

follow-up study is designed to provide much-needed safety data on potential late effects of ART in both mothers and children in Africa.

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Since publication of their article, the authors report no further potential conflict of interest.

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## Trial of ZMapp for Ebola Virus Infection

**TO THE EDITOR:** Davey and colleagues (Oct. 13 issue)<sup>1</sup> are to be commended for completing the ZMapp trial under challenging circumstances. However, in order to determine whether ZMapp represented the only difference across study groups, more detail should have been provided for the between-group comparisons. The ZMapp infusion protocol describes monitoring every 15 to 30 minutes during early dose escalation<sup>1</sup>; however, no description exists for similar monitoring of the patients who received the standard of care. Frequent monitoring of patients receiving ZMapp may have resulted in earlier identification of serious adverse events and improved care delivery, an effect observed in other trials involving severe illness in similar settings.<sup>2</sup> Elevated baseline creatinine levels are associated with Ebola virus disease mortality.<sup>3,4</sup> In the JIKI trial, the elevated baseline creatinine level was lethal in virtually all enrolled patients (97%) with a low cycle-threshold value for the virus (<20).<sup>5</sup> In the ZMapp trial, patients receiving the standard of care appear to have had slightly higher baseline creatinine levels; it was not reported whether there was a significant between-group difference. It is conceivable that such differences between study groups contributed to the improved survival trend attributed to the ZMapp intervention.

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No potential conflict of interest relevant to this letter was reported.

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**THE AUTHORS REPLY:** Jacob and Fletcher raise important issues of potential bias in assessments of survival between the study groups, specifically citing differences in monitoring during follow-up and the possibility of chance imbalances in baseline creatinine levels. As acknowledged in the Discussion section of the article, one limitation of the trial was its open-label strategy (rather than a double-blind, placebo-controlled strategy), which may have influenced bedside monitoring during infusions. Accordingly, we cannot say whether the additional bedside monitoring provided some benefit to ZMapp recipients that was independent of any effect of ZMapp itself. If so, however, it did not translate objectively into any differen-

tial provision of daily measures of supportive care between groups (see Table S3 in the Supplementary Appendix, available with the full text of the article at NEJM.org). Consonant with prevailing recommendations,<sup>1-3</sup> P values for baseline comparisons were not reported (Table 1 of our article). Consistent with other reports, higher baseline creatinine levels (>2 mg per deciliter vs. ≤2 mg per deciliter) were associated with an overall increased risk of death (crude odds ratio, 15.0; P=0.004) in our trial. However, the inclusion of baseline creatinine levels (available for only 44 of 71 patients) as a covariate with location and polymerase-chain-reaction cycle threshold did not alter the odds ratio for mortality with ZMapp versus control (odds ratio, 0.21; 95% confidence interval [CI], 0.03 to 1.48) from that without the inclusion of creatinine levels (odds ratio, 0.24; 95% CI, 0.04 to 1.33).

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## Von Willebrand's Disease

**TO THE EDITOR:** In their review article on von Willebrand's disease, Leebeek and Eikenboom (Nov. 24 issue)<sup>1</sup> state that it is reasonable to measure both levels of factor VIII and ristocetin cofactor activities during surgery in order to monitor the patient's hemostatic response to replacement therapy with concentrates containing both von Willebrand factor and factor VIII. We think that levels of factor VIII alone should be measured because they are the best predictor of hemostasis in patients undergoing surgery.

Patients with alloantibodies to von Willebrand factor<sup>2</sup> have safely undergone surgery with the use of recombinant factor VIII that is devoid of von Willebrand factor.<sup>3,4</sup> This indicates that the control of soft-tissue and surgical bleeding depends on factor VIII rather than on ristocetin cofactor levels, which remain unmeasurable in plasma throughout the postinfusion period because of the neutralizing action of alloantibodies.<sup>3,4</sup> Furthermore, levels of factor VIII increase more than would be predicted from the administered dose, owing to its endogenous stabilization by the infused von Willebrand factor and accumulation of the factor VIII contained in concentrates. Thus, since evidence that surgical hemostasis depends on ristocetin cofactor levels

is lacking, it is important to monitor levels of factor VIII after surgery.

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Dr. Mannucci reports receiving lecture fees from Alexion Pharmaceuticals, Baxalta, Bayer, Grifols, Kedrion Biopharma, and Novo Nordisk. No other potential conflict of interest relevant to this letter was reported.

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**THE AUTHORS REPLY:** Mannucci and Franchini suggest that monitoring patients with von Willebrand's disease during surgery should involve