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5% Albumin compared with Balanced Crystalloid, as intravenous fluid resuscitation in adult patients with sepsis, presenting as an emergency to hospital: Statistical Analysis Plan for the randomised controlled feasibility study, "ABC-Sepsis"

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Abstract

ABC Sepsis is a multi-centre feasibility trial comparing 5% human albumin solution (HAS) with standard of care (balanced crystalloid) as the sole early intravenous resuscitation fluid in adult patients presenting with suspected community acquired sepsis to the emergency department in 15 UK hospitals. This randomised controlled trial recruited 300 participants within 12 hours of presentation, with a National Early Warning Score ≥5 and a clinical diagnosis of community acquired infection.

The primary objectives are feasibility of recruitment to the trial and 30-day mortality between groups. Secondary objectives include in-hospital and 90-day mortality, adherence to trial protocol, quality of life measurements and secondary care costs.

This trial looks to determine the feasibility of conducting a trial to address the current uncertainty around fluid resuscitation of patients with suspected sepsis with the aim of conducting a larger definitive study in this area.

Trial Registration
Clinicaltrials.gov reference: **NCT04540094**

Troubleshooting

1 Introduction

This trial will compare 5% Human Albumin Solution (HAS) with standard care (balanced crystalloid) as intravenous fluid resuscitation in adult patients with community acquired sepsis presenting to the emergency department (ED). The aims are to investigate:

- the feasibility of being able to recruit adults with community acquired sepsis and a National Early Warning Score (NEWS or NEWS2, depending on site usage) of ≥5 in the ED
- the comparative effectiveness, by determining 30-day mortality, of intravenous 5% Human Albumin compared with intravenous balanced crystalloid in the early resuscitation phase of management of adults with community acquired sepsis.

It is a feasibility pilot trial and an open label two-arm, multicentre, pragmatic, parallel group randomised trial. The target sample size is 300 participants from sites.

This document has been compiled according to the Edinburgh Clinical Trials Unit (ECTU) standard operating procedure (SOP) "Statistical Analysis Plans" ECTU_ST_04 and has been written based on information contained in the study protocol version 7.0, dated 02 July 2021.

2 Statistical Methods section from the protocol

All statistical analyses will be governed by a comprehensive Statistical Analysis Plan authored by the study statistician and agreed by the independent Trial Steering Committee. As a feasibility pilot trial, all analyses will be exploratory and mainly descriptive. The primary outcome of recruitment feasibility will be assessed as the proportions who visited the ED that were (a) eligible, and then (b) of those who were eligible that were approached and then (c) of those eligible and approached the proportion that consented to be randomised. The clinical primary outcome of all causes mortality at 30 days will be summarised by randomised treatment group and then analysed using a mixed effects logistic regression adjusting for site and adjusting for pre-specified baseline covariates known to be strong predictors of 30-day mortality. The range of possible treatment effects indicated by the 95% confidence interval around the estimate of difference in 30-day mortality, and that around the 30-day mortality rate in the standard of care group will be used to inform the design of a definitive trial. We plan a number of important predefined exploratory sub-group analyses on the primary outcome including severity of illness at recruitment (NEWS/NEWS2, qSOFA, lactate), age, pre-existing known heart failure, pre-existent chronic kidney disease, baseline albumin. We will also undertake a subgroup analysis of primary outcome for all patients not admitted to a critical bed (HDU or ICU) If the data permits, we will consider additional

analyses exploring compliance (what cumulative dose of novel intervention or standard care was received) using causal models with an instrumental variable approach. Secondary outcomes (e.g. volume of intravenous fluid, length of stay) will be analysed using mixed effects linear models, while the secondary outcomes involving proportions (e.g. proportion receiving renal replacement therapy, vasopressor infusion, invasive ventilation, readmissions within 90 days) will be analysed as per the primary outcome (with a mixed effects logistic regression). The proportions admitted to critical care (HDU or ICU) will be analysed using a proportional odds logistic regression. The safety outcomes will be analysed in a similar way according to their distribution. The quality of life data (at 180 days) will be analysed likewise with a model appropriate to the distribution. We will be interested in understanding the observed patterns of any missing data.

No formal cost-effectiveness analysis in planned, however, if data quality allows, an exploratory estimate of the incremental Quality Adjusted Life Years (QALYs) (at days) and secondary care costs (at 30 days) will be made using the EQ-5D-5L. QALYs will be calculated by estimating a combined survival function and HRQoL function using the EQ-5D. Costs will be estimated by assigning national standard unit costs to inpatient stays (critical care and general ward level), readmissions and additional high costs activities observed in the study. Baseline (pre-admission) HQoL will be estimated using age/sex matched population reference data. In sensitivity analysis, surviving patients or proxies will be asked to provide a retrospective estimate of 1 month pre-admission modified EQ-5D-5L responses.

3 **Overall Statistical Principles**

The intention-to-treat (ITT) population will include all patients who have been randomised into this trial, and who did not withdraw consent for any of their data to be stored in the trial database. Patients will be analysed in the group to which they were allocated, regardless of the intervention they actually received. Analyses will be based on the ITT population, unless otherwise specified; in addition, we will explore the influence of adherence on the range of treatment estimates using a suitably specified per-protocol approach (see Section 4.6, analysis (a)).

Safety data will in the first instance by analysed according to treatment received, and will also be summarised descriptively according to an intention to treat approach.

In general terms, categorical data will be presented using counts and percentages, whilst continuous variables will be presented using the mean, median, standard deviation (SD), minimum, maximum, lower and upper quartiles and number of patients with an observation (N). Data will be split by intervention group and time point where applicable.

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level – but all such tests of hypothesis will be informal and interpreted descriptively. 95% (2-sided) confidence intervals (CIs) will be presented.

Where there is missing data for an outcome variable, in the first instance, those records will be removed from any statistical analysis relating to that outcome variable (complete case analysis), unless otherwise specified. In tabulations, numbers of missing observations will be provided, but percentages will not include them.

Distributional assumptions underlying the statistical analyses may be assessed by visual inspection of residual plots. Normality may be examined by normal probability plots. If the distributional assumptions for the parametric approach are not satisfied, further data transformation (to alleviate substantial skewness (i.e. normalizing) or to stabilise the variance), or other suitable methods will be considered. This will be documented in the statistical results report together with the reasoning supporting the action taken, if applicable.

Sites may be categorised into small sites (less than 10 participants recruited) versus big sites (10 or more participants recruited).

All analysis and data manipulation will be carried out using SAS [1] unless otherwise stated.

Qualitative or health economic analysis will not be covered by this SAP. However, data from the statistics report may be used for health economics analyses.

4 List of Analyses

4.1 Recruitment and retention

Number of patients assessed for eligibility; number of patients who were excluded (with a tabulation of reasons for exclusion); number of patients who were randomised; number of randomised patients who withdrew consent including to use of data; number of patients allocated to each treatment arm; number of patients who completed full follow-up to 90 days or died in that period; number from first randomised who completed follow-up to 180 days for EQ-5D; with a tabulation of reasons for discontinuing early, number of patients included in ITT analysis of main clinical outcome, by allocated treatment and overall; number of patients in safety analysis population, by treatment received and overall.

Graph of cumulative number randomised over time.

Dates first and last patients randomised.

A tabulation of numbers of patients randomised by study site, split by allocated treatment (and overall). For EudraCT reporting purposes, enrolment will also be summarised into age categories 18-64; 65-84; and 85+ years.

4.2 Baseline data

A table showing baseline demographic and clinical characteristics overall and by allocated intervention will include:

a) Age (at randomisation in years)

b) Sex (Male / Female)

c) NEWS Score including individual components (1. Respiratory rate, 2. Oxygen saturations, 3. Temperature, 4. Systolic blood pressure, 5. Heart rate, 6. Glasgow Coma Scale (GCS))

d) Lactate (mmol/l)

e) Vital signs (pulse (bpm), systolic and diastolic blood pressure (mmHg), fraction of inspired oxygen (FiO2) (%))

f) Routine blood results (glucose (mmol/L), eGFR (mL/min/1.73m^2), albumin (g/l), ALT (U/L or iU/L), troponin (ng/l), urea (mmol/L), creatinine (µmol/L), WCC (x10^9/L), Hb (g/l), platelets (x10^9/L), neutrophils (x10^9/L), CRP (mg/l), procalcitonin (ug/L or ng/mL).

g) Expected source of infection (chest, urine, CNS, skin, abdomen, missing, unknown, other)

h) Co-morbidities (cancer, stroke, MI, peripheral vascular disease, heart failure, cardiac obstructive pulmonary disease, chronic kidney disease, diabetes type I/ II & dementia)

i) Average volume of fluid (mL) given prior to randomisation.

No formal statistical testing of the baseline characteristics will be performed. The first relevant observation will be presented if more than one observation was collected.

4.3 Trial treatment details, and adherence

No formal statistical testing will be performed.

The protocol defines:

Crossover Any participant who receives the intervention from the arm they were not allocated to within 24 hours of randomisation will be defined as a crossover and does not need to be recorded as a deviation.

Non-adherence This will be defined as to have occurred in any participant who has not received their allocated fluid prescription for resuscitation within 6 hours of the randomisation and does not need to be recorded as a deviation.

Trial treatment details

Table: Per treatment group, who received their allocated fluid for resuscitation within hours, a table showing the following:

a) Yes, within 75% of that allocated and did not cross over within 0 to 6 hours

b) Yes, within 75% of that allocated and did cross over within 0 to 6 hours

c) Yes, at least 200mls administered, regardless of whether crossover occurred

d) Some received but between 6 hours and less than 12 hours, regardless of whether crossover occurred

e) Some received but between 12 and less than 24 hours, regardless of whether crossover occurred

f) None received or unknown.

Graph: The cumulative distribution function for each of volume and % of allocated resuscitation fluid received, by treatment group, will be plotted separately for each of the time windows 0-6 hours; 0-12 hours; 0-24 hours; 6-24 hours.

Graph: Kaplan-Meier curves will be plotted, by treatment group, for time to crossover.

Further, adherence per treatment group will summarised descriptively using the following measures:

1) Time to start of IMP (randomisation to treatment)

2) Proportion of patients who received their allocated intervention for fluid resuscitation

3) Proportion of patients who received their allocated intervention for maintenance

4) Proportion of patients who received crossover fluid in to 6 hours and volume of crossover fluid received

5) Proportion of patients who received crossover fluid in to 24 hours and volume of crossover fluid received

6) Completion rates for initial bolus administration (within first 6 hours)

7) Proportion of patients who receive any other fluid apart from intervention or control during first 6 hours.

4.4 Primary outcome

1) This will be the proportion of those screened who were randomised (number randomised/ number screened) with a 95% CI.

2) The main clinical outcome is 30-day mortality, under intravenous 5% Human Albumin compared with intravenous balanced crystalloid in the early resuscitation phase of management of adults with community acquired sepsis.

A mixed effects logistic regression model will be used, including a fixed effect for intervention group adjusted for site (as a random effect) and baseline covariates known to be strong predictors of 30-day mortality (age; active cancer; heart failure). The intervention effect will be reported as an odds ratio and 95% confidence interval. The assumptions for mixed effects logistic regression will be assessed to ensure compliance. If this model proves inappropriate, a suitable alternative will be used.

4.5 Subgroup analyses

The following subgroup analyses will also be considered based on a 30 day mortality outcome, provided there are sufficient outcomes per subgroup:

1) Severity of illness at recruitment 1. NEWS/NEWS2 (5-6, 7+)

2) Severity of illness at recruitment 2. qSOFA (≤1, >1)

3) Severity of illness at recruitment 3. lactate (≤2mmol/L, >2mmol/L)

4) Age (<70, ≥70 years)

5) Pre-existing known heart failure (Y/N)

6) Pre-existent chronic kidney disease (Y/N)

7) Admission to a critical care bed (HDU or ICU) (Y/N).

These will initially be assessed by reviewing the number of outcomes per subgroup per site. Where feasible, for each of the subgroup analysis listed above the effect of entering the treatment by subgroup interaction into the mixed effects logistic regression model will be examined. If necessary, sites will be grouped according to region and/or size. The odds ratio, plus 95% confidence interval, will be presented for the interaction. Within subgroup treatment effect odds ratios and confidence intervals will also be presented. No other baseline covariates will be included in these analyses. If feasible, these results will be presented as a Forest plot.

Subgroup analysis findings should be interpreted with caution due to the small number of outcomes anticipated per subgroup and the number of subgroup analyses.

4.6 Other analyses

The following data will be summarised descriptively, by randomised group and overall:

	A	B	C
		Objective	**Endpoints to display**
	1	Assess mortality rate during index hospitalisation, in-hospital and at 90 days	a) In-hospital mortality (index admission) and b) 90-day mortality
	2	Assess the ability to deliver the trial including the time to first dose, data completeness and participant withdrawal	Data completeness (%)
	3	Assess the total volume of intravenous fluid in each arm at 6 hours and 24 hours	Volume of randomised fluid delivered in each arm a) in the first 6hrs and b) more than 6hrs to 24hrs

	A	B	C
	4	Assess the level of critical care interventions administered	Proportion of participants needing critical care intervention: a) Intravenous vasopressors, b) renal replacement therapy and c) invasive ventilation
	5	Investigate the length of hospital stay including critical care (HDU/ICU) admission	a) Proportion of patients admitted to critical care (HDU/ICU) b) Length of stay in critical care (HDU/ICU) c) Length of hospital stay
	6	Investigate the proportion of patients readmitted to hospital in first 90 days after discharge	Proportion of patients readmitted in first 90 days after discharge
	7	Delineate the proportion of patients developing any complications including acute kidney injury, pulmonary oedema and allergy including severe allergic reactions	Proportion of patients developing each, or any, of: a) acute kidney injury (as defined by NICE https://cks.nice.org.uk/acute-kidney-injury#!scenario; b) pulmonary oedema (radiology diagnosis or requirement for rescue management (new diuretic use)); and c) allergy or anaphylaxis (requirement for rescue management (antihistamines, adrenaline, intravenous fluids, steroids))
	For the economist		
	8	To assess patient quality of life measures using EQ-5D-5L questionnaire	Health Related Quality of life (EQ-5D-5L) for the first 50 patients randomised (see section 4.8) a) at baseline b) at 7 days and c) at 180 days
	9	To assess secondary care costs at 30 days	Service use at 30 days: a) number of readmissions, and b) length of stay at ward level and in critical care (HDU/ICU)

In addition, the following exploratory analyses will be considered. If deemed inappropriate based on available data, where feasible, suitable alternatives will be used:

a) If the data permits, the effect of compliance (what cumulative dose of novel intervention or standard care was received) on intervention effect will be explored using a complier average causal effects approach. Descriptive analysis of changes in compliance over time in small and large sites may also be considered.

b) Other continuous outcomes (e.g. volume of intravenous fluid, length of stay) will be analysed using mixed effects linear models, while the other outcomes involving proportions (e.g. proportion receiving renal replacement therapy, vasopressor infusion, invasive ventilation, readmissions within 90 days) will be analysed as per the main clinical outcome (with a mixed effects logistic regression). Site will be included as the random effect.

c) The intervention effect on proportion admitted to critical care (HDU or ICU) will be analysed using mixed effects logistic regression as per the main clinical outcome.

d) The observed patterns of any missing data will be reported by randomised group, across the range of outcomes measured and, where appropriate, by time of measurement. This will inform the missing data handling strategies to be taken forward in the subsequent confirmatory trial.

4.7 Safety

Summary tables of adverse events, by treatment group and overall. Number of events and number of patients who had an event, showing all adverse events, serious adverse events, and non-serious adverse events. Tables will also be presented, stratifying events by MedDRA code; severity; relatedness; expectedness; and outcome.

4.8 Other analyses

For the health economics analyses, EQ-5D-5L index score will be calculated from individual health profiles using UK preference weights. Mean, standard deviation (SD), minimum, median, and maximum scores will be provided for the study population by visit and by randomised treatment. The EQ VAS score (between 0 and 100) will be summarised using mean, SD, minimum, median and maximum scores by visit and by randomised treatment. Patients who are dead at the time of sampling will be assigned a zero index score and a missing VAS response. The numbers and rates of missing data will be reported per measure for each visit.

4.9 Data listings

The following data listings will be provided, ordered by randomised treatment group, participant number and date:
1. Protocol violations

2. Protocol deviations
3. Adverse events
4. Suspected unexpected serious adverse reactions (SUSARs)

5 Validation and QC

Data collection and quality checks will be carried in accordance to SOP ECTU_DM_01. The report will be read and sense checked by a second statistician, who will also reproduce independently the primary outcome analysis (Section 4.4 only).

6 Data sharing

A file, or set of files, containing the final analysis data set will be prepared, along with a data dictionary. These will be made available to the Chief Investigator at the end of the analysis phase.

7 List of Abbreviations

	A	B
	Abbreviation	**Full name**
	AE	Adverse Event
	ALT	Alanine aminotransferase
	AR	Adverse Reaction
	bpm	Beats per minute
	°C	Degrees centigrade
	CHD	Coronary heart disease
	CI	Confidence interval
	CRP	C reactive protein
	CNS	Central nervous system
	CVD	Cardiovascular disease

	A	B
	ECTU	Edinburgh Clinical Trials Unit
	ED	Emergency department
	eGFR	Estimated glomerular filtration rate
	GCS	Glasgow coma scale
	HAS	5% Human Albumin Solution
	HDU	High dependency unit
	HRQol	Health Related Quality of Life
	ICU	Intensive care unit
	IMP	Investigational medicinal product
	IQR	Interquartile range
	ITT	Intention to treat
	KG	Kilogram
	L	Litre
	N	Number
	MI	Myocardial infarction
	mL	Millilitre
	mmHg	Millimetres of mercury
	qSOFA	Quick sepsis-related organ failure assessment
	NEWS/NEWS2	National early warning score

	A	B
	SAE	Serious Adverse Event
	SAP	Statistical analysis plan
	SAR	Serious Adverse Reaction
	SAS	Statistical Analysis Software (a proprietary analysis package) [1]
	SD	Standard deviation
	SOP	Standard Operating Procedure
	SUSAR	Suspected Unexpected Serious Adverse Reaction
	WCC	White cell count
	Y/N	Yes/No

8 References

[1] SAS® Institute Inc. SAS for Windows. SAS Institute Inc.: Cary, NC, U.S.A