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Association for the Advancement of Blood & Biotherapies

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To Whom It May Concern:

The Association for the Advancement of Blood & Biotherapies (AABB) appreciates the opportunity to provide comments in response to the Agency for Healthcare Research and Quality's Key Questions for Pre-Hospital EMS Blood Transfusion.

AABB is an international, not-for-profit association representing institutions and individuals involved in transfusion medicine and biotherapies. The association is committed to "improving lives by making transfusion medicine and biotherapies safe, available and effective worldwide." AABB works toward this vision by developing and delivering standards, accreditation, and educational programs that optimize patient and donor care and safety. AABB individual membership includes physicians, nurses, scientists, researchers, administrators, medical laboratory scientists and technologists, and other health care providers.

Key Question 1: What are the comparative benefits and harms of low-titer group O whole blood transfusion compared with component blood therapy transfusion for patients requiring prehospital hemostatic resuscitation?

Prehospital blood transfusions may improve patients' outcomes. Currently, there are different perspectives among subject matter experts regarding the comparative benefits and harms of low-titer group O whole blood transfusion versus component blood therapy transfusion for patients requiring prehospital hemostatic resuscitation. Ongoing studies are investigating this issue. Additional research and comprehensive data are needed to fully evaluate these critical interventions.

Key Question 2: What are the comparative benefits and harms of low-titer group O whole blood transfusion compared with fluid resuscitation for patients requiring prehospital hemostatic resuscitation?

There is evidence that pre-hospital blood transfusions are lifesaving interventions. These transfusions, whether in the form of low-titer O whole blood or component blood therapy, are generally more beneficial than isotonic fluid alone. Isotonic fluids may dilute clotting factors and red blood cells, potentially worsening outcomes. Whole blood transfusions may provide better hemostatic resuscitation by preserving clotting factors and oxygen-carrying capacity.

For available randomized trial data there are study design characteristics that contribute to heterogeneity (e.g. a mixed comparator of crystalloid and component therapy) or indirectness for the specific question asked above.

Question 3: What are the comparative benefits and harms of component blood therapy transfusion compared with fluid resuscitation for patients requiring prehospital hemostatic resuscitation?

There is strong evidence that pre-hospital blood transfusions are lifesaving interventions. Component blood therapy, like whole blood transfusions, is generally more effective than isotonic fluid resuscitation alone. Isotonic fluids can dilute blood components, potentially leading to coagulopathy and worsening outcomes. Component therapy, by providing targeted transfusion of red blood cells, plasma, and platelets, may better support hemostasis and oxygen delivery.

Multiple randomized trials have compared prehospital component therapy with fluid resuscitation. There is heterogeneity in the specific components in the study intervention arms. For example, there are trials that have used plasma, freeze dried plasma, and RBCs and freeze dried plasma, respectively, as the intervention.

Question 4: What are the comparative benefits and harms of different protocols for the three hemostatic resuscitation interventions (low-titer group O whole blood, component blood therapy, fluid resuscitation) for patients requiring prehospital hemostatic resuscitation?

Prehospital blood transfusions may improve patients' outcomes. However, there are varying perspectives among subject matter experts regarding the comparative benefits and harms of low-titer group O whole blood transfusion versus component blood therapy transfusion for patients requiring prehospital hemostatic resuscitation, especially in certain patient populations, such as patients with current or future child-bearing potential. Ongoing studies aim to clarify these differences in both adults and pediatric trauma populations. Additional research and comprehensive data are needed to fully evaluate these critical interventions.

Key Question 5: What specific areas of future research are essential for closing existing evidence gaps surrounding prehospital hemostatic resuscitation and prehospital blood product transfusion? Consideration should be given to the formulation of precise scientific questions, optimal study design, targeted study populations, and the exploration of various blood transfusion intervention protocols.

There is evidence to support blood transfusions in the pre-hospital setting. As indicated above, additional research and data regarding prehospital blood transfusions are needed to fully define the risks and benefits of the therapy options to different patient populations and to the continued availability of the blood supply.

A comprehensive gap analysis should be conducted to (1) identify research questions, (2) assess EMS capabilities and operational limitations; (3) define the scope of training needed for EMS personnel to safely administer blood in pre-hospital settings, (4) understand blood collectors' operational limitations that may impact the availability of different interventions; (5) evaluate the potential impact of pre-hospital transfusion programs on the hospitals' inventories, which are essential to patient care; and (6) study blood wastage and methods to limit it.

Contextual Question 1: What are the implementation facilitators and barriers of effective prehospital blood product transfusion programs? Distinguishing factors may include emergency medical services agency costs, emergency medical services agency reimbursement, cost effectiveness, blood product maintenance and logistics, partnerships with blood banks, medical oversight including real-time medical direction, and diagnostic tools.

Barriers that limit the implementation of effective prehospital blood transfusion programs include: (1) reimbursement policies and bundled payment rates that are far too low to accommodate the costs of providing blood transfusions; (2) the need for standards and education related to pre-hospital blood transfusions, which is currently being addressed by AABB; and (3) operational challenges.

Reimbursement Policies and Payment Rates

Flawed reimbursement policies and inadequate payment rates limit the widespread availability of pre-hospital blood transfusions. Medicare currently reimburses ambulance services through bundled payments under a fee schedule, which vary in amount based on service level. The payment rates for the existing service levels are far too low to accommodate the cost of providing blood transfusions.

The Centers for Medicare & Medicaid Services (CMS) can facilitate the implementation of effective pre-hospital blood transfusion programs by establishing a service delivery and reimbursement model that incorporates pre-hospital blood transfusions into the emergency medical system. Expanding patients' access to pre-hospital blood transfusions will enable ambulance care teams to better address emergency health care needs in a timely manner, which will improve patients' outcomes and reduce costs to the medical system.

CMS should consider a model that includes a pre-hospital blood product add-on payment that incorporates the costs associated with procuring, storing, and administering blood transfusions. Activities may include, but are not limited to, procuring blood products from entities such as blood collection establishments and hospitals, storing blood products in accordance with safety standards, and transfusing the blood safely and effectively.

Comprehensive reimbursement policies and sufficient payment rates may improve health care quality and lower costs to the Medicare system by reducing hemorrhagic deaths and long-term hospitalizations following ambulance transport. The model can enhance the quality of care provided to Medicare beneficiaries by ensuring that they receive the appropriate level of care that is delivered safely at the right time and place.

Standards and Education Related to Pre-Hospital Blood Transfusions

Throughout the United States, most of the blood supply is collected and transfused by facilities that are accredited by the Association for the Advancement of Blood and Biotherapies (AABB). These AABB-accredited facilities demonstrate high levels of quality and safety by adhering to AABB Standards, which combine internationally accepted quality management requirements

with relevant technical requirements for blood collection establishments, blood banks, and transfusion medicine services.

One of the current challenges with implementing an effective prehospital transfusion program will be mitigated when AABB's Standards for Out-of-Hospital and Prehospital Administration Transfusion Services become available in early 2025 to address all aspects of pre-hospital blood transfusion. AABB recently released for public comment the proposed Standards as part of a robust development process that permits non-members to join AABB members in shaping these important Standards. Examples of Standards that support safe pre-hospital blood transfusions include requirements related to process control, the inspection of blood immediately before transfusion, administration of blood, the use of uncrossmatched blood, and recordkeeping necessary to ensure safety through tracing and tracking of every blood component from donor to patient.

Once finalized, the AABB Standards will lead to the first ever accreditation program for Out-of-Hospital and Prehospital Administration Transfusion Services. These new Standards and the accompanying education programs will be critical resources for emergency management services that wish to implement safe and effective pre-hospital blood transfusion programs. Additionally, the related accreditation program will improve patient care and safety by enhancing the quality of pre-hospital transfusion programs assessed by AABB on a two-year cycle.

Operational Limitations

Blood collectors need to be positioned to support pre-hospital blood transfusion programs. Some operational challenges may include: (1) donor recruitment; (2) manufacturing; (3) supply chain; and (3) the ability to meet demand.

- **Donor Support:** Challenging trends related to blood donor recruitment and retention will impact blood collectors' ability to support pre-hospital blood transfusion programs. For example, over the past 10 years, there has been a 39% decline in younger donors under 30. Blood collectors will need to successfully recruit new Group O donors, who are critical to ensuring that whole blood or red blood cell units are available for pre-hospital transfusion programs. Demand for group O universal type blood by hospitals already outpaces supply most of the time. Thus, blood collectors will incur donor recruitment and operational costs to support pre-hospital blood transfusion programs.
- **Manufacturing:** Manufacturing leukoreduced low titer group O whole blood must be done within 8 hours of collection, which significantly limits the pool of group O donors from which the product can be manufactured. The donors have other restrictions, such as aspirin free, low titer and TRALI safe, placing further constraints on eligible group O donors.
- **Supply Chain:** Blood collection establishments currently rely on a limited number of blood bags to support whole blood collections. There is limited availability of these bags, which restricts the number of potential whole blood collections.
- **Demand:** Blood collection establishments are concerned about being able to meet the increased demand for low-titer group O whole blood - which has the potential to impact blood availability for hospitals. A successful pre-hospital blood transfusion program will require collaboration between blood collectors, hospitals, and local emergency

management services providers. Additionally, it will require robust community engagement to support donor recruitment and retention.

General Comments in Response to the Key Questions

Some published trials have a mixed comparator that may not fit within the paradigm of these proposed questions. For example, a study site may impact the comparison of the intervention of low-titer O whole blood (LTOWB) with components and saline. Additionally, there is variation as to which components were used in trials evaluating prehospital transfusion. This may lead to important heterogeneity and could make meta-analysis challenging. Nevertheless, a rigorous systematic review would likely be useful to summarize current evidence and clearly identify existing knowledge gaps. Additionally, because there are ongoing trials, there may be value to considering a living systematic review that can be updated as more evidence becomes available.

It is important to analyze the potential effect of modifiers. For studies with multiple hemostatic prehospital interventions, it may be appropriate and feasible to conduct subgroup analyses, a network meta-analysis, or sensitivity analyses. Subgroup analyses based on prehospital transit times or rural versus urban location may be of value since there could be differential effects by subpopulation. Additionally, it is not clear whether adverse event rates could be synthesized across studies, but this may be useful even though it is anticipated that rates will be low.

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Thank you for the opportunity to contribute feedback to help inform this important effort. If you have any questions or need additional information, please contact me at 301-215-6554 or lmstone@aabb.org.

Sincerely,

[*Signature on file*]

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