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ATTIRE Clinical Trial Sites

Basildon, Basingstoke, Berkshire, Birmingham, Blackpool, Bournemouth, Bristol, Brighton, Coventry, Derby, Durham, Glasgow RI, Glasgow QE, Glasgow RA, Gloucestershire, Heartlands, Hull, Leeds, Liverpool, Manchester, Newcastle, North Tees, North Tyneside, Nottingham, Oxford, Plymouth, Portsmouth, Royal Free, Royal London, South Tyneside, Southampton, Surrey, Swansea, Whittington and Wigan.

Trial funding

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The 20% Human Albumin Solution used was taken from routine hospital stocks throughout the UK and this was funded wholly by the Wellcome Trust and Department of Health and Social Care grant to Professor O'Brien.

Trial Conduct

ATTIRE was conducted and reported according to the protocol, the Medicines for Human Use (Clinical Trials) Regulations 2004, (amended 2006), the European Union Clinical Trials Directive (2001/20/EC) guidelines, the principles of the International Conference on Harmonisation Good Clinical Practice under oversight of the University College London Comprehensive Clinical Trials Unit (UCL CCTU) and provisions of the Declaration of Helsinki.

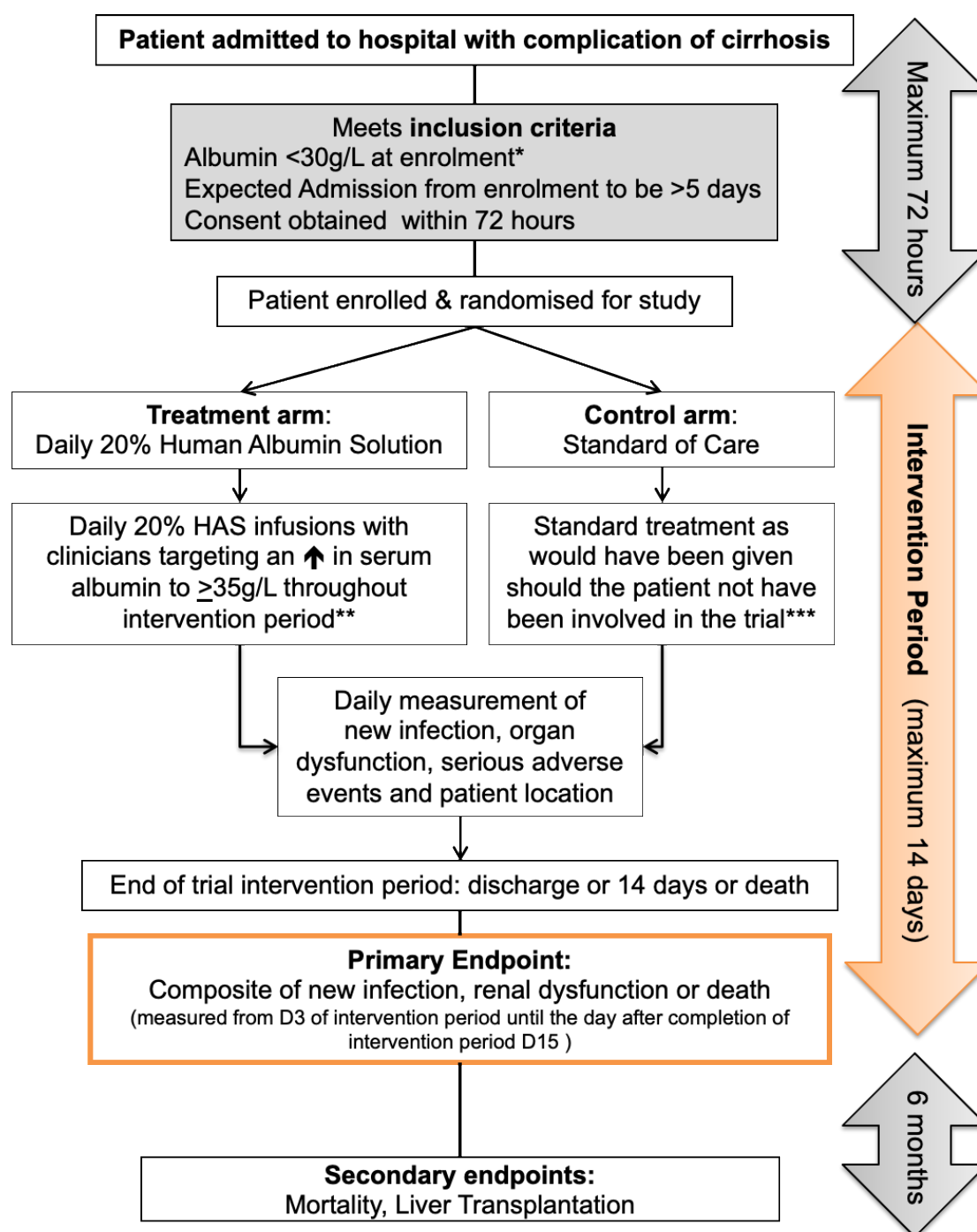
Acknowledgements

The authors acknowledge funding from the Wellcome Trust and Department of Health and Social Care, the National Institute for Health Research Clinical Research Network for providing research nurse support, the University College London Comprehensive Clinical Trials Unit for trial management activities and University College London for sponsoring the trial.

Number of primary randomizations per site

Centre	Randomised
Basildon	38
Basingstoke	10
Berkshire	14
Birmingham	3
Blackpool	38
Bournemouth	1
Bristol	37
Brighton	5
Coventry	34
Derby	17
Durham	22
Glasgow RI	67
Glasgow QE	31
Glasgow RA	38
Gloucestershire	10
Heartlands	10
Hull	35
Leeds	12
Liverpool	31
Manchester	9
Newcastle	23
North Tees	33
North Tyneside	9
Nottingham	22
Oxford	24
Plymouth	29
Portsmouth	28
Royal Free	17
Royal London	37
South Tyneside	10
Southampton	9
Surrey	6
Swansea	27
Whittington	24
Wigan	17
Total	777

Supplementary Figure S1. ATTIRE Study Protocol

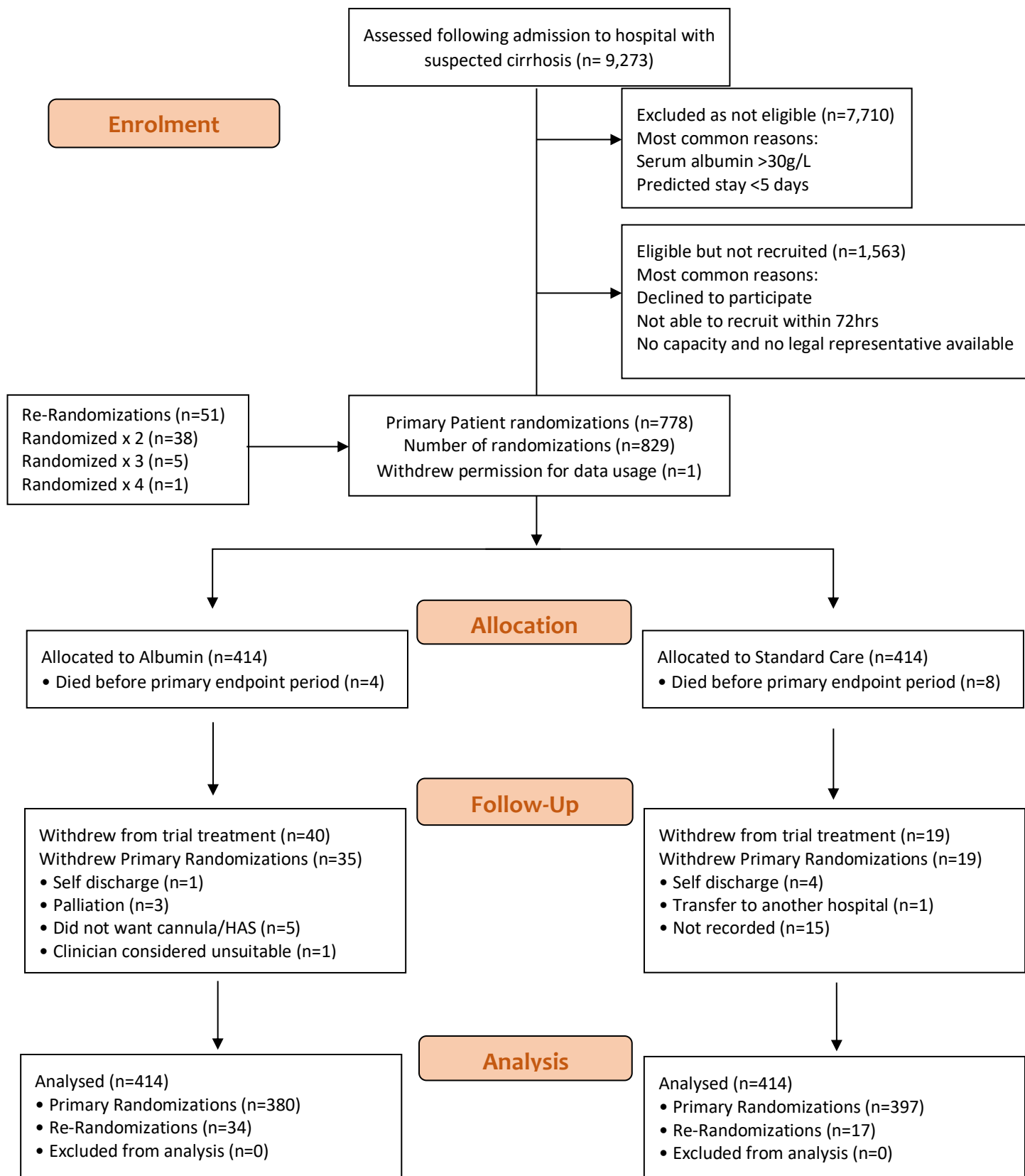


* Which could be any time point on days 1-3 (72 hours) of admission.

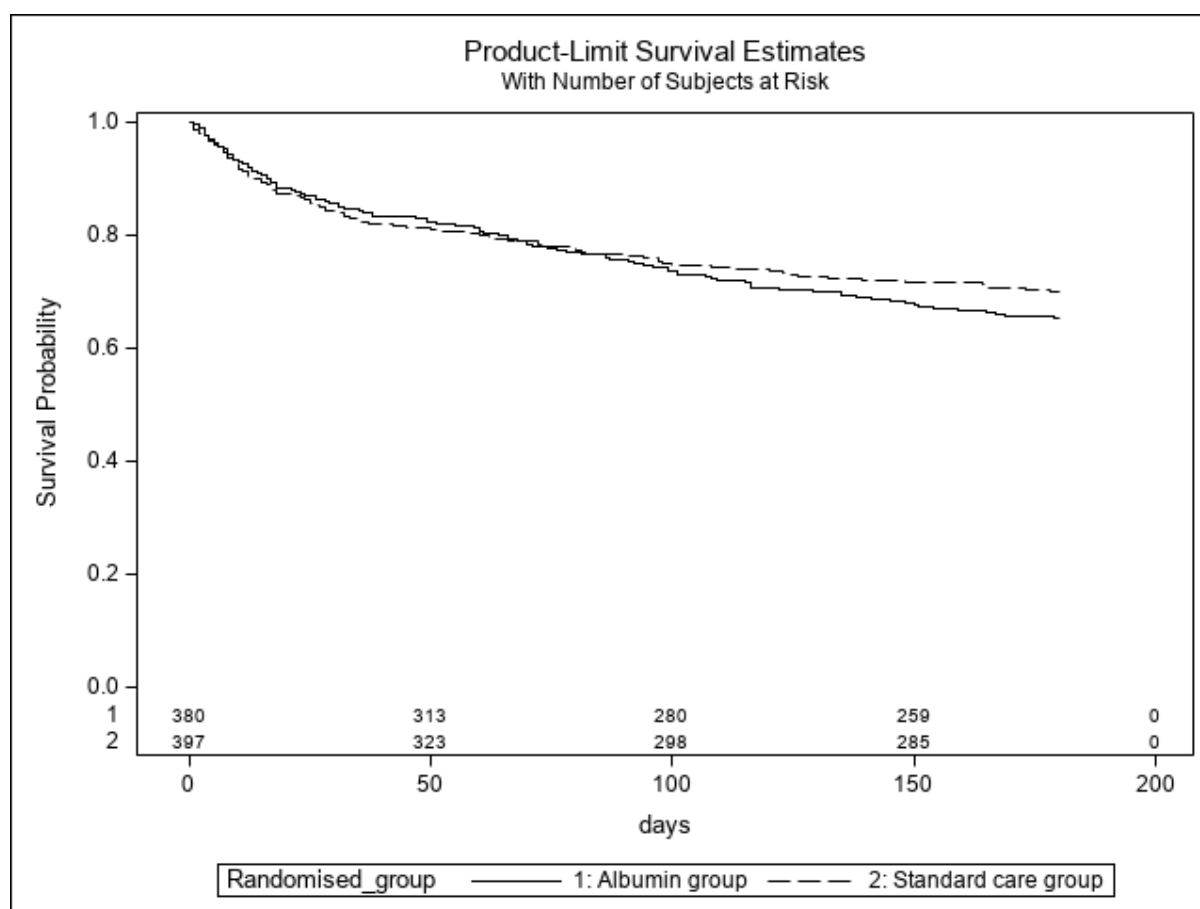
** See table S2 for infusion protocol. The study aim was for treatment arm patients to achieve and sustain a serum albumin $\geq 30\text{g/L}$. This was achieved by asking site clinicians to target a serum albumin of $\geq 35\text{g/L}$.

*** This can only include albumin as recommended in international evidence based guidance: LVP, SBP & HRS.

Supplementary Figure S2. ATTIRE CONSORT Flow Diagram



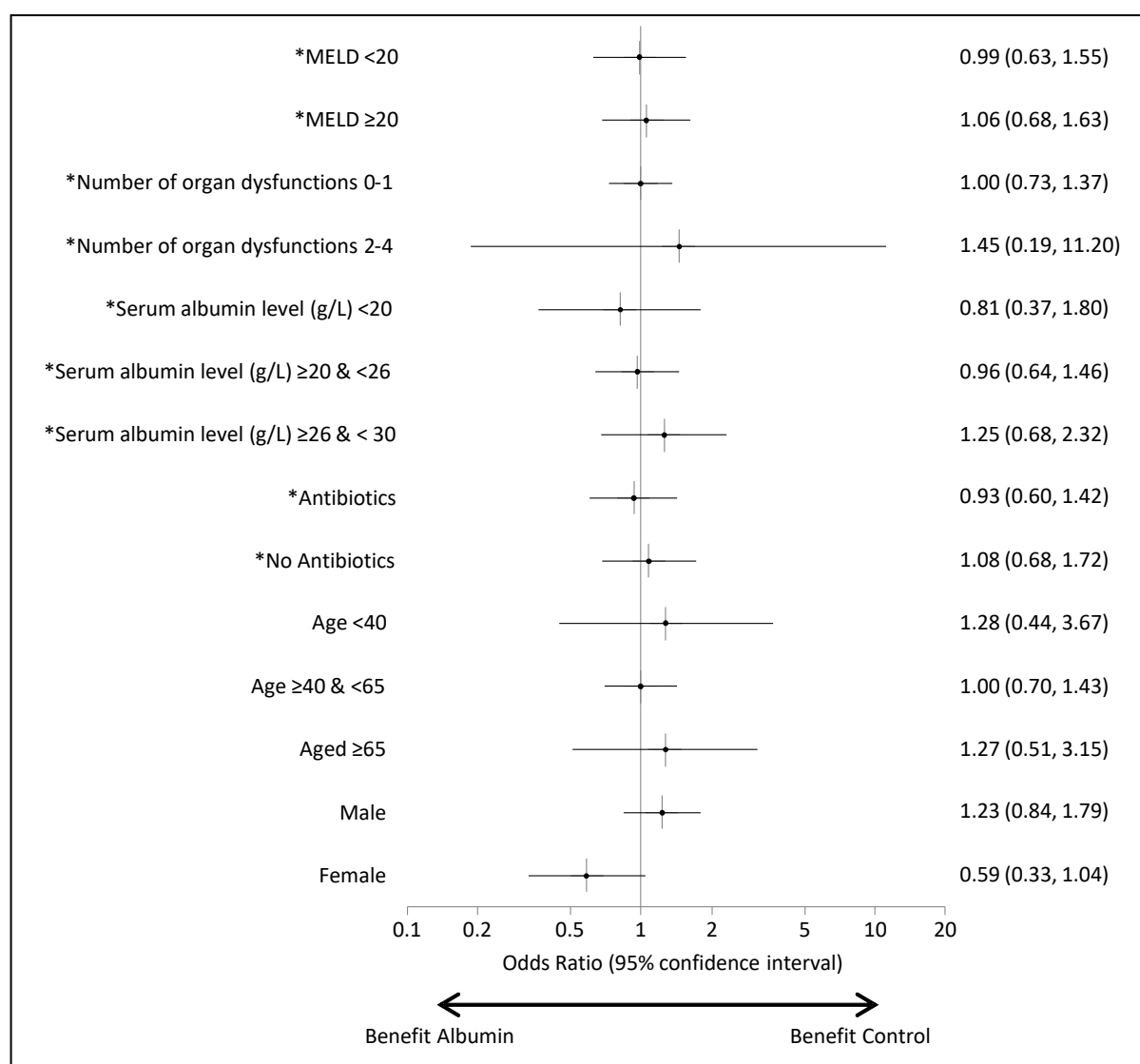
Supplementary Figure S3. Time to Death or Censorship



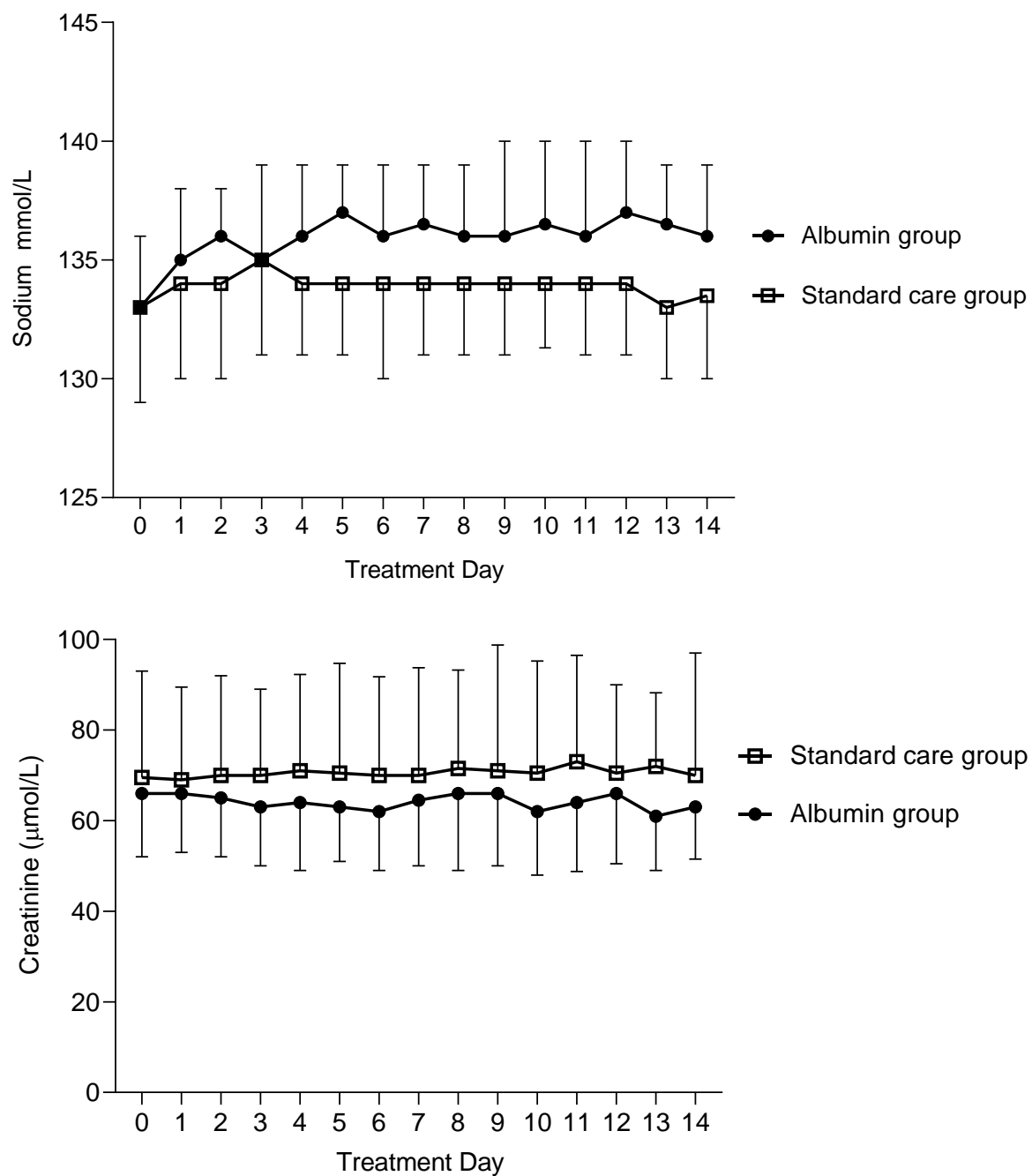
Note: With number of patients at risk

Supplementary Figure S4. Primary outcome subgroup analyses.

* indicates stratification variable



Supplementary Figure S5. Serum Sodium and Creatinine values during trial treatment period. Median and IQR data presented.



Supplementary Tables

Supplementary Table S1. ATTIRE study patient inclusion and exclusion criteria	
Inclusion Criteria	Exclusion Criteria
All patients admitted to hospital with acute onset or worsening of complications of liver cirrhosis	Advanced hepatocellular carcinoma with life expectancy of less than 8 weeks
Over 18 years of age	Patients who will receive palliative treatment only during their hospital admission
Predicted hospital admission > 5 days at trial enrolment, which must be within 72 hours of admission	Patients who are pregnant
Serum albumin <30g/l at screening	Known or suspected severe cardiac dysfunction
Documented informed consent to participate (or consent given by a legal representative)	Any clinical condition which the investigator considers would make the patient unsuitable for the trial
	The patient has been involved in a clinical trial of Investigational Medicinal Products (IMPs) within the previous 30 days that would impact on their participation in this study
	Trial investigators unable to identify the patient (by NHS number)

Supplementary Table S2. Suggested daily dosing protocol for 20% Human Albumin Solution (HAS) administration according to measured serum albumin level	
Patient Serum Albumin Level	Suggested volume of 20% HAS to be infused (rate 100mls/hr)
≥35 g/L	None
30-34 g/L	100mls
26-29 g/L	200mls
20-25 g/L	300mls
<20 g/L	400mls

Supplementary Table S3: Definitions of Extrahepatic Organ Dysfunction				
Definition of baseline organ dysfunction				
Renal	Serum creatinine > 1.5md/dL			
Cerebral	Grade III (Drowsy) or grade IV encephalopathy (coma) using the Westhaven Criteria to grade hepatic encephalopathy			
Circulatory	Mean Arterial Pressure (MAP)* < 60mmHg or if the patient is receiving inotropic/vasopressor support			
Respiratory	SpO ₂ /FiO ₂ of <357			
Definition of new organ dysfunction (Treatment D3 to end of treatment D15)				
Renal	Serum creatinine increase ≥50% compared to value at randomisation, rise in serum creatinine ≥0.3mg/dL within 48 hours or patient initiated on renal replacement therapy <i>Note: patients receiving renal replacement at baseline could not reach this outcome</i>			
Cerebral	Grade III (Drowsy) or grade IV encephalopathy (coma) using the Westhaven Criteria to grade hepatic encephalopathy <i>Note: if the patient has grade III hepatic encephalopathy at baseline they will need to progress to grade IV to reach this endpoint</i>			
Circulatory	i) MAP fall to <60mmHg OR ii) patient is started on inotropic/vasopressor to support blood pressure <i>Note: if MAP <60mmHg at baseline the inotropic/vasopressor support for blood pressure will need to be initiated to reach endpoint</i>			
Respiratory	Any single point increase in SpO ₂ /FiO ₂ as classified in the following scoring system as compared to SpO ₂ /FiO ₂ at baseline:			
		0	1	2
	SpO ₂ /FiO ₂	>357	>214 to ≤357	≤214 or mechanical ventilation for respiratory failure

*MAP = [systolic blood pressure + 2(diastolic blood pressure)]/3

**SpO₂ = oxygen saturations

***FiO₂ = fraction of inspired oxygen

Supplementary Table S4. Daily median amounts of albumin infused per patient (g)					
Group	Treatment Day	Median	Minimum	Maximum	N
Albumin group	1	0	0	180	371
	2	60	0	160	374
	3	40	0	100	361
	4	20	0	120	335
	5	20	0	100	316
	6	20	0	140	285
	7	20	0	120	245
	8	20	0	120	219
	9	20	0	80	182
	10	20	0	120	164
	11	20	0	120	151
	12	20	0	60	141
	13	0	0	80	136
	14	0	0	60	123
	15	0	0	80	114
Standard care group	1	0	0	120	385
	2	0	0	140	387
	3	0	0	180	367
	4	0	0	140	348
	5	0	0	120	330
	6	0	0	100	295
	7	0	0	80	259
	8	0	0	120	227
	9	0	0	100	199
	10	0	0	160	177
	11	0	0	160	163
	12	0	0	60	146
	13	0	0	100	129
	14	0	0	80	119
	15	0	0	140	104

Supplementary Table S5. Supportive analyses for the primary outcome			
For Primary Randomizations			
Analysis description	Albumin n=380	Standard Care n=397	Adjusted odds ratio (95% CI)
Extended end point window (day 1 to day 15)	188 (49.5%)	214 (53.9%)	0.79 (0.58 to 1.07)
Extended end point window (day 2 to day 15)	118 (31.1%)	121 (30.5%)	1.02 (0.75 to 1.40)
Analysis description	Albumin n=376	Standard Care n=389	Adjusted odds ratio (95% CI)
Restricted to those alive at day 3	116 (30.9%)	117 (30.1%)	1.04 (0.76 to 1.42)
Including Re-randomized patients			
Analysis description	Albumin n=414	Standard Care n=414	Adjusted odds ratio (95% CI)
Patient-clustered including re- randomisation‡	128 (30.9%)	127 (30.7%)	1.01 (0.74 to 1.38)
Protocol defined including re- randomisation	125 (30.2%)	128 (30.9%)	0.97 (0.72 to 1.31)
Including all reported deaths including re-randomisation	128 (30.9%)	127 (30.7%)	1.01 (0.75 to 1.36)

‡ model contains random intercept term for patients but not for site.

Supplementary Table S6. Primary outcome subgroup analyses				
		Albumin	Standard Care	Primary Outcome
	Subgroup	Recruited Patients		Adjusted odds ratio (95% CI) ⁺
		no. (%)	no. (%)	
Co-morbidities**	COPD	28 (7.5%)	28 (7.1%)	0.81 (95% CI 0.26 to 2.59)
	Alcohol abuse	310 (82.0%)	305 (77.2%)	1.02 (95% CI 0.73 to 1.44)
	Substance abuse	24 (6.4%)	26 (6.6%)	0.65 (95% CI 0.18 to 2.29)
	Type 2 Diabetes	41 (10.9%)	56 (14.2%)	0.99 (95% CI 0.28 to 3.45)
	Depression	78 (20.8%)	88 (22.4%)	1.46 (95% CI 0.72 to 2.95)
	Hepatitis C	25 (6.7%)	37 (9.4%)	1.29 (95% CI 0.33 to 5.00)
	Malnutrition	80 (21.3%)	64 (16.2%)	0.74 (95% CI 0.36 to 1.52)
	Other	113 (31.0%)	105 (27.1%)	1.03 (95% CI 0.56 to 1.89)
Reason for admission	Infection	80 (21.3%)	82 (20.9%)	0.90 (95% CI 0.45 to 1.80)
	Suspected variceal bleed	52 (13.9%)	63 (16.1%)	2.04 (95% CI 0.81 to 5.18)
	Encephalopathy	80 (21.2%)	69 (17.6%)	0.91 (95% CI 0.44 to 1.86)
	New onset or worsening ascites	236 (62.3%)	281 (71.3%)	0.94 (95% CI 0.64 to 1.39)

* Co-morbidities reported as subgroup when present in at least 5% subject.

\$ Co-morbidities and reason for admission were reported by the patient or taken from the clinical notes. Patients could have >1 co-morbidity or reason for admission.

⁺ Odds ratio for the primary outcome for that subgroup.

Additional Statistical Analyses Section

1. Threshold Analyses addressing loss to follow up

Of the 777 unique patients randomised in ATTIRE, 35 randomised to the ALBUMIN GROUP, and 19 randomised to STANDARD CARE were lost to follow up. Of the 35 ALBUMIN GROUP patients who withdrew, 3 did so after experiencing a qualifying primary event. Of the 19 patients who withdrew in the STANDARD CARE GROUP, 5 withdrew after experiencing a qualifying event. We undertook threshold analyses to examine the degree to which loss to follow up could affect the results of ATTIRE on the primary outcome. We first assumed that all 14 STANDARD CARE patients who withdrew without experiencing a qualifying event had actually experienced such an event, but the ALBUMIN GROUP patients who were lost to follow up prior to experiencing a primary event did not experience such an event. Recalculating the primary outcome with data imputed in this way provides an odds ratio of 0.87 (95% CI 0.64 to 1.18); that is, no evidence of a benefit associated with randomisation to the ALBUMIN GROUP. Conversely, if we assume that the ALBUMIN GROUP patients who were lost actually experienced an event, and those in the STANDARD CARE GROUP did not experience an event, the recalculated odds ratio for the primary outcome with data imputed in this way is 1.50 (95% CI 1.11 to 2.03); therefore loss to follow up in the albumin group could, at extremis, be associated with a worse outcome associated with randomisation to the ALBUMIN GROUP. As the Primary analysis on the intention to treat data set finds no evidence of benefit associated with randomisation to the ALBUMIN GROUP, these threshold analyses with imputed data are supportive of the overall conclusions drawn.

2. Time to Event Analysis

We conducted time to event analysis as a supportive analysis to examine whether the ATTIRE results were sensitive to the analytic approach taken.

In the time to event analysis, the index date was taken as the date of randomisation. The incidence of events that qualified for the primary outcome were identified by day after the index date, with events experienced prior to day 3 censored. Patients were included in the analysis until: they experienced a qualifying primary event; they were discharged; they were deemed medically fit for discharge but remained in hospital for social care reasons; they reached 15 days in hospital. Patients who had not experienced a qualifying primary event at the point they were discharged medically fit or reached 15 days post randomisation were censored at that point.

3. Re-randomization Analyses

We performed primary analyses on all 777 patients following their first randomization, according to the calculated sample size. Given that the natural history of advanced cirrhosis includes recurrent admissions, we permitted re-randomization of patients >30 days since completing previous treatment to allow for wash-out of any effect from previous treatment, accounting for albumin's 21 day half-life. There were 51 re-randomizations. For the primary outcome reported in Table S5 and S7, cluster analysis was performed to account for re-randomization patient response at two time points being correlated (highly so if the patient was re-randomized to the same arm).

For the secondary analyses we treated all outcomes as independent observations (828 patients in total). This was considered appropriate since (a) primary outcome of previous enrolment(s) had been determined, (b) randomisations were independent of previous allocation and (c) 30 days wash-out accounted for albumin's half-life.

We used re-randomisation in line with patients' requiring multiple admissions and to mitigate against recognised recruitment difficulties, yet accept this approach may introduce bias and thus principally report on first randomizations. When all data were included, the results were the same.

4. Poisson Mixed Models for Comparison between Randomised Conditions for Number of Days in Hospital or Number of Days in ICU

Both the outcomes of number of days in hospital and number of days in ICU are naturally count data. All patients will have at least one day in hospital, and the maximum number of hospital days is limited by design to 15 post randomisation. For ICU days, the majority of patients do not experience ICU admission, but those who do may experience several days, again up to a maximum of 15 after randomisation by design. A Poisson Mixed model is used to analyse these data, including the count of days for each patient, the randomised group and stratification variables as fixed effects and site as a random intercept term. The model utilises a conventional $\log(e)$ link function, and Poisson / Gaussian error structures.

An attribute of the Poisson model is that the exponent of the parameter estimate provides a measure of the ratio between treatment conditions, analogous to the relative risk. Thus where the estimate is unitary (1) there is no difference between the treatment conditions. Where the estimate is, say, 1.5 we

infer that a subject who experienced four days in hospital (or ICU) in the control condition would have expected on average to experience $1.5 \times 4 = 6$ days in hospital (or ICU) in the experimental condition.

Supplementary Table S7. Outcomes including Re-randomized Patients*

Outcome	Albumin (N=414)	Standard Care (N=414)	Adjusted Odds Ratio (95% CI)	P-value
Primary outcome – no. (%)				
Protocol defined	125 (30.2%)	128 (30.9%)	0.97 (0.72-1.31)	0.83
Including all reported deaths†	128 (30.9%)	127 (30.7%)	1.01 (0.75-1.36)	
Secondary Outcomes: no. (%)				
Composite endpoint components‡:				
Incidence of new Infection	87 (21.0%)	76 (18.4%)	1.20 (0.85-1.69)	
Incidence of renal dysfunction	45 (10.9%)	62 (15.0%)	0.67 (0.45-1.02)	
Incidence of death	32 (7.7%)	34 (8.2%)	0.94 (0.57-1.55) ⁺	
Mortality at 28 days	56 (13.5%)	65 (15.7%)	0.83 (0.59-1.25)	
Mortality at 3 months	98 (23.7%)	98 (23.7%)	1.01 (0.73-1.41)	
Mortality at 6 months	140 (33.8%)	125 (30.2%)	1.21 (0.90-1.64)	
Incidence of liver transplant§	3 (0.8%)	1 (0.2%)	-	
One or more SAEs¶	53 (12.8%)	50 (12.1%)	1.06 (0.69-1.61)	
Use of terlipressin for:				
a) Renal dysfunction	12 (2.9%)	12 (2.9%)	-	
b) Hypotension	4 (1.0%)	1 (0.24%)	-	
c) Variceal bleeding	32 (7.7%)	32 (7.7%)	-	
Secondary Outcomes - median (IQR)			Adjusted Difference in means (95% CI)	
Total Albumin infused per patient (g)	200 (140–300)	20 (0-120)	142 (126.4-157.8)	
MELD score at end of treatment period	18.39 (14.6-22.7)	17.35 (13.7-21.3)	0.62 (0.03-1.27)	
			Adjusted Relative Risk# (95% CI)	
Total days in ICU during treatment period for all patients	153	118	1.34 (1.04-1.72)	
Duration of hospital stay (days)	8 (6 – 15)	9 (6 – 15)	1.01 (0.96-1.05)	

- * Unless stated time is given the measurement is during the trial treatment period (15 days from randomization). Adjustment by stratification variables and sites as random effects.
- † Includes deaths that occurred on days 1 and 2.
- ‡ Outcomes are defined in the protocol paper.
- ^ Analysed without adjustment because of small number of events. .
- § As reported by sites at 6 months post randomisation.
- ¶ SAE = serious adverse events.
- || Data presented as median (IQR).
- + Departure from Constant Proportional Hazards (Cox Model not reported; P value from log rank test without stratification).
- # Adjusted Poisson Mixed Model - see Additional Statistical Analyses Section.

Number of randomizations per site that include re-randomizations

Centre	Randomised
Basildon	42
Basingstoke	10
Berkshire	18
Birmingham	3
Blackpool	40
Bournemouth	1
Bristol	40
Brighton	5
Coventry	34
Derby	18
Durham	24
Glasgow RI	80
Glasgow QE	32
Glasgow RA	39
Gloucestershire	10
Heartlands	10
Hull	38
Leeds	12
Liverpool	31
Manchester	9
Newcastle	23
North Tees	33
North Tyneside	9
Nottingham	23
Oxford	25
Plymouth	31
Portsmouth	29
Royal Free	19
Royal London	41
South Tyneside	10
Southampton	9
Surrey	6
Swansea	28
Whittington	28
Wigan	19
Total	829

Supplementary Table S8. Additional secondary endpoint analyses*			
	Albumin	Standard Care	Adjusted Odds Ratio (95% CI)\$
Incidence of new cerebral dysfunction	23 (6.1%)	21 (5.3%)	1.12 (0.60 to 2.09)
Incidence of new circulatory dysfunction	26 (6.8%)	20 (5.1%)	1.39 (0.76 to 2.56)
Incidence of new respiratory dysfunction	67 (17.7%)	58 (14.7%)	1.28 (0.87 to 1.90)
Incidence of liver transplant§	3 (0.8%)	1 (0.3%)	
			Adjusted Difference in Means#
MELD score at end of treatment period	18.6 (14.5-22.7)	17.3 (13.6-21.4)	0.59 (-0.09-1.26)
			Adjusted Relative Risk~
Duration of hospital stay (days)	8 (6-15)	9 (6-15)	1.00 (0.96-1.05)
Number of days in ICU during treatment period per patient	0 (0, 0, 15)^	0 (0, 0, 10)^	1.36 (1.06-1.75)
Use of Terlipressin for			
a. Renal dysfunction	12 (3.2%)	12 (3.0%)	-
b. Hypotension	4 (1.1%)	1 (0.25%)	-
c. Variceal bleeding	31 (8.2%)	32 (8.1%)	-

* Unless stated time is given the measurement is during the trial treatment period (15 days from randomization).

§ As reported by sites at 6 months post randomisation. Adjusted for stratification variables and sites as random effects.

|| Data presented as median (IQR).

Difference in means adjusted for stratification variables and sites as random effects.

^ Median (25th Percentile, 75th percentile, Max).

~ Adjusted Poisson Mixed Model see Additional Statistical Analyses Section.

Serious Adverse Events (SAEs) Section

Analyses methods:

- 169 SAEs
- 13 patients had 2 x SAEs (mostly the 2nd was death – but usually caused by a different event)
- Therefore 156 patients had at least 1 SAE
- 10 SAEs were from 8 patients who were in their 2nd randomisation episode therefore these were excluded from the second analysis
- Final total therefore was 159 SAEs from 148 patients

These 159 SAEs have been each assigned ONE primary label (CTCAE classification system) of an event name after internal review. A summary of these 159 events by treatment arm is presented in supplementary table S9. SAE severity by treatment arm is presented in table 3 in the main paper. A causality summary when there was deemed to be any possible causal relationship in the albumin treatment arm is presented per event type in table S10.

Due to the complex nature of these unwell patients, often more than one clinical event was driving a serious adverse event. As there were particular concerns regarding the possibility of albumin infusions precipitating pulmonary edema, portal hypertensive or GI bleeding, an additional analysis was made counting every mention of possible fluid overload/pulmonary edema/GI bleeding in all SAE reports. These data are included in table 3 in the main paper. For this analysis, one SAE report could account for multiple events.

Finally, an external independent review of all respiratory events which could have any possibility of fluid overload contributing to the event was conducted. This was requested by the ATTIRE IDMC and conducted by two independent liver intensive care specialists. The analysis of the 40 events is presented in supplementary figure S5.

Supplementary Table S9: Summary of SAEs (CTCAE classification)			
	Albumin	Standard Care	Grand Total
Blood and lymphatic system disorders	1	1	2
Anemia	1	1	2
Cardiac disorders	1	3	4
Aortic valve disease	0	1	1
Atrial fibrillation	0	1	1
Cardiac arrest	1	0	1
Sinus tachycardia	0	1	1
Gastrointestinal disorders	13	10	23
Ascites	1	0	1
Colonic obstruction	1	0	1
Esophageal varices hemorrhage	5	6	11
Gastric hemorrhage	5	4	9
Pancreatitis	1	0	1
General disorders and administration site conditions	24	31	55
Multi-organ failure	23	31	54
Non-cardiac chest pain	1	0	1
Hepatobiliary disorders	1	0	1
Hepatobiliary disorders - Other: New HCC	1	0	1
Infections and infestations	20	16	36
Infections and infestations - Other: SBP	0	5	5
Joint infection	1	0	1
Lung infection	15	8	23
Sepsis	4	3	7
Injury, poisoning and procedural complications	0	1	1
Fall	0	1	1
Metabolism and nutrition disorders	2	0	2
Hyperkalemia	1	0	1
Hypophosphatemia	1	0	1
Nervous system disorders	5	1	6
Encephalopathy	4	1	5
Seizure	1	0	1
Renal and urinary disorders	2	0	2
Acute kidney injury	2	0	2
Respiratory, thoracic and mediastinal disorders	17	9	26
Adult respiratory distress syndrome	0	2	2
Dyspnea	0	1	1
Hypoxia	1	1	2
Pleural effusion	1	1	2
Pulmonary edema	15	4	19
Vascular disorders	1	0	1
Vascular disorders - Other, aortic dissection	1	0	1
Grand Total	87	72	159

Supplementary Table S10: Causality summary in albumin treatment arm for any event possibly related to treatment					
	Definitely	Probably	Possibly	Unlikely	Unrelated
Esophageal varices hemorrhage	0	0	0	1	4
Gastric hemorrhage	0	0	0	2	3
Lung infection	0	0	1	3	11
Multi-organ failure	0	0	0	6	17
Non-cardiac chest pain	0	0	0	1	0
Pancreatitis	0	0	0	1	0
Pulmonary edema	1*	5	5	3	1
Total	0	5	6	17	36

*20% Human Albumin Solution administered in excess of suggested dosing protocol, which resulted in a serious breach incident.

**Supplementary Figure S6: INDEPENDENT BLINDED REVIEW OF ALL SERIOUS ADVERSE EVENTS WITH A POSSIBILITY OF FLUID OVERLOAD
CONTRIBUTING TO RESPIRATORY IMPAIRMENT**

(29 SAEs in albumin treatment arm, 11 SAEs in standard of care arm reviewed)

How likely is pulmonary oedema/fluid overload after considering all reports?

	Definite	Probable	Possible	Unlikely
Albumin:	n=3	n=12	n=6	n=8
Standard Care:	n=0	n=6	n=1	n=5

How likely is an alternative or additional diagnosis?*

	Definite	Probable	Possible	Unlikely	Definite	Probable	Possible	Unlikely
Albumin:	n=1	n=7	n=3	n=4	n=1	n=13	n=0	n=0
Standard Care:	n=0	n=4	n=0	n=1	n=0	n=6	n=0	n=0

*Most common alternative/additional diagnoses: Pneumonia (20), ARDS/sepsis (13), Blood transfusion associated circulatory overload (2)