Online supplement to:

Randomised trials of human albumin for adults with sepsis: systematic review and meta-analysis with trial sequential analysis of all-cause mortality

Amit Patel,[1,2,3] ***Specialist Registrar & Clinical Lecturer***

Michael A. Laffan,[3] ***Professor & Consultant***

Umeer Waheed,[1] ***Consultant***

Stephen J. Brett,[1] ***Reader & Consultant***

1 Centre for Perioperative Medicine and Critical Care Research, Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, UK

2 MRC Clinical Sciences Centre, Hammersmith Hospital, Imperial College London, London, UK

3 Centre for Haematology, Hammersmith Hospital, Imperial College London, London, UK

Dr Amit Patel

Centre for Perioperative Medicine and Critical Care Research

General Intensive Care Unit, Hammersmith Hospital, Imperial College Healthcare NHS Trust

Du Cane Road, London, W12 0HS, UK

T: (+44) 0208 383 4521

F: (+44) 0208 383 4142

E: amit.patel@imperial.ac.uk

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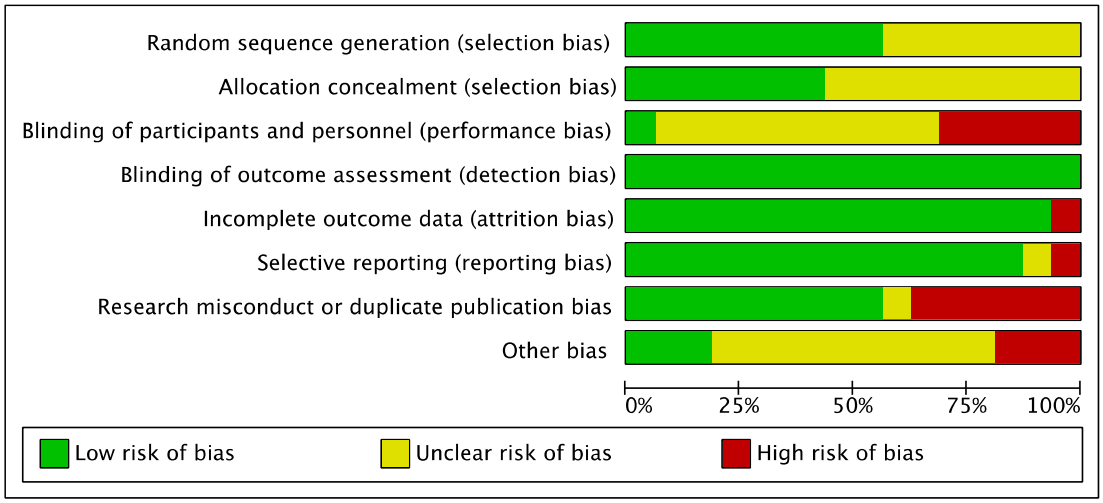
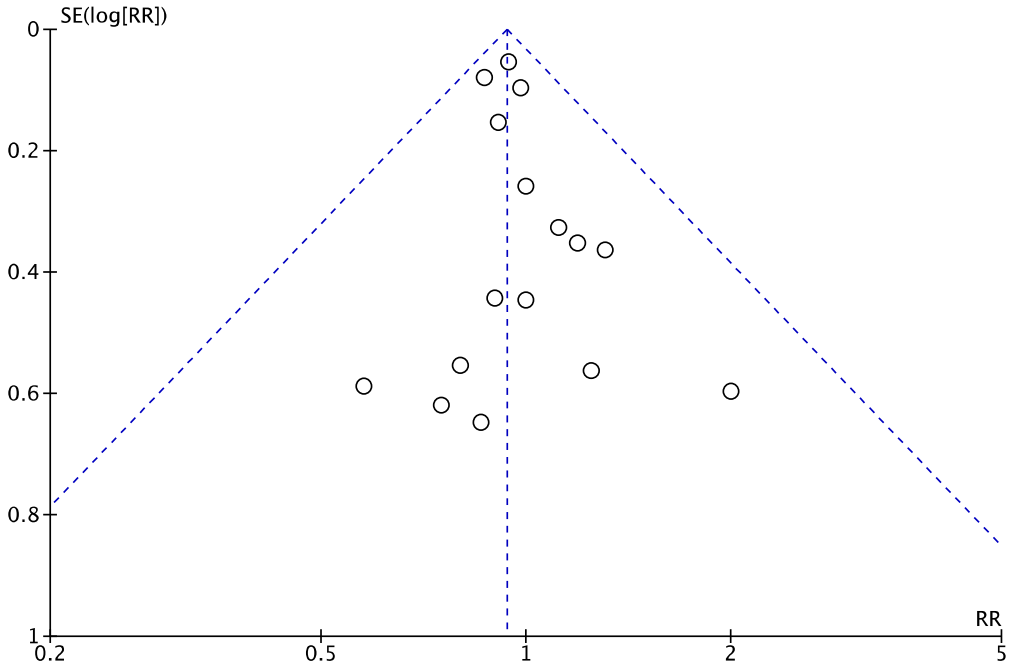
1. Risk of bias graph: reviewer judgements about each risk of bias domain

Risk of bias summary displaying review authors' judgements about each risk of bias domain across all the included studies.

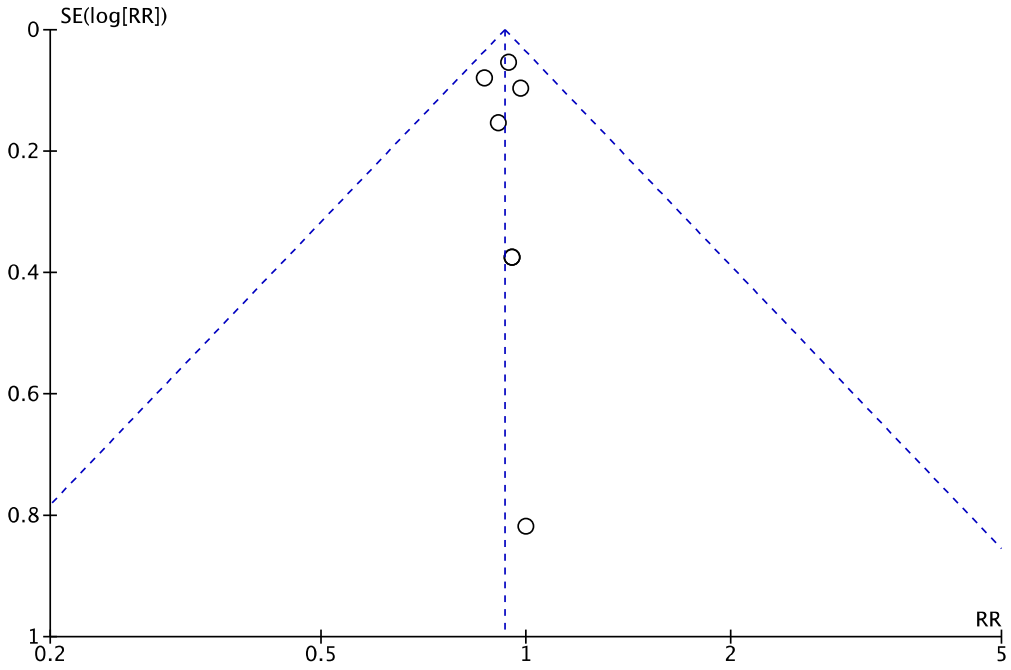


2. Funnel plots for the comparisons of human albumin with control, crystalloid, and colloid fluid

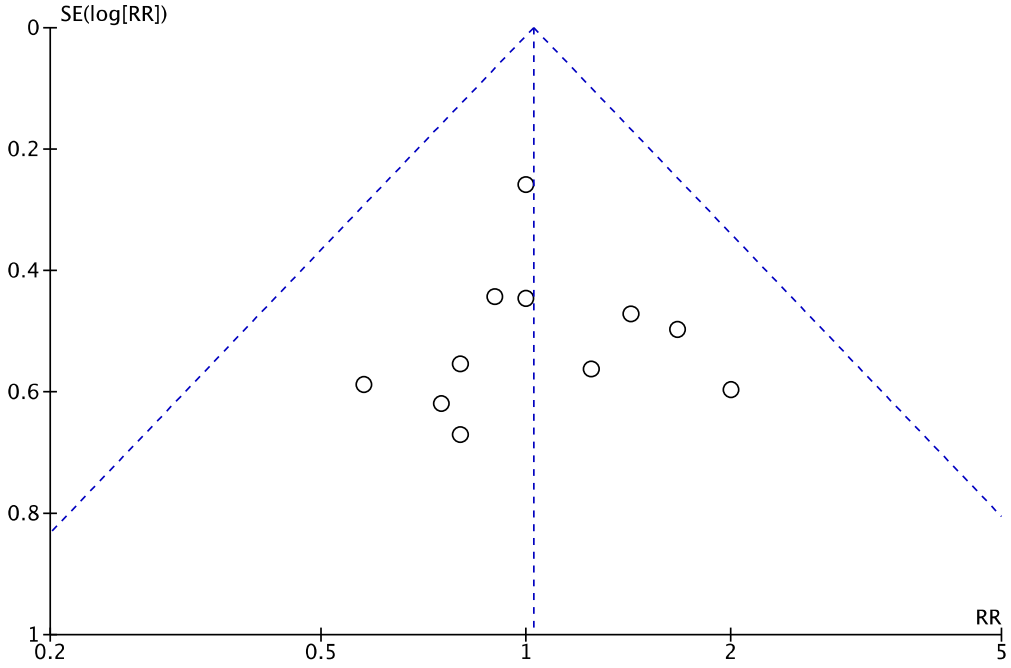
Funnel plot of studies reporting mortality of human albumin compared to control fluids. The relative risk (RR) and its standard error (SE) are plotted.



Funnel plot of studies reporting mortality of human albumin compared to crystalloid fluids. The relative risk (RR) and its standard error (SE) are plotted.



Funnel plot of studies reporting mortality of human albumin compared to colloid fluids. The relative risk (RR) and its standard error (SE) are plotted.



3. Characteristics of patients and albumin treatment

Characteristics of the sixteen randomised critical/intensive care studies included, reported in eighteen articles. The studies are presented alphabetically. Baseline patient characteristics of the albumin intervention group (or study population, @) are presented. Data are presented regarding albumin indication, therapeutic targets, total albumin dose administered, and post treatment albumin level. Abbreviations: Acute Physiology and Chronic Health Evaluation II (APACHE II); Sepsis-related Organ Failure Assessment (SOFA); Simplified Acute Physiology Score II (SAPS II); extravascular lung water (EVLW); acute respiratory distress syndrome (ARDS); colloid oncotic pressure (COP); cardiac index (CI); central venous pressure (CVP); pulmonary capillary wedge pressure (PCWP); pulmonary artery wedge pressure (PAWP); (ITBI); cardiac index (CI); base excess (BE); percentage saturation of mixed venous blood pulmonary artery blood (SvO2); relative risk reduction or increase (RRR(I)); absolute risk reduction or increase (ARR(I)); 95% confidence interval (95% CI); value unclearly or not reported (-); value estimated from a graph (~).

Randomised clinical trial	Primary study endpoint	Baseline medical patients (%)	Mean (SD) or median [IQR]: SAPS II*/ APACHE II§ / SOFA^	Pulmonary site of infection (%)	Mechanical Ventilation (%)	Baseline ARDS (%)	Baseline RRT (%)	Albumin indication	Albumin targets	Total albumin dose (g)	Total albumin volume (L)	Post-intervention albumin (g/L) (mean; SD) [median; IQR]	% RRR(I) / % ARR(I); (95% CI)
ALBIOS 2014[1]	28 day mortality	56.6	48.0 [37-59]* / 8 [6-10]^	38.8	78.5	-	-	Volume expansion and resuscitation with hypoalbuminaemia improvement	Early-goal directed therapy and albumin > 30 g/l	220	1.1	29.4 (3.3) on day 7	-5.8 (-15.5 to +5.1) / -2.5 (-7.0 to +2.1)
Boldt, et al 1995[2]	Coagulation parameters	0	23.4 (3.2)§	-	100	0	-	Volume resuscitation	CVP and/or PCWP 12-16 mmHg	350	1.7	-	0.0 (-39.7 to +65.9) / 0.0 (-33.7 to +33.7)
Boldt, Heesen, et al 1996[3]	Cardio-respiratory and splanchnic perfusion parameters	0	24.0 (2.3)§	-	100	0	-	Volume expansion and resuscitation	CVP and/or PCWP 10-15 mmHg	422	2.1	-	25.0 (-58.5 to +276.6) / 6.7 (-26.0 to +39.4)
Boldt, Müller et al 1996[4]	Platelet function	0	22.8 (3.2)§	-	100	28.6 [severe]	-	Volume expansion and resuscitation	CVP and/or PCWP 12-16 mmHg	358	1.8	-	-20.0 (-73.0 to +137.0) / -7.1 (-41.6 to +27.4)
Boldt, Muller et al 1996[5]	Soluble adhesion molecule parameters	0	20.3 (13.2) §	-	100	-	-	Volume expansion and resuscitation	PAWP 12-18 mmHg	505	2.5	-	100.0 (-38.0 to +545.2) / 21.4 (-12.2 to +55.1)

Dolecek et al 2009[6]	EVLW change	0	8.0 (2)^	66.7	100	0	0	Volume expansion and resuscitation	Normal ITBI (>850 mL/m-2) and cardiac index (CI >3.5 L/min/m-2)	120	0.6	29.5 (5.9)	-42.2 (-81.7 to +82.7) / -9.7 (-30.0 to +10.5)
EARSS 2011[7]	28 day mortality	73.7	51.0 [44-66]*	43.6	82.0	-	22.6	Volume expansion and resuscitation with hypoalbuminaemia improvement	Early-goal directed therapy and albumin > 25 g/l	180	0.9	~28 on day 3	-1.5 (-18.6 to +19.2) / 0.5 (-7.2 to +6.1)
Friedman et al 2008[8]	Haemodynamic parameters	-	-	-	100	100 [moderate]	-	Volume expansion and resuscitation	Physician discretion	16	0.4	-	-10.0 (-62.2 to +114.5) / -3.7 (-33.7 to +26.3)
Haupt et al 1982[9]	COP change	-	Pre-SAPS, APACHE, SOFA scoring	-	-	-	-	Volume expansion and resuscitation	PAWP 10-15 mmHg	155 @	3.1 @	-	19.0 (-40.3 to +137.3) / 11.4 (-33.8 to +56.6)
Metildi et al 1984[10]	Intra-pulmonary shunt fraction change	-	Pre-SAPS, APACHE, SOFA scoring	33.3	100	100 [moderate to severe]	-	Volume expansion and resuscitation	Normal arterial pH, BE, SvO2	170 @	3.4 @	-	-9.1 (-33.0 to +23.3) / -8.3 (-34.6 to +17.9)

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Palumbo et al 2006[11]	Unclear	45.0 @	19.7 (2.7)§	-	100	-	-	Volume expansion and resuscitation	PAWP 15-18 mmHg	-	-	-	-25.0 (-77.7 to +152.4) / -10.0 (-51.6 to +31.6)
Rackow et al 1983[12]	COP change, pulmonary oedema	-	Pre-SAPS, APACHE, SOFA scoring	-	-	-	-	Volume expansion and resuscitation	PAWP 15 mmHg	141 @	2.8 @	-	31.0 (-35.9 to +167.6 / 16.9 (-27.7 to 61.4)
Rackow et al 1989[13]	Cardio-respiratory and coagulation parameters	-	Pre-SAPS, SOFA scoring	50.0	60.0	-	-	Volume expansion and resuscitation	PAWP >15 mmHg or 2 L infused	49	1	-	0.0 (-58.4 to +140.3) / 0.0 (-43.8 to +43.8)
SAFE 2004[14] & 2011[15]	28 day mortality	78.1	21.6 (7.8)§	44.1	56.8	6.5 [moderate to severe]	3.8	Volume expansion and resuscitation with maintenance in ICU	Physician discretion	95	2.4	~≥25 on day 7	-13.0 (-26.0 to +2.1) / -4.6 (-9.9 to +0.7)
van der Heijden et al 2009[16] & Trof et al 2010[17]	EVLW change; COP, CI changes	-	16.0 (2)§	50.0	100	75@ [mild]	-	Volume expansion and resuscitation	CVP-guided fluid loading	300	1.5	27 (3)	-14.3 (-76.0 to +205.6 / -5.6 (-49.5 to +38.4)
Veneman et al 2004[18]	COP	-	22.0 (8)§ @	-	50.0 @	-	-	Volume expansion and resuscitation with hypoalbuminaemia	Haemodynamic and clinical parameters	180	0.9	-	11.6 (-41.1 to +111.5) / 6.5 (-32.3 to +45.3)

improvement

4. Sensitivity, bias and clinical subgroup, and meta-regression analyses for the comparisons of albumin with control fluid

Predefined sensitivity, bias and clinical subgroup, and meta-regression analyses for the comparisons of albumin with control fluid.

Abbreviations: not applicable (NA); Surviving Sepsis Campaign launch (SSC).[19 20]

Human albumin compared to control fluid										
Sensitivity analysis	**Measures of effects size and precision**						**Group heterogeneity**		**Subgroup difference**	
Category	Group or subgroup	Studies	Patients	Point estimate	95% confidence interval	P value	I^2	Chi^2 P value	I^2	Chi^2 P value
Fixed effects model with relative risk	All studies	16	4190	0.94	0.87 to 1.01	0.09	0	0.99	27.1	0.24
	Low or unclear risk of bias	6	3942	0.93	0.85 to 1.00	0.06	0	0.88	NA	NA
	High risk of bias	10	248	1.02	0.83 to 1.24	0.86	0	0.95	NA	NA
Fixed effects model with odds ratio	All studies	16	4190	0.90	0.79 to 1.02	0.09	0	0.99	0	0.32
	Low or unclear risk of bias	6	3942	0.88	0.78 to 1.01	0.06	0	0.90	NA	NA
	High risk of bias	10	248	1.18	0.68 to 2.03	0.56	0	0.97	NA	NA
Random effects model with odds ratio	All studies	16	4190	0.90	0.79 to 1.02	0.09	0	0.99	0	0.32

Trial exclusion: largest[1]	Low or unclear risk of bias	6	3942	0.88	0.78 to 1.01	0.06	0	0.90	NA	NA
	High risk of bias	10	248	1.17	0.67 to 2.05	0.57	0	0.97	NA	NA
	All studies	15	2380	0.94	0.85 to 1.05	0.22	0	0.98	0	0.35
Trial exclusion: greatest weight[1]	Low or unclear risk of bias	5	2132	0.91	0.81 to 1.03	0.13	0	0.81	NA	NA
	High risk of bias	10	248	1.02	0.83 to 1.24	0.86	0	0.95	NA	NA
	All studies	15	2380	0.94	0.85 to 1.05	0.22	0	0.98	0	0.35
Trial exclusion: greatest observed[14 15]	Low or unclear risk of bias	5	2132	0.91	0.81 to 1.03	0.13	0	0.81	NA	NA
	High risk of bias	10	248	1.02	0.83 to 1.24	0.86	0	0.95	NA	NA
	All studies	15	2972	0.96	0.88 to 1.05	0.35	0	0.99	0	0.53
	Low or unclear risk of bias	5	2724	0.95	0.86 to 1.04	0.27	0	0.92	NA	NA
	High risk of bias	10	248	1.02	0.83 to 1.24	0.86	0	0.95	NA	NA

Subgroup analysis		**Relative risk effect size measure with random effects model (Mantel-Haenszel) and precision**					**Group heterogeneity**		**Subgroup difference**	
Category	Subgroups	Studies	Patients	Point estimate	95% confidence interval	P value	I^2	Chi^2 P value	I^2	Chi^2 P value
Selection bias	Low or unclear risk	16	4190	0.94	0.94 to 1.01	0.11	0	0.99	NA	NA
	High risk	0	0	NA	NA	NA	NA	NA	NA	NA
Performance bias	Low or unclear risk	11	4091	0.94	0.87 to 1.01	0.10	0	0.94	0	0.88
	High risk	5	99	0.98	0.77 to 1.25	0.88	0	0.84	NA	NA
Detection bias	Low or unclear risk	16	4190	0.94	0.94 to 1.01	0.11	0	0.99	NA	NA
	High risk	0	0	NA	NA	NA	NA	NA	NA	NA
Attrition bias	Low or unclear risk	15	4157	0.94	0.87 to 1.01	0.10	0	0.98	0	0.60
	High risk	1	33	1.12	0.59 to 2.12	0.74	NA	NA	NA	NA
Reporting bias	Low or unclear risk	15	4157	0.94	0.87 to 1.01	0.10	0	0.98	0	0.60
	High risk	1	33	1.12	0.59 to 2.12	0.74	NA	NA	NA	NA
Research misconduct or duplication	Low or unclear risk	10	4039	0.93	0.86 to 1.00	0.06	0	0.99	38.6	0.20

publication bias										
	High risk	6	151	1.14	0.84 to 1.56	0.40	0	0.88	NA	NA
Other bias	Low or unclear risk	13	4102	0.94	0.87 to 1.01	0.10	0	0.95	0	0.78
	High risk	3	88	1.00	0.65 to 1.53	1.00	0	0.85	NA	NA
Data source bias	Conferences	2	2602	0.95	0.87 to 1.05	0.32	0	0.69	0	0.65
	Journal articles	14	1588	0.94	0.87 to 1.01	0.18	0	0.97	NA	NA
Author bias	Boldt et al	4	116	1.08	0.73 to 1.61	0.70	0	0.67	0	0.48
	Other authors	12	4074	0.94	0.87 to 1.01	0.09	0	0.98	NA	NA
Location bias	Europe	11	2893	0.96	0.87 to 1.05	0.34	0	0.98	0	0.54
	North America	4	79	0.99	0.77 to 1.27	0.95	0	0.71	NA	NA
	Australasia	1	1218	0.87	0.74 to 1.02	0.09	NA	NA	NA	NA
Small study bias	Multicentre	3	3820	0.93	0.86 to 1.02	0.08	0	0.58	0	0.54
	Single centre	13	370	0.99	0.82 to 1.20	0.94	0	0.98	NA	NA
Time bias	Post-SSC	6	2744	0.95	0.86 to 1.04	0.25	0	0.96	0	0.79
	Pre-SSC	10	1446	0.93	0.82 to 1.05	0.24	0	0.87	NA	NA
Disease severity (sepsis versus severe sepsis and/or septic shock)	Severe sepsis and/or septic shock	11	3854	0.94	0.87 to 1.01	0.09	0	0.96	0	0.55
	Sepsis	5	336	1.15	0.73 to 1.51	0.80	0	0.79	NA	NA
Disease severity (sepsis versus severe sepsis versus septic shock)	All studies	16	4190	0.94	0.87 to 1.01	0.08	0	0.88	0	0.76
	Septic shock	4	1962	0.92	0.83 to 1.02	0.10	0	0.45	NA	NA
	Severe sepsis	8	2070	0.95	0.85 to 1.06	0.35	0	0.67	NA	NA
	Sepsis	5	336	1.15	0.73 to 1.51	0.80	0	0.79	NA	NA
Intervention method	Predefined	4	2691	0.95	0.87 to 1.05	0.31	0	0.77	0	0.64
	Variable	16	1499	0.92	0.81 to 1.04	0.18	0	0.96	NA	NA
Intervention type	Hypooncotic (4-5% albumin)	7	1363	0.90	0.79 to 1.03	0.13	0	0.92	0	0.47
	Hyperoncotic (20% albumin)	9	2827	0.96	0.87 to 1.05	0.35	0	0.92	NA	NA

Intervention timing	Early (<24 hours)	6	3907	0.93	0.86 to 1.01	0.10	0	0.89	0	0.69
	Not described/other timing	10	283	0.98	0.80 to 1.20	0.82	0	0.93	NA	NA
Time of mortality observation	90 day	2	2602	0.95	0.87 to 1.05	0.32	0	0.69	0	0.72
	28-30 day	3	1307	0.88	0.75 to 1.02	0.09	0	0.58	NA	NA
	Hospital	5	122	0.99	0.78 to 1.26	0.96	0	0.80	NA	NA
	ICU	6	160	1.03	0.72 to 1.48	0.88	0	0.86	NA	NA

Meta-regression analysis		Mixed effect meta-regression (unrestricted maximum likelihood) slope effect size, precision, and heterogeneity					
Category	Covariate	Studies	Patients	Point estimate	95% confidence interval	P value	Tau^2
Baseline mortality risk	Comparison group mortality	16	4190	0.0007	-0.0046 to 0.0061	0.79	0
Baseline septic shock	Vasopressor use	12	4096	0.0018	-0.0177 to 0.0544	0.32	0
Baseline septic shock	Lactate	8	2742	0.0136	-0.0589 to 0.0860	0.71	0
Baseline pulmonary site infection	Pulmonary infection	7	3944	-0.0584	-0.0267 to 0.0150	0.58	0
Baseline invasive ventilation	Invasive ventilation	14	4155	0.0018	-0.0041 to 0.0076	0.56	0
Baseline ARDS	ARDS	8	1452	0.0276	-0.0031 to 0.0037	0.87	0
Baseline RRT	RRT	3	2066	0.0072	-0.0059 to 0.0203	0.28	0
Baseline hypoalbuminaemia	Baseline albumin level	6	3933	-0.0124	-0.0407 to 0.0159	0.39	0
Intervention duration	Days of intervention	16	4190	-0.0100	-0.0330 to 0.0160	0.45	0
Daily intervention exposure	Daily albumin dose	15	4170	0.0013	-0.0013 to 0.0038	0.33	0
Total intervention exposure	Total albumin dose	15	4170	0.0006	-0.0005 to 0.0018	0.26	0
Total intervention exposure volume	Total albumin volume	15	4170	-0.0172	-0.1141 to	0.73	0

					0.0798		
Early intervention response	Day 1 post intervention albumin	4	3844	0.0007	-0.0454 to 0.0440	0.97	0
Intervention response	Post intervention albumin level	5	3900	0.0173	-0.0268 to 0.0613	0.44	0
Intervention response	Post intervention increase in albumin level	5	3903	0.0116	-0.0120 to 0.0352	0.34	0

5. Sensitivity, bias and clinical subgroup, and meta-regression analyses for the comparisons of albumin with crystalloid fluid

Predefined sensitivity, bias and clinical subgroup, and meta-regression analyses for the comparisons of albumin with crystalloid fluid.

Abbreviations: not applicable (NA); Surviving Sepsis Campaign launch (SSC).[19 20]

Human albumin compared to crystalloid fluid										
Sensitivity analysis		Measures of effects size and precision					Group heterogeneity		Subgroup difference	
Category	Group or subgroup	Studies	Patients	Point estimate	95% confidence interval	P value	I^2	Chi^2 P value	I^2	Chi^2 P value
Fixed effects model with relative risk	All studies	7	3878	0.93	0.86 to 1.01	0.07	0	0.98	0	0.98
	Low or unclear risk of bias	4	3832	0.93	0.86 to 1.01	0.08	0	0.78	NA	NA
	High risk of bias	3	46	0.93	0.70 to 1.23	0.59	0	0.99	NA	NA
Fixed effects model with odds ratio	All studies	7	3878	0.89	0.78 to 1.01	0.07	0	0.97	0	0.71
	Low or unclear risk of bias	4	3832	0.89	0.78 to 1.01	0.08	0	0.80	NA	NA
	High risk of bias	3	46	0.66	0.14 to 3.13	0.60	0	0.93	NA	NA
Random effects model with odds ratio	All studies	7	3878	0.89	0.78 to 1.01	0.07	0	0.97	0	0.71
	Low or unclear risk of bias	4	3832	0.89	0.78 to 1.01	0.08	0	0.80	NA	NA

Trial exclusion: largest[1]	High risk of bias	3	46	0.66	0.14 to 3.16	0.61	0	0.93	NA	NA
	All studies	6	2068	0.92	0.82 to 1.02	0.13	0	0.96	0	0.98
	Low or unclear risk of bias	3	2022	0.92	0.81 to 1.04	0.16	0	0.61	NA	NA
	High risk of bias	3	46	0.92	0.71 to 1.20	0.53	0	0.99	NA	NA
Trial exclusion: greatest weight[1]	All studies	6	2068	0.92	0.82 to 1.02	0.13	0	0.96	0	0.98
	Low or unclear risk of bias	3	2034	0.92	0.81 to 1.04	0.16	0	0.61	NA	NA
	High risk of bias	3	46	0.92	0.71 to 1.20	0.53	0	0.99	NA	NA
Trial exclusion: greatest observed[14 15]	All studies	6	2660	0.95	0.87 to 1.04	0.25	0	1.00	0	0.81
	Low or unclear risk of bias	3	2614	0.95	0.87 to 1.05	0.32	0	0.92	NA	NA
	High risk of bias	3	46	0.92	0.71 to 1.20	0.53	0	0.99	NA	NA

Subgroup analysis		Relative risk effect size measure with random effects model (Mantel-Haenszel) and precision					Group heterogeneity		Subgroup difference	
Category	Subgroups	Studies	Patients	Point estimate	95% confidence interval	P value	I^2	Chi^2 P value	I^2	Chi^2 P value
Selection bias	Low or unclear risk	7	3878	0.93	0.86 to 1.01	0.07	0	0.98	NA	NA
	High risk	0	0	NA	NA	NA	NA	NA	NA	NA
Performance bias	Low or unclear risk	4	3832	0.93	0.86 to 1.01	0.08	0	0.76	0	0.91
	High risk	3	46	0.92	0.71 to 1.20	0.53	0	0.99	NA	NA
Detection bias	Low or unclear risk	7	3878	0.93	0.86 to 1.01	0.07	0	0.98	NA	NA
	High risk	0	0	NA	NA	NA	NA	NA	NA	NA
Attrition bias	Low or unclear risk	7	3878	0.93	0.86 to 1.01	0.07	0	0.98	NA	NA
	High risk	0	0	NA	NA	NA	NA	NA	NA	NA
Reporting bias	Low or unclear risk	7	3878	0.93	0.86 to 1.01	0.07	0	0.98	NA	NA
	High risk	0	0	NA	NA	NA	NA	NA	NA	NA
Research misconduct or duplication publication bias	Low or unclear risk	5	3856	0.93	0.86 to 1.01	0.07	0	0.89	0	0.93
	High risk	2	22	0.95	0.57 to 1.60	0.85	0	1.00	NA	NA

Other bias	Low or unclear risk	7	3878	0.93	0.86 to 1.01	0.07	0	0.98	NA	NA
	High risk	0	0	NA	NA	NA	NA	NA	NA	NA
Data source bias	Conferences	2	2602	0.95	0.87 to 1.05	0.32	0	0.69	0	0.38
	Journal articles	5	1276	0.88	0.77 to 1.01	0.08	0	1.00	NA	NA
Author bias	Boldt et al	0	0	NA	NA	NA	NA	NA	NA	NA
	Other authors	7	3878	0.93	0.86 to 1.01	0.07	0	0.98	NA	NA
Location bias	Europe	3	2614	0.95	0.87 to 1.05	0.32	0	0.92	0	0.63
	North America	3	46	0.92	0.71 to 1.20	0.53	0	0.99	NA	NA
	Australasia	1	1218	0.87	0.74 to 1.02	NA	NA	NA	NA	NA
Small study bias	Multicentre	3	3820	0.93	0.86 to 1.01	0.08	0	0.58	0	0.95
	Single centre	4	58	0.92	0.71 to 1.20	0.54	0	0.10	NA	NA
Time bias	Post-SSC	3	2614	0.95	0.87 to 1.05	0.32	0	0.92	0	0.37
	Pre-SSC	4	1264	0.88	0.77 to 1.01	0.08	0	0.98	NA	NA
Disease severity (sepsis versus severe sepsis and/or septic shock)	Severe sepsis and/or septic shock	7	3878	0.93	0.86 to 1.01	0.07	0	0.98	NA	NA
	Sepsis	0	0	NA	NA	NA	NA	NA	NA	NA
Disease severity (sepsis versus severe sepsis versus septic shock)	All studies	7	3878	0.93	0.86 to 1.00	0.05	0	0.63	0	0.56
	Septic shock	4	1949	0.91	0.82 to 1.01	0.06	0	0.77	NA	NA
	Severe sepsis	4	1929	0.96	0.83 to 1.10	0.55	0	0.29	NA	NA
	Sepsis	0	0	NA	NA	NA	NA	NA	NA	NA
Intervention method	Predefined	2	2602	0.95	0.87 to 1.05	0.32	0	0.69	0	0.32
	Variable	5	1276	0.88	0.77 to 1.01	0.08	0	1.00	NA	NA
Intervention type	Hypooncotic (4-5% albumin)	5	1276	0.88	0.77 to 1.01	0.08	0	1.00	0	0.33
	Hyperoncotic (20% albumin)	2	2602	0.95	0.87 to 1.05	0.32	0	0.69	NA	NA
Intervention timing	Early (<24 hours)	4	3832	0.93	0.86 to 1.01	0.12	0	0.78	0	0.93
	Not described/other	3	46	0.92	0.71 to 1.20	0.53	0	0.99	NA	NA

	timing									
Time of mortality observation	90 day	2	2602	0.95	0.87 to 1.05	0.32	0	0.69	0	0.82
	28-30 day	1	1218	0.87	0.74 to 1.02	0.09	NA	NA	NA	NA
	Hospital	3	46	0.92	0.71 to 1.20	0.53	0	0.99	NA	NA
	ICU	1	12	1	0.20 to 4.95	1	NA	NA	NA	NA

Meta-regression analysis	Mixed effect meta-regression (unrestricted maximum likelihood) slope effect size, precision, and heterogeneity						
Category	Covariate	Studies	Patients	Point estimate	95% confidence interval	P value	Tau^2
Baseline mortality risk	Comparison group mortality	7	3878	0.0000	-0.0055 to 0.0054	0.98	0
Baseline septic shock	Vasopressor use	6	3854	0.0018	-0.0018 to 0.0055	0.33	0
Baseline septic shock	Lactate	5	2636	0.0117	-0.0895 to 0.0661	0.77	0
Baseline pulmonary site infection	Pulmonary infection	5	3856	-0.0026	-0.0272 to 0.0221	0.83	0
Baseline invasive ventilation	Invasive ventilation	5	3856	0.0258	-0.0042 to 0.0093	0.45	0
Baseline ARDS	ARDS	3	1241	0.0005	-0.0031 to 0.0042	0.79	0
Baseline RRT	RRT	2	2010	NA	NA	NA	NA
Baseline hypoalbuminaemia	Baseline albumin level	4	3832	-0.0129	-0.0427 to 0.0189	0.45	0
Intervention duration	Days of intervention	7	3878	-0.0054	-0.0337 to 0.0229	0.71	0
Daily intervention exposure	Daily albumin dose	7	3878	0.0003	-0.0025 to 0.0031	0.82	0
Total intervention exposure	Total albumin dose	7	3878	0.0006	-0.0009 to 0.0022	0.41	0
Total intervention exposure volume	Total albumin volume	7	3878	-0.0405	-0.1401 to 0.0592	0.43	0
Early intervention response	Day 1 post intervention albumin	4	3832	0.0074	-0.0454 to 0.0440	0.97	0

Intervention response	Post intervention albumin level	4	3832	0.0182	-0.0259 to 0.0624	0.42	0
Intervention response	Post intervention increase in albumin level	4	3832	0.0124	-0.0114 to 0.0362	0.31	0

6. Sensitivity, bias and clinical subgroup, and meta-regression analyses for the comparisons of albumin with colloid fluid

Predefined sensitivity, bias and clinical subgroup, and meta-regression analyses for the comparisons of albumin with colloid fluid.

Abbreviations: not applicable (NA); Surviving Sepsis Campaign launch (SSC);[19 20] hydroxyethyl starch (HES)

Human albumin compared to colloid fluid										
Sensitivity analysis		Measures of effects size and precision					Group heterogeneity		Subgroup difference	
Category	Group or subgroup	Studies	Patients	Point estimate	95% confidence interval	P value	I^2	Chi^2 P value	I^2	Chi^2 P value
Fixed effects model with relative risk	All studies	13	299	1.02	0.77 to 1.35	0.87	0	0.92	26.7	0.24
	Low or unclear risk of bias	3	116	0.76	0.41 to 1.40	0.38	0	0.83	NA	NA
	High risk of bias	8	183	1.14	0.83 to 1.58	0.87	0	0.92	NA	NA
Fixed effects model with odds ratio	All studies	13	299	1.04	0.64 to 1.71	0.87	0	0.91	32.2	0.23
	Low or unclear risk of bias	3	116	0.67	0.28 to 1.61	0.37	0	0.88	NA	NA
	High risk of bias	8	183	1.29	0.70 to 2.37	0.41	0	0.88	NA	NA
Random effects model with odds ratio	All studies	13	299	1.04	0.63 to 1.71	0.89	0	0.91	29.1	0.24
	Low or unclear risk of bias	3	116	0.67	0.28 to 1.61	0.37	0	0.88	NA	NA

Trial exclusion: largest[6]	High risk of bias	8	183	1.29	0.69 to 2.39	0.42	0	0.88	NA	NA
	All studies	12	243	1.08	0.82 to 1.44	0.58	0	0.95	0	0.52
	Low or unclear risk of bias	2	60	0.87	0.42 to 1.79	0.70	0	0.88	NA	NA
	High risk of bias	8	183	1.13	0.83 to 1.53	0.45	0	0.89	NA	NA
Trial exclusion: greatest weight[2]	All studies	12	269	1.06	0.77 to 1.48	0.34	0	0.86	31.3	0.23
	Low or unclear risk of bias	3	116	0.77	0.42 to 1.43	0.41	0	0.83	NA	NA
	High risk of bias	7	153	1.21	0.82 to 1.79	0.34	0	0.86	NA	NA
Trial exclusion: greatest observed power[5]	All studies	12	271	1.01	0.76 to 1.34	0.97	0	0.95	0	0.34
	Low or unclear risk of bias	3	116	0.77	0.42 to 1.43	0.41	0	0.83	NA	NA
	High risk of bias	7	155	1.08	0.78 to 1.49	0.64	0	0.93	NA	NA

Subgroup analysis		Relative risk effect size measure with random effects model (Mantel-Haenszel) and precision					Group heterogeneity		Subgroup difference	
Category	Subgroups	Studies	Patients	Point estimate	95% confidence interval	P value	I^2	Chi^2 P value	I^2	Chi^2 P value
Selection bias	Low or unclear risk	11	299	1.04	0.79 to 1.38	0.76	0	0.92	NA	NA
	High risk	0	0	NA	NA	NA	NA	NA	NA	NA
Performance bias	Low or unclear risk	7	232	0.98	0.70 to 1.37	0.90	0	0.85	0	0.51
	High risk	4	67	1.20	0.73 to 1.95	0.47	0	0.72	NA	NA
Detection bias	Low or unclear risk	11	299	1.04	0.79 to 1.38	0.76	0	0.92	NA	NA
	High risk	0	0	NA	NA	NA	NA	NA	NA	NA
Attrition bias	Low or unclear risk	11	299	1.04	0.79 to 1.38	0.76	0	0.92	NA	NA
	High risk	0	0	NA	NA	NA	NA	NA	NA	NA
Reporting bias	Low or unclear risk	11	299	1.04	0.79 to 1.38	0.76	0	0.92	NA	NA
	High risk	0	0	NA	NA	NA	NA	NA	NA	NA
Research misconduct or duplication publication bias	Low or unclear risk	5	156	0.83	0.52 to 1.32	0.42	0	0.96	33.0	0.22
	High risk	6	143	1.19	0.84 to 1.67	0.33	0	0.80	NA	NA

Other bias	Low or unclear risk	8	111	1.08	0.75 to 1.55	0.68	0	0.77	0	0.79
	High risk	3	88	1.00	0.65 to 1.53	1.00	0	0.85	NA	NA
Data source bias	Conferences	0	0	NA	NA	NA	NA	NA	NA	NA
	Journal articles	11	299	1.04	0.79 to 1.38	0.76	0	0.92	NA	NA
Author bias	Boldt et al	4	116	1.08	0.73 to 1.61	0.70	0	0.67	0	0.8
	Other authors	7	183	1.01	0.69 to 1.48	0.96	0	0.81	NA	NA
Location bias	Europe	8	252	0.96	0.70 to 1.33	0.81	0	0.90	0	0.33
	North America	3	47	1.31	0.77 to 2.23	0.32	0	0.73	NA	NA
	Australasia	0	0	NA	NA	NA	NA	NA	NA	NA
Small study bias	Multicentre	0	0	NA	NA	NA	NA	NA	NA	NA
	Single centre	11	299	1.04	0.79 to 1.38	0.76	0	0.92	NA	NA
Time bias	Post-SSC	4	136	0.77	0.44 to 1.33	0.35	0	0.95	38.1	0.20
	Pre-SSC	7	163	1.16	0.84 to 1.60	0.36	0	0.87	NA	NA
Disease severity	Severe sepsis and/or septic shock	7	141	1.04	0.68 to 1.59	0.86	0	0.71	0	0.98
	Sepsis	5	158	1.05	0.73 to 1.51	0.80	0	0.79	NA	NA
	All studies	11	299	1.04	0.79 to 1.38	0.76	0	0.92	8.0	0.34
	Septic shock	2	27	1.54	0.78 to 3.01	0.21	0	0.82	NA	NA
	Severe sepsis	4	114	0.80	0.46 to 1.39	0.43	0	0.90	NA	NA
	Sepsis	5	158	1.05	0.73 to 1.51	0.80	0	0.79	NA	NA
Intervention method	Predefined	2	98	0.77	0.38 to 1.53	0.45	0	0.54	0	0.34
	Variable	9	201	1.11	0.82 to 1.50	0.51	0	0.92	NA	NA
Intervention type	Hypooncotic (4-5% albumin)	5	107	1.13	0.74 to 1.74	0.57	0	0.83	0	0.62
	Hyperoncotic (20% albumin)	6	192	0.99	0.69 to 1.41	0.94	0	0.74	NA	NA
Intervention timing	Early (<24 hours)	2	48	1.04	0.45 to 2.42	0.93	0	0.61	0	0.99
	Not described/other timing	9	251	1.05	0.78 to 1.40	0.77	0	0.84	NA	NA

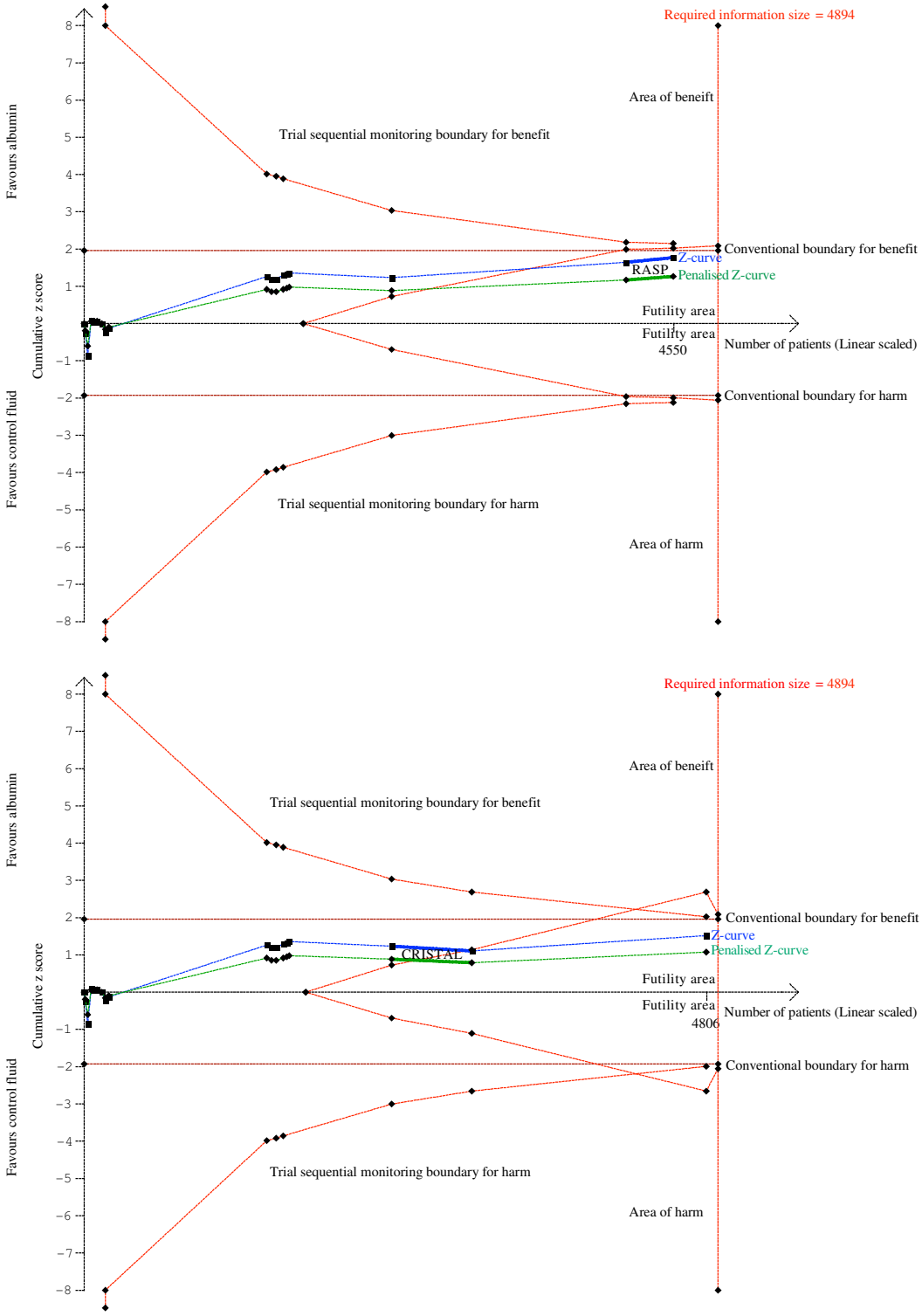
Time of mortality observation	90 day	0	0	NA	NA	NA	NA	NA	0	0.52
	28-30 day	1	56	0.58	0.18 to 1.83	0.35	NA	NA	NA	NA
	Hospital	4	89	1.18	0.75 to 1.86	0.47	0	0.76	NA	NA
	ICU	6	154	1.02	0.71 to 1.47	0.90	0	0.85	NA	NA
Colloid type: hydroxyethyl starch (HES)	6% tetrastarch 130 kDa	2	76	0.65	0.28 to 1.51	0.32	0	0.76	26.3	0.24
	Other HES	9	223	1.11	0.83 to 1.48	0.50	0	0.93	NA	NA
Colloid type: Gelatin	Gelatin	1	12	1.00	0.20 to 4.95	1	NA	NA	NA	NA

Meta-regression analysis		Mixed effect meta-regression (unrestricted maximum likelihood) slope effect size, precision, and heterogeneity					
Category	Covariate	Studies	Patients	Point estimate	95% confidence interval	P value	Tau^2
Baseline mortality risk	Comparison group mortality	11	299	0.0022	-0.0143 to 0.0187	0.79	0
Baseline septic shock	Vasopressor use	8	229	0.0090	-0.0162 to 0.0144	0.91	0
Baseline septic shock	Lactate	5	99	0.0025	-0.2359 to 0.02409	0.98	0
Baseline pulmonary site infection	Pulmonary infection	3	100	-0.0287	-0.1103 to 0.0529	0.49	0
Baseline invasive ventilation	Invasive ventilation	9	272	0.0000	-0.0243 to 0.024	0.93	0
Baseline ARDS	ARDS	6	210	0.0009	-0.0100 to 0.0080	0.83	0
Baseline RRT	RRT	1	56	NA	NA	NA	NA
Baseline hypoalbuminaemia	Baseline albumin level	2	80	NA	NA	NA	NA
Intervention duration	Days of intervention	11	299	-0.0077	-0.1318 to 0.1163	0.90	0
Daily intervention exposure	Daily albumin dose	10	279	0.0015	-0.0032 to 0.0061	0.54	0
Total intervention exposure	Total albumin dose	10	279	0.0004	-0.0001 to 0.0023	0.64	0
Total intervention exposure volume	Total albumin volume	10	279	0.2861	-0.0681 to	0.11	0

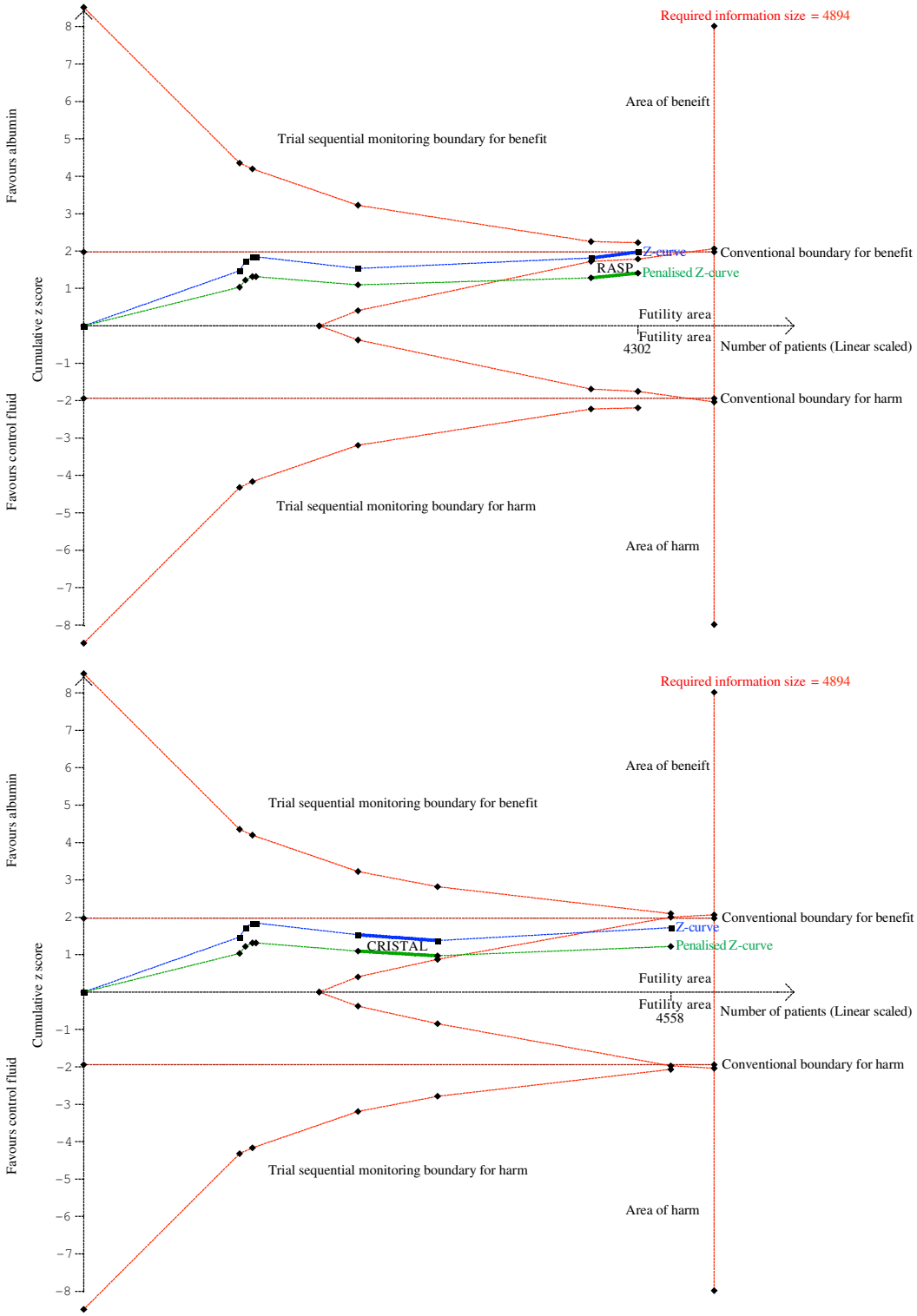
					0.6404		
Early intervention response	Day 1 post intervention albumin	1	24	NA	NA	NA	NA
Intervention response	Post intervention albumin level	2	80	NA	NA	NA	NA
Intervention response	Post intervention increase in albumin level	2	80	NA	NA	NA	NA

7. Trial sequential analysis model with RASP or CRISTAL for human albumin compared to control fluid, with or without exclusion of studies at high risk of bias

The graphs show trial sequential analysis of sixteen primary trials reporting all-cause mortality comparing pooled human albumin solutions to control fluids. They both model the possible effect of RASP[21] or CRISTAL[22] as a bold type-face segment of the cumulative z score. RASP[21] is an on-going double-blinded randomised clinical trial that was given a hypothetical relative risk of 0.9. CRISTAL[22] is an open label randomised trial that compared colloid and crystalloid fluids but albumin infusion was permitted for hypoalbuminaemia in all treatment groups, which was not subject to randomisation. CRISTAL is included in this exploratory model for clinical interest only. A diversity adjusted information size of 4894 patients was calculated for both models using α=0.05 (two sided), β=0.20 (power 80%), an anticipated relative risk of 10.0%, and an event proportion of 38.6% in the control arm. The blue cumulative z score was constructed using a random effects model, and the green curve represents an adjusted z score. For the RASP model, the relative risk was 0.94, P=0.08, consistent with the conclusion of no mortality benefit with human albumin. Trial sequential analysis correction for random error and repeated hypothesis testing of 95% confidence interval (0.87 to 1.01; D^2=0%) did not alter this finding. Using the exploratory CRISTAL model also did not alter this conclusion (relative risk 0.94, P=0.13; 95% confidence interval 0.88 to 1.02; D^2=0%).


Required information size = 4894
Area of beneift
Trial sequential monitoring boundary for benefit
Favours albumin
Cumulative z score
Favours control fluid
Conventional boundary for benefit
Z-curve
RASP
Penalised Z-curve
Futility area
Futility area
4550
Number of patients (Linear scaled)
Conventional boundary for harm
Trial sequential monitoring boundary for harm
Area of harm
Required information size = 4894
Area of beneift
Trial sequential monitoring boundary for benefit
Favours albumin
Cumulative z score
Favours control fluid
Conventional boundary for benefit
Z-curve
CRISTAL
Penalised Z-curve
Futility area
Futility area
4806
Number of patients (Linear scaled)
Conventional boundary for harm
Trial sequential monitoring boundary for harm
Area of harm

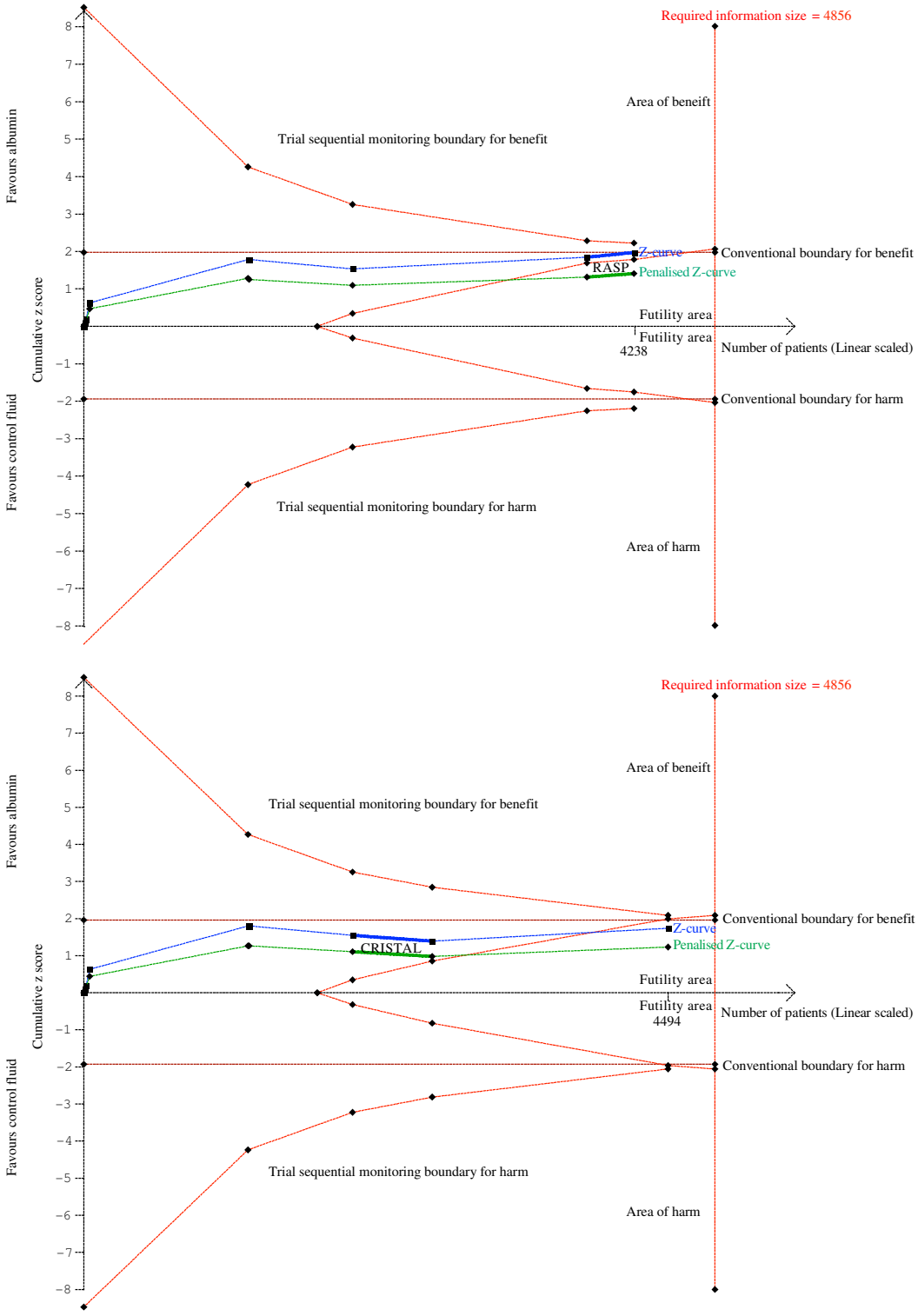
The graphs show trial sequential analysis of six primary trials, after exclusion of studies that were at high risk of bias, reporting all-cause mortality comparing pooled human albumin solutions to control fluids. They both model the possible effect of RASP[21] or CRISTAL[22] as a bold type-face segment of the cumulative z score. RASP[21] is an on-going double-blinded randomised clinical trial that was given a hypothetical relative risk of 0.9. CRISTAL[22] is an open label randomised trial that compared colloid and crystalloid fluids but albumin infusion was permitted for hypoalbuminaemia in all treatment groups, which was not subject to randomisation. CRISTAL is included in this exploratory model for clinical interest only. A diversity adjusted information size of 4894 patients was calculated for both models using α=0.05 (two sided), β=0.20 (power 80%), an anticipated relative risk of 10.0%, and an event proportion of 38.6% in the control arm. The blue cumulative z score was constructed using a random effects model, and the green curve represents an adjusted z score. For the RASP model, the relative risk was 0.94 and P=0.05. However, trial sequential analysis correction for random error and repeated hypothesis testing of the 95% confidence interval (0.85 to 1.02; D^2=0%), was consistent with no benefit with albumin given that the z score touched only the conventional boundary of benefit but not the trial sequential monitoring boundary for benefit. The penalised z score does not cross the conventional boundary of benefit. Adding RASP is very unlikely to be associated with harm, as the z score would need to cross the boundary of futility. Using the exploratory CRISTAL model did not alter conclusion of no mortality benefit with human albumin (relative risk 0.93, P=0.08; 95% confidence interval 0.86 to 1.01; D^2=0%).


Required information size = 4894
Area of beneift
Trial sequential monitoring boundary for benefit
Favours albumin
Cumulative z score
Z-curve
RASP
Penalised Z-curve
Conventional boundary for benefit
Futility area
Futility area
4302
Number of patients (Linear scaled)
Conventional boundary for harm
Favours control fluid
Trial sequential monitoring boundary for harm
Area of harm
Required information size = 4894
Area of beneift
Trial sequential monitoring boundary for benefit
Favours albumin
Cumulative z score
Conventional boundary for benefit
Z-curve
CRISTAL
Penalised Z-curve
Futility area
Futility area
4558
Number of patients (Linear scaled)
Conventional boundary for harm
Favours control fluid
Trial sequential monitoring boundary for harm
Area of harm

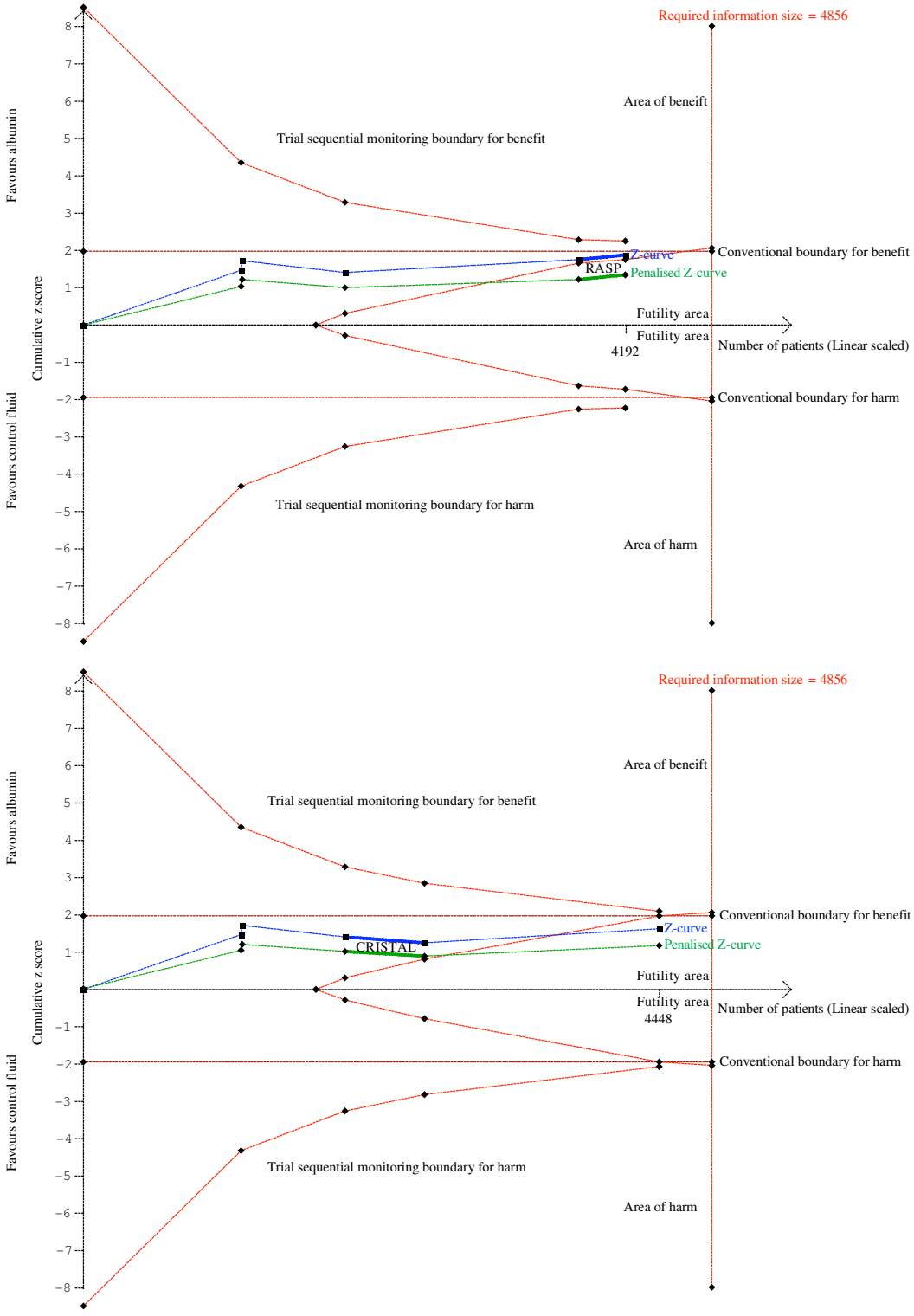
8. Trial sequential analysis models with RASP or CRISTAL for human albumin compared to crystalloid fluid, with or without exclusion of studies at high risk of bias

The graphs show trial sequential analysis of seven primary trials reporting all-cause mortality comparing pooled human albumin solutions to crystalloid fluid. They both model the possible effect of RASP[21] or CRISTAL[22] as a bold type-face segment of the cumulative z score. RASP[21] is an on-going double-blinded randomised clinical trial that was given a hypothetical relative risk of 0.9. CRISTAL[22] is an open label randomised trial that compared colloid and crystalloid fluids but albumin infusion was permitted for hypoalbuminaemia in all treatment groups, which was not subject to randomisation. CRISTAL is included in this exploratory model for clinical interest only. A diversity adjusted information size of 4856 patients was calculated for both models using α=0.05 (two sided), β=0.20 (power 80%), an anticipated relative risk of 10.0%, and an event proportion of 38.8% in the control arm. The blue cumulative z score was constructed using a random effects model, and the green curve represents an adjusted z score. For the RASP model, the relative risk was 0.93 and P=0.05. Trial sequential analysis correction for random error and repeated hypothesis testing of the 95% confidence interval (0.85 to 1.01; D^2=0%) was consistent with no benefit with albumin. The cumulative z score touches the conventional boundary of benefit but not the trial sequential monitoring boundary of benefit. Harm seems unlikely with this RASP model as the z score would need to cross the futility area to touch the trial sequential monitoring boundary of harm. Using the exploratory

CRISTAL model did not alter the conclusion of no mortality benefit (relative risk 0.94, P=0.09; 95% confidence interval 0.86 to 1.01; D^2=0%).

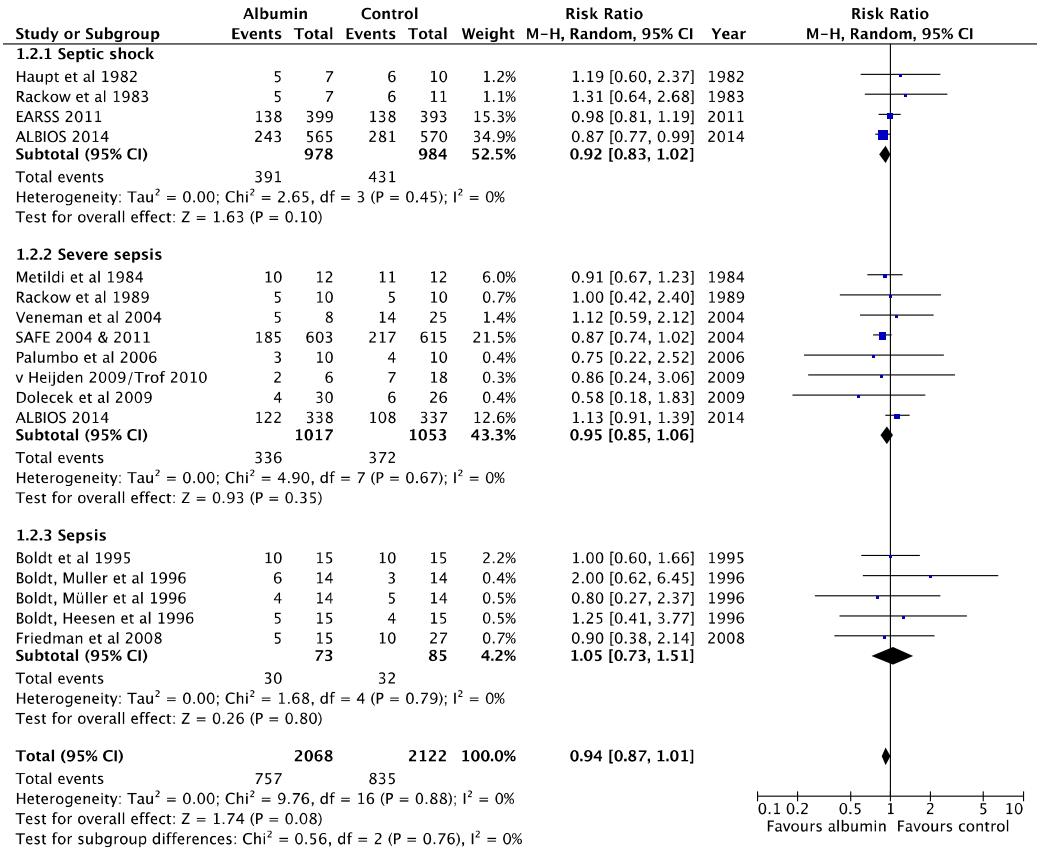


The graphs show trial sequential analysis of four primary trials reporting all-cause mortality comparing pooled human albumin solutions to control fluidsThey both model the possible effect of RASP[21] or CRISTAL[22] as a bold type-face segment of the cumulative z score. RASP[21] is an on-going double-blinded randomised clinical trial that was given a hypothetical relative risk of 0.9. CRISTAL[22] is an open label randomised trial that compared colloid and crystalloid fluids but albumin infusion was permitted for hypoalbuminaemia in all treatment groups, which was not subject to randomisation. CRISTAL is included in this exploratory model for clinical interest only. A diversity adjusted information size of 4856 patients was calculated for both models using α=0.05 (two sided), β=0.20 (power 80%), an anticipated relative risk of 10.0%, and an event proportion of 38.8% in the control arm. The blue cumulative z score was constructed using a random effects model, and the green curve represents an adjusted z score. For the RASP model, the relative risk was 0.93 and P=0.06. Trial sequential analysis correction for random error and repeated hypothesis testing of 95% confidence interval (0.85 to 1.01; D^2=0%) was consistent with no mortality benefit. The cumulative z score is between the futility boundary and the conventional boundary of benefit, but not the trial sequential monitoring boundary of benefit. Harm also seems unlikely with this RASP model as the z score would need to cross the futility area to touch the trial sequential monitoring boundary of harm. Using the exploratory CRISTAL model did not alter the conclusion of no mortality benefit (relative risk 0.94, P=0.11; 95% confidence interval 0.86 to 1.02; D^2=0%).

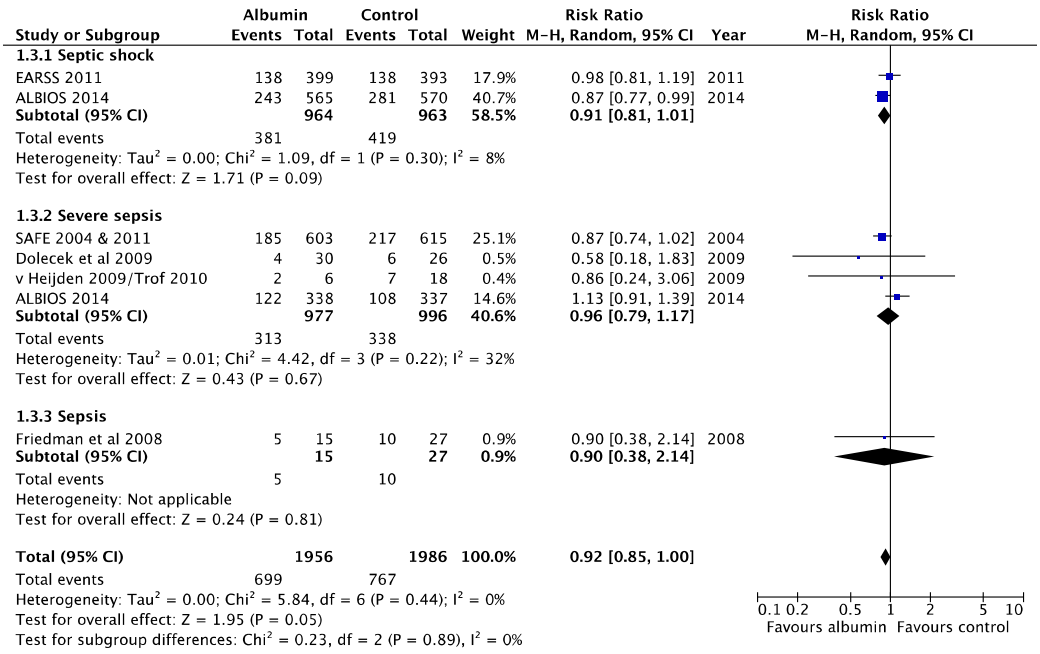

Required information size = 4856
Area of beneift
Trial sequential monitoring boundary for benefit
Favours albumin
Cumulative z score
Favours control fluid
Conventional boundary for benefit
Z-curve
RASP
Penalised Z-curve
Futility area
Futility area
4192
Number of patients (Linear scaled)
Conventional boundary for harm
Trial sequential monitoring boundary for harm
Area of harm
Required information size = 4856
Area of beneift
Trial sequential monitoring boundary for benefit
Favours albumin
Cumulative z score
Favours control fluid
Conventional boundary for benefit
Z-curve
CRISTAL
Penalised Z-curve
Futility area
Futility area
4448
Number of patients (Linear scaled)
Conventional boundary for harm
Trial sequential monitoring boundary for harm
Area of harm

9. Forest plots and trial sequential analyses for the comparisons of human albumin compared to control fluid by sepsis subgroup, with or without exclusion of studies at high risk of bias

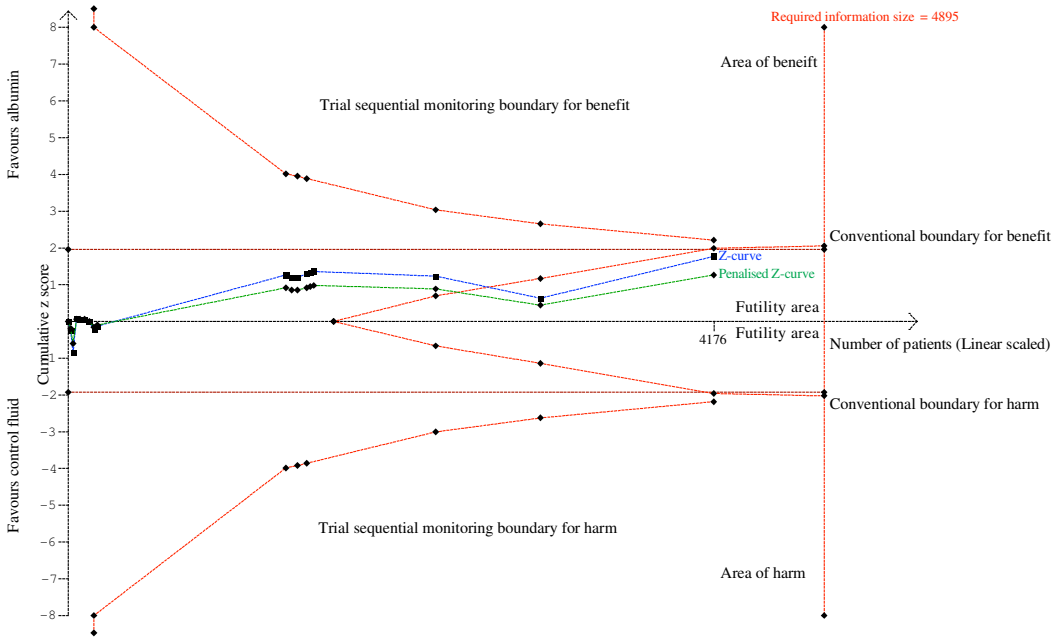
Forest plot of the relative risk of all-cause mortality in patients exposed to human albumin solutions compared to control fluid stratified by sepsis severity subgroup for all studies. Squares to the left of the line indicate that albumin reduced the risk of mortality; horizontal lines indicate 95% confidence intervals; square size represents relative study weight; the diamond indicates the aggregated random effects relative risk (95% confidence interval; M-H (Mantel-Haenszel). Data from ALBIOS[1] were separated into severe sepsis and septic shock subgroups as 90 day mortality outcome data were available. Studies are ordered chronologically within subgroups.

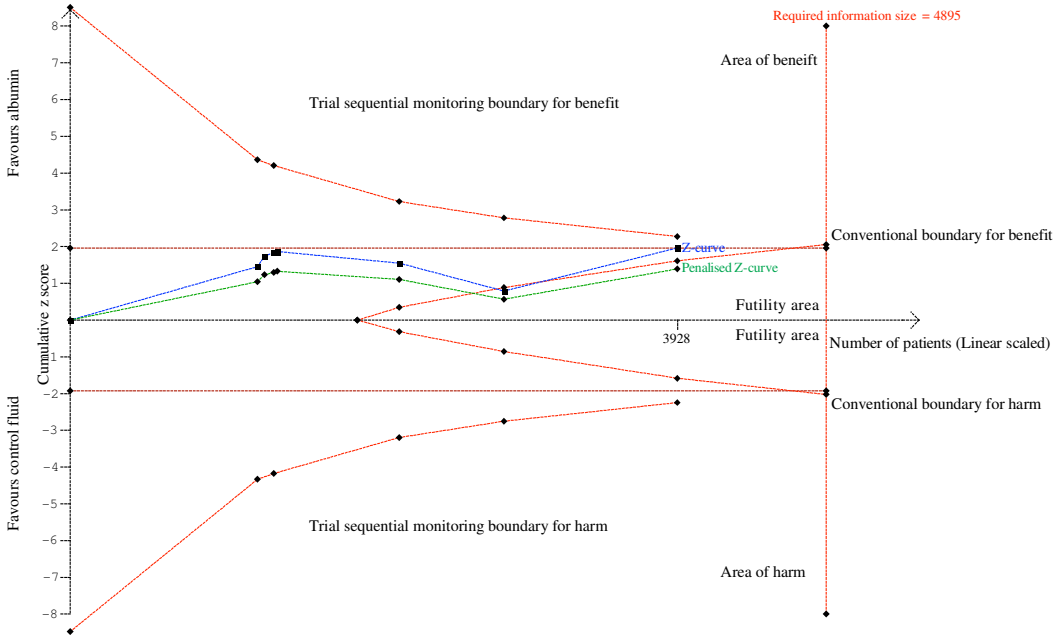

Albumin
Control
Risk Ratio
Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
1.2.1 Septic shock
Haupt et al 1982 5 7 6 10 1.2% 1.19 [0.60, 2.37] 1982
Rackow et al 1983 5 7 6 11 1.1% 1.31 [0.64, 2.68] 1983
EARSS 2011 138 399 138 393 15.3% 0.98 [0.81, 1.19] 2011
ALBIOS 2014 243 565 281 570 34.9% 0.87 [0.77, 0.99] 2014
Subtotal (95% CI) 978 984 52.5% 0.92 [0.83, 1.02]
Total events 391 431
Heterogeneity: Tau² = 0.00; Chi² = 2.65, df = 3 (P = 0.45); I² = 0%
Test for overall effect: Z = 1.63 (P = 0.10)
1.2.2 Severe sepsis
Metildi et al 1984 10 12 11 12 6.0% 0.91 [0.67, 1.23] 1984
Rackow et al 1989 5 10 5 10 0.7% 1.00 [0.42, 2.40] 1989
Veneman et al 2004 5 8 14 25 1.4% 1.12 [0.59, 2.12] 2004
SAFE 2004 & 2011 185 603 217 615 21.5% 0.87 [0.74, 1.02] 2004
Palumbo et al 2006 3 10 4 10 0.4% 0.75 [0.22, 2.52] 2006
v Heijden 2009/Trof 2010 2 6 7 18 0.3% 0.86 [0.24, 3.06] 2009
Dolecek et al 2009 4 30 6 26 0.4% 0.58 [0.18, 1.83] 2009
ALBIOS 2014 122 338 108 337 12.6% 1.13 [0.91, 1.39] 2014
Subtotal (95% CI) 1017 1053 43.3% 0.95 [0.85, 1.06]
Total events 336 372
Heterogeneity: Tau² = 0.00; Chi² = 4.90, df = 7 (P = 0.67); I² = 0%
Test for overall effect: Z = 0.93 (P = 0.35)
1.2.3 Sepsis
Boldt et al 1995 10 15 10 15 2.2% 1.00 [0.60, 1.66] 1995
Boldt, Muller et al 1996 6 14 3 14 0.4% 2.00 [0.62, 6.45] 1996
Boldt, Müller et al 1996 4 14 5 14 0.5% 0.80 [0.27, 2.37] 1996
Boldt, Heesen et al 1996 5 15 4 15 0.5% 1.25 [0.41, 3.77] 1996
Friedman et al 2008 5 15 10 27 0.7% 0.90 [0.38, 2.14] 2008
Subtotal (95% CI) 73 85 4.2% 1.05 [0.73, 1.51]
Total events 30 32
Heterogeneity: Tau² = 0.00; Chi² = 1.68, df = 4 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)
Total (95% CI) 2068 2122 100.0% 0.94 [0.87, 1.01]
Total events 757 835
Heterogeneity: Tau² = 0.00; Chi² = 9.76, df = 16 (P = 0.88); I² = 0%
Test for overall effect: Z = 1.74 (P = 0.08)
Test for subgroup differences: Chi² = 0.56, df = 2 (P = 0.76), I² = 0%
0.1 0.2 0.5 1 2 5 10
Favours albumin Favours control

Forest plot of the relative risk of all-cause mortality in patients exposed to human albumin solutions compared to control fluid stratified by sepsis severity subgroup after exclusion of studies at high risk of bias. Squares to the left of the line indicate that albumin reduced the risk of mortality; horizontal lines indicate 95% confidence intervals; square size represents relative study weight; the diamond indicates the aggregated random effects relative risk (95% confidence interval; M-H (Mantel-Haenszel). Data from ALBIOS[1] were separated into severe sepsis and septic shock subgroups as 90 day mortality outcome data were available. Studies are ordered chronologically within subgroups.

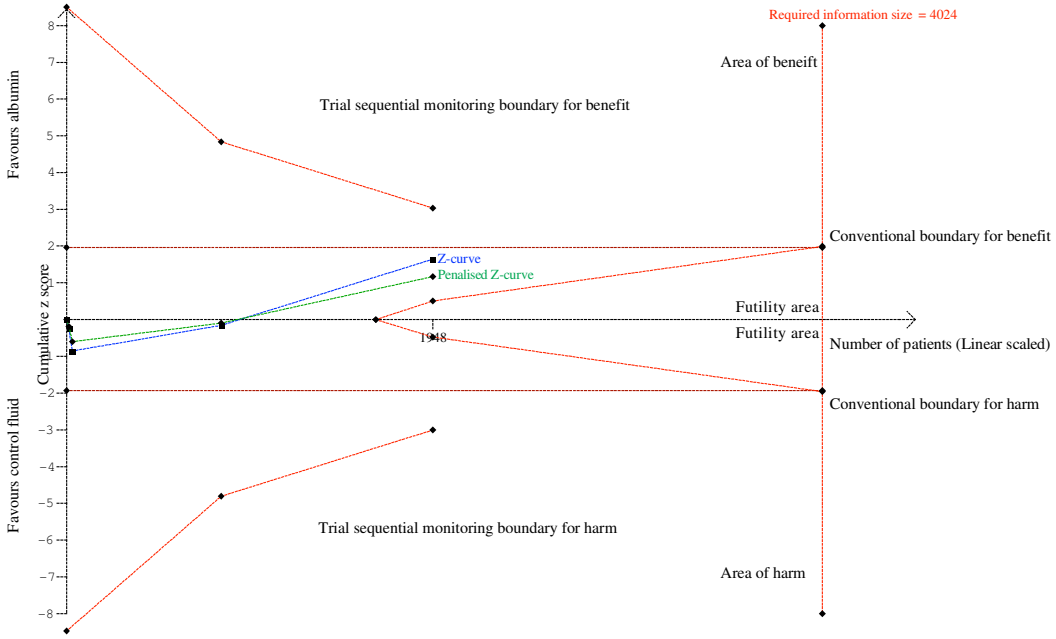


The graphs show trial sequential analysis of studies reporting all-cause mortality comparing pooled human albumin solutions to control fluids. The upper graph included all studies and the lower graph had excluded studies at high risk of bias. A diversity adjusted information size of 4895 patients was calculated for both models using α=0.05 (two sided), β=0.20 (power 80%), an anticipated relative risk of 10.0%, and an event proportion of 38.6% in the control arm. When all studies are included, the relative risk is 0.94 and P=0.08; D^2=0%. The blue cumulative z curve was constructed using a random effects model, and the green curve represents an adjusted z curve. The cumulative z score has crossed the futility boundary consistent with no survival benefit. After excluding studies at high risk of bias the relative risk point estimate becomes 0.92, and P=0.05. The trial sequential analysis corrected 95% confidence interval (0.84 to 1.01; D^2=0%) indicates there does not seem to be robust evidence of albumin benefit.


Required information size = 4895
Area of beneift
Trial sequential monitoring boundary for benefit
Favours albumin
Cumulative z score
Conventional boundary for benefit
Z-curve
Penalised Z-curve
Futility area
Futility area
4176
Number of patients (Linear scaled)
Favours control fluid
Conventional boundary for harm
Trial sequential monitoring boundary for harm
Area of harm


Required information size = 4895
Area of beneift
Trial sequential monitoring boundary for benefit
Favours albumin
Cumulative z score
Conventional boundary for benefit
Z-curve
Penalised Z-curve
Futility area
Futility area
3928
Number of patients (Linear scaled)
Favours control fluid
Conventional boundary for harm
Trial sequential monitoring boundary for harm
Area of harm

The graphs show trial sequential analysis of studies reporting all-cause mortality comparing pooled human albumin solutions to control fluids in patients with septic shock where mortality outcome data were available. The upper graph included all studies and the lower graph had excluded studies at high risk of bias. A diversity adjusted information size was calculated for both models using α=0.05 (two sided), β=0.20 (power 80%), an anticipated relative risk of 10.0%, and an event proportion of 43.5% in the control arm. The blue cumulative z curve was constructed using a random effects model, and the green curve represents an adjusted z curve. When all studies are included the relative risk is 0.94 and P=0.08. The trial sequential analysis corrected 95% confidence interval (0.78 to 1.07; D^2=0% is consistent with no overall survival benefit with albumin. After excluding studies at high risk of bias the relative risk point estimate becomes 0.91 but the conclusion does not change. Exploratory modelling with the addition of CRISTAL would move the z score close to the futility boundary whether studies at high risk of bias are included or excluded (graphs not shown).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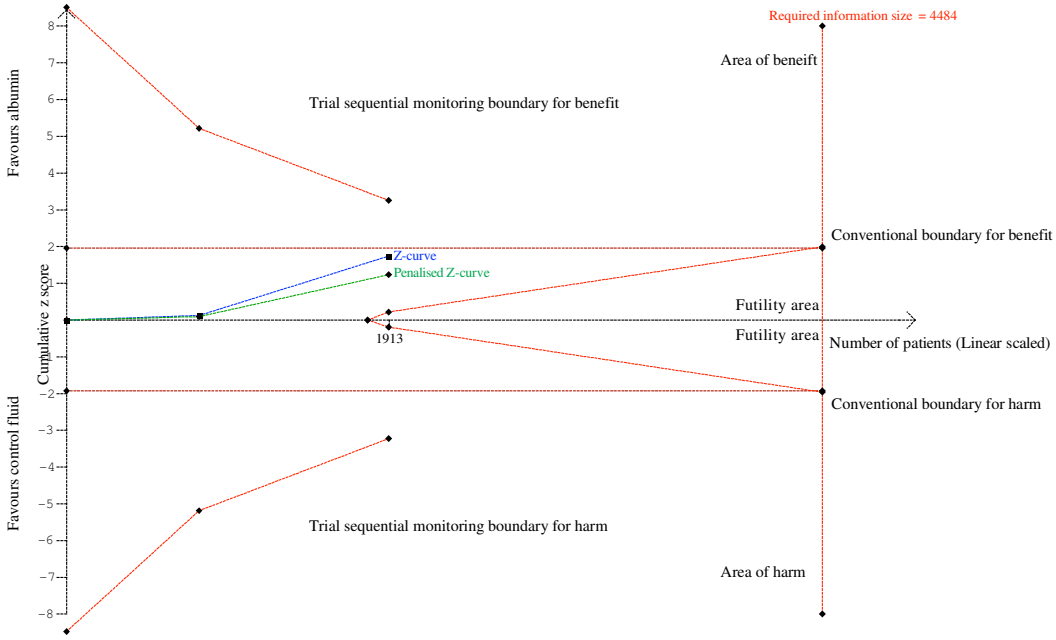
Area of beneift
Trial sequential monitoring boundary for benefit
Favours albumin
Cumulative z score
Favours control fluid
Conventional boundary for benefit
Z-curve
Penalised Z-curve
Futility area
Futility area
1948
Number of patients (Linear scaled)
Conventional boundary for harm
Trial sequential monitoring boundary for harm
Area of harm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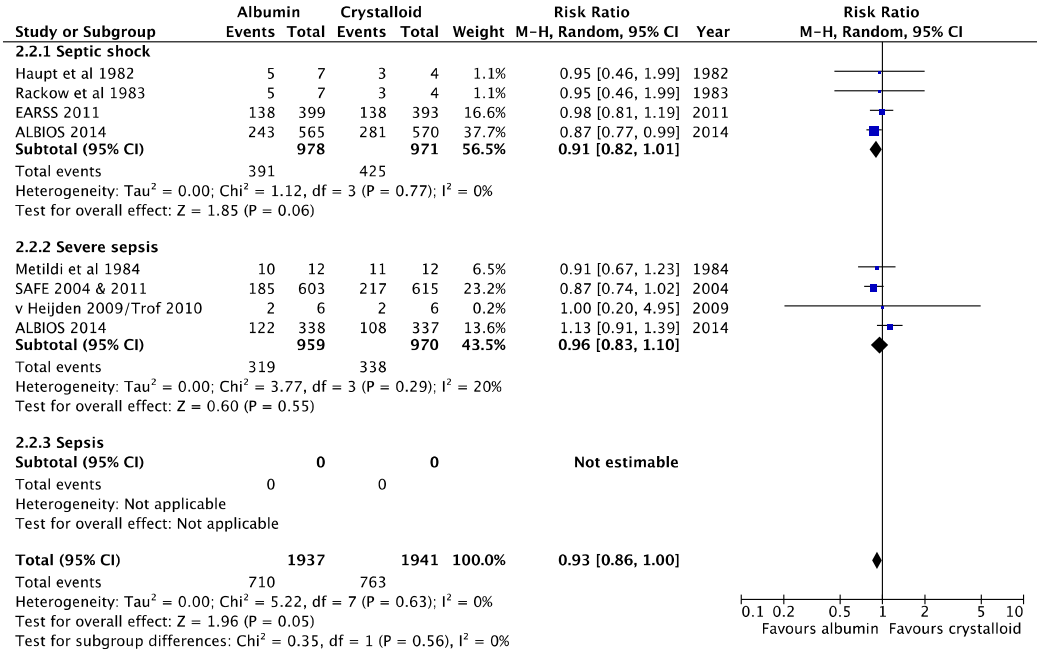
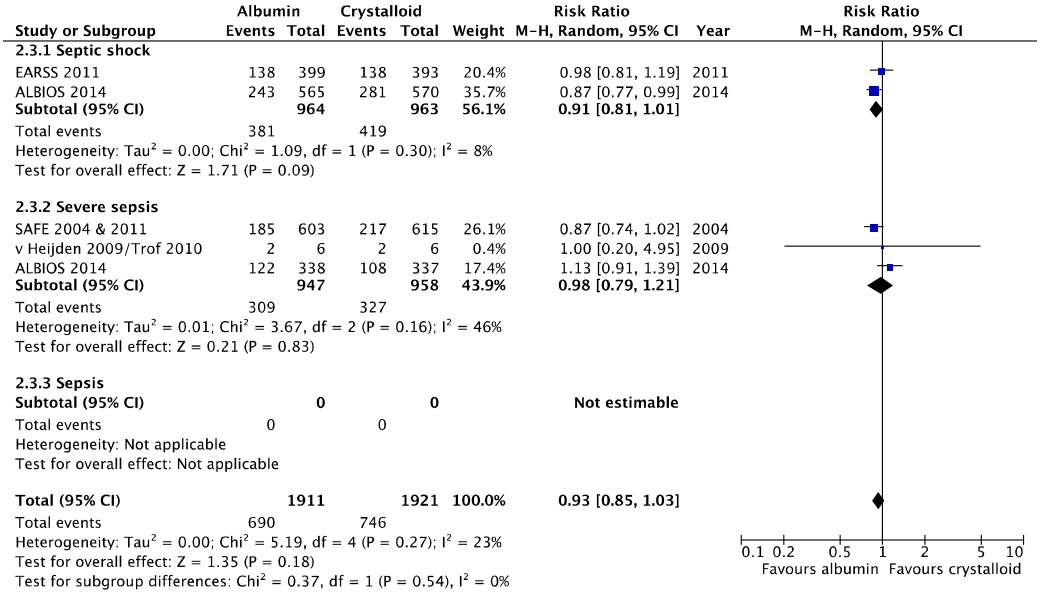
Area of beneift
Trial sequential monitoring boundary for benefit
Favours albumin
Cumulative z score
Favours control fluid
Conventional boundary for benefit
Z-curve
Penalised Z-curve
Futility area
Futility area
1913
Number of patients (Linear scaled)
Conventional boundary for harm
Trial sequential monitoring boundary for harm
Area of harm

10. Forest plots and trial sequential analyses for the comparisons of human albumin compared to crystalloid fluid by sepsis subgroup, with or without exclusion of studies at high risk of bias

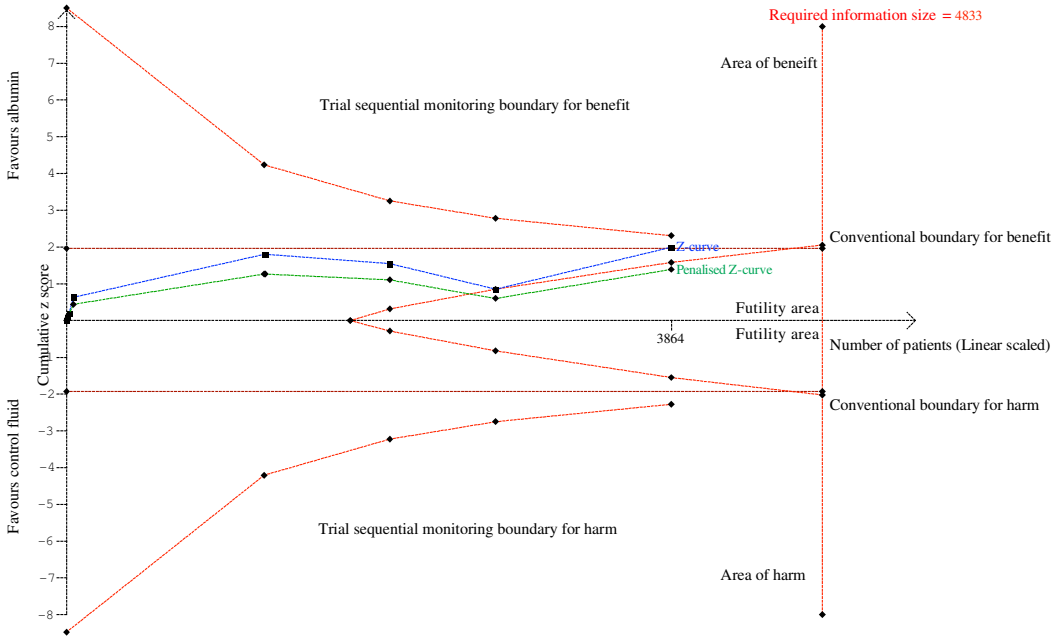
Forest plot of the relative risk of all-cause mortality in patients exposed to human albumin solutions compared to crystalloid fluids stratified by sepsis severity subgroup for all studies. Squares to the left of the line indicate that albumin reduced the risk of mortality; horizontal lines indicate 95% confidence intervals; square size represents relative study weight; the diamond indicates the aggregated random effects relative risk (95% confidence interval; M-H (Mantel-Haenszel). Data from ALBIOS[1] were separated into severe sepsis and septic shock subgroups as 90 day mortality outcome data were available. Studies are ordered chronologically within subgroups.

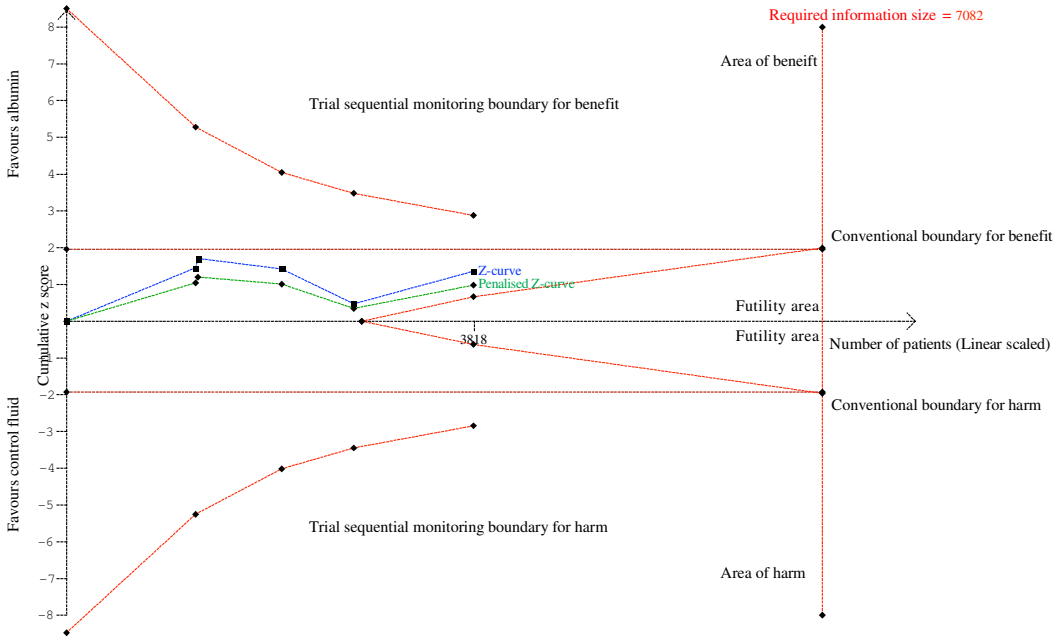


Forest plot of the relative risk of all-cause mortality in patients exposed to human albumin solutions compared to crystalloid fluid, stratified by sepsis severity subgroup after exclusion of studies at high risk of bias. Squares to the left of the line indicate that albumin reduced the risk of mortality; horizontal lines indicate 95% confidence intervals; square size represents relative study weight; the diamond indicates the aggregated random effects relative risk (95% confidence interval; M-H (Mantel-Haenszel). Data from ALBIOS[1] were separated into severe sepsis and septic shock subgroups as 90 day mortality outcome data were available. Studies are ordered chronologically within subgroups.

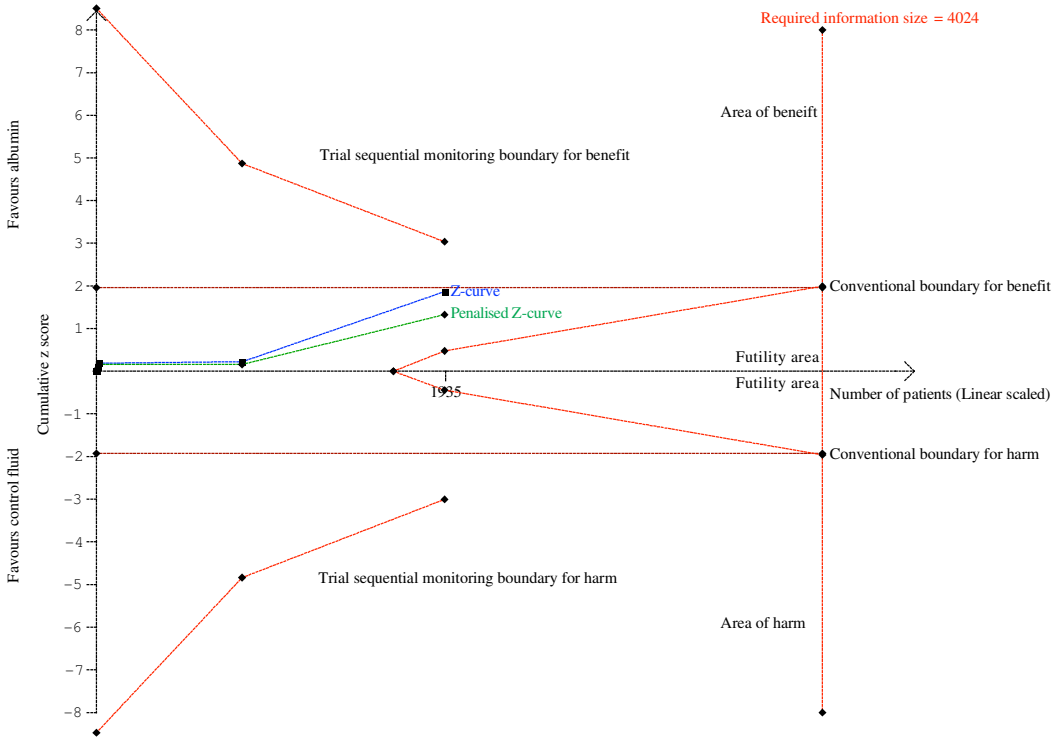


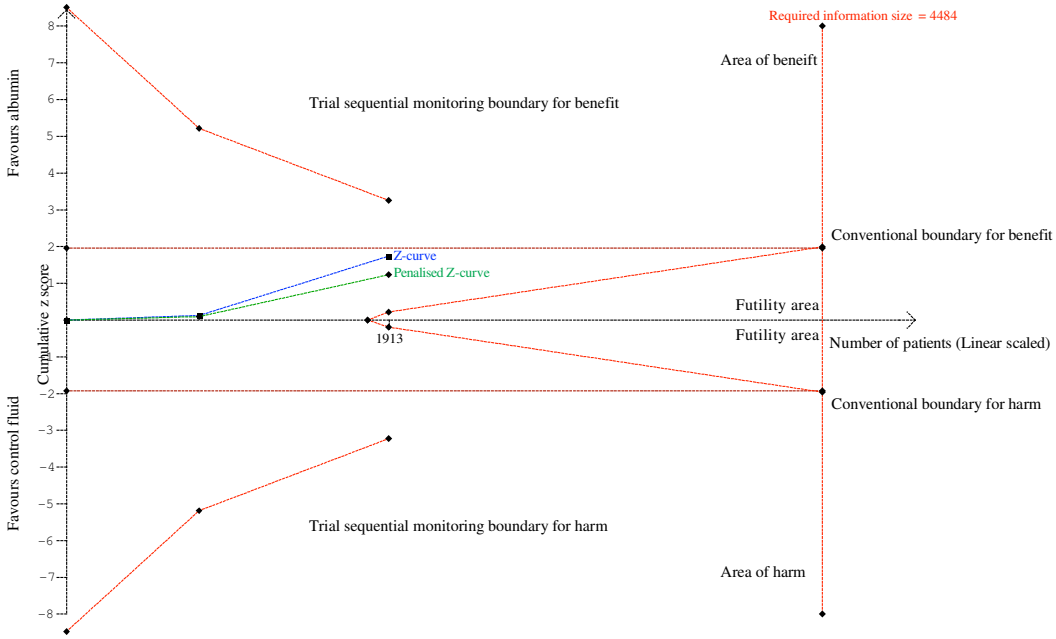
The graphs show trial sequential analysis of studies reporting all-cause mortality comparing pooled human albumin solutions to crystalloid fluids. The upper graph included all studies and the lower graph had excluded studies at high risk of bias. A diversity adjusted information size was calculated for both models using α=0.05 (two sided), β=0.20 (power 80%), an anticipated relative risk of 10.0%, and an event proportion of 38.8% in the control arm. The blue cumulative z curve was constructed using a random effects model, and the green curve represents an adjusted z curve. When all studies are included the relative risk is 0.93 and P=0.05. The trial sequential analysis corrected 95% confidence interval (0.84 to 1.01; D^2=0%) is consistent with no survival benefit, although this possibility cannot be completely excluded. After excluding studies at high risk of bias the relative risk point estimate remains 0.93 and P=0.18. The trial sequential analysis corrected 95% confidence interval (0.81 to 1.08; D^2=0%) is still consistent with no reduction in mortality. There does not seem to be robust evidence of albumin benefit after correction for repetitive testing and spare data.


Required information size = 4833
Area of beneift
Trial sequential monitoring boundary for benefit
Favours albumin
Cumulative z score
Favours control fluid
Z-curve
Penalised Z-curve
Conventional boundary for benefit
Futility area
Futility area
3864
Number of patients (Linear scaled)
Conventional boundary for harm
Trial sequential monitoring boundary for harm
Area of harm


Required information size = 7082
Area of beneift
Trial sequential monitoring boundary for benefit
Favours albumin
Cumulative z score
Favours control fluid
Z-curve
Penalised Z-curve
Conventional boundary for benefit
Futility area
Futility area
3818
Number of patients (Linear scaled)
Conventional boundary for harm
Trial sequential monitoring boundary for harm
Area of harm

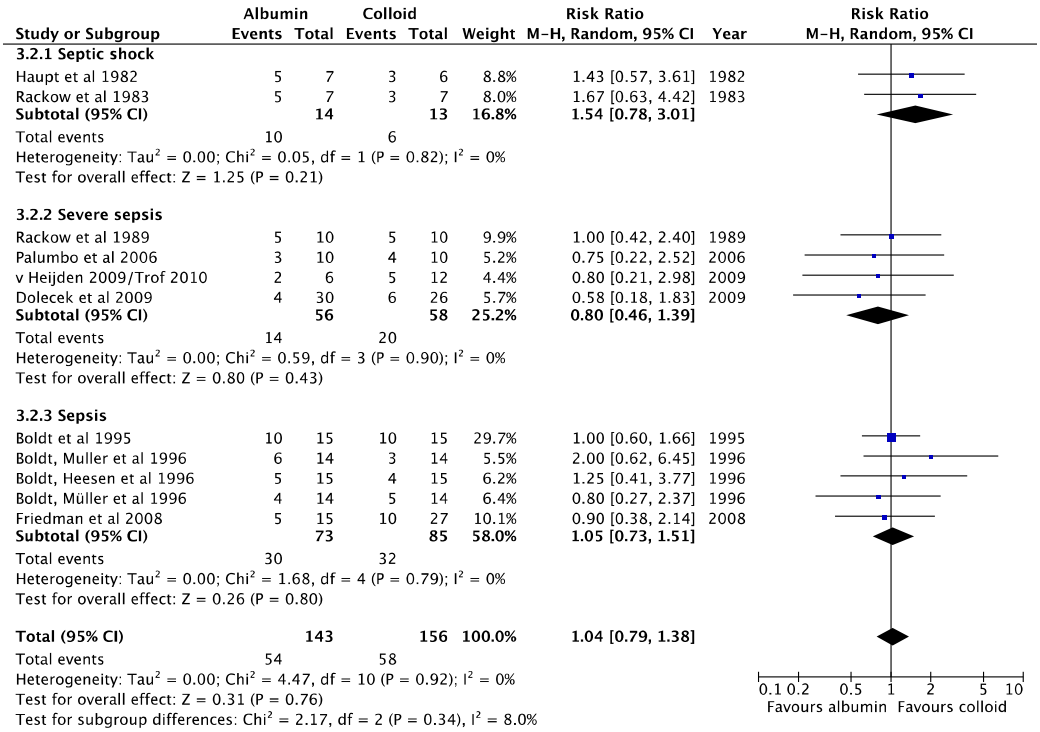
The graphs show trial sequential analysis of studies reporting all-cause mortality comparing pooled human albumin solutions to crystalloid fluids in patients with septic shock where mortality outcome data were available. The upper graph included all studies, and the lower graph had excluded studies at high risk of bias. A diversity adjusted information size was calculated for both models using α=0.05 (two sided), β=0.20 (power 80%), an anticipated relative risk of 10.0%, and an event proportion of 43.5% in the control arm. The blue cumulative z curve was constructed using a random effects model, and the green curve represents an adjusted z curve. When all studies are included the relative risk is 0.91 and P=0.06. The trial sequential analysis corrected 95% confidence interval (0.77 to 1.06; D^2=0%) is consistent with no overall survival benefit with albumin. After excluding studies at high risk of bias the relative risk point estimate remained 0.91 and P=0.08. The conclusion did not change. Exploratory modelling with the addition of CRISTAL would move the z score close to the futility boundary whether studies at high risk of bias are included or excluded (graphs not shown).


Required information size = 4024
Area of beneift
Trial sequential monitoring boundary for benefit
Favours albumin
Cumulative z score
Z-curve
Penalised Z-curve
Conventional boundary for benefit
Futility area
Futility area
1935
Number of patients (Linear scaled)
Conventional boundary for harm
Favours control fluid
Trial sequential monitoring boundary for harm
Area of harm

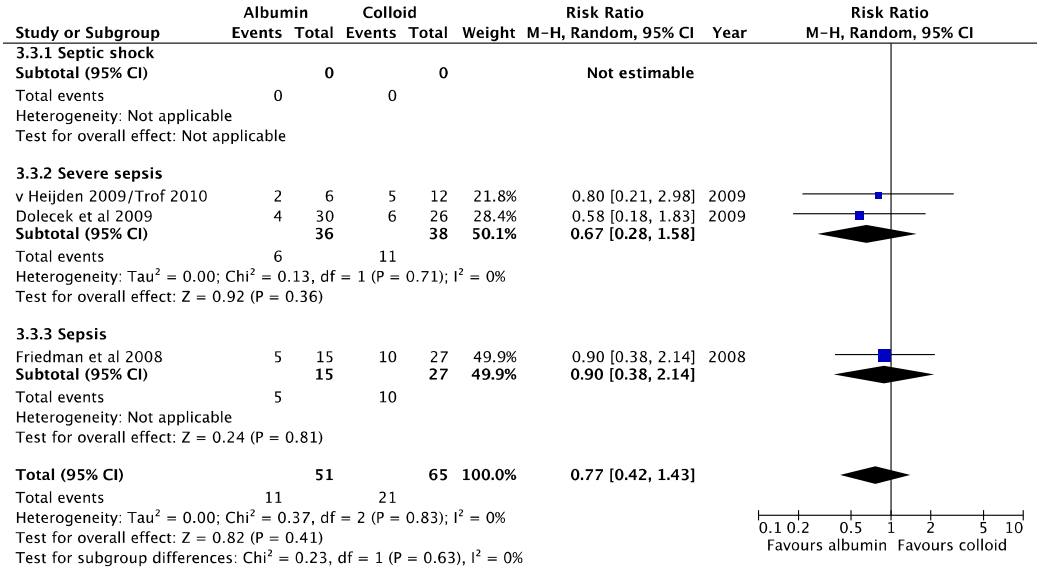

Required information size = 4484
Area of beneift
Trial sequential monitoring boundary for benefit
Favours albumin
Cumulative z score
Z-curve
Penalised Z-curve
Conventional boundary for benefit
Futility area
Futility area
1913
Number of patients (Linear scaled)
Conventional boundary for harm
Favours control fluid
Trial sequential monitoring boundary for harm
Area of harm

11. Forest plots of human albumin compared to colloid fluid by sepsis subgroup, with or without exclusion of studies at high risk of bias

Forest plot of the relative risk of all-cause mortality in patients exposed to human albumin solutions compared to colloid fluid stratified by sepsis severity subgroup. Squares to the left of the line indicate that albumin reduced the risk of mortality; horizontal lines indicate 95% confidence intervals; square size represents relative study weight; the diamond indicates the aggregated random effects relative risk (95% confidence interval; M-H (Mantel-Haenszel). Studies are ordered chronologically within subgroups.



Forest plot of the relative risk of all-cause mortality in patients exposed to human albumin solutions compared to colloid fluid stratified by sepsis severity subgroup after exclusion of studies at high risk of bias. Squares to the left of the line indicate that albumin reduced the risk of mortality; horizontal lines indicate 95% confidence intervals; square size represents relative study weight; the diamond indicates the aggregated random effects relative risk (95% confidence interval; M-H (Mantel-Haenszel). Studies are ordered chronologically within subgroups.



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