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FEAST trial – external validity, interpretation and ethical conduct (Word count 481)

Kathryn Maitland, Abdel Babiker, Sarah Kiguli and Elizabeth Molyneux on behalf of the FEAST trial Group.

The FEAST team investigators acknowledge that the assimilation of the FEAST trial results is challenging¹, since they question decades of practice in resource-rich countries and our understanding of the pathophysiology of shock in severe infection. This is precisely why carefully conducted randomised clinical trials are so important, since they generate robust data to guide and change clinical practice. We now welcome discussion of the possible explanations and interpretations of our findings.

Professor Duke's recent commentary in *The Lancet* (28 May 2011)² contains two main criticisms of FEAST: (1) That the inclusion criteria were broader than those used in most shock classification systems, prompting him to question any extrapolation of the results to children with 'shock'; (2) That final diagnoses were not reported, although the characteristics of the trial population suggested that many of the children had conditions (severe anaemia, pneumonia, meningitis/encephalopathy) that may be adversely affected by bolus administration. Finally, he voices concern over the protocol amendment to increase the volume of fluid boluses.

First, fluid boluses were associated with increased mortality, regardless of the clinical criteria used to define shock, including the stringent definition used by WHO (presence of cold hands or feet with both capillary refill time of 4 or more seconds and a weak, fast pulse). Of the children in this category who received fluid boluses, 48% died, compared to 20% in the no bolus arm, an absolute risk difference of 28 percent (95% CI 3.4% - 52.5%) (Appendix Table 5)¹. Table 5 also shows increased mortality among children with moderate hypotension (192 children) and those with any one of the WHO clinical criteria for shock who received bolus therapy (1890 children). Second, final clinical diagnoses are shown in Appendix Table 2, Professor Duke's concern regarding children with oxygen saturation <90%, 'many of whom probably had pneumonia', is countered by the greater mortality associated with boluses among children **without** hypoxaemia than in those with hypoxaemia: risk ratio 1.91 vs 1.09 (p=0.04 for heterogeneity).

Finally, Professor Duke expresses concern that the protocol amendment to increase the volume of boluses was made at a time when it was already clear that boluses were harmful. This is incorrect; the Independent Data Monitoring Committee (IDMC) would not have permitted the trial to continue if there had been safety concerns at any of the interim analyses. The amendment was proposed by the study team (who were blinded to all interim results) in June 2010, because they were concerned that the trial might fail to reach a conclusive result, since bolus volumes were much lower than standard practice in resource-rich countries. The amendment was endorsed by the Trial Steering Committee. The published data includes additional children recruited after the penultimate review of the IDMC but before the implementation of the amendment from August 2010, following ethical committee approval. The investigators unanimously support recommendations made by the IDMC in the conduct of the FEAST trial.

1. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, et al. Mortality after Fluid Bolus in African Children with Severe Infection. *N Engl J Med*. 2011 May 26.

2. Duke T. What the African fluid-bolus trial means. *Lancet*. 2011 Jun 15.