although many of the principles in the document can be applied to pediatric patients, we recommend involving local pediatric specialists when creating OHT guidelines for this population.

Conclusion

This nationwide consensus document covers a wide range of important domains in the development of OHT protocols. It should support CCTOs in establishing and standardizing OHT, to ensure efficient and equitable use of this valuable resource.

Conclusion
References


Competing interests: Brodie Nolan reports research funding from Canadian Blood Services and Physicians’ Services Incorporated Foundation. Andrew Shih reports payments for consulting on educational materials in relation to bleeding management from Octapharma Canada and payments for advisory board participation in relation to clotting factor concentrates from CSL Behring. He has received speaker honoraria from Octapharma Canada and CSL Behring. Octapharma Canada reimbursed travel expenses for attending a meeting for the FARES-II trial comparing clotting factor concentrates to plasma in cardiac surgery. He is vice-chair of the National Advisory Committee on Blood and Blood Products. No other competing interests were declared.

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Data sharing: Anonymized data can be shared on reasonable request by contacting the corresponding author.

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