

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011. DOI: [10.1056/NEJMoa1101549](https://doi.org/10.1056/NEJMoa1101549).

## **Contributory Listings**

The FEAST trial was designed by KM, ML, AGB and DMG with input from SK, ROO, CE, POO, SA, RO and HR. The trial was conducted at clinical centers in Uganda by SK, ROO, CE, POO, RO, in Tanzania by GM and HR and in Kilifi, Kenya by SA. The trial management (MM), monitoring (GO and MW) and data management (NW) was run out of the KEMRI-Wellcome Trust Programme, Clinical Trial Facility, Kilifi in consultation and collaboration with DMG, JC, MT, ECR and AGB of the MRC CTU. ECR and AGB wrote the trial analysis plan, which was reviewed and approved by TMG and TSC. ECR conducted the analyses, under supervision from AGB. The writing group were involved in the collection, interpretation of the data; and the drafting and revision of the manuscript for intellectual content; and the approval of the final manuscript. The first draft was written by the first author, together with DMG, AGB, ECR and ML and with contributions from members of the writing group. All authors vouch for the completeness and accuracy of the data presented. All authors had access to all the study data and participated in the decision to submit the manuscript for publication.

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Appendix Table 1: Baseline characteristics for children with severe hypotension enrolled into FEAST B.

	Albumin- bolus	Saline- bolus	Total
<b>Demographic/Anthropometry</b>	<b>13</b>	<b>16</b>	<b>29</b>
Age (months); median (IQR)	28 (22-84)	21 (10-47)	26 (11-47)
Female (%)	5 (38%)	8 (50%)	13 (45%)
MUAC $\leq$ 11.5cm (%)‡	1 (13%)	0 (0%)	1 (6%)
<b>Triage parameters</b>			
Axillary Temperature $>39^{\circ}\text{C}$ (%)	0 (0%)	1 (6%)	1 (4%)
Hypothermia (temperature $<36^{\circ}\text{C}$ ) (%)	5 (42%)	3 (19%)	8 (29%)
Respiratory distress (%)	13 (100%)	12 (86%)	25 (93%)
Respiratory rate; mean (SD)	44 (21.5)	53.4 (20.1)	49.6 (20.8)
Oxygen saturation $<90\%$ (%) †	3 (60%)	6 (55%)	9 (56%)
Bradycardia ( $< 80$ beats/min) (%)	4 (33%)	2 (14%)	6 (23%)
Severe Tachycardia (%)	5 (42%)	6 (43%)	11 (42%)
Weak radial pulse (%)	11 (85%)	14 (88%)	25 (86%)
Capillary refilling time: (2 or more secs) (%)	1 (8%)	3 (19%)	4 (14%)
(3 or more secs) (%)	10 (77%)	11 (69%)	21 (72%)
Temperature gradient (%) §	10 (77%)	14 (88%)	24 (83%)
Systolic blood pressure; median (IQR)	59 (51-60)	56 (47-59)	57 (51-59)
Dehydration (%)*	8 (62%)	5 (31%)	13 (45%)
Severe pallor (mucous membranes)	10 (77%)	11 (69%)	21 (72%)
Prostration (%) ‡	2 (15%)	6 (38%)	8 (28%)
Coma (%) ¶	10 (77%)	9 (56%)	19 (66%)
Convulsions in this illness (%)	2 (15%)	0 (0%)	2 (7%)
Hemoglobinuria (dark urine) (%)	2 (15%)	3 (19%)	5 (17%)
Jaundice (reported) (%)	6 (46%)	6 (38%)	12 (41%)
<b>Laboratory assessments*</b>			
Malaria parasitemia <sup>§</sup> positive (%)	8 (62%)	5 (31%)	13 (45%)
Hemoglobin $<5\text{g/dl}$ (%)	7 (58%)	6 (38%)	13 (46%)
$>10\text{g/dl}$ (%)	3 (25%)	2 (13%)	5 (18%)
Glucose $<2.5$ mmol/L (%)	2 (17%)	3 (20%)	5 (18%)
$<3.0$ mmol/L (%)	2 (15%)	3 (20%)	5 (18%)
Lactate $\geq 5\text{mmol/L}$ (%)	10 (83%)	10 (63%)	20 (71%)
Base deficit $>8$ (%)	8 (100%)	9 (90%)	17 (94%)
Severe acidemia (ph $<7.2$ )	4 (50%)	5 (50%)	9 (50%)
Hyperkalemia ( $>6.5\text{mmol/L}$ )	3 (28%)	5 (50%)	8 (44%)
HIV antibody positive (%)	0 (0%)	2 (13%)	2 (7%)
Blood culture done (% positive)	7 (0%)	8 (25%)	15 (13%)
CSF culture done (% positive)	3 (0%)	2 (0%)	5 (0%)

‡ MUAC: mid-upper arm circumference;

† Oxygen saturation and pulse rate recorded by pulse oximeter;

§ Temperature gradient was assessed using the back of hand running up from the toe to the knee: a positive temperature gradient: notable temperature change from cold (dorsum of foot) to warm (knee).

\* Dehydration defined as sunken eyes or decreased skin turgor.

‡ prostration: inability to sit upright if  $>8$ months or breast feed if  $<8$ m;

¶ coma: inability to localise a painful stimulus

\* Venous blood was obtained at admission for immediate analyses with handheld blood analyser

(i-STAT, Abbott Laboratories, Abbott Park, IL, USA), hemoglobin (HemOcue, Ångelholm Sweden),

blood glucose and lactate and HIV antibody testing. Not all parameters were available- so denominators vary.

Blood smears for malaria parasites were prepared for immediate reading and subsequent quality control.

Admission blood cultures were collected at certain centers only.

§ All *Plasmodium falciparum* apart from 3 *Plasmodium vivax* and 1 *Plasmodium ovale*.

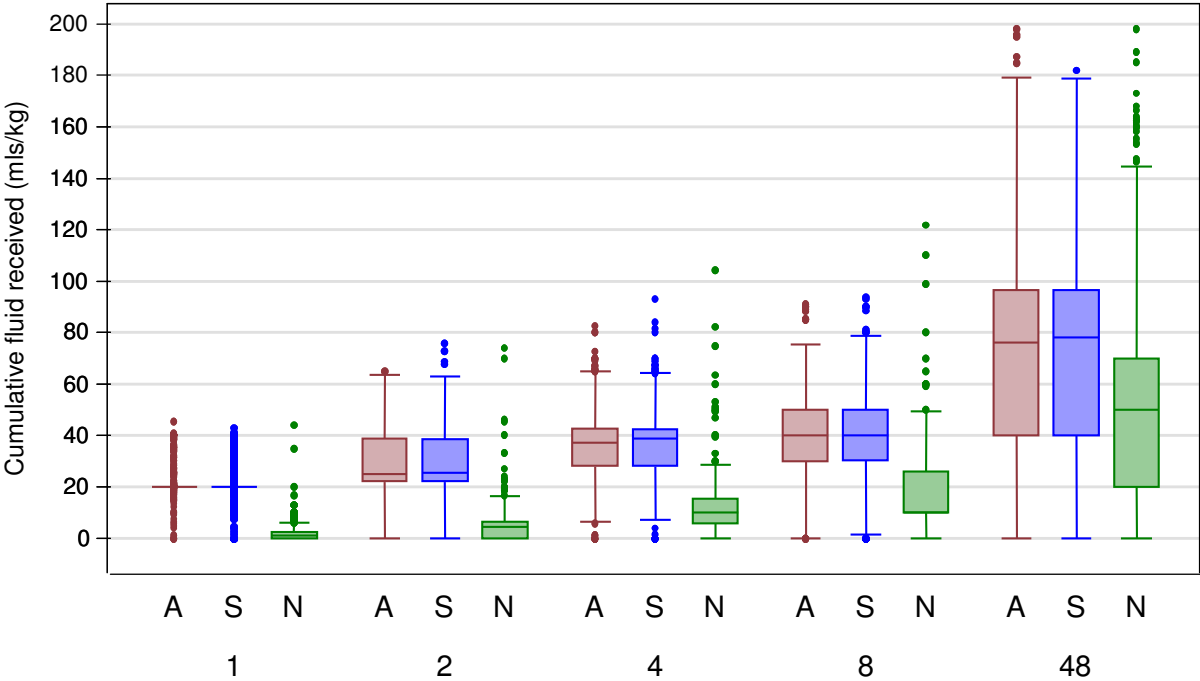
Appendix Table 2. 'Working' diagnoses made by clinician by 48 hours after admission.

	Treatment Group			Total
	Albumin	Saline	Control	
Children randomised	1050	1047	1044	3141
<b>Working diagnosis<sup>†</sup> (more than one permitted)</b>				
Severe malaria	688 (66%)	693 (66%)	698 (67%)	2079 (66%)
Severe anemia	468 (45%)	449 (43%)	428 (41%)	1345 (43%)
Lower respiratory tract infection	455 (43%)	442 (42%)	418 (40%)	1315 (42%)
Sepsis/septicemia	172 (16%)	158 (15%)	140 (13%)	470 (15%)
Upper respiratory tract infection	117 (11%)	108 (10%)	125 (12%)	350 (11%)
Meningitis	26 (3%)	34 (3%)	39 (4%)	99 (3%)
HIV/AIDS	26 (6%)	18 (2%)	28 (3%)	72 (2%)
Other*	330 (31%)	313 (30%)	339 (32%)	982 (31%)

† Multiple diagnoses were recorded. Since WHO pneumonia criteria encompass any child with respiratory distress or impaired consciousness this diagnosis was frequently recorded. Previous studies have shown that children with metabolic acidosis would be labelled as pneumonia (LRTI) according to WHO criteria, with up to up to 45% of children admitted with respiratory signs indicative of severe LRTI probably had malaria as the primary diagnosis (English et al TRSHTM 1996). WHO guidelines do not recognised sepsis as a specific entity, thus infrequently diagnosed. Few children had chest x-rays or other investigations and therefore working diagnoses should be considered with these caveats in mind.

\* Other includes: urinary tract infection (64), sickle cell disease (56), malnutrition (44), developmental delay/cerebral palsy(41), gastroenteritis (32), other chest condition(29), tuberculosis(28), hepatitis(26), encephalitis(25), abscess/cellulitis(3), mild/moderate anemia(91).

Appendix Figure 1: Box and Whisker plot describing median (IQR) and lower and upper adjacent values for all cumulative fluid (bolus, blood and maintenance) received at each clinical review time point by arm.



	1 hour			2 hours			4 hours			8 hours			48 hours		
	A	S	N	A	S	N	A	S	N	A	S	N	A	S	N
Number of children received fluids	1045	1041	640	1045	1041	781	1045	1041	820	1044	1041	832	1044	1041	865
Total fluid median (IQR)	20 (20,20)	20 (20,20)	1.2 (0,2.5)	25.1 (22,39)	25.5 (22,39)	4.5 (0, 6.7)	37.1 (29, 43)	38.7 (28,43)	10 (6,15)	40 (30,50)	40 (30,50)	10.1 (10,26)	76.2 (40,97)	78.1 (40,97)	50 (20,70)

A Albumin-bolus, S Saline-bolus, N No bolus control

Note: At 1 hour, the IQR in the bolus arms is zero and so no upper and lower adjacent values are plotted. There were 5, 6 and 179 children in the albumin-bolus, saline-bolus and no bolus control arms respectively that received no intravenous fluid during the trial. Values are truncated at 200mls/kg for the 48 hour time point.

Appendix Table 3a) Median (IQR) and mean (SD) (mls/kg/hr) of all fluids administered during trial by each time point.

	ALBUMIN-BOLUS				SALINE- BOLUS				NO BOLUS CONTROL			
	all fluids	Bolus	Blood	Maintenance	all fluids	Bolus	Blood	Maintenance	all fluids	Bolus	Blood	Maintenance
Total number enrolled.	1050	1050	1050	1050	1047	1047	1047	1047	1044	1044	1044	1044
<b>Total fluid received in first 1 hour</b>												
number of children that received fluid (%)	1045 (99%)	1045 (99%)	26 (2%)	10 (1%)	1041 (99%)	1041 (99%)	38 (4%)	15 (1%)	640 (61%)	2* (0.2%)	207 (20%)	439 (42%)
median amount of fluid (IQR) mls/kg/hr in those that received fluid	20 (20,20)	20 (20,20)	0.1 (0.07, 1.5)	0.06 (0.06, 2.2)	20 (20,20)	20 (20,20)	0.1 (0.07, 1.2)	0.06 (0.05, 0.07)	2.2 (1.4, 3.2)	28.3 (12.8, 43.7)	2.8 (1.6, 4.4)	1.9 (1.3, 2.7)
mean amount of fluid (sd) mls/kg/hr in those that received fluid	22.2 (6.6)	22.2 (6.5)	1.7 (4.0)	1.0 (1.7)	22.2 (6.7)	22.2 (6.7)	1.6 (3.6)	0.1 (0.2)	2.7 (2.9)	28.3 (21.8)	3.2 (2.2)	2.3 (2.3)
median amount of fluid (IQR) mls/kg/hr in all children alive	20 (20,20)	20 (20,20)	0 (0, 0)	0 (0,0)	20 (20,20)	20 (20,20)	0 (0,0)	0 (0,0)	1.2 (0, 2.5)	0 (0,0)	0 (0,0)	0 (0, 1.8)
mean amount of fluid (SD) mls/kg/hr in all children alive	22.1 (6.7)	22.1 (6.7)	0.04 (0.7)	0.01 (0.2)	22.1 (6.9)	22.1 (6.9)	0.06 (0.7)	0.002 (0.02)	1.7 (2.6)	0.05 (1.4)	0.6 (1.6)	1.0 (1.9)
<b>Total fluid received in second hour</b>												
number alive at beginning of second hour	1032	1032	1032	1032	1030	1030	1030	1030	1031	1031	1031	1031
number of children that received fluid (%)	829 (80%)	390 (38%)	284 (28%)	237 (23%)	852 (83%)	368 (36%)	324 (31%)	227 (22%)	775 (75%)	7 (0.7%)	294 (29%)	514 (50%)
number of children with impaired perfusion at beginning of second hour	586 (57%)	586 (57%)	586 (57%)	586 (57%)	596 (58%)	596 (58%)	596 (58%)	596 (58%)	702 (68%)	702 (68%)	702 (68%)	702 (68%)
median amount of fluid (IQR) mls/kg/hr in those that received fluid	5.9 (3.2, 17.8)	18.2 (13.5, 19.7)	4.8 (3.9, 5.9)	2.3 (1.7, 3.0)	6.0 (3.3, 17.4)	18.2 (14.2, 19.7)	5.5 (4.3, 6.2)	2.1 (1.3, 2.6)	3.3 (2.9, 5.7)	27.0 (20.1, 40)	6.01 (3.8, 6.6)	2.9 (2.5, 3.3)
mean amount of fluid (sd) mls/kg/hr in those that received fluid	9.5 (7.4)	15.2 (6.5)	5.1 (2.2)	2.4 (2.4)	9.5 (7.5)	15.7 (6.5)	5.6 (2.9)	2.1 (1.2)	4.4 (3.6)	28.0 (9.4)	5.7 (2.3)	3.0 (2.0)
median amount of fluid (IQR) mls/kg/hr in all children alive	4.5 (1.7, 16.2)	0 (0, 16.0)	0 (0, 2.3)	0 (0,0)	5.0 (1.7, 16)	0 (0, 15.6)	0 (0, 4.0)	0 (0,0)	2.9 (0.2, 4.2)	0 (0, 0)	0 (0, 3.3)	0 (0, 2.9)
mean amount of fluid (SD) mls/kg/hr in all children alive	7.7 (7.6)	5.7 (8.4)	1.4 (2.5)	0.6 (1.5)	7.8 (7.7)	5.6 (8.5)	1.8 (3.1)	0.5 (1.0)	3.3 (3.6)	0.2 (2.4)	1.6 (2.8)	1.5 (2.1)
<b>Total fluid received in third and fourth hours</b>												
number alive at beginning of third hour	1021	1021	1021	1021	1018	1018	1018	1018	1021	1021	1021	1021
number of children that received fluid (%)	823 (81%)	226 (22%)	328 (32%)	499 (49%)	825 (81%)	204 (20%)	354 (35%)	489 (48%)	795 (78%)	5 (0.5%)	318 (31%)	600 (59%)
median amount of fluid (IQR) mls/kg/hr in those that received fluid	3.4 (2.8, 5.7)	1.3 (0.4, 2.4)	5.5 (3.6, 6.2)	2.8 (2.1, 3.3)	3.5 (2.7, 6.1)	1.2 (0.6, 2.3)	5.9 (3.7, 6.6)	2.6 (1.9, 2.8)	2.9 (2.6, 4.8)	12.0 (10.7, 13.1)	4.6 (2.9, 6.0)	2.7 (2.3, 2.9)
mean amount of fluid (sd) mls/kg/hr in those that received fluid	4.1 (2.2)	1.9 (2.5)	5.0 (1.7)	2.6 (0.9)	4.1 (2.2)	1.8 (2.1)	5.2 (1.9)	2.4 (1.0)	3.9 (2.2)	14.4 (8.8)	4.4 (1.9)	2.7 (1.1)
median amount of fluid (IQR) mls/kg/hr in all children alive	3.3 (1.4, 5.0)	0 (0, 0)	0 (0, 3.3)	0 (0, 2.7)	2.8 (1.4, 5.2)	0 (0,0)	0 (0, 4.0)	0 (0, 2.5)	2.8 (1.6, 4.1)	0 (0,0)	0 (0, 2.5)	1.9 (0, 2.8)
mean amount of fluid (SD) mls/kg/hr in all children alive	3.3 (2.5)	0.4 (1.4)	1.6 (2.5)	1.3 (1.5)	3.3 (2.6)	0.4 (1.2)	1.8 (2.7)	1.2 (1.4)	3.0 (2.5)	0.1 (1.1)	1.4 (2.3)	1.6 (1.6)

<b>Total fluid received in fifth to eighth hour</b>												
number alive at beginning of fifth hour	1006	1006	1006	1006	1003	1003	1003	1003	1010	1010	1010	1010
number of children that received fluid (%)	737 (73%)	4 (0.4%)	263 (26%)	643 (64%)	739 (74%)	5 (0.5%)	251 (25%)	663 (66%)	608 (60%)	3 (0.3%)	170 (17%)	543 (54%)
median amount of fluid (IQR) mls/kg/hr in those that received fluid	1.8 (1.0, 3.1)	1.3 (0.3, 2.3)	0.9 (0.5, 2.4)	1.6 (0.9, 2.5)	1.9 (1.1, 2.8)	4.7 (2.4, 5)	0.7 (0.3, 2.1)	1.7 (1.0, 2.5)	2.0 (0.7, 3.0)	5 (1.7, 10)	1.4 (0.6, 2.6)	1.7 (0.6, 2.5)
mean amount of fluid (sd) mls/kg/hr in those that received fluid	2.1 (1.5)	1.3 (1.2)	1.5 (1.4)	1.8 (1.2)	2.1 (1.4)	3.7 (1.6)	1.3 (1.4)	1.8 (1.1)	2.1 (1.6)	5.6 (4.2)	1.8 (1.5)	1.8 (1.4)
median amount of fluid (IQR) mls/kg/hr in all children alive	1.1 (0, 2.6)	0 (0,0)	0 (0, 0.2)	0.8 (0, 2.0)	1.3 (0, 2.5)	0 (0,0)	0 (0, 0.01)	1.0 (0, 2.1)	0.4 (0, 2.3)	0 (0,0)	0 (0, 0)	0.2 (0, 1.8)
mean amount of fluid (SD) mls/kg/hr in all children alive	1.5 (1.6)	0.01 (0.1)	0.4 (1.0)	1.1 (1.3)	1.6 (1.5)	0.02 (0.3)	0.3 (0.9)	1.2 (1.2)	1.3 (1.6)	0.02 (0.4)	0.3 (0.9)	0.9 (1.3)
<b>Total fluid received in eighth to forty-eighth hour</b>												
number alive at beginning of eighth hour	991	991	991	991	984	984	984	984	997	997	997	997
number of children that received fluid (%)	734 (74%)	4 (0.4%)	210 (21%)	689 (70%)	741 (75%)	2 (0.2%)	208 (21%)	704 (72%)	758 (76%)	3 (0.3%)	181 (18%)	721 (72%)
median amount of fluid (IQR) mls/kg/hr in those that received fluid	1 (0.8, 1.3)	0.5 (0.4, 0.5)	0.5 (0.3, 0.5)	1 (0.8, 1.3)	1 (0.8, 1.3)	0.3 (0.03, 0.6)	0.5 (0.3, 0.5)	1 (0.8, 1.3)	1.1 (0.8, 1.3)	1 (0.2, 1)	0.5 (0.3, 0.5)	1 (0.8, 1.3)
mean amount of fluid (sd) mls/kg/hr in those that received fluid	1.1 (0.6)	0.5 (0.1)	0.4 (0.2)	1.0 (0.5)	1.1 (0.6)	0.3 (0.4)	0.4 (0.2)	1.1 (0.6)	1.1 (0.6)	0.7 (0.4)	0.4 (0.2)	1.1 (0.6)
median amount of fluid (IQR) mls/kg/hr in all children alive	1.0 (0, 1.3)	0 (0,0)	0 (0,0)	0.8 (0, 1.2)	0.9 (0.1, 1.3)	0 (0,0)	0 (0,0)	0.8 (0, 1.3)	1 (0.2, 1.3)	0 (0,0)	0 (0,0)	0.8 (0, 1.3)
mean amount of fluid (SD) mls/kg/hr in all children alive	0.8 (0.7)	0.002 (0.03)	0.1 (0.2)	0.7 (0.6)	0.8 (0.7)	0.001 (0.02)	0.1 (0.2)	0.8 (0.7)	0.9 (0.7)	0.002 (0.04)	0.1 (0.2)	0.8 (0.7)

\*One child received study fluid for severe hypotension, one child received treatment for severe dehydration and vomiting.

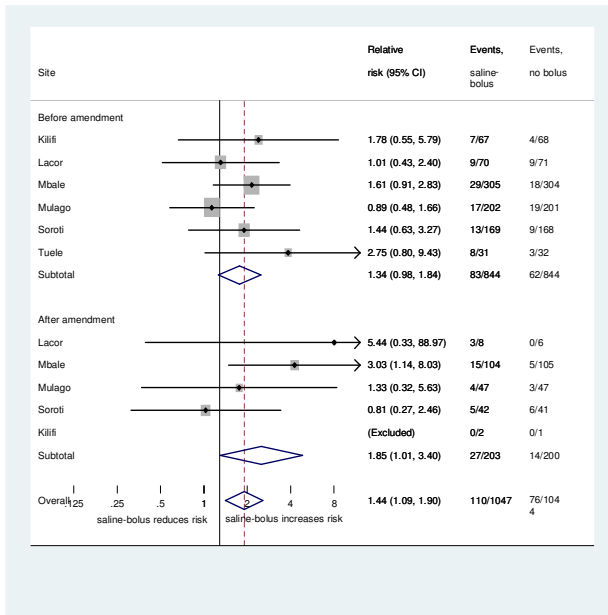


Appendix Table 3b) Cumulative median (IQR) and mean (SD) (mls/kg) of all fluids administered during trial by each time point.

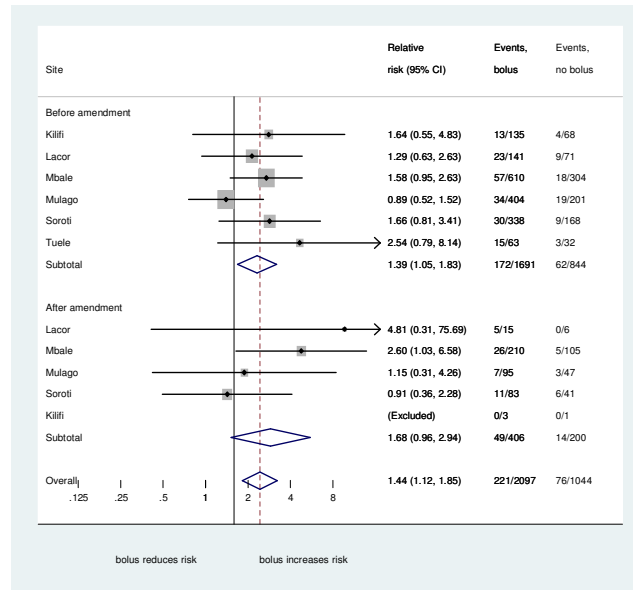
	ALBUMIN-BOLUS				SALINE-BOLUS				NO BOLUS CONTROL			
	Overall	Bolus	Blood	Maintenance	Overall	Bolus	Blood	Maintenance	Overall	Bolus	Blood	Maintenance
Total number enrolled.	1050	1050	1050	1050	1047	1047	1047	1047	1044	1044	1044	1044
<b>Total fluid received in first 1 hour</b>												
number of children that received fluid (%)	1045 (99%)	1045 (99%)	26 (2%)	10 (1%)	1041 (99%)	1041 (99%)	38 (4%)	15 (1%)	640 (61%)	2 (0.2%)	207 (20%)	439 (42%)
median amount of fluid (IQR) mls/kg	20 (20,20)	20 (20,20)	0 (0, 0)	0 (0,0)	20 (20,20)	20 (20,20)	0 (0,0)	0 (0,0)	1.2 (0, 2.5)	0 (0,0)	0 (0,0)	0 (0, 1.8)
mean amount of fluid (SD) mls/kg	22.1 (6.7)	22.1 (6.7)	0.04 (0.7)	0.01 (0.2)	22.1 (6.9)	22.1 (6.9)	0.06 (0.7)	0.002 (0.02)	1.7 (2.6)	0.05(1.4)	0.6 (1.6)	1.0 (1.9)
<b>Total fluid received by end of second hour</b>												
number of children that received fluid (%)	1045 (99%)	1045	284 (27%)	238 (23%)	1041 (99%)	1041	325 (31%)	227 (22%)	781 (75%)	7 (0.7%)	296 (28%)	524 (50%)
median amount of fluid (IQR) mls/kg	25.1 (21.9,38.9)	20 (20, 38.9)	0 (0, 2.0)	0 (0,0)	25.5 (22.0,38.6)	20 (20, 38.5)	0 (0, 4.1)	0 (0,0)	4.5 (0, 6.7)	0 (0,0)	0 (0, 3.5)	0.1 (0, 4.6)
mean amount of fluid (SD) mls/kg	29.6 (10.8)	27.7 (11.5)	1.4 (2.7)	0.6 (1.5)	29.8 (11.1)	27.6 (11.7)	1.8 (3.2)	0.5 (1.0)	4.9 (5.6)	0.2 (3.3)	2.2 (4.2)	2.5 (3.8)
<b>Total fluid received by end of fourth hours</b>												
number of children that received fluid (%)	1045 (99%)	1045	330 (31%)	501 (48%)	1041 (99%)	1041	363 (35%)	492 (47%)	820 (79%)	8 (0.8%)	340 (33%)	628 (60%)
median amount of fluid (IQR) mls/kg	37.1 (28.0,42.8)	20 (20, 40)	0 (0, 10)	0 (0, 6.1)	38.7 (27.9,42.5)	20 (20,40)	0 (0, 11.9)	0 (0, 5.4)	10 (5.8,15.4)	0 (0,0)	0 (0, 10)	5 (0,10)
mean amount of fluid (SD) mls/kg	36.1 (11.6)	28.5 (12.4)	4.5 (7.3)	3.0 (3.8)	36.3 (11.6)	28.3 (12.4)	5.3 (8.0)	2.7 (3.5)	10.8 (9.2)	0.4 (4.9)	4.9 (7.7)	5.5 (6.3)
<b>Total fluid received by end of eighth hour</b>												
number of children that received fluid (%)	1045 (99%)	1045	366 (35%)	670 (64%)	1041 (99%)	1041	397 (38%)	684 (65%)	832 (80%)	10 (1%)	374 (36%)	725 (69%)
median amount of fluid (IQR) mls/kg	40 (30,50)	20 (20,40)	0 (0, 16.5)	10 (0,10)	40 (30.4,50)	20 (20,40)	0 (0, 18.9)	10 (0,10)	10.1 (10,25.9)	0 (0,0)	0 (0, 15.6)	10 (0,10)
mean amount of fluid (SD) mls/kg	42.0 (13.9)	28.6 (12.4)	6.1 (8.9)	7.4 (7.0)	42.3 (13.5)	28.4 (12.4)	6.6 (9.1)	7.4 (6.7)	15.7 (12.9)	0.5 (5.2)	6.1 (8.7)	9.2 (9.3)
<b>Total fluid received by end of forty-eighth hour</b>												
number of children that received fluid (%)	1045 (99%)	1045	472 (45%)	715 (68%)	1041 (99%)	1041	487 (47%)	739 (71%)	865 (83%)	13 (1%)	449 (43%)	767 (73%)
median amount of fluid (IQR) mls/kg	76.2 (40,96.5)	20 (20,40)	0 (0, 20)	40 (0, 59.6)	78.1 (40, 96.6)	20 (20,40)	0 (0,20)	40 (0, 58.1)	50 (20, 70)	0 (0,0)	0 (0,20)	40 (0, 60)
mean amount of fluid (SD) mls/kg	72.6 (34.6)	28.6 (12.4)	9.5 (12.1)	34.5 (30.9)	73.9 (36.1)	28.4 (12.4)	9.8 (12.2)	35.8 (32.2)	48.9 (36.7)	0.5 (5.4)	8.9 (11.6)	39.5 (34.8)

## Appendix Figure 2: Primary endpoint of mortality at 48 hours by clinical site

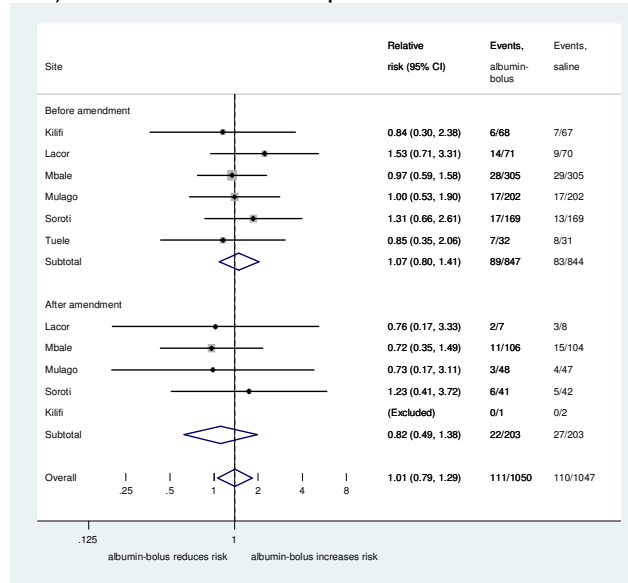
### i) Saline-bolus compared to no bolus



### iii) Any bolus compared to no bolus



### ii) Albumin-bolus compared to Saline-bolus



Appendix Table 4a) ERC adjudication of non-fatal solicited events

	Albumin-bolus	Saline-bolus	No bolus control	Total
<b>Non-fatal events within 48 hours.</b>				
Pulmonary edema (PE)				
events reported	1	0	0	1
events accepted (%)	1 (100%)	0	0	1 (100%)
Adjudicated relationship to fluids: possible/probable	1	0	0	1
Raised intracranial pressure (RICP)				
events reported	2	0	1	3
events accepted (%)	2 (100%)	0	1 (100%)	3 (100%)
Adjudicated relationship to fluids: unrelated/unlikely	1	0	0	1
possible/probable	1	0	0	1
uncertain	0	0	1	1
Allergic reaction reported				
events reported	4	4	3	11
events accepted (%)	3 (75%)	2 (50%)	2 (67%)	7 (64%)
Adjudicated relationship to fluids: unrelated/unlikely	0	2	2	4
possible/probable	1	0	0	1
uncertain	2	0	0	2
<b>Neurological sequelae at 28 days</b>				
events reported	33	29	26	88
events accepted (%)	22 (67%)	19 (66%)	20 (77%)	61 (69%)
Adjudicated relationship to fluids: unrelated/unlikely	17	17	20	54
possible/probable	1	0	0	1
uncertain	4	2	0	6

Appendix Table 4b): ERC adjudicated causes of death.

	Treatment Group			Total
	Albumin-bolus	Saline-bolus	No bolus control	
Total enrolled	1050	1047	1044	3141
<b>Diseases that led to death</b>				
<b>Total deaths</b>	128	126	91	345
<b>Primary disease that led to death</b>				
malaria	56	50	42	148
meningitis	7	10	7	24
pneumonia	21	21	13	55
septicemia	11	10	8	29
anemia	13	11	4	28
other*	9	9	7	25
insufficient information	11	15	10	36
<b>Secondary condition leading to death (can have more than one)</b>				
malaria	14	9	7	30
meningitis	1	2	0	3
pneumonia	16	15	11	42
septicemia	17	20	8	45
anemia	22	25	14	61
hypoglycemia	9	15	11	35
HIV	4	5	5	14
other **	16	14	9	39
insufficient information	3	4	3	10
<b>Solicited events possibly/probably present and contributing to death</b>				
Pulmonary Edema (PE)	13	6	5	24
Adjudicated relationship to fluids:				
Unlikely related	2	3	1	6
Possibly probably related	0	0	1	1
Uncertainly related	10	2	3	15
Insufficient information	1	1	0	2
Raised Intracranial Pressure (RICP)	14	18	10	42
Adjudicated relationship to fluids:				
Unlikely related	8	13	6	27
Possibly probably related	0	0	0	0
Uncertainly related	4	4	4	12
Insufficient information	2	1	0	3
Allergic Reaction	0	2	0	2
Adjudicated relationship to fluids:				
Unlikely related	0	2	0	2

Most diagnoses derived from clinical information, other than malaria few were supported by laboratory or clinical investigation

\* Acute diarrhoea (1), DIC (1), Encephalopathy(6), HIV (1), Hepatic encephalopathy(3), Hepatic failure(1), Hypoglycemia (1), Intravascular hemolysis (1), Laryngotracheitis (1), Pneumothorax (2), Renal failure (2), Sickle cell crisis(1), Sickle cell disease(1), Tetanus(1), Trauma(1), Tuberculosis (1)

\*\*Acute abdomen (1), Cellulitis(1), DIC (1), Downs Syndrome (1), Empyema(1), Encephalopathy(1), Epilepsy(2), Herpes Zoster(1), Hydrocephalus(3), Hyperkalemia(4), Intravascular hemolysis(1), Jaundice(1), Lower urinary tract infection (2), Malnutrition (3), Metabolic disorder(1), Raised urea(1), Renal failure(1), Sickle cell disease(5), Thrombocytopenia(1), Transfusion reaction (1), Tuberculosis(1)

Appendix Table 5: Risk ratios for mortality at 48 hours in various subgroups.

Subgroup	Events/Total (%)			Risk ratios			
	Albumin-bolus	Saline-bolus	No bolus control	Saline-bolus vs no bolus	Albumin-bolus vs no bolus	Albumin-bolus vs Saline-bolus	Bolus vs no bolus
<b>Overall</b>	111/1050 (10.6%)	110/1047 (10.5%)	76/1044 (7.3%)	1.44 (1.09-1.90)	1.45 (1.10-1.92)	1.00 (0.78-1.29)	1.45 (1.13-1.86)
Malaria +	57/590 (9.7%)	53/612 (8.7%)	34/591 (5.8%)	1.51 (0.99-2.28)	1.68 (1.12-2.53)	1.11 (0.78-1.59)	1.59 (1.10-2.31)
Malaria -	53/454 (11.7%)	55/430 (12.8%)	38/446 (8.5%)	1.50 (1.01-2.22)	1.37 (0.92-2.04)	0.91 (0.64-1.30)	1.43(1.01-2.04)
p-value heterogeneity				0.99	0.48	0.43	0.69
adjusted Risk ratio				1.50 (1.13-2.00)	1.51 (1.14-2.01)	1.01 (0.79-1.30)	1.51 (1.17-1.94)
Coma	39/156 (25.0%)	39/161 (24.2%)	33/140 (23.6%)	1.03 (0.69-1.54)	1.06 (0.71-1.59)	1.03 (0.70-1.51)	1.04 (0.73-1.49)
No Coma	72/892 (8.1%)	71/885 (8.0%)	43/904 (4.8%)	1.69 (1.17-2.44)	1.70 (1.18-2.45)	1.00 (0.70-1.38)	1.69 (1.21-2.36)
p-value heterogeneity				0.07	0.09	0.92	0.05
adjusted Risk ratio				1.39 (1.06-1.82)	1.41 (1.08-1.85)	1.02 (0.79-1.30)	1.40 (1.10-1.79)
Before amendment	89/847 (10.5%)	83/844 (9.8%)	62/844 (7.4%)	1.34 (0.98-1.83)	1.43 (1.05-1.95)	1.07 (0.80-1.42)	1.38 (1.05-1.83)
After amendment	22/203 (10.9%)	27/203 (13.3%)	14/200 (7.0%)	1.90 (1.03-3.51)	1.54 (0.82-2.93)	0.81 (0.48-1.38)	1.72 (0.98-3.05)
p-value heterogeneity				0.32	0.83	0.38	0.5
adjusted Risk ratio				1.44 (1.09-1.91)	1.45 (1.10-1.91)	1.01 (0.78-1.39)	1.45 (1.13-1.86)
Severe anemia (hb<5)	52/323 (16.1%)	49/332 (14.8%)	30/332 (9.0%)	1.63 (1.06-2.51)	1.78 (1.17-2.72)	1.09 (0.76-1.56)	1.71 (1.16-2.51)
No severe anemia (hb>5)	56/701 (8.0%)	58/683 (8.5%)	43/683 (6.3%)	1.35 (0.92-1.97)	1.27 (0.87-1.86)	0.94 (0.66-1.34)	1.31 (0.93-1.84)
p-value heterogeneity				0.51	0.24	0.56	0.31
adjusted Risk ratio				1.47(1.10-1.95)	1.48 (1.11-1.96)	1.01 (0.78-1.29)	1.47 (1.14-1.90)
Acidosis (lactate>5)	80/357 (22.4%)	77/407 (18.9%)	59/395 (14.9%)	1.27 (0.93-1.73)	1.50 (1.11-2.03)	1.18 (0.90-1.57)	1.38 (1.05-1.81)
No acidosis (lactate<5)	25/643 (3.9%)	24/582 (4.1%)	11/597 (1.8%)	2.24 (1.11-4.53)	2.11 (1.05-4.25)	0.94 (0.54-1.63)	2.17 (1.13-4.14)
p-value heterogeneity				0.14	0.38	0.47	0.2
adjusted Risk ratio				1.42 (1.08-1.88)	1.60 (1.21-2.12)	1.12 (0.87-1.44)	1.50 (1.17-1.93)
Acidosis (base deficit>8)	70/380 (18.4%)	58/360 (16.1%)	34/330 (10.3%)	1.56 (1.05-2.32)	1.79 (1.22-2.62)	1.14 (0.83-1.57)	1.68 (1.18-2.39)
No acidosis (base deficit<8)	10/330 (3.0%)	10/329 (3.0%)	10/350 (2.9%)	1.06 (0.45-2.52)	1.06 (0.45-2.51)	1.00 (0.42-2.37)	1.06 (0.50-2.24)
p-value heterogeneity				0.43	0.28	0.77	0.28
adjusted Risk ratio				1.46 (1.02-2.09)	1.63 (1.15-2.31)	1.12 (0.83-1.51)	1.54 (1.12-2.13)
WHO shock score*	85/632 (13%)	93/645 (14%)	61/613 (10%)	1.45 (1.07-1.96)	1.35 (0.99-1.84)	0.93 (0.71-1.23)	1.40 (1.06-1.84)
Not satisfying WHO shock score criteria	26/416 (6%)	17/399 (4%)	14/428 (3%)	1.30 (0.65-2.61)	1.91 (1.01-3.61)	1.47 (0.81-2.66)	1.61 (0.89-2.91)
p-value heterogeneity				0.78	0.34	0.18	0.67
adjusted Risk ratio				1.42 (1.08-1.88)	1.45 (1.10-1.91)	1.02 (0.79-1.30)	1.44 (1.12-1.85)
Moderate hypotension <sup>‡</sup>	16/66 (24%)	18/69 (26%)	9/57 (16%)	1.65 (0.80-3.39)	1.53 (0.73-3.20)	0.93 (0.52-1.66)	1.60 (0.81-3.11)
No hypotension	91/964 (9%)	89/967 (9%)	65/977 (7%)	1.38 (1.02-1.88)	1.42 (1.05-1.93)	1.03 (0.78-1.35)	1.40 (1.07-1.84)
p-value heterogeneity				0.66	0.85	0.76	0.72
adjusted Risk ratio				1.41 (1.07-1.88)	1.43 (1.08-1.90)	1.01 (0.79-1.30)	1.43 (1.11-1.83)
Severe dehydration <sup>§</sup>	12/78 (15%)	26/95 (28%)	8/58 (13%)	1.98 (0.97-4.08)	1.11 (0.49-2.55)	0.56 (0.30-1.04)	1.59 (0.79-3.21)
No dehydration	98/971 (10%)	82/947 (9%)	67/984 (7%)	1.27 (0.93-1.73)	1.48 (1.10-2.00)	1.16 (0.88-1.54)	1.38 (1.05-1.81)
p-value heterogeneity				0.27	0.53	0.03	0.71
adjusted Risk ratio				1.37 (1.03-1.81)	1.44 (1.09-1.90)	1.03 (0.80-1.33)	1.40 (1.09-1.81)

\*Child has any one of: capillary refill time (CRT) of 4 seconds or more, weak pulse or cold limbs.

Stringent WHO guidelines for shock of CRT 4 or more and cold hands and weak pulse was only detected in 65 patients (mortality 11 (42%),13 (54%) and 3 (20%) in the albumin-bolus, saline-bolus and control arms respectively).

<sup>‡</sup> Moderate hypotension: systolic blood pressure [ $<12$ months : 50-75mmHg] or [12months to 5years : 60-75mmHg] or [ $>5$ years : 70-85mmHg]

<sup>§</sup> Severe dehydration defined as decreased skin turgor or sunken eyes.