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In Reply

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Dr Moore and colleagues raise issues regarding clinical trial end points. The 24-hour and 30-day regulatory end points commonly used are based on convenient clock and calendar periods rather than the physiology of patients with severe and multiple injuries at high risk of hemorrhagic death. Regarding potential bias in the determination of hemostasis and death due to exsanguination, these end points were prespecified by investigators as clinically relevant and operationalized to avoid bias. Each death was reviewed by the attending surgeon and then adjudicated by an external clinician blinded to group assignment.

Concern that “the 1:1:1 cohort reportedly had superior hemostasis and delayed deaths from bleeding, whereas the 1:1:2 group did not” is explained by the main findings. More severely injured patients survived in the 1:1:1 group; therefore, it is plausible that these survivors continued to be at higher risk of hemorrhagic death than those in 1:1:2 group. Importantly, there were no differences between the 2 groups in any of 23 prespecified complications. Most patients enrolled in the PROPPR trial received massive transfusions and these randomized data clearly show that the 1:1:1 transfusion approach is safe and decreased exsanguination. Most clinicians caring for patients with trauma would consider the 8% improvement in hemostasis ($P = .006$) a clinically important difference. Moore and colleagues imply that a 1:1:2 ratio, which results in a similar number of blood products transfused during resuscitation and fewer products during 24 hours, is the preferred strategy from a resource use perspective. We disagree and suggest that the 6.5-U difference is outweighed by improved hemostasis and decreased exsanguination in the 1:1:1 group.

The question of goal-directed vs ratio-driven resuscitation was not addressed in the PROPPR trial. Our large, multi-center randomized trial of 680 patients with severe injuries provides substantially stronger evidence for clinical utility than the 2 small single-center studies referenced. Not described is the delay in obtaining data from thrombelastography or rotational thromboelastometry, putting patients with massive and rapid bleeding at risk of death while waiting for the laboratory results. For patients who are bleeding, what products are transfused while waiting for laboratory values to return? For this reason, goal-directed transfusion therapy may be useful, but only when bleeding has slowed considerably and laboratory values are returned fast enough to be clinically useful.¹ We think that combining

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the 2 approaches, using a 1:1:1 ratio early and goal-directed after bleeding significantly slows, is the optimal way to use the strengths of both approaches.²

We agree with Dr McCurdy and colleagues that the definition of massive transfusion has evolved, largely in recognition of survival bias inherent in the traditional definition.³ We did not use any definition of massive transfusion as an outcome or to define a subgroup; doing so would have introduced survival or collider bias, or both.⁴ Because approximately 50% of patients in the PROPPR trial experienced a penetrating injury, we will be exploring the issue of mechanism in the future. The platelet-first strategy in the 1:1:1 group was based on data from the Prospective, Observational, Multicenter Major Trauma Transfusion study, in which platelets were often administered late or not at all.⁵

We agree with Drs Helwani and Gillihan that “the evidence suggests that the 1:1:1 ratio offers benefits that outweigh potential harms.” We also agree that the competing risk of death due to serious head injury likely diluted the main effect we reported.⁴ Multiple secondary analyses are under way, exploring subsets of patients with traumatic brain injury, those with massive bleeding, and those with available thrombelastography data.

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