In Reply:

Dr. Faraoni *et al.* are concerned about our proposal for prophylactic erythrocyte transfusion in anemic patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).[1] We welcome this opportunity to address their concerns, for we are confident that a critical and unbiased review of available options for reducing transfusion-related adverse events in anemic cardiac surgical patients will illustrate the advantages of our proposal.

First, let's look at the benefits and risks of erythrocyte transfusion in anemic patients, as the risk-benefit profile of any intervention depends on the context. The benefits of erythrocyte transfusion in the setting of progressive anemia are indisputable (despite not being backed by randomized trials—yet another illustration that "clinical trials, useful as they are, are not the only means of evaluation,"[2] but that's another story): at some point, progressive anemia, left untreated, kills![3] When anemic patients undergo cardiac surgery with CPB, which is associated with substantial blood loss and hemodilution, they invariably become more anemic and in many cases become profoundly anemic. For example, in the control arm of our study,[1] fully 29% of patients whose baseline hemoglobin was 10–12 g/dl became profoundly anemic (hemoglobin less than 7 g/dl), despite the use of antifibrinolytic drugs, retrograde autologous prime, and the addition of erythrocyte in the prime as deemed appropriate. In a substantial proportion of these patients, withholding erythrocyte transfusion can lead to serious adverse events and death.[3] It is simply disingenuous to argue that, in such a setting, erythrocyte transfusions are "useless."

Clearly, however, erythrocyte transfusions have serious hazards, which can be categorized into two groups based on whether their pathophysiology is (relatively) well understood or not.[4] The first group includes transmission of infectious agents, hemolytic transfusion reactions, transfusion-associated circulatory overload, and transfusion-related acute lung injury. However, the current risk for these hazards is extremely low, at approximately 1 in 10,000 transfusions,[5] which is comparable with the annual near-term fatality risk associated with the daily use of aspirin by an otherwise healthy 50-yr-old man.[6]

The second group of hazards, which include organ dysfunction and death,[4] potentially are much more concerning. Although their pathophysiology has not been fully elucidated, a major contributing factor is thought to be the changes that occur to erythrocytes during storage.[4] Although these storage-related changes have been well described, their clinical significance remains a matter of debate. On the one hand, numerous observational studies have found that the risk of organ dysfunction and death is approximately 2-fold higher in transfused than in nontransfused patients,[7] but these types of studies have a major limitation in that they are unable to adequately control for confounding by indication (transfused patients are invariably sicker and have more blood loss than nontransfused patients, and these factors are not measured and thus cannot be controlled for in observational studies). On the other hand, there is evidence that hospitals with high transfusion rates have the same risk-adjusted mortality rate as hospitals with low transfusion rates (eTable of cited reference),[8] which would not be the case if transfusions increased mortality.

We believe that storage-related changes are indeed hazardous, but these hazards become clinically significant only in susceptible patients (*e.g.*, patients with pre-existing anemia) in whom transfusion is accompanied by other stressors, such cardiac surgery, CPB, and profound anemia.[1,9] We believe that, under these circumstances, the risks of storage-related hazards dwarf the 1-in-10,000 risk of serious hazards outlined. If we can eliminate the storage-related hazards, we can, in essence, make transfusions as safe as taking an aspirin a day. Prophylactic erythrocyte transfusions in the right patient population may be able to achieve this goal, because they can effectively treat anemia, prevent the occurrence of profound anemia during surgery, reduce or eliminate the need for intraoperative erythrocyte transfusions, and allow time for the transfused erythrocytes to be rejuvenated and the patient to recover from the storage-related effects of the transfusion before being exposed to additional stressors, all without increasing overall transfusions. These advantages were illustrated in our pilot trial: in the treatment and control arms, the incidence of profound anemia was 3% and 29%, respectively, ($P = 0.01$) and the median (twenty-fifth and seventy-fifth percentiles) intraoperative erythrocytes transfused were 0 (0, 2) and 2 (1, 4) units ($P = 0.0002$), respectively. Moreover, overall transfusions were similar, and all but one patient in the control arm received 2 units or more perioperative erythrocytes and that one patient received 1 unit.[1]

What about alternatives such as erythropoietin stimulating agents (ESAs)? We believe this option, although quite viable, is inferior for two reasons. First, ESAs are simply not as uniformly efficacious as 2 units of erythrocytes, and in fact a substantial number of cardiac surgical patients have a blunted response to ESAs.[10] Second, ESAs have several major hazards, including thromboembolic complications, cancer progression, and death.† Their short-term and, in particular, long-term safety in cardiac surgery is a matter of conjecture. In one of the largest randomized studies in cardiac surgery with CPB to date, there were 9 deaths among 126 patients randomized to ESA therapy *versus* 0 deaths among 56 patients randomized to placebo ($P = 0.06$).[10] At this time, according to the prescribing information, the use of ESAs "is not indicated for use in patients undergoing cardiac or vascular surgery."† The studies cited by Dr. Faraoni *et al.* in support of the use of ESAs in cardiac surgery with CPB either have major limitations or are not applicable. The study by Emmert *et al.* included only 16 Jehovah's Witness

† See prescribing information at www.procrit.com. Accessed June 7, 2012.

patients, and of them only 3 received ESAs.[11] The study by Weltert *et al.* included only patients undergoing off-pump cardiac surgery and thus cannot be used to address safety and efficacy for on-pump surgery.[12] The study by Yoo *et al.* included only 74 patients (not much larger than our pilot trial) and seems to have not been properly blinded.[13] Moreover, in that study transfusions were guided by the hemoglobin concentration, so it is hard to understand why the ESA group had a markedly lower intraoperative transfusion need than the control group (0.7 ± 0.7 *vs.* 1.2 ± 1.1 units/patient) when the two groups had very similar postinduction hemoglobin concentrations (11.6 ± 1.2 g/dl *vs.* 11.5 ± 1.4 g/dl) and reticulocyte counts (80 ± 24 *vs.* 75 ± 27 $\times 10^3/\mu$l). Thus, these studies do not provide strong support for the use of ESAs in cardiac surgery with CPB.

Finally, Dr. Faraoni *et al.* state that our results should be viewed with caution, with which we strongly agree because it was a *pilot* study. We specifically stated that "it would be inappropriate to modify clinical practice based on the results of this pilot study." We did conclude that the intervention "reduces perioperative anemia and erythrocyte transfusions, and may reduce plasma iron levels," and we stand by this conclusion because it is supported by the results. We also noted that "large multicenter trials adequately powered to determine if this intervention reduces postoperative acute kidney injury are warranted." To that end, we have created a multidisciplinary research team at 20 institutions and have applied for peer-reviewed funding to conduct such a trial. Given that definitive safety and efficacy data are also lacking for alternative interventions aimed at reducing perioperative transfusions, such as but not limited to ESAs and acute normovolemic hemodilution, the only logical conclusion is that these interventions also should not be used outside of clinical trials that are properly designed to determine their overall risk-benefit profiles.

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Table Your Contaminated Equipment during Induction

To the Editor:

Mecham's and Hopf's "A proposal to minimize work area contamination during induction" brought up some interesting points.[1] Preparing an area to isolate items contaminated during anesthesia induction is a good idea that deserves attention. However, we propose that the clean towel not be placed on the patient's chest, as depicted. Rather, the towel should be placed "at a site easily reached," as the authors also suggested.[1] A towel on the chest, covered with contaminated and bulky items (such as gloves, mask, laryngoscope), will need to be moved to confirm endotracheal tube position *via* auscultation of breath sounds and the epigastrium, crucial parts of the intubation process.[2,3] The patient's chest is not always a stable, flat surface, thus items may fall off of the towel and onto the floor. Using a Mayo stand or similar