HHS Public Access

Author manuscript

J Trauma Acute Care Surg. Author manuscript; available in PMC 2022 August 01.

Published in final edited form as:

J Trauma Acute Care Surg. 2021 August 01; 91(2): S19–S25. doi:10.1097/TA.0000000000003300.

Recommended Primary Outcomes for Clinical Trials Evaluating Hemostatic Blood Products and Agents in Patients with Bleeding: Proceedings of a National Heart Lung and Blood Institute and United States Department of Defense Consensus Conference

Philip C. Spinella, MD[1], **Nahed El Kassar, MD, PhD**[2], **Andrew P. Cap, MD, PhD**[3], **Andrei L. Kindzelski, MD, PhD**[2], **Christopher S. Almond, MD**[3], **Alan Barkun, MD, MSc**[4], **Terry B. Gernsheimer, MD**[5], **Joshua N. Goldstein, MD, PhD**[6], **John B. Holcomb, MD**[7], **Alfonso Iorio, MD, PhD**[8], **Dennis M. Jensen, MD**[9], **Nigel S. Key, MB, ChB**[10], **Jerrold H. Levy, MD**[11], **Stephan A. Mayer, MD**[12], **Ernest E. Moore, MD**[13], **Simon J. Stanworth, MD, DPhil**[14], **Roger J. Lewis, MD, PhD**[15,16], **Marie E. Steiner, MD, MS**[17], **Hemostasis Trials Outcomes Working Group**[†]

[1]Division of Critical Care, Department of Pediatrics, Washington University School of Medicine, St. Louis, MO, USA

[2]National Heart Lung and Blood Institute, NIH, Bethesda, MD

[3]US Army Institute of Surgical Research, Ft Sam Houston, TX

[4]Division of Gastroenterology, McGill University and the McGill University Health Centre Montréal, Québec, Canada

[5]Division of Hematology, University of Washington, Seattle WA 98195 USA

[6]Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

[7]Department of Surgery, Center for Injury Science, Division of Acute Care Surgery, University of Alabama at Birmingham, Birmingham, AL

[8]Division of Hematology and Thromboembolism, Department of Medicine and Department of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton Ontario L8S 4K Canada

[9]Division of Gastroenterology, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, CA 90095

[10]Division of Hematology and Blood Research Center, Department of Medicine, University of North Carolina, Chapel Hill, NC 27599

[11]Department of Anesthesiology and Critical Care, Duke University Medical Center, Durham, NC 27710 USA

[†]A complete list of conflicts of interest and working group members is provided in the Supplementary Appendix.

Corresponding Author Philip C. Spinella, MD, 10th floor NWT, box 8100, 1 Children's Place, St Louis, MO 63110, Office: (314) 286 0858, pspinella@wustl.edu.

[12]Departments of Neurology and Neurosurgery, Westchester Medical Center, New York Medical College, Valhalla NY 10595

[13]Ernest E Moore Shock Trauma Center at Denver Health, Department of Surgery, University of Colorado Denver, Denver, Colorado 80204 USA

[14]Oxford University, Oxford, United Kingdom, The John Radcliffe Hospital, Oxford, GBR NHSBT, Oxford, United Kingdom

[15]Berry Consultants LLC, Austin TX 78746

[16]Department of Emergency Medicine, David Geffen School of Medicine at UCLA, Los Angeles California 90095 USA

[17]Department of Pediatrics, Division of Pediatric Hematology and Oncology, Division of Pediatric Critical Care Medicine, University of Minnesota Medical School, Minneapolis, MN 55455 USA

Introduction

The treatment of conditions associated with bleeding is a common challenge in clinical medicine, and, accordingly, the focus of a substantial volume of clinical research. Interventions may target supportive care to manage the bleeding and prevent complications, or those aimed at controlling the bleeding source.[1] Across multiple clinical settings, there is an increased risk of morbidity and mortality if bleeding occurs at a rapid rate, results in copious volume loss, or occurs in a critical organ system. The importance of timelines is reiterated by data following traumatic injury which indicates the median time to death due to hemorrhage is 2 hr.[2] Alternatively, in the setting of intracranial hemorrhage, mortality and residual disability are highly correlated with the volume of the lesion.[3, 4]

High-quality evidence guiding optimal transfusion and other supportive therapies to reduce bleeding are needed to improve outcomes for patients either with severe bleeding or hemostatic disorders that are associated with poor outcomes. Alongside challenges in performing high-quality clinical trials in patient populations that are at risk of bleeding or who are actively bleeding, the interpretation of research evaluating hemostatic agents has been limited by inconsistency in the choice of primary trial outcomes. This lack of standardization of primary endpoints or outcomes decreases the ability of clinicians to assess the validity of endpoints, compare research results across studies, impairs meta-analytic efforts, and ultimately delays the translation of research results into clinical practice.

To address this challenge, an international panel of experts was convened by the National Heart Lung and Blood Institute (NHLBI) and the United States (US) Department of Defense (DoD) on September 23rd and 24th 2019 to develop expert opinion, consensus-based recommendations for primary clinical trial outcomes for pivotal trials in pediatric and adult patients with six categories in various clinical settings. This publication documents the conference proceedings from the workshop funded by the National Heart Lung and Blood Institute (NHLBI) and the United States (US) Department of Defense (DoD) that consolidated expert opinion regarding clinically meaningful outcomes across a wide range

of disciplines to provide guidance for outcomes of future trials of hemostatic products and agents for patients with active bleeding.

Methods

An international working-group of experts in the clinical treatment of bleeding, hemostasis research, and clinical research methodology was assembled. Members were identified based on current and prior research activities, relevant expertise, and roles within relevant organizations to ensure diversity of perspectives across clinical and scientific domains. The executive committee of the workshop in collaboration with the subgroup leaders finalized the list of members for each subgroup. Members chosen were predominantly from the US with a few exceptions due to the limitation in funding for travel. The members of the working group and their affiliations are listed in the Appendix.

The working group was organized into six subgroups, each addressing the assessment of bleeding in a clinical setting: 1) traumatic injury; 2) intracranial hemorrhage; 3) cardiac surgery (including mechanical circulatory support); 4) gastrointestinal hemorrhage; 5) inherited bleeding disorders; and 6) hypoproliferative thrombocytopenia. Each subgroup was balanced to include a breadth of clinical perspectives, clinical and translational research expertise, clinical trialists, and at least one epidemiologist or statistician.

The recommendations were intended to establish valid, clinically relevant outcomes for late-stage human trials evaluating hemostatic interventions, devices, or agents and to support alignment among investigators, sponsors, and regulators. The scope of the recommendations was limited to primary outcomes in pivotal clinical trials in adults. Some subgroups included pediatric recommendations.

For each bleeding category, working-group members considered prior experience with previously published clinical trial outcomes in their respective fields including strengths and weaknesses of each possible outcome. Particular note was taken of prior work in which the discrepancy between regulatory guidance and human physiology complicated the choice of primary endpoints and contributed to difficulty in clinical interpretation of results.[5] The selection of primary outcomes was guided by expected or demonstrated sensitivity to beneficial treatment effects, clinical and logistical feasibility, and broad applicability within each bleeding category. Most importantly, the primary outcomes were chosen based on their merits as clinically meaningful endpoints in the opinion of the expert panel. As a result, formal literature searches for each subgroup were not performed since clinical relevance or meaningfulness is qualitative and not quantitative. A literature search of what outcomes have been used before would not have achieved the goal of developing consensus statement for recommendations of outcomes that are of clinical value. Each subgroup did reference the literature to provide biologic rationale for expert opinion recommendations when available.

Each subgroup's recommendations were developed based on structured discussions through a series of teleconferences over 12 months and augmented with in-person meetings, to create preliminary recommendations for outcomes to consider. The subgroups refined these recommendations based on additional literature review, consideration of clinical relevance,

feasibility, and biologic rationale, to create a list of outcomes appropriate for primary and secondary trial outcomes for pivotal clinical trials.

In September 2019, members of the working group met in Bethesda, MD, along with representatives of funding and regulatory agencies and additional meeting registrants, including members of industry, to discuss and finalize recommendations. During the two-day meeting recommendations from all subgroups were discussed and modified. The simultaneous integration of multiple endpoints in a single analysis, using innovative analytic techniques were considered as well (e.g., a gatekeeping approach with multiple endpoints).[6] Finalization of the recommendations for outcomes occurred in the symposium breakout sessions, followed by a public review by all attendees. All expert opinion recommendations were voted on by subgroup members with at least 85% indicating agreement.

Summary of Recommendations and Rationale

Synopses of the recommendations for primary clinical trial outcomes and the associated rationales are provided below and summarized in Table 1.

Traumatic Injury

The trauma subgroup focused on hemostatic outcomes of clinical trials for patients with life-threatening bleeding excluding isolated traumatic brain injury (TBI) and burns. Historically, 30-day survival has been the standard primary outcome for all injury trials,[7, 8] but the biological rationale for this arbitrary endpoint is not consistent with the physiological effects of effective hemostatic interventions.[9] Assessing mortality at later time points results in more deaths occurring in both the experimental and control groups, for reasons other than lack of hemostasis, more commonly due to TBI and inflammatory complications.[2, 9] Early, effective hemostatic interventions may result in significant differences within hours of injury, however, the same absolute mortality difference that was statistically significant at 3 to 6 hours, may lose significance at 24 hours or 30 days due to the decrease in statistical power and dilution of the target outcome (hemorrhagic deaths) by other death causes not directly treatable by hemostatic interventions (e.g., TBI, multiple organ failure).[5, 9, 10]

For patients with traumatic injury, a 3 to 6-hour all-cause mortality is recommended as a primary outcome for hemostatic interventions, with robust evaluation of late safety-related outcomes [11]. This recommendation is supported by multiple RCTs and large observational studies that indicate that the vast majority of hemorrhage-related fatalities occur within 3 to 6 hours after injury.[2, 5 12–20] The recommendation of using all-cause mortality is justified by the known difficulties in objectively ascribing a primary cause of death in patients with combined hemorrhage and TBI. While conceptually appealing, a standard, objective definition of hemorrhagic only death may be impossible given that its major competing risk, TBI, occurs along with hemorrhage up to 38% of the time.[5, 9] Exclusion of isolated TBI patients based on physical exam alone may be difficult, if not impossible, before randomization, especially in the pre-hospital and very early hospital setting.[2, 5, 9, 12, 13, 21–23]

In children with life-threatening traumatic hemorrhage, a primary outcome of death at either 6 or 24 hours is recommended [11]. In a recent prospective observational study of 208 children younger than 16 years (median 10 years), the median time to death from hemorrhage was 2.9 hours (personal communication, Spinella PC, December 11, 2019). The percent of the deaths that occurred from hemorrhage was 70% by 6 hours and 90% by 24 hours. At both 6 and 24 hours after hospital admission, 60% of the deaths were due to hemorrhage, with the other 40% from CNS injury. Further work is needed to define the primary cause and timing of death based on age groups (18–12, 11–6, and < 6 years).

The FDA has agreed with both above adult and pediatric recommended primary outcomes in recently submitted pre-IND applications for trials comparing whole blood to blood components in both populations (personal communication, Holcomb JB and Spinella PC, March 29, 2021).

Intracranial Hemorrhage

The intracranial hemorrhage subgroup focused on hemostatic outcomes for clinical trials in patients with spontaneous and traumatic intracranial hemorrhage (ICH). ICH is the most devastating form of bleeding that can occur in the human body, with the highest rate of mortality and residual disability.[3]

Conventional outcomes for hemostatic therapies for intracranial bleeding to date have focused on measurements of hematoma volume – almost universally the change in hemorrhage volume at 24 hours – and global functional outcome at 90 days. Fortunately, intracranial bleeding is easy to quantify with extreme precision using computed tomographic (CT) scanning, allowing for accurate and valid measurement of blood volume to the nearest milliliter.[24, 25]

For patients with spontaneous or traumatic intracranial hemorrhage the recommended optimal primary outcome is a global patient-centered clinical outcome scale measured between 30–180 days after the event. For studies that may lack sufficient power for this, a combined clinical and radiographic endpoint (such as poor outcome associated with ICH expansion) is an acceptable second choice. Preferred outcome scales include Modified Rankin Scale, Extended Glasgow Outcome Scale, or a similar patient-centered outcome measure that is relevant for the disease entity. The high degree of correlation between final hemorrhage volume, mortality, and functional outcome makes hemorrhage volume or growth a reasonable endpoint for trials of hemostatic therapies when there is insufficient power to use patient-centered outcome scales in the primary outcome.[24–28]

Cardiac Surgery/Mechanical Circulatory Support

The cardiac surgery subgroup considered primary outcomes for clinical trials of hemostatic therapies for bleeding associated with cardiac surgery and with the use of mechanical circulatory support (MCS), primarily extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VADs). For MCS, however, it was noted that both hemorrhage and thrombotic events are clinically important with the risk of thromboembolic events limiting the use of some hemostatic treatments; the MCS subgroup thus also considered

thromboembolic endpoints. The lack of consensus definitions for clinically important bleeding and thrombosis makes optimal endpoints for clinical trials of hemostatic strategies in cardiac surgery and MCS challenging.

Conventional primary endpoints for cardiac surgery trials include the volume of allogeneic transfusions,[29] time to anastomotic hemostasis,[30] postoperative drainage tube/chest tube output,[31] the need for reoperation,[31] or combinations of these metrics (i.e., bleeding scores).[32, 33] Limitations of these approaches, with attendant challenges in interpretation, include heterogeneity in bleeding risk among different surgical procedures and variability in surgical technique, thresholds for reoperation, and transfusion practices.

For patients with bleeding secondary to cardiothoracic surgery, a primary efficacy endpoint of total allogeneic blood products (units vs ml/kg) administered intraoperatively and postoperatively to day 5 or hospital discharge is recommended. To control extraneous variation across centers and/or providers, a pre-specified bleeding management protocol/algorithm is critical.[29, 34–36]

Conventional endpoints for ECMO/VAD trials are derived from INTERMACS,[37] ELSO,[38] and other registries' definitions. Previously utilized endpoints are variable and include survival, transfusion requirements, clinically important bleeding, stroke, and thrombotic complications.[39, 40] Importantly, the optimal hemostatic strategy in the setting of MCS requires a balance between the risks of hemorrhage and thrombosis; any primary outcome that fails to take both into account risks yielding clinically inappropriate results.

For clinical trials of patients on ECMO, the recommended primary outcome is a 5-point ordinal score of both thrombosis and bleeding severity adapted from the consensus definitions in Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The score should be applied during the initial 10 days of treatment, as patient attrition often occurs over this period; the initial resuscitation phase (24–48 hours) and late maintenance phase (>24–48 hours) should also be evaluated.. Existing ELSO definitions of bleeding or thrombosis should serve as individual safety points.[37]

For VAD studies, the recommended primary endpoint is freedom from disabling stroke (CTCAE ≥ Gr3) through 180 days. Assessments should be obtained through Day 2, < 30 days and ≥ 30 days. Recommended primary safety endpoints include thrombosis and bleeding complications defined by INTERMACS.[37] Thrombotic/bleeding rates may vary over time, so both early (<30 days) and late rates (≥30 days) should be assessed. The 5-point ordinal bleeding/thrombosis scale proposed for ECMO is also feasible to validate in the VAD population.

Gastrointestinal Hemorrhage

Endpoints used in the assessment of treatments for gastrointestinal hemorrhage have included initial or immediate hemostasis based on visual examination. New technologies (e.g., Doppler probe) may be useful in the future to better define when treatments have achieved more durable initial hemostasis at index endoscopy.[41] Definitions for these have varied or are based on technology with limited availability. Furthermore, these immediate

endpoints only partially determine subsequent longer-term outcomes, such as patient morbidity and mortality.

The primary outcome we recommended for all types of acute GI bleeding (UGI, small bowel, & colon) was a composite outcome of the following: further bleeding after randomization leading to RBC transfusion, urgent intervention (repeat endoscopy; surgery or interventional radiology) or death. The time period to assess this endpoint was suggested to be 30 days. Persistent bleeding may be defined as the inability to achieve hemostasis after 3 to 5 minutes of observation following what is felt by the operator to be the optimal attempt at endoscopic hemostasis based on visual cues using the studied modality. A proposed consensus definition for rebleeding is to include: 1) the post-intervention development of hematemesis or bloody nasogastric (NG) aspirate > 6 hours after endoscopy, 2) melena after normalization of stool color,3) hematochezia after normalization of stool color or after melena, 4) the development of tachycardia (heart rate ≥ 110 beats per minute) or hypotension (systolic blood pressure ≤ 90 mm Hg) after ≥ 1 hour of hemodynamic stability (i.e. no tachycardia or hypotension) in the absence of an alternative explanation, 5) a hemoglobin drop of ≥ 2 g /dl after two consecutive stable hemoglobin values (< 0.5 g /dl decrease) ≥ 3 hours apart, 6) the presence of tachycardia or hypotension that does not resolve within 8 hours after index endoscopy despite appropriate hemodynamic resuscitation in the absence of an alternative explanation and associated with persistent melena or hematochezia, and 7) a persistently dropping hemoglobin of > 3 g /dl in 24 hours associated with persistent melena or hematochezia.[42] Mortality is chosen as part of a composite outcome measure owing to its clinical importance and because its direction and incremental decrease evolve with therapy in the same general direction and amplitude (in very general terms) as those of persistent bleeding and rebleeding. The time horizon to be covered by all bleeding-related mortality needs to take into consideration the varying natural history of GI bleeding etiologies, especially non-variceal (30 days) [42, 43] versus variceal (usually measured in 42-day cumulative mortality rates).[44]

Inherited Bleeding Disorders

The subgroup considered outcomes for patients with hemophilia as a model since they had been comprehensively studied. They are usually grouped into 6 domains: 1) bleeding and hemostasis; 2) joint health; 3) co-morbidities and mortality; 4) overall physical functioning and participation; 5) health-related quality of life (HRQoL); and 6) cost and resource use.[45, 46]

For the treatment of acute bleeding or for the prevention of surgical bleeding the recommended primary outcome is a composite scoring system[45, 47] incorporating the number of infusions required, rating on a clinical scale, and need for re-intervention [48]. These outcomes have been successfully used to evaluate replacement therapy over several decades and recommended by the International Society of Thrombosis and Hemostasis Scientific Subcommittee on Factor VIII and IX.[47]

For the prevention of bleeding events the recommended primary outcome is an annualized bleeding rate, quantifying the number of bleeding events over a period

of time.[45] There is a body of evidence linking the bleeding rate to the progression of joint disease as measured by joint scores.[48, 49]

For the long term and overall impact of bleeding, which is the ultimate goal in patients with inherited bleeding disorders, the recommended primary outcome is a composite of joint function (measured via an objective clinical scale or a patient reported functional score),[50] chronic pain (measured via a validated scale),[51] and HRQoL (both generic and specific)[46] as proposed in a core outcome set for hemophilia gene therapy trials.[48, 52]

Hypoproliferative Thrombocytopenia

Bleeding is common in patients with bone marrow failure, and an important risk factor is severe thrombocytopenia; the strength of this relationship might vary depending on the clinical situation.[53, 54] Conventional endpoints for hemostatic therapies for hypoproliferative thrombocytopenia have included platelet count increments as a surrogate marker of bleeding risk and scoring systems for clinical bleeding. **For patients with bleeding secondary to hypoproliferative thrombocytopenia, the recommended primary outcome for trials that examine the efficacy of blood products or hemostatic agents is the WHO Bleeding Assessment Score**. Specifically, we recommend a WHO Grade of 2 or greater as a primary outcome in clinical trials of platelet threshold and efficacy.[55–57]

Limitations to the use of the WHO Bleeding Assessment Score for data collection and analysis of bleeding have been recognized.[58, 59] WHO Grade 2 bleeding, the most common grade, includes bleeding into the skin which is difficult to quantify and daily changes may be subjective, whereas Grade 2 mucosal bleeding may be more readily evaluated. Widespread endothelial and mucosal damage occur in patients with hematologic malignancy as a result of disease, infection, and therapy. Whether visible mucosal and cutaneous bleeding represent “window” into vascular and hemostatic health or merely the manifestation of mild and clinically insignificant blood loss is not known. The extent or severity of microvascular bleeding actually may not be fully captured by examination of the skin or mouth. As a composite outcome, WHO Grade 2 or greater bleeding includes Grades 3 (gross blood loss) and Grade 4 (debilitating blood loss), but the incidences of these clinically more meaningful events are low. There is uncertainty whether Grade 2 bleeding is predictive of more severe forms of Grades 3 and 4 bleeding, and whether isolated Grade 3 and 4 bleeding can occur without notable Grade 2 bleeding.[60, 61]

Conclusions

Advancements in treatment for hemorrhage to improve patient outcomes, require high quality trials rigorously evaluating effects on valid, clinically relevant endpoints. Expert opinion from an international group of clinical experts and trialists has been leveraged to provide recommendations for primary outcomes for pivotal trials of hemostatic therapies. These recommendations attempt to harmonize the objectives of investigators, funding agencies, and regulatory agencies to facilitate the development and performance of high quality trials examining hemostatic blood products and agents in bleeding patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

References

1. Levy JH, Dutton RP, Hemphill JC 3rd, et al. Multidisciplinary approach to the challenge of hemostasis. Anesth Analg. Feb 1 2010;110(2):354–64. doi:doi: 10.1213/ANE.0b013e3181c84ba5 [PubMed: 20007735]
2. Tisherman SA, Schmicker RH, Brasel KJ, et al. Detailed description of all deaths in both the shock and traumatic brain injury hypertonic saline trials of the Resuscitation Outcomes Consortium. Ann Surg. Mar 2015;261(3):586–90. doi:10.1097/SLA.0000000000000837 [PubMed: 25072443]
3. Hemphill JC 3rd, Greenberg SM, Anderson CS, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. Jul 2015;46(7):2032–2060. doi:doi: 10.1161/STR.0000000000000069 [PubMed: 26022637]
4. Christoforidis GA, Slivka A, Mohammad Y, Karakasis C, Avutu B, Yang M. Size matters: hemorrhage volume as an objective measure to define significant intracranial hemorrhage associated with thrombolysis. Stroke. Jun 2007;38(6):1799–804. doi:10.1161/strokeaha.106.472282 [PubMed: 17463318]
5. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. Feb 3 2015;313(5):471–82. doi:10.1001/jama.2015.12 [PubMed: 25647203]
6. Yadav K, Lewis RJ. Gatekeeping strategies for avoiding false-positive results in clinical trials with many comparisons. JAMA. Oct 10 2017;318(14):1385–1386. doi:doi: 10.1001/jama.2017.13276 [PubMed: 29049572]
7. Carrico CJ, Holcomb JB, Chaudry IH, Pulse Trauma Work Group. Post Resuscitative and Initial Utility of Life Saving Efforts. Scientific priorities and strategic planning for resuscitation research and life saving therapy following traumatic injury: report of the PULSE Trauma Work Group. Acad Emerg Med. Jun 2002;9(6):621–626. doi:doi: 10.1111/j.1553-2712.2002.tb02303.x [PubMed: 12045079]
8. U.S. Food and Drug Administration, U.S. Department of Health and Human Services. CFR - Code of Federal Regulations 21CFR50.24. Available from: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.24. Accessed: 2019 Dec 27. Silver Spring, Maryland.
9. Fox EE, Holcomb JB, Wade CE, Bulger EM, Tilley BC, Proppr Study Group. Earlier endpoints are required for hemorrhagic shock trials among severely injured patients. Shock. May 2017;47(5):567–573. doi:doi: 10.1097/SHK.0000000000000788 [PubMed: 28207628]
10. Chang R, Kerby JD, Kalkwarf KJ, et al. Earlier time to hemostasis is associated with decreased mortality and rate of complications: Results from the Pragmatic Randomized Optimal Platelet and Plasma Ratio trial. J Trauma Acute Care Surg. Aug 2019;87(2):342–349. doi:10.1097/TA.0000000000002263 [PubMed: 31349348]
11. Holcomb JB, Moore EE, Sperry JL, et al. Evidence-Based and Clinically Relevant Outcomes for Hemorrhage Control Trauma Trials. Ann Surg. Mar 1 2021;273(3):395–401. doi:10.1097/SLA.0000000000004563 [PubMed: 33065652]
12. Sperry JL, Guyette FX, Brown JB, et al. Prehospital Plasma during Air Medical Transport in Trauma Patients at Risk for Hemorrhagic Shock. N Engl J Med. Jul 26 2018;379(4):315–326. doi:10.1056/NEJMoa1802345 [PubMed: 30044935]
13. Moore HB, Moore EE, Chapman MP, et al. Plasma-first resuscitation to treat haemorrhagic shock during emergency ground transportation in an urban area: a randomised trial. Lancet. Jul 28 2018;392(10144):283–291. doi:10.1016/S0140-6736(18)31553-8 [PubMed: 30032977]
14. Schreiber MA, Meier EN, Tisherman SA, et al. A controlled resuscitation strategy is feasible and safe in hypotensive trauma patients: results of a prospective randomized pilot trial. J Trauma Acute Care Surg. Apr 2015;78(4):687–95; discussion 695–7. doi:10.1097/TA.0000000000000600 [PubMed: 25807399]

15. CRASH-2 trial collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. Jul 3 2010;376(9734):23–32. doi:doi: 10.1016/S0140-6736(10)60835-5 [PubMed: 20554319]

16. Gonzalez E, Moore EE, Moore HB, et al. Goal-directed Hemostatic Resuscitation of Trauma-induced Coagulopathy: A Pragmatic Randomized Clinical Trial Comparing a Viscoelastic Assay to Conventional Coagulation Assays. Ann Surg. Jun 2016;263(6):1051–9. doi:10.1097/SLA.0000000000001608 [PubMed: 26720428]

17. Moore EE, Moore FA, Fabian TC, et al. Human polymerized hemoglobin for the treatment of hemorrhagic shock when blood is unavailable: the USA multicenter trial. J Am Coll Surg. Jan 2009;208(1):1–13. doi:10.1016/j.jamcollsurg.2008.09.023 [PubMed: 19228496]

18. Roberts I, Shakur H, Coats T, et al. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health Technol Assess. Mar 2013;17(10):1–79. doi:10.3310/hta17100

19. Bulger EM, May S, Kerby JD, et al. Out-of-hospital hypertonic resuscitation after traumatic hypovolemic shock: a randomized, placebo controlled trial. Ann Surg. Mar 2011;253(3):431–41. doi:10.1097/SLA.0b013e3181fcdb22 [PubMed: 21178763]

20. Hauser CJ, Boffard K, Dutton R, et al. Results of the CONTROL trial: efficacy and safety of recombinant activated Factor VII in the management of refractory traumatic hemorrhage. J Trauma. Sep 2010;69(3):489–500. doi:10.1097/TA.0b013e3181edf36e [PubMed: 20838118]

21. Brenner A, Arribas M, Cuzick J, et al. Outcome measures in clinical trials of treatments for acute severe haemorrhage. Trials. Oct 1 2018;19(1):533. doi:10.1186/s13063-018-2900-4 [PubMed: 30285839]

22. Del Junco DJ, Bulger EM, Fox EE, et al. Collider bias in trauma comparative effectiveness research: the stratification blues for systematic reviews. Injury. May 2015;46(5):775–80. doi:10.1016/j.injury.2015.01.043 [PubMed: 25766096]

23. del Junco DJ, Fox EE, Camp EA, Rahbar MH, Holcomb JB, Group PS. Seven deadly sins in trauma outcomes research: an epidemiologic post mortem for major causes of bias. J Trauma Acute Care Surg. Jul 2013;75(1 Suppl 1):S97–103. doi:10.1097/TA.0b013e318298b0a4 [PubMed: 23778519]

24. Zimmerman RD, Maldjian JA, Brun NC, Horvath B, Skolnick BE. Radiologic estimation of hematoma volume in intracerebral hemorrhage trial by CT scan. AJNR Am J Neuroradiol. Mar 2006;27(3):666–70. [PubMed: 16552014]

25. Broderick JP, Brott TG, Duldner JE, Tomsick T, Huster G. Volume of intracerebral hemorrhage. A powerful and easy-to-use predictor of 30-day mortality. Stroke. Jul 1993;24(7):987–93. doi:10.1161/01.str.24.7.987 [PubMed: 8322400]

26. Rost NS, Smith EE, Chang Y, et al. Prediction of functional outcome in patients with primary intracerebral hemorrhage: the FUNC score. Stroke. Aug 2008;39(8):2304–9. doi:10.1161/STROKEAHA.107.512202 [PubMed: 18556582]

27. Steiner T, Juvela S, Unterberg A, et al. European Stroke Organization guidelines for the management of intracranial aneurysms and subarachnoid haemorrhage. Cerebrovasc Dis. 2013;35(2):93–112. doi:doi: 10.1159/000346087 [PubMed: 23406828]

28. MRC CRASH Trial Collaborators, Perel P, Arango M, et al. Predicting outcome after traumatic brain injury: practical prognostic models based on large cohort of international patients. BMJ. Feb 23 2008;336(7641):425–9. doi:doi: 10.1136/bmj.39461.643438.25 [PubMed: 18270239]

29. Levy JH, Pifarre R, Schaff HV, et al. A multicenter, double-blind, placebo-controlled trial of aprotinin for reducing blood loss and the requirement for donor-blood transfusion in patients undergoing repeat coronary artery bypass grafting. Circulation. Oct 15 1995;92(8):2236–44. doi:10.1161/01.cir.92.8.2236 [PubMed: 7554207]

30. Khoynezhad A, DelaRosa J, Moon MR, et al. Facilitating hemostasis after proximal aortic surgery: results of The PROTECT Trial. Ann Thorac Surg. May 2018;105(5):1357–1364. doi:10.1016/j.athoracsur.2017.12.013 [PubMed: 29337125]

31. Colson PH, Gaudard P, Fellahi JL, et al. Active bleeding after cardiac surgery: a prospective observational multicenter study. PLoS One. 2016;11(9):e0162396. doi:doi:10.1371/journal.pone.0162396
32. Dyke C, Aronson S, Dietrich W, et al. Universal definition of perioperative bleeding in adult cardiac surgery. J Thorac Cardiovasc Surg. May 2014;147(5):1458–1463.e1. doi:doi: 10.1016/j.jtcvs.2013.10.070
33. Mariscalco G, Gherli R, Ahmed AB, et al. Validation of the European Multicenter Study on Coronary Artery Bypass Grafting (E-CABG) Bleeding Severity Definition. Ann Thorac Surg. May 2016;101(5):1782–8. doi:10.1016/j.athoracsur.2015.10.028 [PubMed: 26707003]
34. Karkouti K, von Heymann C, Jespersen CM, et al. Efficacy and safety of recombinant factor XIII on reducing blood transfusions in cardiac surgery: a randomized, placebo-controlled, multicenter clinical trial. J Thorac Cardiovasc Surg. Oct 2013;146(4):927–39. doi:10.1016/j.jtcvs.2013.04.044 [PubMed: 23820174]
35. Alderman EL, Levy JH, Rich JB, et al. Analyses of coronary graft patency after aprotinin use: results from the International Multicenter Aprotinin Graft Patency Experience (IMAGE) trial. J Thorac Cardiovasc Surg. Nov 1998;116(5):716–30. doi:10.1016/S0022-5223(98)00431-0 [PubMed: 9806378]
36. Gill R, Herbertson M, Vuylsteke A, et al. Safety and efficacy of recombinant activated factor VII: a randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. Circulation. Jul 7 2009;120(1):21–7. doi:10.1161/CIRCULATIONAHA.108.834275 [PubMed: 19546387]
37. STS National Database™. STS INTERMACS (The Society of Thoracic Surgeons, Interagency Registry for Mechanically Assisted Circulatory Support). Available from: https://www.uab.edu/medicine/intermacs/intermacs-documents. Accessed: 2020 May 5. University of Alabama at Birmingham, Alabama.
38. © Copyright 2020 Extracorporeal Life Support Organization. Extracorporeal Life Support Organization (ELSO) Registry. Available from: https://www.elso.org/Registry/DataDefinitions,Forms,Instructions.aspx. Accessed: 2020 May 5. Ann Arbor, Michigan.
39. Eckman PM, John R. Bleeding and thrombosis in patients with continuous-flow ventricular assist devices. Circulation. Jun 19 2012;125(24):3038–47. doi:10.1161/CIRCULATIONAHA.111.040246 [PubMed: 22711669]
40. Dalton HJ, Reeder R, Garcia-Filion P, et al. Factors Associated with Bleeding and Thrombosis in Children Receiving Extracorporeal Membrane Oxygenation. Am J Respir Crit Care Med. Sep 15 2017;196(6):762–771. doi:10.1164/rccm.201609-1945OC [PubMed: 28328243]
41. Jensen DM, Kovacs TOG, Ohning GV, et al. Doppler Endoscopic Probe Monitoring of Blood Flow Improves Risk Stratification and Outcomes of Patients With Severe Nonvariceal Upper Gastrointestinal Hemorrhage. Gastroenterology. May 2017;152(6):1310–1318 e1. doi:10.1053/j.gastro.2017.01.042 [PubMed: 28167214]
42. Laine L, Spiegel B, Rostom A, et al. Methodology for randomized trials of patients with nonvariceal upper gastrointestinal bleeding: recommendations from an international consensus conference. Am J Gastroenterol. Mar 2010;105(3):540–50. doi:10.1038/ajg.2009.702 [PubMed: 20029415]
43. Lau JY, Barkun A, Fan DM, Kuipers EJ, Yang YS, Chan FK. Challenges in the management of acute peptic ulcer bleeding. Lancet. Jun 8 2013;381(9882):2033–43. doi:10.1016/S0140-6736(13)60596-6 [PubMed: 23746903]
44. de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol. Sep 2015;63(3):743–52. doi:10.1016/j.jhep.2015.05.022 [PubMed: 26047908]
45. Chai-Adisaksopha C, Hillis C, Thabane L, Iorio A. A systematic review of definitions and reporting of bleeding outcome measures in haemophilia. Haemophilia. Nov 2015;21(6):731–5. doi:10.1111/hae.12750 [PubMed: 26179330]
46. Limperg PF, Terwee CB, Young NL, et al. Health-related quality of life questionnaires in individuals with haemophilia: a systematic review of their measurement properties. Haemophilia. Jul 2017;23(4):497–510. doi:doi: 10.1111/hae.13197 [PubMed: 28429867]

47. Blanchette VS, Key NS, Ljung LR, et al. Definitions in hemophilia: communication from the SSC of the ISTH. J Thromb Haemost. Nov 2014;12(11):1935–9. doi:10.1111/jth.12672 [PubMed: 25059285]
48. Aquino CC, Borg Debono V, Germini F, et al. Outcomes for studies assessing the efficacy of hemostatic therapies in persons with congenital bleeding disorders. Haemophilia. Mar 2021;27(2):211–220. doi:10.1111/hae.14247 [PubMed: 33550614]
49. Manco-Johnson MJ, Abshire TC, Shapiro AD, et al. Prophylaxis versus episodic treatment to prevent joint disease in boys with severe hemophilia. N Engl J Med. Aug 9 2007;357(6):535–44. doi:10.1056/NEJMoa067659 [PubMed: 17687129]
50. Gouw SC, Timmer MA, Srivastava A, et al. Measurement of joint health in persons with haemophilia: A systematic review of the measurement properties of haemophilia-specific instruments. Haemophilia. Jan 2019;25(1):e1–e10. doi:doi: 10.1111/hae.13631 [PubMed: 30427100]
51. Schäfer GS, Valderramas S, Gomes AR, Budib MB, Wolff ÁL, Ramos AA. Physical exercise, pain and musculoskeletal function in patients with haemophilia: a systematic review. Haemophilia. May 2016;22(3):e119–129. doi:doi: 10.1111/hae.12909 [PubMed: 27075748]
52. Iorio A, Skinner MW, Clearfield E, et al. Core outcome set for gene therapy in haemophilia: Results of the coreHEM multistakeholder project. Haemophilia. Jul 2018;24(4):e167–172. doi:doi: 10.1111/hae.13504 [PubMed: 29781145]
53. Slichter SJ, Kaufman RM, Assmann SF, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. N Engl J Med. Feb 18 2010;362(7):600–13. doi:10.1056/NEJMoa0904084 [PubMed: 20164484]
54. Stanworth SJ, Estcourt LJ, Powter G, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. N Engl J Med. May 9 2013;368(19):1771–80. doi:10.1056/NEJMoa1212772 [PubMed: 23656642]
55. World Health Organization (WHO). WHO handbook for reporting results of cancer treatment. World Health Organization. Available from: https://apps.who.int/iris/handle/10665/37200. Accessed: 2020 May 5. vol 48th Edition. 1979.
56. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer. Jan 1 1981;47(1):207–14. doi:10.1002/1097-0142(19810101)47:1<207::aid-cncr2820470134>3.0.co;2-6 [PubMed: 7459811]
57. Dyer C, Alquist CR, Cole-Sinclair M, et al. A multicentred study to validate a consensus bleeding assessment tool developed by the biomedical excellence for safer transfusion collaborative for use in patients with haematological malignancy. Vox Sang. Apr 2018;113(3):251–259. doi:doi: 10.1111/vox.12627 [PubMed: 29318636]
58. Estcourt LJ, Heddle N, Kaufman R, et al. The challenges of measuring bleeding outcomes in clinical trials of platelet transfusions. Transfusion. Jul 2013;53(7):1531–43. doi:10.1111/trf.12058 [PubMed: 23305609]
59. Webert KE, Arnold DM, Lui Y, Carruthers J, Arnold E, Heddle NM. A new tool to assess bleeding severity in patients with chemotherapy-induced thrombocytopenia (CME). Transfusion. Nov 2012;52(11):2466–2474; quiz 2465. doi:doi: 10.1111/j.1537-2995.2012.03634.x [PubMed: 22486274]
60. Heddle NM, Cook RJ, Tinmouth A, et al. A randomized controlled trial comparing standard- and low-dose strategies for transfusion of platelets (SToP) to patients with thrombocytopenia. Blood. Feb 12 2009;113(7):1564–73. doi:10.1182/blood-2008-09-178236 [PubMed: 19109560]
61. Stanworth SJ, Hudson CL, Estcourt LJ, Johnson RJ, Wood EM, TOPPS Study Investigators. Risk of bleeding and use of platelet transfusions in patients with hematologic malignancies: recurrent event analysis. Haematologica. Jun 2015;100(6):740–747. doi:doi: 10.3324/haematol.2014.118075 [PubMed: 25795717]

Table 1.

Recommendations for primary outcomes for trials examining hemostatic blood products and agents

Clinical Condition	Primary Outcome Recommendations
Traumatic Injury (excluding isolated traumatic brain injury and burn injury)	For patients with traumatic injury, a 3 to 6-hour all-cause mortality is recommended as a primary outcome for hemostatic interventions, with robust evaluation of late safety-related outcomes In children with life-threatening traumatic hemorrhage, a primary outcome of death at either 6 or 24 hours is recommended.
Intracranial Hemorrhage	For patients with spontaneous or traumatic intracranial hemorrhage the recommended optimal primary outcome is a global patient-centered clinical outcome scale measured between 30–180 days after the event. For studies that may lack sufficient power for this, a combined clinical and radiographic endpoint (such as poor outcome associated with ICH expansion) is an acceptable second choice.
Cardiac Surgery/ Mechanical Circulatory Support	For patients with bleeding secondary to cardiothoracic surgery, a primary efficacy endpoint of total allogeneic blood products (units vs ml/kg) administered intraoperatively and postoperatively to day 5 or hospital discharge is recommended. For clinical trials of patients on ECMO, the recommended primary outcome is a 5-point ordinal score of both thrombosis and bleeding severity adapted from the consensus definitions in Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For VAD studies, the recommended primary endpoint is freedom from disabling stroke (CTCAE ≥ Gr3 through 180 days.
Gastrointestinal Hemorrhage	For patients with acute gastrointestinal bleeding, the recommended primary outcome is a composite measure consisting of further bleeding (including persistent bleeding and rebleeding with primary assessment in 7 days),[42] and cause-specific or bleed-related mortality at 30–42 days.
Inherited Bleeding Disorders	For the treatment of acute bleeding or for the prevention of surgical bleeding the recommended primary outcome is a composite scoring system incorporating the number of infusions required, rating on a clinical scale, and need for re-intervention For the prevention of bleeding events the recommended primary outcome is an annualized bleeding rate, quantifying the number of bleeding events over a period of time. For the long term and overall impact of bleeding, which is the ultimate goal in patients with inherited bleeding disorders, the recommended primary outcome is a composite of joint function (measured via an objective clinical scale or a patient reported functional score),[50] chronic pain (measured via a validated scale), and HRQoL (both generic and specific)[46] as proposed in a core outcome set for hemophilia gene therapy trials.
Hypoproliferative Thrombocytopenia	For patients with bleeding secondary to hypoproliferative thrombocytopenia, the recommended primary outcome for trials that examine the efficacy of blood products or hemostatic agents is the WHO Bleeding Assessment Score. Specifically, we recommend a WHO Grade of 2 or greater as a primary outcome in clinical trials of platelet threshold and efficacy.