Evidence-Based and Clinically Relevant Outcomes for Hemorrhage Control Trauma Trials

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Objective: To address the clinical and regulatory challenges of optimal primary endpoints for bleeding patients by developing consensus-based recommendations for primary clinical outcomes for pivotal trials in patients within 6 categories of significant bleeding, (1) traumatic injury, (2) intracranial hemorrhage, (3) cardiac surgery, (4) gastrointestinal hemorrhage, (5) inherited bleeding disorders, and (6) hypoproliferative thrombocytopenia.

Background: A standardized primary outcome in clinical trials evaluating hemostatic products and strategies for the treatment of clinically significant

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bleeding will facilitate the conduct, interpretation, and translation into clinical practice of hemostasis research and support alignment among funders, investigators, clinicians, and regulators.

Methods: An international panel of experts was convened by the National Heart Lung and Blood Institute and the United States Department of Defense on September 23 and 24, 2019. For patients suffering hemorrhagic shock, the 26 trauma working-group members met for almost a year, utilizing biweekly phone conferences and then an in-person meeting, evaluating the strengths and weaknesses of previous high quality studies. The selection of the recommended primary outcome was guided by goals of patient-centeredness, expected or demonstrated sensitivity to beneficial treatment effects, biologic plausibility, clinical and logistical feasibility, and broad applicability.

Conclusions: For patients suffering hemorrhagic shock, and especially from truncal hemorrhage, the recommended primary outcome was 3 to 6-hour all-cause mortality, chosen to coincide with the physiology of hemorrhagic death and to avoid bias from competing risks. Particular attention was recommended to injury and treatment time, as well as robust assessments of multiple safety related outcomes.

Keywords: endpoints, transfusion, trauma

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To address the clinical and regulatory challenges of optimal primary endpoints for bleeding patients, an international panel of experts was convened by the National Heart Lung and Blood Institute and the United States Department of Defense on September 23 and 24, 2019.[1] Their charge was to develop consensus-based recommendations for primary clinical outcomes for pivotal trials in patients within 6 categories of significant bleeding, (1) traumatic injury, (2) intracranial hemorrhage, (3) cardiac surgery, (4) gastrointestinal hemorrhage, (5) inherited bleeding disorders, and (6) hypoproliferative thrombocytopenia. A summary paper describing the comprehensive recommendations has been submitted.[2]

The goal of our trauma-focused committee is to recommend clinically relevant outcomes for trials evaluating hemostatic blood products and technology, which will be acceptable to funding and regulatory agencies. Our recommendations cover mechanical injury, including blunt and penetrating trauma, but exclude burns and isolated traumatic brain injury (TBI). It is important to characterize the bleeding trauma patient in a sequence of related but distinct clinical scenarios, each of which require tailored interventions: (1) acute phase (0 to 6 hours postinjury) characterized by loss of blood and shock, with or without coagulopathy, requiring immediate mechanical bleeding control and damage-control resuscitation; (2) intermediate phase (6 to 24 hours postinjury), during which severe TBI and/or physiologic derangement may result in death, and (3) late phase, when the consequences of dysfunctional immuno-inflammatory responses, thrombotic complications, and/or prolonged immobility and mechanical ventilation manifest (eg, infections, acute respiratory distress syndrome, multiple organ failure, venous thromboembolic events).

CURRENT PRIMARY OUTCOMES

Trauma deaths from hemorrhage occur very early, within hours of the injury, while those from isolated TBI occur later, often 24 to 36 hours after hospital admission.[3–12] An assessment of 2 Resuscitation Outcomes Consortium (ROC) randomized controlled trials (RCTs) revealed that 82% of the deaths within 24 hours were in the shock/hemorrhage cohort (median of 2 hours post admission) and 72% in the cohort with both shock and TBI (median of 4 hours), compared with 46% of deaths in the isolated TBI cohort (median of 29 hours), while sepsis and multiple organ failure accounted for only 2% of all deaths in these trials.[3] A recent review of deaths in trauma-focused RCTs showed that median time to hemorrhagic death, in trauma systems with rapid transport from injury to hospital, varied from 2.0 to 2.6 hours from admission.[4] Alarhayem et al[8] have shown a precipitous rise in patient mortality in patients with severe truncal injury (irrespective of mechanism) within 30 minutes of injury. Consistent with these timelines, recent studies document the significant survival benefit of interventions occurring either prehospital or within minutes to hours of hospital arrival.[13–19]

Three recent RCTs evaluating different hemostatic interventions depict the proportion of deaths due to hemorrhage and TBI within specific time intervals (Table 1).[5,6,10] Hemorrhage-related deaths were responsible for most of the deaths occurring within 6 hours, while TBI-related deaths peaked after that time. Although in PAMPer[6] and COMBAT[10] several deaths were attributed to the category ''other/unknown'' when distinction between TBI and

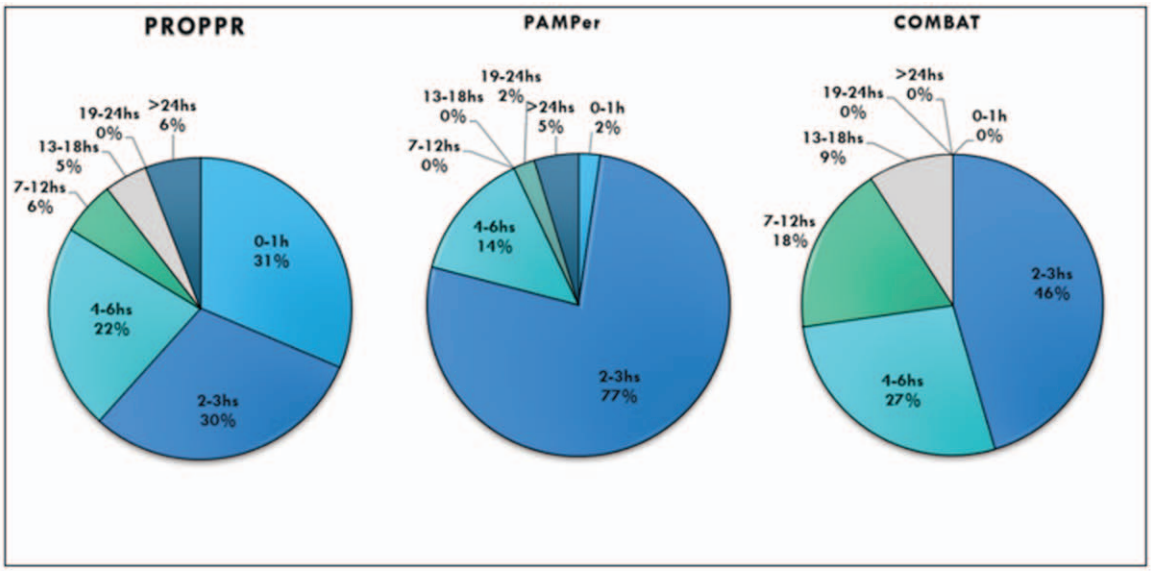
TABLE 1. Proportion of Deaths Attributable to Traumatic Brain Injury (TBI) and Hemorrhage Within Each Time Interval in 3 Randomized Controlled Trials

	PROPPR[5] (n = 680) Time Zero= Randomization in-Hospital Entry Criteria: ≥ 1 unit of Blood Product and Assessment of Blood Consumption score>1 or Physician's Prediction of Massive Transfusion Need			PAMPer[6] (n = 501) Time Zero=Scene Arrival Entry Criteria: Air Transported and SBP <70 mm Hg or SBP <90 mm Hg + HR>108 bpm			COMBAT[10] (n = 144) Time Zero=Dispatch Entry Criteria: Ground Transported and SBP <70 mm Hg or SBP <90 mm Hg + HR >108 bpm		
Hours	Number of Deaths Within the Time Interval	No. (%) Deaths in the Interval Attributed to TBI	No. (%) Deaths in the Interval Attributed to Hemorrhage	Number of Deaths Within the Time Interval	No. (%) Deaths in the Interval Attributed to TBI	No. (%) Deaths in the Interval Attributed to Hemorrhage	Number of Deaths Within the Time Interval	No. (%) Deaths in the Interval Attributed to TBI	No. (%) Deaths in the Interval Attributed to Hemorrhage
1–3	58	7 (12.1)	53 (91.4)	57	9 (15.8)	34 (59.6)	8	2 (25.0)	5 (62.5)
4–6	21	3 (14.3)	19 (90.5)	12	5 (41.7)	6 (50.0)	3	3 (100.0)	0 (0.0)
7–12	10	6 (60.0)	5 (50.0)	11	9 (81.8)	0.0%	2	2 (100.0)	0 (0.0)
13–18	7	2 (28.6)	4 (57.1)	9	8 (88.9)	0 (0.0)	1	0 (0.0)	1 (100.0)
19–24	5	5 (100.0)	0 (0.0)	3	1 (33.3)	1 (33.3)	0	0 (0.0)	0 (0.0)
>24	63	39 (61.9)	5 (7.9)	46	10 (21.7)	2 (4.3)	2	0 (0.0)	0 (0.0)
Total	164			138			16		

All studies excluded lethal traumatic brain injury (TBI).

Among patients who received at least 1 unit of red blood cells/24 h, the proportion of deaths due to hemorrhage within 1–3 h was 82% in PAMPer and 100% in COMBAT, and within 4–6 h, it was 40% in PAMPer and 100% in COMBAT.

HR indicates heart rate; SBP, systolic blood pressure.



- PROPPR [5] (n = 680) Time zero= randomization in-hospital; Entry criteria: > 1 unit of blood product and Assessment of Blood Consumption score>1 or physician's prediction of massive transfusion need
- PAMPer (n = 501) [6] Time zero=scene arrival; Entry criteria: Air transported and SBP<70mmHg or SBP <90mmHg + HR>108bpm
- COMBAT (n = 144) [10] Time zero=dispatch; Entry criteria: Ground transported and SBP<70mmHg or SBP <90mmHg + HR>108bpm

Note: Among patients requiring ≥ 1 unit of red blood cells/24 hours, 85% of the hemorrhagic deaths in PAMPer and 50% in COMBAT occurred ≤6 hours.

FIGURE 1. Distribution of all hemorrhagic deaths over time in 3 randomized controlled trials.

hemorrhage was not possible, in PROPPR[5] deaths were accounted for in both categories (thus the percentages may add to >100%). Almost all hemorrhage-related fatalities happened within 24 hours with the vast majority declared within 3 to 6 hours. This is illustrated in Figure 1, which shows the percentage of all hemorrhagic deaths occurring within 1, 2 to 3, 4 to 6 hours, and so forth. As described below, the time ''zero'' of these trials (eg, time of injury, randomization, hospital admission, etc) differed, making precise comparisons by time-intervals impossible. In addition, PAMPer[6] and COMBAT[10] enrolled injured patients in the field, for whom the diagnosis of hemorrhagic shock could not be precisely ascertained, thus resulting in a lower proportion of hemorrhagic deaths in the first few hours due to contamination by TBI. In contrast, PROPPR[5] tested an in-hospital intervention in patients who required at least 1 unit of red blood cells and Assessment of Blood Consumption score[20] greater than 1 or physician's prediction of need for massive transfusion, thus increasing the certainty of the hemorrhagic shock diagnosis, and the percentage of subjects dying from hemorrhage within 6 hours of hospital admission (91%). Yet, despite such disparities between these 3 recent hemostasis-aimed RCTs, 2 major conclusions can be drawn: most hemorrhagic deaths occur within 6 hours of injury and hemorrhage causes most deaths within the first 6 hours.

From a regulatory view, 30-day survival has been the standard primary outcome for all injury trials,[21–23] but the biological rationale for this arbitrary endpoint is not consistent with the physiological effects of effective hemostatic interventions, nor with the above-mentioned sequential clinical scenarios that are typical of critically injured patients.[4] 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.[3,4,24] 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 (eg, TBI, infections).[4,5,9]

Increasing the number of patients included in such trials could overcome the above-mentioned issues, as demonstrated in the CRASH-2 trial testing anti-fibrinolytic therapy, which required over 20,000 patients to demonstrate a survival benefit, and showed a difference in outcome within 3 hours of hospital arrival.[17] The PROPPR transfusion RCT provides an example of the scale of the problem.[5] On the basis of the results of this large (n = 680) and expensive (32.5 million dollars) multicenter study, an enrollment greater than 5800 patients would have been required to achieve significant differences at 30 days with a hospital-based intervention, dramatically (and likely prohibitively) increasing cost, number of sites, and study duration.[4] Therefore, the use of the traditional 30-day mortality outcome may require extremely large trials, likely delaying the testing and translation to practice of life-saving interventions. Of course, the experimental treatment might have harmful effects

TABLE 2. Assessment of Truncation by Death in the PROPPR Study[5]

	All Patients								Survival ≥ 3 h							
	Controls			Treatment			|SMD|	*P*	Controls			Treatment			|SMD|	*P*
	Median or %	LQ	UQ	Median or %	LQ	UQ			Median or %	LQ	UQ	Median or %	LQ	UQ		
Age, y	34	24	50	34.5	25	51	0.03	0.56	34	25	51	34	25	50	0.02	0.85
Female sex	17%			22%			0.06	0.11	17%			22%			0.05	0.11
Blunt injury	51%			55%			0.11	0.28	50%			55%			0.11	0.28
Glasgow Coma Scale	14	3	15	14	3	15	0.02	0.90	14	3	15	14	3	15	0.05	0.37
Systolic Blood pressure, mm Hg	102	80	125	102	81	126	0.07	0.55	103	82	126	103	81	126	0.06	0.76
Diastolic blood pressure, mm Hg	68	50	91	70	53	90	0.03	0.54	69	50	93	70	53	90	0.01	0.78
Respiratory rate, rpm	20	17	26	20	18	26	0.04	0.67	21	17	26	20	18	26	0.03	0.65
Heart rate, bpm	113	93	130	115	97	135	0.12	0.25	113	93	130	114	97	134	0.09	0.46
Revised trauma score	6.38	4.09	7.84	6.82	4.09	7.84	0.01	0.98	6.9	4.09	7.84	6.9	4.09	7.84	0.06	0.44
Minutes from EMS call to randomization	37	55	25	36	52	27	0.04	0.66	38	55	25	36	52	28	0.03	0.75
Minutes from EMS arrival to randomization	28	43	19	27	40	20	0.01	0.89	28	43	19	27	40	20	0.00	0.96
Minutes from hospital arrival to randomization	26	16	41	28	17	47	0.12	0.11	27	16	42	29	16	47	0.11	0.16
First lactate, mmol/L	6.2	3.6	9.5	6.0	3.9	9.1	0.04	0.99	5.6	3.5	8.8	5.9	3.7	9	0.08	0.70
First base excess, mEq/L	-8.5	-12.8	-4.7	-8.0	-12.5	-3.8	0.07	0.26	-8.0	-12.0	-4.1	-7.8	-12.0	-3.7	0.00	0.65
First prothrombin time/INR	1.3	1.2	1.54	1.26	1.15	1.54	-0.05	0.19	1.3	1.19	1.51	1.25	1.14	1.5	0.05	0.26
First hemoglobin	11.9	10.1	13.2	11.7	10.1	13.4	0.05	0.82	11.9	10.1	13.3	11.9	10.2	13.4	0.05	0.70
Pre- randomization Plasma: RBC ratio	0	0	0.5	0	0	0.7	0.03	0.75	0	0	0.5	0	0	0.7	0.04	0.60
Pre- randomization Platelets: RBC ratio	0	0	0	0	0	0	0.08	0.32	0	0	0	0	0	0	0.08	0.33
Injury Severity Score	26	17	38	27	17	41	0.06	0.45	26	17	37	26	17	41	0.05	0.52

INR indicates international normalized ratio; RBC, red blood cells; SMD, absolute standardized mean difference.

manifested through death due to other causes or later complications, thus monitoring these later causes of morbidity and mortality is essential to assess the safety of early experimental interventions.[25,26]

Successful randomized trials of hemostatic interventions may confound important later outcomes [eg, acute respiratory distress syndrome (ARDS), multiple organ failure (MOF), venous thromboembolism (VTE), infections] because of the "truncation-by-death" phenomenon, that is, how much early survival differences affect the comparability of the study groups regarding later outcomes.[27–29] If the experimental intervention reduces early hemorrhage-related mortality relative to the control (ie, saves patients who would have otherwise died under the control therapy), the survivors of the experimental and control treatments are now different (and the equalization of their injury severity afforded by the randomization is potentially lost). This subsequent disparity between study groups may affect the internal validity of the comparison of outcomes other than death, unless appropriate statistical approaches are used to estimate the so-called survivor-average causal effect (SACE).[27] To our knowledge, there has been no assessment of the magnitude of such bias in trauma focused RCTs. We analyzed 2 RCTs with large effects at early times postinjury, namely PROPPR[5] (Table 2) and PAMPer[6] (Table 3). We hypothesized that if truncation by death occurred, then the survivors of the initial few hours in the control and experimental groups would differ regarding demographic characteristics, injury severity and physiologic

TABLE 3. Assessment of Truncation by Death in the PAMPer Study[6]

	All Patients*								Survival ≥48 h							
	Control			Experimental			SMD	*P*	Control			Experimental			SMD	*P*
	Median or %	LQ	UQ	Median or %	LQ	UQ			Median or %	LQ	UQ	Median or %	LQ	UQ		
Age, y	46	27	60	44	31	61	0.03	0.76	45			45			0.09	0.36
Female sex	26%			29%			0.07	0.42	26%			28%			0.03	0.74
Blunt trauma	83%			81%			0.05	0.55	80%			81%			0.01	0.91
Scene to Hospital Minutes	40	33	52	42	34	52.5	0.13	0.14	40	33	52	42	34	53	0.13	0.21
Injury Severity Score	21	12	29.5	22	14	33	0.11	0.25	21	12	29	22	13	33	0.1	0.32
Max AIS-Head/Neck	1	0	3	2	0	3	0.07	0.41	0	0	3	2	0	3	0.12	0.23
Field Systolic blood pressure, mm Hg	69	61	81	71	64	81	0.11	0.28	70	64	82	73	65	82	0.01	0.73
Field heart rate, bpm	115	96	126	117	103	128	0.08	0.21	115.5	100	127	117	104	128	0	0.59
Field Glasgow Coma Scale	10	3	15	11	3	15	0.03	0.72	13	3	15	13	3	15	0.02	0.87
Field Shock Index, bpm/mm Hg	1.5	1.4	1.8	1.5	1.4	1.8	0.02	0.67	1.5	1.4	1.8	1.5	1.4	1.7	0.08	0.79

LQ indicates lower quartile; Max AIS, Maximum Abbreviated Injury Scale; SMD, absolute standardized mean difference; UQ, upper quartile.
*Values may differ slightly from values in the initial publication[6] because patients with mixed blunt and penetrating trauma were removed.

derangement as well as time to randomization. Specifically, the survivors in the experimental group would be more severely ill (and would have died under the control intervention) than the survivors of the control group. For PROPPR,[5] we analyzed the patients who survived ≥3 hours, when the mortality ratio between experimental and control groups was highest. As summarized in Table 2, the survivors of the initial 3-hour period remained comparable (absolute standardized mean difference, |STD| <0.02, nonsignificant *P* values). For PAMPer,[6] we compared individuals who survived ≥48 hours (Table 3), and observed that the groups remained comparable. We also examined the incidence of late outcomes in both trials. Both the PROPPR[5] and PAMPer trials[6] observed similar rates of ARDS (PROPPR: 14% for both groups; PAMPer: 19% in the experimental group versus 21% in the control group, $P = 0.50$ unadjusted for multiple comparisons). Under the truncation-by-death assumption, if the survivors of the experimental groups were sicker than the survivors of the control group due to unobserved/unmeasured confounders, this would increase the ARDS incidence in the experimental group and lead to biased estimates of the effect of the interventions on ARDS incidence.[27] This effect was not seen, thus truncation by death did not appear to have occurred in these 2 studies. We recommend that investigators carefully plan data collection for hemostasis trials keeping in mind the need for assessment of truncation-by-death.

Other challenges in the design of traumatic hemorrhage randomized trials abound, starting with the process to obtain exception from informed consent (EFIC) under regulations for emergency research granted by Title 21, Code of Federal Regulation Section 50.24.[22,30–32] With greater experience, these studies have become fairly routine and over 95% of enrolled subjects complete the studies. In trials conducted with individual or legally authorized representative consent before randomization, obtaining consent necessarily delays the start of the study, thus selecting patients who survived the initial hemorrhage and consent process.[33] This results in systematic differences between study participants and the eligible study population, by enrolling patients with lower mortality from hemorrhage and limiting the generalizability of the research findings. EFIC trials allow the intervention to start sooner relative to the injury event, thus increasing their external validity, while on the other hand, prehospital studies (Table 1) deal with increased difficulty in identifying patients at high risk of adverse outcomes.[4,10]

The design and analysis must account for the high early case-fatality rate, which then declines precipitously within the first few hours to preserve external and internal validity. Threats to internal validity are mostly related to disparities between the study groups, supposedly equalized by the randomization process. If, for example, the hemostatic experimental intervention takes longer to initiate than the control therapy (or vice versa), a powerful confounding is introduced. Intent-to-treat analysis (ie, analysis of patients according to assigned group at randomization time), starting the ''clock'' at the same time for all study groups, taking accurate records of all key times and use of appropriate statistical techniques (eg, survival analysis accounting from time from injury) are crucial to maximize internal validity in such cases.

RECOMMENDED PRIMARY OUTCOMES

Due to the diverse nature of potential interventions and the population evaluated, we recommend flexibility in the determination of the primary outcome of hemostatic interventions. We propose that 3 to 6-hour all-cause mortality should be considered an acceptable primary outcome for hemostatic interventions, with robust evaluation of late safety-related outcomes. This recommendation is supported by RCTs and large observational studies that indicate that the vast majority of hemorrhage-related fatalities occur within 3 to 6 hours after injury.[2,5,6,10,18,19,33–35] Adding time to the primary endpoint definition underscores the importance of clearly defining the starting time-point: (ie, time of injury, EMS dispatch, arrival of EMS, hospital admission, randomization, intervention initiation, etc). Prehospital times vary significantly depending on location of the incident and mode of transport, and are therefore especially important to document as accurately as possible.[36–38] Emphasizing the issue of ''start time,'' Alarhayem et al[8] have shown that the peak time to death is within 30 minutes of injury, irrespective of mechanism. Although we recognize that each trial would have to focus on a different starting point depending on the intervention under evaluation, it is essential that all hemostatic intervention trials document the above-mentioned time-points, including time to hemostasis after intervention.[9,39] Although practical considerations may limit the precise time determination of very early interventions, it is clear that interventions as close to the injury time as possible are more likely to result in greater separation between groups and improved early and long term outcomes. On the contrary, conducting enrollment closer to time of injury will lead to greater uncertainty in the diagnosis of hemorrhagic shock and TBI, thus potentially diluting the effect of hemostatic interventions, as noted above in the comparison of recent hemostasis-aimed RCTs, (Table 1).

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. Although 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] Exclusion of isolated TBI patients based on physical examination alone may be difficult, if not impossible, before randomization, especially in the pre-hospital and very early hospital setting.[40,41] We also recognize that different interventions will exert their effect over different time-periods after injury, thus we suggest that phase 2 or exploratory studies be conducted to fully understand the biologic plausibility and time course of interventions, while controlling for the unavoidable confounding effect of coexisting TBI or an unanticipated complication of the hemorrhage control intervention.[4] Because of the difficulty in defining hemorrhagic death, we recommend (especially in those without complete autopsy or whole-body computed tomography scans) the use of time-specific, all-cause mortality (eg, within 3 to 6 hours) as an objective outcome for hemostasis trials.[4,39] We do recommend, however, that all hemostatic-related trials include a pre-planned stratified analysis by TBI status, and exploratory phase 2 studies to understand biological significance of the proposed intervention. Furthermore, we recommend against the use of post randomization intervention-related criteria (eg, transfusions, tourniquets, emergency operative procedures, etc) in enrollment and subgroup analysis, as these are subject to bias (survivor, collider, and intervention biases), and variably utilized across centers.[40,41] However, given the lack of current accurate predictors of hemorrhage, we believe it is acceptable to use transfusion as a pre-randomization entry criteria to facilitate identifying and enrolling eligible bleeding patients into hemorrhage control studies (Table 1).

In sum, there is good evidence to support that the critical window for demonstrating differences in outcomes in trials aiming at reducing hemorrhage-related deaths is within 3 to 6 hours after injury, which is entirely consistent with the biological mechanisms.

PEDIATRIC TRAUMA DATA

Although there are abundant data for trauma in adults, the scenario in the pediatric population is much more complex. Anatomic, physiologic, and injury mechanism differences yield vastly

different causes of death following trauma across the spectrum infant (0 to 1 year), toddler (1 to 3 years), preschool (3 to 5 years), school age (6 to 11 years), and adolescent (12 to 18 years) with TBI dominating the younger the patient.[42] The incidence of hemorrhage-related trauma death has not been well documented in children, yet blunt thoracoabdominal trauma resulting in hemorrhage is the second leading cause of traumatic death in children.[43] Most reports suggest adolescents are similar to adults and thus adult recommendations for hemostasis studies could be similar.[44] However, the hemorrhagic death data in children younger than 12 years of age are limited and virtually nonexistent in those younger than 6 years. In a recent prospective observational study of 207 children with traumatic injury 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 percentage 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 central nervous system injury. Thus, in children with life-threatening traumatic hemorrhage we recommend a primary outcome of death at either 6 or 24 hours. However, further work is needed to define the primary cause and timing of death based on age groups (18 to 12, 11 to 6, and $<$ 6 years).

CONCLUSION

The choice of primary outcome for hemorrhage control studies in seriously injured patients clearly depends on the research question, but given that the majority of deaths from hemorrhage in injured patients occur within a few hours of injury, we propose that an acceptable primary endpoint for pivotal randomized studies of hemorrhage control interventions is within 3 to 6 hours after injury. This 3 to 6-hour time-period captures when a hemorrhage control intervention is likely to produce a survival difference. We recognize that different interventions will exert their effect over different time-periods after injury, thus we suggest that exploratory studies be conducted to fully understand the biologic plausibility and time course of interventions, while controlling for the unavoidable confounding effect of coexisting TBI or an unanticipated later complication(s) of the hemorrhage control intervention.

Study designs incorporating adaptive and Bayesian principles should be encouraged.[45] Adaptive designs allow for prospectively planned modifications, based on accumulating study data. These designs can reduce resource requirements, shorten enrollment time, and increase the chance of study success. Bayesian analyses are more interpretable, because they yield the actual probability of a specific treatment effect, rather than a *P* value. This helps to avoid the dichotomization of trials into ''significant'' and ''not significant.'' Bayesian frameworks also offer more flexibility when it comes to formulating meaningful decision criteria, such as when to declare a trial successful, or when to stop a trial early. In conjunction with a range of prior probability distributions, they can provide more nuanced results, and are particularly powerful when combined with an adaptive trial design.

Lastly, substantial experience in the recent wars support the survival benefit of early hemostatic interventions.[46–50] Randomized study design after injury should continue to investigate the findings of this hard won knowledge, translating improved care to the civilian patients.

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