Study Protocol

Feasibility of 5% Albumin compared with Balanced Crystalloid, as intravenous fluid resuscitation in adult patients with sepsis, presenting as an emergency to hospital: ABC Sepsis trial

Co-sponsors	The University of Edinburgh & Lothian Health Board ACCORD The Queen's Medical Research Institute 47 Little France Crescent Edinburgh EH16 4TJ
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PROTOCOL APPROVAL SIGNATURE PAGE

Feasibility of 5% Albumin compared with Balanced Crystalloid, as intravenous fluid resuscitation in adult patients with sepsis, presenting as an emergency to hospital

ABC Sepsis

EudraCT: 2020-0013520-18

The undersigned accept the content of this protocol in accordance with the appropriate regulations and agree to adhere to it throughout the execution of the study.

Prof Alasdair Gray	Alasdair Gray Alasdair Gray (Jul 27, 2021 10:14 GMT+1)	Jul 27, 2021
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For multi-site trials, the Principal Investigator must sign below to document that the protocol has been read and understood.

Principal Investigator	**Signature**	**Site**	**Date**

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LIST OF ABBREVIATIONS

ACCORD	Academic and Clinical Central Office for Research & Development - Joint office for The University of Edinburgh and Lothian Health Board
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CRF	Case Report Form
CSR	Clinical Study Report
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
eCRF	Electronic Case Report Form
ECTU	Edinburgh Clinical Trials Unit
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HAS	5% Human Albumin Solution
HRQol	Health Related Quality of Life
IB	Investigator Brochure
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
NIMP	Non-Investigational Medicinal Product
QA	Quality Assurance
REC	Research Ethics Committee

SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

TRIAL SUMMARY

Trial Title	Feasibility of 5% Human Albumin Solution compared with Balanced Crystalloid, as intravenous fluid resuscitation in adult patients with sepsis, presenting as an emergency to hospital
Study Acronym	ABC Sepsis
Clinical Phase	Phase III
Trial Design	Open label two-arm, multicentre, pragmatic, parallel group randomised trial
Trial Participants	Adult patients with community acquired sepsis recruited from the Emergency Department and Medical and Surgical Assessment Units in ~ 15 UK NHS Hospitals.
Planned Number of Participants	300
Planned Number of Sites	~15
Countries Anticipated to be Involved in Trial	UK
Treatment Duration	6 hours
Follow up Duration	90 days; except first 50 patients (180 days)
Total Planned Trial Duration	24 months
Primary Objective	This trial aims to investigate: • the feasibility of being able to recruit adults with community acquired sepsis and a National Early Warning Score (NEWS/NEWS2) of ≥5 in the Emergency Department • 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.
Primary Endpoint	• Recruitment rate from screening logs • 30 day mortality

Secondary Objectives	1. To assess the mortality rate during index hospitalisation, in-hospital and at 90 days; 2. To assess the ability to deliver the trial including the time to first dose, data completeness and participant withdrawal; 3. To quantify the proportion of patients who receive any other fluid apart, from the one being studied, in the first 6 hours after recruitment; 4. To assess the total volume of intravenous fluid in each arm at 6 hours and 24 hours 5. To assess the level of critical care interventions administered; 6. To investigate the length of hospital stay including critical care (HDU/ICU) admission; 7. To investigate the proportion of patients readmitted to hospital in first 90 days after discharge; 8. Delineate the proportion of patients developing any complications including acute kidney injury, pulmonary oedema and allergy including severe allergic reactions; 9. To assess patient quality of life measures using EQ-5D-5L questionnaire; 10. To assess secondary care costs at 30 days.

Secondary Endpoints	1. In-hospital mortality and 90-day mortality; 2. Time to start of IMP; 3. Data completeness; 4. Study withdrawal; 5. Volume of randomised fluid delivered in each arm in the first 6hrs and 24hrs; 6. Proportion of participants needing critical care intervention: Intravenous vasopressors, renal replacement therapy and invasive ventilation; 7. Proportion of patients who receive any other fluid apart from intervention or control in first 6 hrs after recruitment; 8. Proportion of patients admitted to critical care (HDU/ICU); length of stay in critical care (HDU/ICU); 9. Length of hospital stay; 10. Proportion of patients readmitted in first 90 days after discharge. 11. Proportion of patients developing any of: acute kidney injury (Defined by NICE (https://cks.nice.org.uk/acute-kidney-injury#!scenario); pulmonary oedema (Radiology diagnosis or requirement for rescue management (new diuretic use); and allergy or anaphylaxis (Requirement for rescue management (antihistamines, adrenaline, intravenous fluids, steroids)). 12. Health Related Quality of life (EQ-5D-5L) at 7 and 180 days for the first 50 patients. 13. Secondary care costs at 30 days (calculated from readmissions and length of stay at ward level and in critical care (HDU/ICU).
IMP(s)	5% Human Albumin Solution
IMP Route of Administration	Intravenous, peripheral or central
Lay Summary of Trial	The aim of this research study is to compare two different fluids (Human Albumin Solution (HAS) and Balanced Crystalloid that are given via a drip to patients with severe infection (sepsis). We plan to see which fluid is better, and to see if they have a role in improving a patient's recovery time, reducing complications and the length of time they stay in hospital. This study plans to find out if there is evidence that one fluid is better overall to determine the need for a subsequent definitive trial.

1. INTRODUCTION

1.1 BACKGROUND

This trial will investigate the feasibility of delivering an early intravenous fluid resuscitation trial comparing 5% human albumin solution (HAS), (current recommended second line fluid therapy in septic shock) as first line therapy with a balanced crystalloid (routine care; currently recommended first line therapy in international sepsis guidelines) [1,2] in adults with sepsis. Previous trials and meta-analyses show that HAS has a potential benefit in patients with sepsis.
The trial intervention will be delivered in the critical first hours of hospital treatment. Patients will be enrolled in Emergency departments (ED) and Medical and Surgical Assessment Units (AAU). We aim to recruit in all groups of sepsis patients who require intravenous fluid resuscitation, not the minority whose care is delivered or will ultimately be delivered in critical care. This maximises generalisability and relevance to the NHS and is very different from previous HAS or previous international sepsis resuscitation trials. Most sepsis in UK hospitals is not managed in critical care; critical care patients are estimated to comprise around only 5-10% of all patients with suspected sepsis [3,4]. We propose an efficient trial design to investigate feasibility and potential effect size for the proposed primary effectiveness outcome, 30-day mortality.

HAS is a potentially ideal resuscitation fluid for sepsis, but this study is needed because: **1.** Evidence for HAS is promising but inconclusive; **2.** HAS is costly (x25-50 greater than balanced crystalloid; £2-4; Albumin 5% group £106); **3.** HAS has not been studied in large sepsis resuscitation trials outside the critical care setting or early during the resuscitation phase; **4.** All previous data relates to critical care management, only 5-10% of eligible patients receive critical care in the UK [3,4, unpublished data from Plymouth, Aberdeen]; **5.** Based on a survey of pharmacists, HAS use is increasing in Critical Care in the UK and globally [5] but use is minimal in Emergency Care [6,7]; **6.** The International Surviving Sepsis Campaign guidelines [1] advise initial intravenous fluid resuscitation with crystalloids: *'using HAS in addition to crystalloids…in patients with sepsis and septic shock when patients require substantial amounts of crystalloids'* (low evidence). NICE guideline 51[2] states: *'Consider HAS for fluid resuscitation only in patients with sepsis and shock';* and **7.** It is considered an important question for treating clinicians with a clear willingness to participate in a trial if funded [31/31 respondents in survey completed prior to grant application].

Adult patients presenting to UK EDs and AAUs with community acquired infection and abnormal vital signs (NEWS/NEWS2 ≥5) are common. Multiple data sets suggest that this sepsis patient cohort constitute around 1-1.5% of all emergency attendances [3, 4, unpublished data from Plymouth, Aberdeen]. This group has a mean age around 70, with a median length of stay 10 days and have significant mortality during index hospitalisation, around 20%. Patients who are older and/or more severely unwell with shock have significantly higher mortality. Overall, data suggest that a patient dies from sepsis every 20 minutes in the UK. Survivors suffer step reductions in health status, with reduced quality of life and functional status [8]. Key issues include cognitive decline and psychological morbidity, and increased risk of subsequent cardiovascular events, renal failure, and infections. Early sepsis management is likely to contribute

causally to long-term outcomes, by reducing subsequent inflammation, immune suppression, and organ dysfunction [9]. Guidelines highlight the importance of early antibiotics and intravenous fluid resuscitation, but the delivery of early fluids is logistically challenging and its direct association with outcomes is uncertain [10]. The proposed primary/secondary clinical outcomes all directly reflect or impact on population health and wellbeing. Our focus is on early sepsis intervention, which has plausibility for modifying short and long-term outcomes. We chose not to study an exclusively ICU population, because, in this population, the intervention is later, selection bias is possible, and disease modification is less plausible. This trial will uniquely include all sepsis presenting to hospitals (>90% of sepsis patients in the NHS are managed in a general ward setting), for whom there is very limited research evidence around the timing and type or volume of intravenous fluid resuscitation. This initial study will establish whether a definitive study comparing 5% HAS with the current standard of balanced crystalloid fluid is feasible in this population and setting. If this study is feasible, it will inform the design and conduct of a larger definitive trial with results that will be generalisable to all patients with community acquired sepsis. The cost of sepsis is high, both during index admission and subsequent 'survivorship' [10]. The excess treatment costs for HAS are likely to be around £110/patient, substantially increasing current fluid costs, but HAS use has already increased 2-3 fold in many hospitals since 2012 consistent with data from outside the UK [6]. The potential economic gains (health/social) from effective early sepsis interventions are substantial and lifelong so our definitive study will include a health economic evaluation which will provide key information to guide HAS use in the NHS. For example, a reduction of 1 patient day in ICU would save around £1500 (equivalent to 12-13 units of HAS).

The main types of intravenous resuscitation fluid*:* The two classes of commonly used intravenous resuscitation fluids are crystalloids ("normal" saline and balanced crystalloid) and colloids (hydroxyethyl starch and albumin) [6,7]. Current UK and international guidelines recommend balanced crystalloids as the first line choice of intravenous fluid in the resuscitation of adult patients with sepsis [1,2]. Recent international and UK data suggest that the use of non-balanced crystalloid remains widespread especially in emergency care settings [6,7]. Starch based colloids are no longer recommended because they were associated with harm in large sepsis and critical care trials.

Supporting randomised controlled trials, meta-analyses and current research: Three large trials include data directly comparing HAS with crystalloid, one included a heterogeneous critical care population using iso-oncotic 4% albumin [31,32] and two only recruited sepsis populations admitted to critical care with hyper-oncotic solution of 20% albumin [33,34]. The reduction in the risk of death from septic shock with albumin as compared to crystalloid fluid was consistent across all three trials and ranged between 2.3% to 6.4% at 28 and 90 days respectively. In the Saline *vs.* Albumin Fluid Evaluation (SAFE) trial [31], in a general ICU population, HAS had no overall effect but the sepsis sub-group suggested lower mortality. This subgroup demonstrated a 5.2% mortality difference when adjusted for relevant baseline characteristics (35.5% *vs*. 30.2%; OR 0.71, 95% CI 0.52–0.97, p = 0.03). [32]. However, this post hoc analysis was at best hypothesis generating. The ALBIOS trial

[33] studied ICU patients with severe sepsis (comparing 20% HAS infusion with crystalloid) and found no overall effect on mortality, but lower mortality with HAS in the sub-group with septic shock (RR 0.87; 95% CI 0.77 to 0.99), equating to an absolute risk reduction of 5.3%; HAS also improved cardiovascular stability although, importantly, the treatment goal in this study was serum albumin concentration, not haemodynamic or end organ perfusion markers. The EARSS study in France, recruited 798 patients with septic shock of less than 6 hours duration, but only in ICUs. These patients were randomised to receive: 100 ml of 20% albumin or 1000 ml of 0.9% saline every 8 hours for 3 days. Almost all patients had severe hypoalbuminemia at study inclusion. There were no significant differences in 28 day mortality rates between the two groups (24.1 *vs.* 26.3%). This study has never been published in full [34].

Several meta-analyses (MA) analysed these data plus results from a number of smaller trials. A MA of 5,534 patients (5 trials) comparing HAS with crystalloids (3,658 severe sepsis; 2,180 septic shock) found HAS was associated with a non-significant difference in 90-day mortality in severe sepsis (odds ratio (OR) 0.88; 95% CI, 0.76 to 1.01; p = 0.08) and significantly reduced mortality in septic shock (OR 0.81; 95% CI, 0.67 to 0.97; p = 0.03) [35]. A MA of 3878 patients (7 trials) found a non-significant difference in mortality with HAS (RR 0.93; 95% CI 0.86 to 1.01; p=0.07), with possibly greater effects in septic shock (RR 0.91; 0.82 to 1.01; p=0.06) [36]. Differences between the MAs are likely to relate to the differences in included trials and methodologies, and small total number of participants.
Importantly, none of these trials compare HAS to balanced crystalloid as the early resuscitation fluid in a pre-ICU setting despite these data being extrapolated in guidelines to precisely this environment. A search of trial registries 12th June 2020) found no ongoing trials addressing this research question. These MA support the need for a trial of HAS in early sepsis, powered for a clinically plausible effect size. In this study we will investigate feasibility of delivering a pragmatic trial during the resuscitation phase of treatment of adults with sepsis and provide pilot data that will inform the size of treatment effect between HAS and balanced crystalloid for the planned primary outcome – 30-day mortality - enabling an accurate sample size to be calculated for a subsequent definitive trial.

1.2 RATIONALE FOR STUDY

Rationale for balanced compared with non-balanced crystalloid as comparator:
There has been increasing concern relating to the potential adverse effects of crystalloids such as 0.9% “normal” saline due to the harmful effects of the high chloride content being associated with hyperchloraemic metabolic acidosis [11] and resultant increased risk of acute kidney injury [12]. More recently, three large pragmatic trials have shown divergent results in relation to the potential harm associated with non-balanced crystalloids. The SPLIT trial showed no difference in the rates of acute kidney injury in ICU patients [13], whereas the SALT-ED in Emergency Department [14] and SMART in ICU patients [15] showed a reduced risk of acute kidney injury and other important clinical outcomes with balanced crystalloids when compared with non-balanced crystalloids. We chose to mandate balanced crystalloid based on these recent large trials, We consider this an important stipulation in this feasibility trial given heterogeneity of use of balanced crystalloid in ED.

Mechanism of action of Human Albumin Solution: It is widely believed that colloids exhibit properties that result in them being superior to crystalloids for expansion of the intravascular space, enhancing cardiac output and thus end organ oxygenation and perfusion. Additionally, due to their larger molecules, they do not leak through the endothelial layer into the interstitium resulting in less tissue oedema than with crystalloids [14-16]. These properties should lead to less fluid resuscitation volume requirement for a given physiological effect, often cited as a ratio of 3:1 [14]. Recent understanding of the pathophysiological effects of sepsis on the glycocalyx in the endothelial wall suggest HAS might have important protective effects that could translate into clinical benefit; however, this potential benefit is controversial and unsubstantiated in clinical trials [15]. Importantly, glycocalyx injury is exacerbated by rapid fluid expansion and hypervolaemia, both of which may occur during early fluid resuscitation. HAS has a number of additional biological properties that may benefit oxygen delivery and end organ perfusion over and above circulating volume expansion in patients with infection and sepsis. Albumin is a key antioxidant in plasma scavenging oxygen free radicals [17-23] and acts as a transport protein binding inflammatory mediators [24]. Moreover, in animal models albumin improves myocardial function and oxygenation [25]. Laboratory studies suggest it is an essential component of the endothelium and may affect vascular permeability and endothelial dysfunction in sepsis [26-29]. As noted above, laboratory evidence suggests it may reduce damage to the glycocalyx in patients with sepsis [30].

Relevance and importance for current UK clinical practice now: The vast majority of patients with community acquired sepsis are managed in general wards in the NHS. This group is extremely common and has long lengths of hospital stay. The mortality rate for this patient group remains stubbornly high and there is limited scope for evidence based practice to lower it further. One possible beneficial intervention is intravenous fluid resuscitation. There is a paucity of evidence around type, timing and volume of intravenous fluid and this trial directly addresses this area. If HAS was shown to be superior the impact for NHS practice would be substantial, would improve patient experience and relieve suffering and would radically change the current NICE and international guidelines [1,2]. Conversely, if HAS is shown not to be superior, then the non-evidence based current drift of clinicians to extrapolate use of HAS to all sepsis settings could be curtailed, which would ensure patients only receive necessary treatment and also have significant cost savings for UK and international healthcare. The importance of this subject area to clinicians is evident by the clear support for a trial in this area from a recent international survey [6] and a 31/31 respondent agreement to participate rate from our recent survey.

2. STUDY OBJECTIVES

2.1 OBJECTIVES

2.1.1 Primary Objective

This trial aims to investigate:

- the feasibility of being able to recruit adults with community acquired sepsis and a National Early Warning Score (NEWS or NEWS2) of ≥5 in the Emergency Department
- 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.

2.1.2 Secondary Objectives

1. To assess the mortality rate during index hospitalisation, in-hospital and at 90 days;
2. To assess the ability to deliver the trial including the time to first dose, data completeness and participant withdrawal;
3. To quantify the proportion of patients who receive any other fluid apart, from the one being studied, in the first 6 hours after recruitment;
4. To assess the total volume of intravenous fluid in each arm at 6 hours and 24 hours
5. To assess the level of critical care interventions administered;
6. To investigate the length of hospital stay including critical care (HDU/ICU) admission;
7. To investigate the proportion of patients readmitted to hospital in first 90 days after discharge;
8. Delineate the proportion of patients developing any complications including acute kidney injury, pulmonary oedema and allergy including severe allergic reactions;
9. To assess patient quality of life measures using EQ-5D-5L questionnaire;
10. To assess secondary care costs at 30 days.

2.2 ENDPOINTS

2.2.1 Primary Endpoint

1. Recruitment rate from screening logs
2. 30-day mortality

2.2.2 Secondary Endpoints

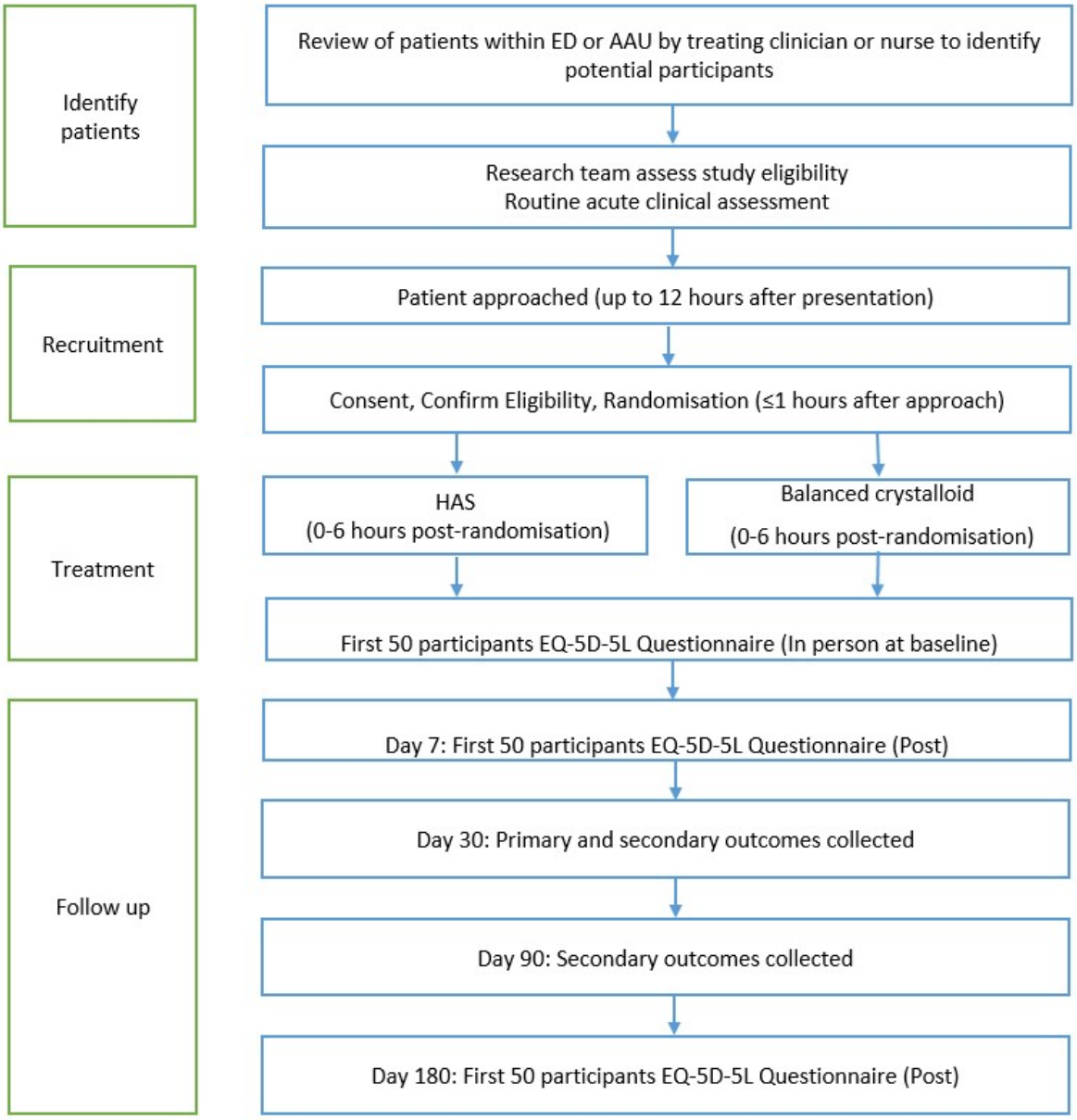
1. In-hospital mortality and 90-day mortality;
2. Time to start of IMP;
3. Data completeness;
4. Study withdrawal;
5. Volume of randomised fluid delivered in each arm in the first 6hrs and 24hrs;
6. Proportion of participants needing critical care intervention: Intravenous vasopressors, renal replacement therapy and invasive ventilation;

7. Proportion of patients who receive any other fluid apart from intervention or control in first 6 hrs after recruitment;
8. Proportion of patients admitted to critical care (HDU/ICU); length of stay in critical care (HDU/ICU);
9. Length of hospital stay;
10. Proportion of patients readmitted in first 90 days after discharge;
11. Proportion of patients developing any of: acute kidney injury (Defined by NICE (https://cks.nice.org.uk/acute-kidney-injury#!scenario); pulmonary oedema (Radiology diagnosis or requirement for rescue management (new diuretic use); and allergy or anaphylaxis (Requirement for rescue management (antihistamines, adrenaline, intravenous fluids, steroids));
12. Health Related Quality of life (EQ-5D-5L) at 7 and 180 days for the first 50 patients;
13. Secondary care costs at 30 days (calculated from readmissions and length of stay at ward level and in critical care (HDU/ICU).

3. STUDY DESIGN

This trial will be an open label two-arm, multicentre, pragmatic, parallel group randomised trial of adult patients with community acquired sepsis recruited from the Emergency Department and Medical and Surgical Assessment Units across ~15 UK NHS Hospitals. The treatment phase will be the first 6 hours following randomisation. 30-day and 90-day follow up will be conducted using routine data only. The exception to this will be the first 50 patients enrolled in the study, Health Related Quality of Life (HRQoL) will be measured using the EQ-5D-5L at baseline, 7 days and at 180 days. At baseline, the participant or their relative will be asked to recall the quality of life 4 weeks prior to the index hospital admission (modified EQ-5D-5L). Questionnaires will be administered by direct participant/relative completion or postal survey with telephone follow up for non-responders after two mailings two weeks apart.

3.1 Study Flowchart



4. STUDY POPULATION

4.1 NUMBER OF PARTICIPANTS

We aim to recruit 300 participants, from adults presenting to an Emergency Department or Medical/Surgical Assessment Units with signs or symptoms of community acquired sepsis and a NEWS (or NEWS2 if adopted by recruiting site) score of ≥5. Recruitment will take place over approximately 12 months.

4.2 INCLUSION CRITERIA

Adult patients (18 years or older) who present to UK NHS hospitals with community acquired sepsis meeting all of the 5 criteria:

1. Clinically suspected or proven infection resulting in principal reason for acute illness;
2. NEWS/NEWS2 score ≥5;
3. Hospital presentation within last 12hrs;
4. Clinician decision has been made that immediate (within 1 hour of assessment) intravenous fluid resuscitation is needed; and;
5. Ability to obtain informed consent.

4.3 EXCLUSION CRITERIA

1. >1 litre of intravenous crystalloid fluid or any intravenous HAS administered prior to eligibility assessment;
2. Clinically judged to require immediate surgery (within one hour of eligibility assessment);
3. Chronic renal replacement therapy;
4. Known allergy/adverse reaction to HAS;
5. Known contraindications to balanced crystalloid as per reference SmPC.
6. Known adverse reaction to blood products;
7. Palliation/end of life care (explicit decision by patient/family/carers in conjunction with clinical team that any active treatment beyond symptomatic relief is not appropriate);
8. Religious beliefs precluding HAS administration;
9. Previous recruitment in the trial;
10. Known recent severe traumatic brain injury (within 3 months);
11. Patients with permanent incapacity;
12. Known to have participated in interventional phase of another CTIMP study within the last 30 days.

4.4 CO-ENROLMENT

4.4.1 Observational Studies

Co-enrolment in observational studies will be permitted. For example, with studies that involve only the collection of data (e.g. questionnaires) or tissue samples (e.g. blood).

4.4.2 Interventional Phase CTIMP-CTIMP Co-enrolment

Enrolling a participant in the interventional phase of more than one CTIMP (i.e. a participant receiving IMP(s) from more than one trial concurrently) is not permitted and participants will be excluded from the study if they have participated in another CTIMP within 30 days. This is to maintain participant safety, avoid drug interactions and to ensure there is appropriate levels of research burden.

4.4.3 CTIMP-CTIMP Co-enrolment

In cases where participants are in long term follow-up (e.g. where follow data only is being collected) co-enrolment may be permitted. In such instances, the CTIMP-CTIMP Co-enrolment Checklist (POL008-F01) must be completed by the Sponsor

Representative(s) in conjunction with the CI prior to the co-enrolment proceeding. Where necessary, the combined risk assessment may need to be appraised as per ACCORD SOP GS002 (Combined Risk Assessment)

4.4.4 CTIMP-Non-CTIMP Co-enrolment

Participants who are active in the interventional phase of a non-CTIMP can be co-enrolled to a CTIMP provided the CTIMP-non-CTIMP Co-enrolment Checklist (POL008-F02) is be completed by the Sponsor Representative(s) in conjunction with the CI prior to the co-enrolment proceeding. In addition, when considering permitting co-enrolment, investigators should be mindful of the potential burden upon participants, their families and research staff.

4.4.5 Accidental/Unintentional Co-Enrolment Identified Retrospectively

Investigators should aim to prevent accidental/unintentional co-enrolment by ensuring electronic and paper medical notes are checked for documentation of trial participation and by routinely asking participants if they are enrolled in another study prior to recruitment. The Sponsor's representatives require that incidents of accidental/unintentional co-enrolment be reported to the Sponsor as a protocol deviation/violation so they can determine the appropriate course of action.

5. PARTICIPANT SELECTION AND ENROLMENT

5.1 IDENTIFYING PARTICIPANTS

There will be no trial specific screening tests performed. The patient will receive routine acute clinical assessment including severity of illness assessment (vital signs and blood lactate measurement - which is needed to complete the randomisation) and be treated in accordance to current UK guidelines (Sepsis 6) [2,37]. The results of these will inform trial eligibility and the patient may be approached as soon as these are available. Patients may be approached up to 12 hours after presentation if their clinical condition means that fluid resuscitation needs to commence. This time window has been chosen as it allows the longest reasonable period for recruitment from arrival where the patient could be deemed to be receiving acute assessment.
Patient and clinician will be unaware of treatment allocation until after randomisation.
The research team, where it is locally agreed that they are part of the clinical care team, will identify patients using triage information and clinical or electronic records in the Emergency Department, Medical or Surgical Assessment Units or any other area used for acute assessment in the recruiting site. In this case, it is anticipated they would identify patients and make the first approach. Any member of the clinical team who has received general and trial specific training and is on the delegation log may also identify patients in this way.

Where researchers are <u>not</u> considered to be part of the care team, the researcher should ask a member of the direct care team to identify suitable patients and ask permission from the patient to be approached by the researcher to discuss participation.

5.1.2 Pregnant Participants

Pregnancy is not an exclusion criteria as the interventions are thought to be safe for use during pregnancy according to their representative Summary of Product Characteristics (SPC). The safety of Human Albumin Solution for use in human pregnancy has not been established in controlled clinical trials. However, clinical experience with albumin suggests that no harmful effects on the course of pregnancy, or on the foetus and the neonate are to be expected. Human Albumin is also a normal constituent of human blood. Compound Sodium Lactate solution can be used safely during pregnancy and lactation as long as the electrolyte and fluid balance is controlled.

5.2 CONSENTING PARTICIPANTS

The consent pathway below will be followed to determine the appropriate mechanism of consent to use for an individual participant and details where consent to continue is needed.

5.2.1. Patient consent

Potentially eligible participants who are willing to take part in the study, and have capacity to do so, will be asked to provide written informed consent. Consent will be obtained by trained members of the clinical team or members of the research team who have been delegated this responsibility. The Investigator is responsible for the delivery of processes to ensure informed consent is obtained before any protocol specific procedures are carried out. The decision of a patient to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.

The patient will be given a Patient Information Sheet (PIS), which will explain the aims of the trial and the potential risks and benefits of the study treatments. If necessary, a Summary PIS will be provided first to provide a brief outline of the study and allow potential participants to decide whether or not they wish to proceed and before the full Patient Information Sheet is provided.

The patient will be given enough time to consider the trial and ask questions regarding their participation in the trial. Due to the need to start treatment within one hour, there may not be long for the participant to consider the trial. Ideally, a period of 30-40 minutes will be given but it may be only 10-15 minutes due to the need for fluid resuscitation to begin. The research teams are experienced at recruiting patients in the emergency environment and given the nature of the intervention and the burden of the trial we believe this to be reasonable. Potential participants will receive adequate oral and written information. The oral explanation to the patient will be performed by a member of the research team or a trained and delegated member of the clinical team and must cover all the elements specified in the Participant Information Sheet and Consent Form. The patient must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information. The patient must be given sufficient time to consider all the information provided. It should be emphasised that the patient may withdraw their consent to participate at any time without loss of

benefits to which they otherwise would be entitled. The participant will be informed and agree to their medical records being inspected by representatives of the sponsor(s). The Investigator or delegated member of the trial team and the participant will sign and date the Consent Form to confirm that consent has been obtained. If the participant is unable to sign the consent form for themselves then the witnessed verbal consent form can be used and written consent does not need to be obtained in addition to this. The original consent form will be filed in the Investigator Site File (ISF), the participant will receive a copy of this document and a copy filed in the participant's medical notes.

Capacity will be assessed by the Principal Investigator (PI) or a clinician responsible for the treatment of the participant. This assessment of capacity will be documented in the participant's medical records.

5.2.2. Personal/Professional Representative consent

If a patient is not considered to have capacity to consent, then a Personal Representative or Professional Representative will be approached for consent.

In Scotland this is defined as:

1. Personal legal representative i.e. Adult's Welfare Guardian or Welfare Attorney, or if not appointed the adult's nearest relative.
2. Professional legal representative i.e. a doctor responsible for the medical treatment of the adult if they are independent of the study, or a person nominated by the healthcare provider.

In England and Wales this is defined as:

1. Personal legal representative i.e. a person not connected with the conduct of the trial who is suitable to act as the legal representative by virtue of their relationship with the adult and is available and willing to do so.
2. Professional legal representative i.e. a doctor responsible for the medical treatment of the adult if they are independent of the study, or a person nominated by the healthcare provider.

If a Personal Representative is present, they will be given information about the trial in the Personal Representative Information Sheet. The Personal Representative will be given enough time to consider the trial and ask questions regarding their relative's participation in the trial. Ideally, a period of 30-40 minutes will be given but this may be only 10-15 minutes due to the need for fluid resuscitation to begin within one hour.

The Personal Representative will be told they are being asked to give consent on behalf of the incapacitated adult, that they are free to decide whether they wish to make this decision or not and that they are being asked to consider what the adult would want, and to set aside their own personal views when making this decision. They will be informed that their relative will be asked whether or not they wish to continue in the study once they have regained capacity to do so.

If they indicate they have had time to consider the trial, the impact on their relative and provided with the opportunity to have any trial related questions they will be asked to

provide written consent. The Investigator or delegated member of the trial team and the Personal Representative will sign and date the Consent Form to confirm that consent has been obtained. The original consent form will be filed in the Investigator Site File (ISF), the participant will receive a copy of this document and a copy filed in the participant's medical notes.

Consent via Telephone

Every effort will be made to approach and consent the Personal Representative in person. If the Personal Representative is only contactable by telephone then the informed consent process is permitted via telephone or an appropriate video conferencing technology such as NHS near me, provided the following:

• The Representative who is being contacted has previously had the opportunity to discuss the clinical aspects of the patient's care with the clinical team;

• A member of the clinical team has sought permission for the Personal Representative to be contacted by a member of the clinical or research team regarding potential involvement in the study;

• The approach to discuss consent is clearly separate to any discussions made between the representative and the clinical team.

A member of the research team will contact the Personal Representative by telephone/videoconferencing technology to explain what the study entails and answer any questions they may have. The Personal Representative will be given time to read and consider the information sheet. In situations where the Personal Representative does not have a copy of the PIS this will be read to them. Ideally, a period of 30-40 minutes will be given but this may be only 10-15 minutes due to the need for fluid resuscitation to begin within one hour. If the Personal Representative chooses to enrol the patient onto the study, verbal consent will be obtained by a member of the research team who conducted the interview and will sign the consent form. This will be witnessed by an independent member of staff.

A copy of the signed Personal Rep Witness consent form will be sent to the Personal Representative electronically or by post along with a Personal Representative PIS and Consent form for signature by the Personal Representative. All efforts will be made to obtain a signature on the Personal Representative Consent form either electronically or by post However, in the absence of this signature, a consent form completed by a member of the research team and witnessed by an independent member of staff will be acceptable.

If there is no response from the Personal Representative one further reminder can be send after one month. If the Personal Representative does not return the signed consent form but does not ask for the participant to be withdrawn from the trial, the Professional Representative consent will remain valid and the patient will remain in the trial.

If a Personal Representative objects to the inclusion of the patient in the trial, their views will be respected.

The participant must also receive information, according to their capacity of understanding, about the trial and its risks and benefits.

If there is not a Personal Representative immediately available (within 30 minutes), a Professional Representative will be approached to determine if it is appropriate for the patient to be entered into the trial so that treatment could be commenced within one hour. A Personal Representative should be approached for consent to continue as soon as they are available, and it is feasible to do so. If the Personal Representative is unable to visit the hospital in person the consent form will be sent to them by post. The Personal Representative will be asked to return the signed consent form if they wish to remain in the trial, or contact the study team if they wish to be withdrawn. If the patient does not return the signed consent form but does not ask to be withdrawn from the trial, the Professional Representative consent will remain valid.

5.2.3. Deferred Consent

Patients who have “life threatening features” and who lack temporary capacity due to their current illness can be recruited to the trial using deferred consent if there is no Personal/Professional Representative to give consent on their behalf within 30 minutes so that treatment can be commenced within one hour. The decision to defer consent should be made by an ST4 (or above) or consultant who has appropriate trial training and this should be clearly documented.

The patient would be enrolled into the trial and receive their allocated treatment. Consent would be sought as soon as possible from a Personal Representative (or a Professional Representative if they are available sooner). If a Personal/Professional Representative declines to give consent for continuation at this stage, their wishes will be respected and the withdrawal process in section 5.6 will be followed.

5.2.4. When the participant regains capacity

If and when the participant regains capacity to consent (as assessed by a clinician), they will be given a Recovered Capacity PIS which will explain what has happened to them so far and seek written consent for continued participation in the trial. This will be done as soon as it is feasibly possible. If the participant is happy to continue they will be asked to provide written consent. The Investigator or delegated member of the trial team and the participant will sign and date the Consent Form to confirm that consent has been obtained. The original consent form will be filed in the Investigator Site File (ISF), the participant will receive a copy of this document and a copy filed in the participant’s medical notes.

In the event that a patient is not able to be approached for consent to remain in the trial prior to hospital discharge, the local research team will seek written consent by sending a PIS and consent form by post. The patient will be asked to return the signed consent form if they wish to remain in the trial, or contact the study team if they wish to be withdrawn. If there is no response, one further reminder can be send after one month by post. If the patient does not return the signed consent form but

does not ask to be withdrawn from the trial, the Professional Representative and/or Personal Representative consent will remain valid and the patient will remain in the trial.

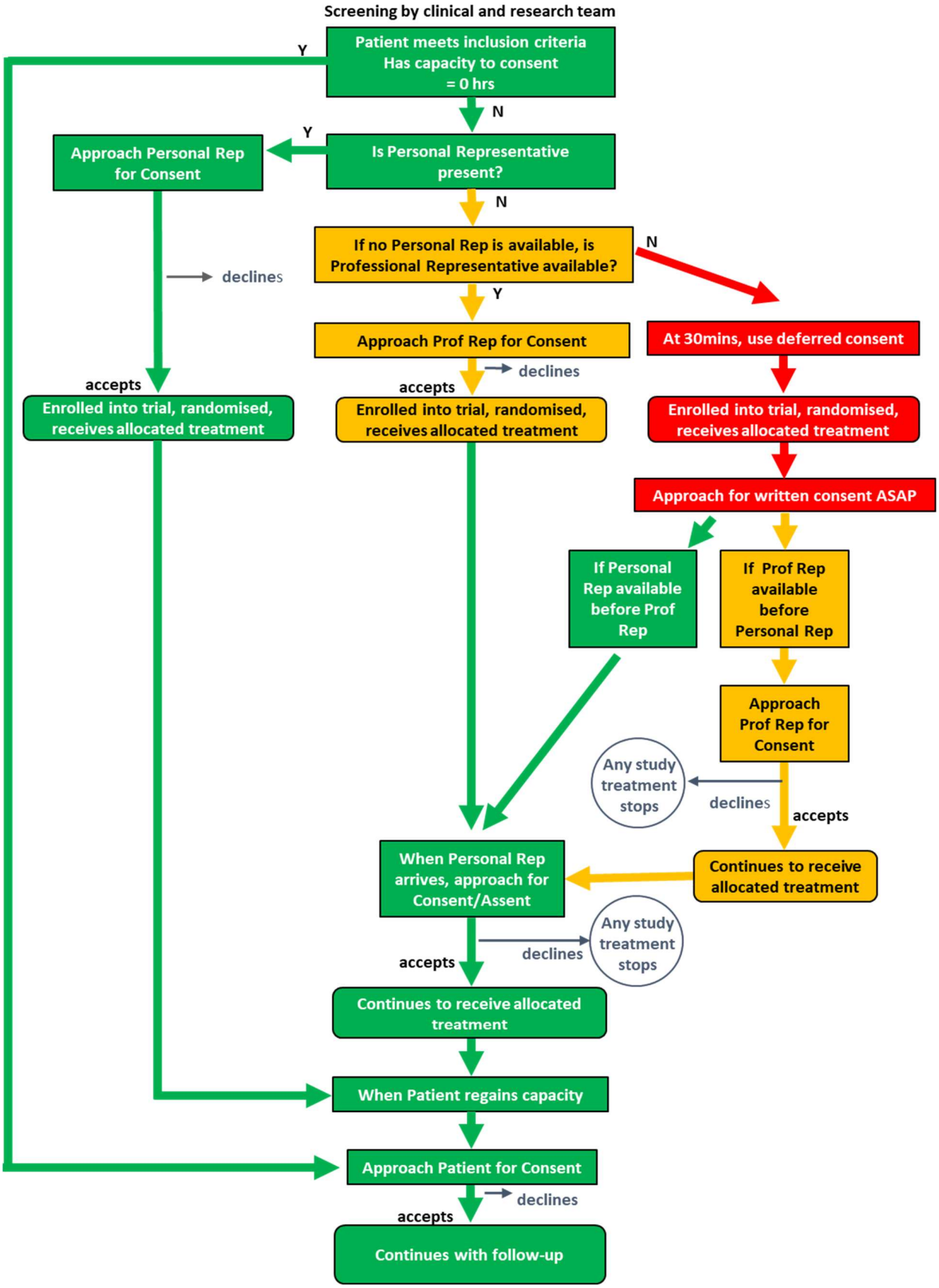
If the participant is not happy to continue, the withdrawal process in section 5.6 will be followed.

For any patient who was included but does not regain full capacity, consent from the Personal Representative will stand, or from the Professional Representative where there is no Personal Representative. Where no consent is given by any legal representative, i.e. deferred consent is used and no subsequent consent obtained, or a participant dies before any consent obtained the patient data collected would be destroyed.
Patients with permanent incapacity will not be recruited and this is an exclusion criteria.

5.2.5. Witnessed Methods of Obtaining Signatures

Consent will normally be recorded in writing, dated and signed or otherwise marked by the participant or their legal representative. In most instances this will take the form of a face to face consent process with a wet ink signature.

If face to face consent is not possible or feasible, verbal consent over the phone or video-call will be utilised, this will be witnessed and recorded in writing. If a verbal witnessed consent procedure is utilised we will also attempt to obtain a written signature from the participant or their legal representative by posting the consent form to them for signature and return.


Screening by clinical and research team
Patient meets inclusion criteria
Has capacity to consent
= 0 hrs
Y
N
Is Personal Representative present?
Y
Approach Personal Rep for Consent
N
If no Personal Rep is available, is Professional Representative available?
N
Y
declines
Approach Prof Rep for Consent
At 30mins, use deferred consent
declines
accepts
Enrolled into trial, randomised, receives allocated treatment
accepts
Enrolled into trial, randomised, receives allocated treatment
Enrolled into trial, randomised, receives allocated treatment
Approach for written consent ASAP
If Personal Rep available before Prof Rep
If Prof Rep available before Personal Rep
Approach Prof Rep for Consent
Any study treatment stops
declines
accepts
When Personal Rep arrives, approach for Consent/Assent
Continues to receive allocated treatment
Any study treatment stops
declines
accepts
Continues to receive allocated treatment
When Patient regains capacity
Approach Patient for Consent
declines
accepts
Continues with follow-up

5.3 SCREENING FOR ELIGIBILITY

Participant eligibility will be verified by a clinical trial physician. Confirmation of eligibility will be recorded on the eligibility form/eCRF and within the participants' medical records.

5.4 INELIGIBLE AND NON-RECRUITED PARTICIPANTS

Patients who are eligible for inclusion but are not recruited will be recorded on the screening log to provide data to comply with CONSORT reporting for randomised controlled trials. The Data Protection Act will be complied with at all times.

5.5 RANDOMISATION

5.5.1 Randomisation Procedures

After assessment for eligibility and consent, the researcher or a delegated member of the clinical team will collect the baseline data necessary to complete the pre-randomisation information on the eCRF (a blood lactate measurement is required in order to complete the randomisation). Vital signs and blood lactate taken within the last hour can be used to make the assessment. Use of clinical care results taken prior to consent is permitted. If greater than one hour ago, a further blood lactate should be measured prior to randomisation. Randomisation will be carried out using a web-based randomisation service (managed by the Edinburgh Clinical Trials Unit (ECTU)) that ensures allocation concealment. Randomisation will be carried out within 12 hours of arrival at the hospital and within one hour of the decision being made that fluid resuscitation should be commenced. Once a patient is randomised, they will remain in the study and have all outcomes recorded regardless of compliance with randomised pathway allocation, unless they specifically withdraw consent to have data stored. Consented patients will be randomised on a 1:1 basis to albumin or balanced crystalloid in addition to standard care and will be stratified by age(<70 and ≥70) and lactate (<2 and ≥2) and study site.

5.5.2 Treatment Allocation

5% Human Albumin Solution will be compared to balanced crystalloid. This is an open label study.

1. 5% Human Albumin Solution arm

Participants will receive 5% albumin as their sole resuscitation fluid in the first six hours following recruitment to the study. See section 6.3 for dosing and 6.5 for overdose. All other care will be as per local protocol.

2. Balanced crystalloid arm

Participants will receive balanced crystalloid as their sole resuscitation fluid in the first six hours following recruitment to the study. All other care will be as per local protocol.

5.5.3 Emergency Unblinding Procedures

The study will be not be blinded, treating clinicians will be aware of which treatment the participant is receiving.

5.6 WITHDRAWAL OF STUDY PARTICIPANTS

Participants are free to withdraw from the study at any point or a participant can be withdrawn by the Investigator or their Personal/Professional Representative. If withdrawal occurs, the primary reason for withdrawal will be documented in the participant's eCRF, if possible. The participant/their Representative will have the option of withdrawal from:

1. Study treatment with continuation of the collection of clinical and safety data;
2. All aspects of the trial but continued use of data collected up to that point. To safeguard rights, the minimum personal information possible will be collected.

Randomised patients who wish to be withdrawn from the study before they have undertaken any study related procedures will be withdrawn from the study and another participant will be recruited to replace them. Data on the original participant will be kept on the eCRF/database.

We anticipate ~1% withdrawal as previously found in the 3CPO, RATPAC and RAPID-CTCA trials [38-40].

6. INVESTIGATIONAL MEDICINAL PRODUCT AND COMPARATOR

6.1 STUDY DRUG

6.1.1 Study Drug Identification

5% Human Albumin Solution.

6.1.2 Study Drug Manufacturer

Not applicable. Any preparation of 5% Human Albumin Solution which has marketing authorisation in the UK to be used for this indication and is stocked by local hospital pharmacies at the participating sites, may be prescribed in this study.

6.1.3 Marketing Authorisation Holder

An example of a Human Albumin Solution MA Holder is Octapharma Limited and the MA number is PL 10673/0030. This is being listed for representative purposes only.

6.1.4 Labelling and Packaging

No specific arrangements are planned for labelling since we will use the licensed medicinal products that are currently available in the UK.

6.1.5 Storage

The 5% HAS will be supplied by the local hospital pharmacy department at each participating site. The interventions will be kept in a secure place at each hospital pharmacy under conditions specified in the local internal procedures.

6.1.6 Destruction of Trial Drug

Not applicable as using hospital routine supplies.

6.1.7 Summary of Product Characteristics (SPC) Booklet or Investigators Brochure

The NHS does not have a preferred brand or generic HAS. Each hospital pharmacy may stock several brands and these may change over the course of the study. The pharmacy can dispense any brand of HAS currently in stock. A representative Summary of Product Characteristics (SPC) (is provided in a separate document with a cover sheet and signature page (signed and verified by the CI and Sponsor) and is filed in the TMF.

6.2 COMPARATOR DRUG

6.2.1 Study Drug Identification

Intravenous “balanced” crystalloid.

6.2.2 Study Drug Manufacturer

Not applicable. Any preparation of intravenous “balanced” crystalloid which has marketing authorisation in the UK to be used for this indication and is stocked by local hospital pharmacies at the participating sites, may be prescribed in this study.

6.2.3 Marketing Authorisation Holder

An example of an Intravenous “balanced” crystalloid MA Holder is Baxter Healthcare Ltd and the MA number is PL 00116/0332. This is being listed for representative purposes only.

6.2.4 Labelling and Packaging

No specific arrangements are planned for labelling since we will use the licensed medicinal products that are currently available in the UK.

6.2.5 Storage

The balanced crystalloid will be supplied by the local hospital pharmacy department at each participating site. It will be kept in a secure place at each hospital pharmacy under conditions specified in the local internal procedures.

6.2.6 Destruction of Trial Drug

Not applicable as using hospital routine supplies.

6.2.7 Summary of Product Characteristics (SPC) Booklet or Investigators Brochure

The NHS does not have a preferred brand or generic intravenous “balanced” crystalloid. Each hospital pharmacy may stock several brands and these may change over the course of the study. The pharmacy can dispense any brand of intravenous “balanced” crystalloid currently in stock. A representative Summary of Product Characteristics (SPC) is provided in a separate document with a cover sheet and signature page (signed and verified by the CI and Sponsor) and is filed in the TMF

6.3 DOSING REGIME

Participants allocated to the treatment arm will receive intravenous 5% Human Albumin Solution (HAS) administered as the sole intravenous resuscitation fluid during the initial 6-hour resuscitation period. It is anticipated that most participants will receive approximately 10ml/kg in the first 3 hours using 250-500ml rapid infusion (bolus) of HAS for resuscitation based on clinical judgement, using clinical assessment supplemented by technology within the usual scope of practice. After 3 hours, further HAS boluses for resuscitation up to 6 hours post-randomisation will be at clinical discretion and will be documented in the eCRF. Both vital signs and lactate, if measured, prior to treatment starting and at 1,3,5,7 hours (+/-30mins) after randomisation, will be recorded in the eCRF as well as source data worksheets or medical notes.

To avoid contamination, participants in the HAS arm should not receive balanced crystalloid or other fluid as a resuscitation fluid in the first 6 hours post randomisation. If the treating clinician believes resuscitation to euvolaemia has been completed within the 6hour period post randomisation and wishes to commence slow maintenance fluid within this timeframe using balanced crystalloid, this should be at a rate of no more than 125ml/hour. The reason for the fluid should be clearly recorded in the eCRF i.e., maintenance rather than resuscitation. In the subsequent event of further clinical deterioration during the intervention timeframe requiring resuscitation fluid, further boluses of HAS should be administered and documented as further bolus fluid for resuscitation.

Participants allocated to the usual care arm will receive intravenous balanced crystalloid administered as the sole intravenous fluid during the initial 6 hour resuscitation period post randomisation. It is anticipated that most participants will receive approximately 30ml/kg in the first 3 hours using 250-1000ml rapid infusion (bolus) of balanced crystalloid for fluid resuscitation based on clinical judgement, using clinical assessment supplemented by technology within the usual scope of practice. Thereafter, further crystalloid boluses for resuscitation up to 6 hours will be at the discretion of the clinical team and will be documented in the eCRF. Both vital signs and lactate, if measured, prior to treatment starting and at 1,3,5,7 hours (+/-30mins), will be recorded in the eCRF as well as source data or medical notes.

Participants in the balanced crystalloid arm should not receive HAS or any other fluid as a resuscitation fluid in the first 6 hours. If the treating clinician wishes to administer maintenance rather than resuscitation fluid this should only be done after resuscitation is complete and should be at a rate of no more than 125ml/hour. The reason for the fluid should be clearly recorded in the eCRF i.e., maintenance rather than resuscitation. In the subsequent event of further clinical deterioration during the intervention timeframe requiring resuscitation fluid, further boluses of balanced crystalloid should be administered and documented as further bolus fluid for resuscitation.

For any participants requiring operative intervention during the 6 hours post randomisation treatment allocation should be maintained where possible in theatre and in critical care after but allow for anaesthetic discretion/judgement around other fluid and blood product use.

6.3.1 Difference between current/planned care pathways

There will be no difference between treatment arms other than intravenous resuscitation fluid in the first 6 hours of care after recruitment. Other care will follow national sepsis guidelines.

6.4 PARTICIPANT ADHERENCE

Adherence with fluid prescription will be a feasibility outcome and will be recorded as part of the eCRF. This does not need to be reported to the Sponsor as a deviation/violation.

6.5 CROSSOVER OF TREATMENT ARMS

If a participant receives the intervention from the arm they were not allocated to within 24hours of randomisation then this will be recorded as an outcome in the eCRF at discharge. This does not need to be reported to the Sponsor as a deviation/violation.

6.6 OVERDOSE

There are no specific overdose features expected, beyond those associated with excessive intravenous fluid administration. Excess fluid administration will be handled in line with standard practice.

6.7 OTHER MEDICATIONS

6.7.1 Non-Investigational Medicinal Products

There are no NIMPs for this study.

6.7.2 Permitted Medications

Not applicable.

6.7.3 Prohibited Medications

Not applicable.

6.7.4 Concomitant Medications

No concomitant medications will be recorded as part of the eCRF. These will be documented in the medical records and will only be recorded where they are relevant to AE/SAE reporting.

7. STUDY ASSESSMENTS

7.1 STUDY ASSESSMENTS

The following study assessments will be completed:

	Screening	Baseline (Day 0)	Day 1-6	Day 7	Discharge	Day 30 #	Day 90 #	Day 180
Consent	X							
Eligibility	X							
Randomisation		X						
Demographics/Medical History/estimated weight		X						
Routine blood results*		X	X	X				
Routine urine and other culture results		X						
Vital Signs/lactate**		X						
IMP administration/adherence		X						
Interventions		X						
Mortality					X	X	X	
Length of stay/ Ward/HDU/ICU stay					X		X	
Readmissions							X	
Acute kidney injury/ Pulmonary oedema/ Allergy/anaphylaxis					X			
Adverse Events		X	X	X				
EQ-5D-5L***		X		X				X

* Daily (+/- 12 hours) for any routine bloods collected up to 7 days. If bloods (or individual parameters) are not requested by the clinical team, this will not be recorded as a deviation.
**Both vital signs and lactate, if measured, will be recorded prior to treatment starting and at 1,3,5 and 7 hours after randomisation (+/-30mins). Lactates up to 24hours post-randomisation, if measured, will be recorded at 9,11,13,15,17,19,21,23 hours (+/-30mins).
***First 50 participants only.
As Day 30 and Day 90 follow up is collected from the medical records it can be reviewed and recorded in the eCRF up to 7 days after the time point so it captures all admissions/events up to and including Day 30 and 90.

For the first 50 participants enrolled in the study, HRQoL will be measured using the EQ-5D-5L at baseline, 7 days and at 180 days. If questionnaires are not completed on the specified day or are not returned by the participant, this will not be reported as a deviation. Vital status will be checked either using local electronic medical records or contact with participant GP prior to contacting participant. Outcome measures will be obtained via the medical notes.

7.2 LONG TERM FOLLOW UP ASSESSMENTS

There is no long term follow up for this study – most participants will be followed up for 90 days only, with the first 50 participants being followed up for 180 days.

8. DATA COLLECTION

Data will be collected from consent until final follow up visit. Site-specific source data plans will be created to indicate where protocol required information will be originally documented. Source data worksheets created by the Edinburgh Clinical Trials Unit (ECTU) will be made available, but their use is optional. The eCRF can be used as source data for some data points (this should be noted on the source data plan by the site).
Study data will be entered onto an eCRF (case report form) developed by ECTU.

8.1 CASE REPORT FORMS

Patients will have data collected during index hospitalisation, comprising of age, sex at birth, past medical history. Data will be collected from NHS records and will include: eligibility criteria, consent and baseline demographics; estimated weight, co-morbidities; vital signs, routine blood results including baseline kidney function, liver function and albumin; relevant investigations or interventions including surgery, vasopressor use, renal replacement therapy, invasive ventilation, chest x-rays, prescriptions; time of start of IMP; length of stay including critical care, repeat hospitalisations, adverse events and decisions regarding treatment escalation planning and resuscitation. Detail will also be collected on the trial intervention including timing and volume of fluids. Length of stay and repeat hospitalisation will be recorded as part of follow up.

Study Data Collected on eCRF
Primary Outcome
30-day mortality
Recruitment rate from screening logs
Secondary Outcomes
In-hospital mortality and 90-day mortality
Time to start of IMP
Data completeness
Study withdrawal
Volume of randomised fluid delivered in each arm in the first 6hrs and 24hrs
Proportion of participants needing critical care intervention: Intravenous vasopressors, renal replacement therapy and invasive ventilation
Proportion of patients who receive any other fluid apart from intervention or control in first 6 hrs after recruitment
Proportion of patients admitted to critical care (HDU/ICU); length of stay in critical care (HDU/ICU)
Length of hospital stay
Proportion of patients readmitted in first 90 days after discharge

Proportion of patients developing any of: acute kidney injury (Defined by NICE (https://cks.nice.org.uk/acute-kidney-injury#!scenario); pulmonary oedema (Radiology diagnosis or requirement for rescue management (new diuretic use); and allergy or anaphylaxis (Requirement for rescue management (antihistamines, adrenaline, intravenous fluids, steroids)).
Health Related Quality of life (EQ-5D-5L) at 7 and 180 days for the first 50 patients.
Secondary care costs at 30 days (calculated from readmissions and length of stay at ward level and in critical care (HDU/ICU)

8.2 TRIAL DATABASE

Data collected about the participants will be entered into a specially designed password protected online accessed secure database (REDCAP; http://www.project-redcap.org) the server of which is held within the University of Edinburgh. Data can be entered directly to the database using is as an eCRF if the research team prefer. Following data analysis, the database will be archived by programmers in ECTU. This archived eCRF/database will be stored indefinitely on University of Edinburgh servers once user access has been disabled. Access to the archived database will be controlled by the Chief Investigator.

9. DATA MANAGEMENT

This trial will be coordinated from ECTU. Data will be collected at each site by local investigators and uploaded to the eCRF/database. If a participant or their representative withdraws a previously given informed consent or refuses to consent for continuation in the trial, or if the participant dies and no participant consent is available, the patient's data will be handled as follows: Data collected up to the point of withdrawal will be used in an intention to treat analysis. All data on adverse events, including those routinely collected as outcomes, will be collected and reported as required by the relevant authorities. Where no consent is given by any legal representative, i.e. deferred consent is used and no subsequent consent obtained, or a participant dies before any consent obtained, the patient data collected would be destroyed.

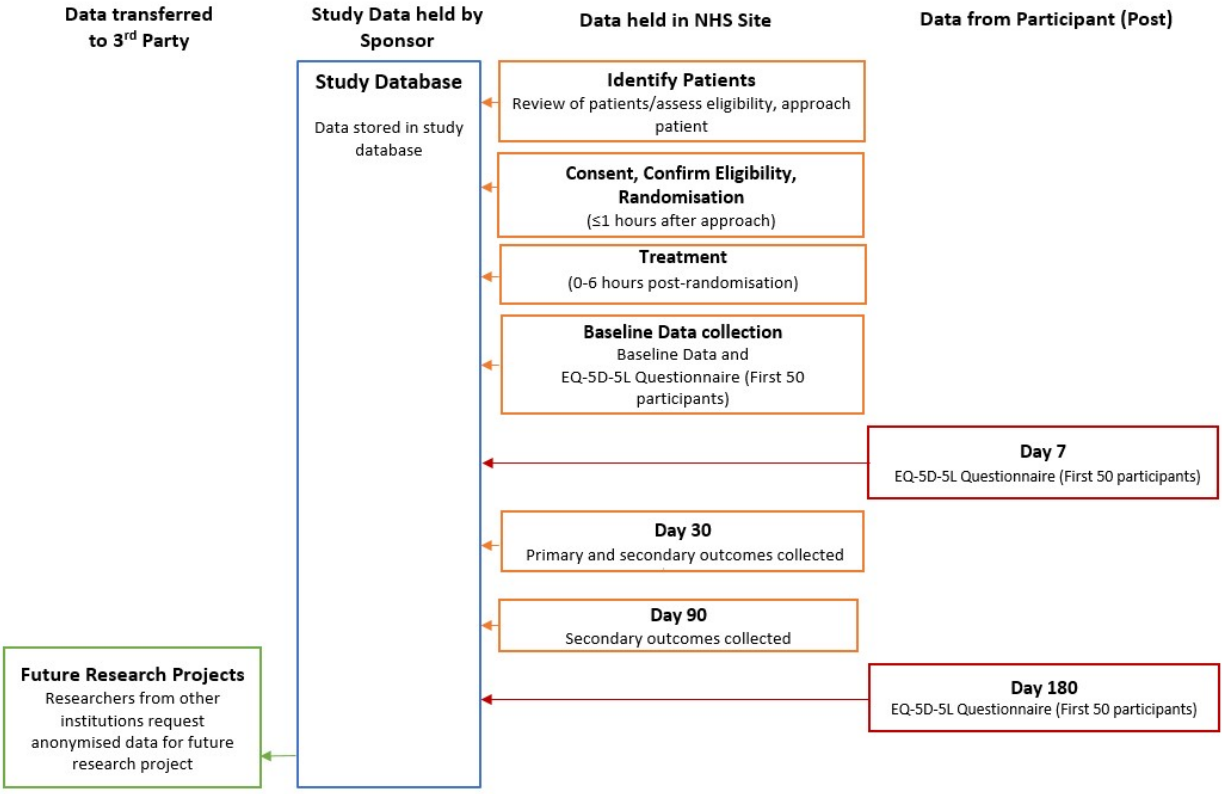
9.1.1 Data Information Flow

The following personal data will be collected as part of the study: Name; Initials; Home Address; Sex at birth; Date of birth and Health Information. The Name; Home Address and Phone Number of the personal representative will be collected if required to obtain consent.

The name and address will only be collected for the purposes of sending a letter to the GP informing them their participant is taking part, to send the study questionnaires to the first 50 participants and to send consent forms (if required). This personal data will be kept at the study site.

Personal data will be stored by the study team on NHS computers (desktop and laptop). Computers will be password protected and kept in locked offices. All paper files containing personal data will be held in filing cabinets in NHS offices that will be locked when unattended. Access to the study documents will be by the study team only.

Personal data will also be stored on University computers hosting the study database. Edinburgh Clinical Trials Unit will provide and maintain a secure web based bespoke database compliant with the relevant regulations and Sponsor SOPs. Data will be entered by those staff delegated to do so on the delegation log held at site.



9.1.3 Data Controller

The University of Edinburgh and NHS Lothian are joint data controllers along with any other entities involved in delivering the study that may be a data controller in accordance with applicable laws (e.g. the site).

9.1.4 Data Breaches

Any data breaches will be reported to the University of Edinburgh and NHS Lothian Data Protection Officers who will onward report to the relevant authority according to the appropriate timelines if required.

10. STATISTICS AND DATA ANALYSIS

10.1 SAMPLE SIZE CALCULATION

A pragmatic sample size of 300 was based on projected recruitment over 12 months study period in around 15 centres. It is anticipated that this will provide sufficient data to demonstrate feasibility and inform design of a fully powered study

As a pilot feasibility study, no formal sample size calculation is appropriate. However, indicatively on the first primary outcome of recruitment feasibility, an acceptance rate of 50% would be estimated with a 95% confidence interval of 44% to 56% if 300 from 600 of those eligible agreed to be randomised. For the second primary outcome of death at 30 days, indicatively if the standard of care had a 30-day mortality of 35%,

with 300 randomised the study would have 90% power at a 5% level of significance to detect an approximate 50% relative reduction of 17%, to 18%.

10.2 PROPOSED ANALYSES

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 180 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.

11. PHARMACOVIGILANCE

The Investigator is responsible for the detection and documentation of events meeting the criteria and definitions detailed below.

5% Human Albumin Solution has a well-documented safety profile. Although the Summary of Product Characteristics suggests that rare cases of anaphylactic events might be associated with albumin administration, there is no evidence that the albumin treatment regime used in this trial is associated with an increased risk of anaphylaxis. Nevertheless, data on anaphylaxis events will be collected as secondary outcomes and will be presented to the independent Data Monitoring Committee (DMC) for unblinded review.
Full details of contraindications and side effects that have been reported following administration of the IMP can be found in the relevant Summary of Product Characteristics (SPC) Booklet.

11.1 DEFINITIONS

An **adverse event** (AE) is any untoward medical occurrence in a clinical trial participant which does not necessarily have a causal relationship with an investigational medicinal product (IMP).
An **adverse reaction** (AR) is any untoward and unintended response to an IMP which is related to any dose administered to that participant.
A **serious adverse event** (SAE), **serious adverse reaction** (SAR). Any AE or AR that at any dose:

- results in death of the clinical trial participant;
- is life threatening*;
- requires in-patient hospitalisation^ or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- consists of a congenital anomaly or birth defect;
- results in any other significant medical event not meeting the criteria above.

*Life-threatening in the definition of an SAE or SAR refers to an event where the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

^Any hospitalisation that was planned prior to enrolment will not meet SAE criteria. Any hospitalisation that is planned post enrolment will meet the SAE criteria.

A suspected unexpected serious adverse reaction (SUSAR) is any AR that is classified as serious and is suspected to be related to the IMP, that it is not consistent with the information about the IMP in the Summary of Product Characteristics (SPC) booklet or Investigators Brochure.

11.2 IDENTIFYING AEs AND SAEs

Participants will be asked about the occurrence of AEs/SAEs during the study and the medical records will be reviewed to identify these. AEs and SAEs will only be recorded and reported from consent until 7 days after randomisation due to the well-known safety profiles of the interventions. Open-ended and non-leading verbal questioning of

the participant will be used to enquire about AE/SAE occurrence. Participants will also be asked if they have been admitted to hospital, had any accidents, used any new medicines or changed concomitant medication regimens. If there is any doubt as to whether a clinical observation is an AE, the event will be recorded.
AEs and SAEs may also be identified via information from support departments e.g. laboratories.

11.3 RECORDING AEs AND SAEs

When an AE/SAE occurs, it is the responsibility of the Investigator, or another suitably qualified physician in the research team who is delegated to record and report AEs/SAEs, to review all documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator will then record all relevant information in the eCRF/AE log and on the SAE form (if the AE meets the criteria of serious).
Information to be collected includes dose, type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

11.3.1 Pre-existing Medical Conditions

Pre-existing medical conditions (i.e. existed prior to informed consent) should be recorded as medical history and only recorded as adverse events if medically judged to have worsened during the study.

11.3.2 Worsening of the Underlying Condition during the Trial

Medical occurrences or symptoms of deterioration that are expected due to the participant's underlying condition should be recorded in the patient's medical notes and only be recorded as AEs on the AE log if medically judged to have unexpectedly worsened during the study. Events that are consistent with the expected progression of the underlying disease should not be recorded as AEs.

11.4 ASSESSMENT OF AEs AND SAEs

Each AE must be assessed for seriousness, causality, severity and ARs must be assessed for expectedness by the Principal Investigator or another suitably qualified physician in the research team who has been delegated this role. For randomised double blind studies, AEs will be assessed as though the participant is taking active IMP. SUSARs will be unblinded by ACCORD before they are reported to REC and CA (by ACCORD). The Chief Investigator (CI) may not downgrade an event that has been assessed by an Investigator as an SAE or SUSAR, but can upgrade an AE to an SAE, SAR or SUSAR if appropriate.

11.4.1 Assessment of Seriousness

The Investigator will make an assessment of seriousness as defined in Section 11.1.

11.4.2 Assessment of Causality

The Investigator will make an assessment of whether the AE/SAE is likely to be related to the IMP according to the definitions below.

Unrelated: where an event is not considered to be related to the IMP.

Possibly Related: The nature of the event, the underlying medical condition, concomitant medication or temporal relationship make it possible that the AE has a causal relationship to the study drug. Where non Investigational Medicinal Products (NIMPs) e.g. rescue/escape drugs are given: if the AE is considered to be related to an interaction between the IMP and the NIMP, or where the AE might be linked to either the IMP or the NIMP but cannot be clearly attributed to either one of these, the event will be considered as an AR. Alternative causes such as natural history of the underlying disease, other risk factors and the temporal relationship of the event to the treatment should be considered and investigated. The blind should not be broken for the purpose of making this assessment.

11.4.3 Assessment of Expectedness

If the event is an AR the evaluation of expectedness will be made based on knowledge of the reaction and the relevant product information documented in the SPC Booklet

The event may be classed as either:
Expected: the AR is consistent with the toxicity of the IMP listed in the SPC Booklet.
Unexpected: the AR is not consistent with the toxicity in the SPC Booklet.
Fatal and life threatening SARs should usually be considered unexpected. Fatal SARs can only be expected for IMPs with an MA in the EU, when it is clearly stated in the list of ARs of the SPC (Section 4.8) that the IMP causes fatal SARs.

11.4.4 Assessment of Severity

The Investigator will make an assessment of severity for each AE/SAE/SAR/SUSAR and record this on the eCRF/AE log or SAE form according to one of the following categories:
Mild: an event that is easily tolerated by the participant, causing minimal discomfort and not interfering with every day activities.
Moderate: an event that is sufficiently discomforting to interfere with normal everyday activities.
Severe: an event that prevents normal everyday activities.
Note: the term ‘severe’, used to describe the intensity, should not be confused with ‘serious’ which is a regulatory definition based on participant/event outcome or action criteria. For example, a headache may be severe but not serious, while a minor stroke is serious but may not be severe.

11.5 RECORDING OF AEs

All adverse events identified between consent and 7 days after randomisation for each participant will be recorded in the medical notes for each participant. Only those events which would meet the criteria of seriousness and also qualify for reporting to the sponsor (see section 11.6.2) will be recorded on AE logs/ SAE forms and will be assigned the appropriate MedDRA Systems Organ Class (SOC) code.

11.6 REPORTING OF SAEs/SARs/SUSARs

Once the Investigator becomes aware that an SAE has occurred in a study participant, the information will be reported to the ACCORD Research Governance **within 24 hours**. If the Investigator does not have all information regarding an SAE, they

should not wait for this additional information before notifying ACCORD. The SAE report form can be updated when the additional information is received.
The SAE report will provide an assessment of causality and expectedness at the time of the initial report to ACCORD according to Sections 10.4.2, Assessment of Causality and 10.4.3, Assessment of Expectedness.

The SAE form will be transmitted via email to safety@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.
All reports sent to ACCORD and any follow up information will be retained by the Investigator in the Investigator Site File (ISF).

11.6.2 Reporting of SAEs/SARs/SUSARs and exemptions

All SAEs that meet the definition given in section 11.1 and occur between consent and 7 days afterwards should be reported to the Sponsor unless they meet the exemption criteria below. These are outcome events are anticipated to occur in this participant group and will be exempt from reporting to the Sponsor:

Death related to infection (including multi-organ failure)

Critical care (HDU/ICU) admission

Acute kidney injury

Pulmonary oedema,

Allergy or anaphylaxis

Events That Are Common in the Trial Population:

The primary event of infection is classified as a pre-existing condition. As such, the occurrence or expected progression of infection or sepsis-related events including death will occur. In addition, participants are likely to have many minor adverse events during the course of the trial. These events will be recorded in the medical records and assessed in the same way as AE/SAEs. However, they are not usually recorded as AEs/SAEs, unless they are thought to be related to participant involvement in the trial.

Abdominal pain, nonspecific or related to a pre-existing condition

Accidents (domestic, traffic, occupational) including falls

Agitation or Anxiety

Atrial fibrillation or another cardiac dysrhythmia

Bleeding

Blood result abnormality (outside lab reported normal range) requiring no clinical intervention

Breathlessness related to a pre-existing condition e.g. COPD

Chest pain, non-specific or related to a pre-existing condition

Confusion or delirium

Constipation

Deep vein thrombosis/venous thromboembolism

Diarrhoea and/or vomiting

Dizziness or light headedness including vertigo

Dysphagia

Embolism

Fatigue, tiredness or sleepiness (somnolence)

Gastrointestinal disturbance, non-specific

Headache

Hypotension (if related to infection)

Hypoxia (if related to infection)

Incontinence, urinary or faecal

Malignancy, new diagnosis or new treatment for existing diagnosis

Mild ankle swelling not requiring treatment

Mood disorders

Muscle twitching

Any musculoskeletal condition e.g. arthritis or mechanical back pain

Peripheral vascular disease

Pneumothorax

Pressure sores or skin ulceration

Procedures occurring as part of the management of infection e.g. urinary catheter, central venous line, arterial line, intubation

Seizure

Sinus tachycardia (if related to infection)

Visual Loss e.g. cataract or macular degeneration or retinal detachment

Weight loss

Any other known complications of, or symptoms related to infection or sepsis

11.7 REGULATORY REPORTING REQUIREMENTS

ACCORD is responsible for pharmacovigilance reporting on behalf of the co-sponsors (The University of Edinburgh and NHS Lothian).

ACCORD has a legal responsibility to notify the regulatory competent authority and relevant ethics committee (Research Ethics Committee (REC) that approved the trial). Fatal or life threatening SUSARs will be reported no later than 7 calendar days and all other SUSARs will be reported no later than 15 calendar days after ACCORD is first aware of the reaction.

ACCORD (or delegate) will inform Investigators at participating sites of all SUSARs and any other arising safety information.

ACCORD will be responsible for providing safety line listings and assistance; however, it is the responsibility of the Investigator to prepare the Development Safety Update

Report. This annual report lists all SARs and SUSARs reported during that time period. The responsibility of submitting the Development Safety Update Report to the regulatory authority and RECs, lies with ACCORD.

11.8 FOLLOW UP PROCEDURES

After initially recording an AE or recording and reporting an SAE, the Investigator should make every effort to follow each event until a final outcome can be recorded or reported as necessary. Follow up information on an SAE will be reported to the ACCORD office.

If, after follow up, resolution of an event cannot be established, an explanation should be recorded on the eCRF or AE log or additional information section of SAE form.

11.9 PREGNANCY

Although pregnancy is not considered an AE or SAE; as a matter of safety, the Investigator will be required to record any female participant's pregnancy identified from consent until 7 days afterwards. The Investigator will need to record the information on a Pregnancy Notification Form and submit this to the ACCORD office within 14 days of being made aware of the pregnancy.

All pregnant female participants will be followed up until the outcome of the pregnancy.

12. TRIAL MANAGEMENT AND OVERSIGHT ARRANGEMENTS

12.1 TRIAL MANAGEMENT GROUP

The trial will be coordinated by a Trial Management Group, consisting of the grant holders (Chief Investigator and Principal Investigator in Edinburgh), A Trial Manager and coordinating nurse.

The Trial Manager will oversee the study and will be accountable to the Chief Investigator. The Trial Manager will be responsible for checking the eCRF/database for completeness, plausibility and consistency. Any queries will be resolved by the Investigator or delegated member of the trial team.

A Delegation Log will be prepared for each site, detailing the responsibilities of each member of staff working on the trial.

12.2 TRIAL STEERING COMMITTEE

A Trial Steering Committee (TSC) will be established to oversee the conduct and progress of the trial. The terms of reference of the Trial Steering Committee, the draft template for reporting and the names and contact details are detailed in CR015 DMC & TSC Charters.

12.3 DATA MONITORING COMMITTEE

An independent Data Monitoring Committee (DMC) will be established to oversee the safety of participants in the trial. The terms of reference of the Data Monitoring Committee and the names and contact details are detailed in CR0015 DMC & TSC Charters. The DMC Charter will be signed by the appropriate individuals prior to the trial commencing.

12.4 INSPECTION OF RECORDS

Investigators and institutions involved in the study will permit trial related monitoring and audits on behalf of the sponsor, REC review, and regulatory inspection(s). In the event of an audit or monitoring, the Investigator agrees to allow the representatives of the sponsor direct access to all study records and source documentation. In the event of regulatory inspection, the Investigator agrees to allow inspectors direct access to all study records and source documentation.

12.5 RISK ASSESSMENT

A study specific risk assessment will be performed by representatives of the co-sponsors, ACCORD monitors and the QA group, in accordance with ACCORD governance and sponsorship SOPs. Input will be sought from the Chief Investigator or designee. The outcomes of the risk assessment will form the basis of the monitoring plans and audit plans. The risk assessment outcomes will also indicate which risk adaptions could be incorporated into to trial design.

12.6 STUDY MONITORING AND AUDIT

ACCORD clinical trial monitors, or designees, will perform monitoring activities in accordance with the study monitoring plan. This will involve on-site visits and remote monitoring activities as necessary. ACCORD QA personnel, or designees, will perform study audits in accordance with the study audit plan. This will involve investigator site audits, study management audits and facility (including 3rd parties) audits as necessary.

13. GOOD CLINICAL PRACTICE

13.1 ETHICAL CONDUCT

The study will be conducted in accordance with the principles of the International Conference on Harmonisation Tripartite Guideline for Good Clinical Practice (ICH GCP). Before the study can commence, all required approvals will be obtained and any conditions of approvals will be met.

13.2 REGULATORY COMPLIANCE

The study will not commence until a Clinical Trial Authorisation (CTA) is obtained from the appropriate Regulatory Authority. The protocol and study conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

13.3 INVESTIGATOR RESPONSIBILITIES

The Investigator is responsible for the overall conduct of the study at the site and compliance with the protocol and any protocol amendments. In accordance with the principles of ICH GCP, the following areas listed in this section are also the responsibility of the Investigator. Responsibilities may be delegated to an appropriate member of study site staff.

Delegated tasks must be documented on a Delegation Log and signed by all those named on the list prior to undertaking applicable study-related procedures.

13.3.1 Informed Consent

The Investigator is responsible for ensuring informed consent is obtained before any study specific procedures are carried out. The decision of a participant to participate in clinical research is voluntary and should be based on a clear understanding of what is involved.
Participants must receive adequate oral and written information – appropriate Participant Information and Informed Consent Forms will be provided. The oral explanation to the participant will be performed by the Investigator or qualified delegated person, and must cover all the elements specified in the Participant Information Sheet and Consent Form. The participant must be given every opportunity to clarify any points they do not understand and, if necessary, ask for more information.

The participant must be given sufficient time to consider the information provided. It should be emphasised that the participant may withdraw their consent to participate at any time without loss of benefits to which they otherwise would be entitled.

The participant will be informed and agree to their medical records being inspected by regulatory authorities and representatives of the sponsor(s).

The Investigator or delegated member of the trial team and the participant will sign and date the Informed Consent Form(s) to confirm that consent has been obtained. The original will be signed in the Investigator Site File (ISF). The participant will receive a copy of the signed consent form and a copy will be filed in the participant's medical notes.

13.3.2 Study Site Staff

The Investigator must be familiar with the IMP, protocol and the study requirements. It is the Investigator's responsibility to ensure that all staff assisting with the study are adequately informed about the IMP, protocol and their trial related duties.

13.3.3 Data Recording

The Principal Investigator is responsible for the quality of the data recorded in the eCRF at each Investigator Site.

13.3.4 Investigator Documentation

Prior to beginning the study, each Investigator will be asked to provide particular essential documents to the ACCORD Research Governance & QA Office, including but not limited to:

- An original signed Investigator's Declaration (as part of the Clinical Trial Agreement documents);
- Curriculum vitae (CV) signed and dated by the Investigator indicating that it is accurate and current.
- ACCORD will ensure all other documents required by ICH GCP are retained in a Trial Master File (TMF) or Sponsor File, where required. The Principal Investigator will ensure that the required documentation is available in local Investigator Site files ISFs. Under certain circumstances the TMF responsibilities may be delegated to the research team by ACCORD.

13.3.5 GCP Training

All study staff must hold evidence of appropriate GCP training.

13.3.6 Confidentiality

All laboratory specimens, evaluation forms, reports, and other records must be identified in a manner designed to maintain participant confidentiality. All records must be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant. The Investigator and study site staff involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

13.3.7 Data Protection

All Investigators and study site staff involved with this study must comply with the requirements of the appropriate data protection legislation (including where applicable the General Data Protection Regulation with regard to the collection, storage, processing and disclosure of personal information. Access to personal information will be restricted to individuals from the research team treating the participants, representatives of the sponsor(s) and representatives of regulatory authorities.
Computers used to collate the data will have limited access measures via user names and passwords. Published results will not contain any personal data that could allow identification of individual participants.

14. STUDY CONDUCT RESPONSIBILITIES

14.1 PROTOCOL AMENDMENTS

Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the participant in the case of an urgent safety measure, must be reviewed and approved by the Chief Investigator.
Proposed amendments will be submitted to the Sponsor for classification and authorisation.
Amendments to the protocol must be submitted in writing to the appropriate REC, Regulatory Authority and local R&D for approval prior to implementation.

14.2 PROTOCOL NON COMPLIANCE

14.2.1 Definitions

Deviation - Any change, divergence, or departure from the study design, procedures defined in the protocol or GCP that does not significantly affect a subjects rights, safety, or well-being, or study outcomes.
Violation - A deviation that may potentially significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.

14.2.2 Protocol Waivers

Prospective protocol deviations, i.e. protocol waivers, will not be approved by the sponsors and therefore will not be implemented, except where necessary to eliminate

an immediate hazard to study participants. If this necessitates a subsequent protocol amendment, this should be submitted to the REC, Regulatory Authority and local R&D for review and approval if appropriate.

14.2.3 Management of Deviations and Violations

Protocol deviations will be recorded in a protocol deviation log and logs will be submitted to the sponsors every 3 months. Each protocol violation will be reported to the sponsor within 3 days of becoming aware of the violation.Deviation logs / violation forms will be transmitted via email to QA@accord.scot. Only forms in a pdf format will be accepted by ACCORD via email. Where missing information has not been sent to ACCORD after an initial report, ACCORD will contact the Investigator and request the missing information. The Investigator must respond to these requests in a timely manner.

14.3 URGENT SAFETY MEASURES

The Investigator may implement a deviation from or change to the protocol to eliminate an **immediate hazard** to trial participants without prior approval from the REC and the MHRA. This is defined as an urgent safety measure and the investigator must contact the Clinical Trial Unit at the MHRA and discuss the issue with a medical assessor immediately (+44 (0) 20 3080 6456).
The Investigator will then notify the MHRA (clintrialhelpline@mhra.gsi.gov.uk), the REC and ACCORD, in writing of the measures taken and the reason for the measures within 3 days by submitting a substantial amendment.

14.4 SERIOUS BREACH REQUIREMENTS

A serious breach is a breach which is likely to effect to a significant degree:
(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial.
If a potential serious breach is identified by the Chief investigator, Principal Investigator or delegates, the co-sponsors (QA@accord.scot) must be notified within 24 hours. It is the responsibility of the co-sponsors to assess the impact of the breach on the scientific value of the trial, to determine whether the incident constitutes a serious breach and report to regulatory authorities and research ethics committees as necessary.

14.5 STUDY RECORD RETENTION

All study documentation will be kept for a minimum of 5 years from the protocol defined end of study point. When the minimum retention period has elapsed, study documentation will not be destroyed without permission from the sponsor.

14.6 END OF STUDY

The end of study is defined as the last patient's last 90 day follow up.
The Investigators and/or the trial steering committee and/or the co-sponsor(s) have the right at any time to terminate the study for clinical or administrative reasons.
The end of the study will be reported to the REC, Regulatory Authority, R&D Office(s) and co-sponsors within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants of the premature study closure and ensure that

the appropriate follow up is arranged for all participants involved. End of study notification will be reported to the co-sponsors via email to resgov@accord.scot.
In accordance with ACCORD SOP CR011, a Clinical Study Report (CSR) will be provided to the Sponsor (QA@accord.scot) and REC within 1 year of the end of the study.
Upon completion of the study, the Investigator will upload clinical trial results onto the EudraCT database on behalf of the Sponsor.
The Investigator will submit a short confirmatory e-mail to the MHRA (CT.Submission@mhra.gsi.gov.uk) once the result-related information has been uploaded to EudraCT, with 'End of trial: result-related information: EudraCT XXXX-XXXXXX-XX' as the subject line. The Sponsor(s) will be copied in this e-mail (QA@accord.scot). It should be noted that you will not get an acknowledgment e-mail or letter from the MHRA.

14.7 INSURANCE AND INDEMNITY

The co-sponsors are responsible for ensuring proper provision has been made for insurance or indemnity to cover their liability and the liability of the Chief Investigator and staff.
The following arrangements are in place to fulfil the co-sponsors' responsibilities:

- The Protocol has been authored by the Chief Investigator and researchers employed by the University and collaborators. The University has insurance in place (which includes no-fault compensation) for negligent harm caused by poor protocol design by the Chief Investigator and researchers employed by the University.
- Sites participating in the study will be liable for clinical negligence and other negligent harm to individuals taking part in the study and covered by the duty of care owed to them by the sites concerned. The co-sponsors require individual sites participating in the study to arrange for their own insurance or indemnity in respect of these liabilities. Sites which are part of the United Kingdom's National Health Service have the benefit of NHS Indemnity.
- Sites out with the United Kingdom will be responsible for arranging their own indemnity or insurance for their participation in the study, as well as for compliance with local law applicable to their participation in the study.
- The manufacturer supplying IMP has accepted limited liability related to the manufacturing and original packaging of the study drug and to the losses, damages, claims or liabilities incurred by study participants based on known or unknown Adverse Events which arise out of the manufacturing and original packaging of the study drug, but not where there is any modification to the study drug (including without limitation re-packaging and blinding).

15. REPORTING, PUBLICATIONS AND NOTIFICATION OF RESULTS

15.1 AUTHORSHIP POLICY

Ownership of the data arising from this study resides with the study team. On completion of the study, the study data will be analysed and tabulated, and a clinical study report will be prepared in accordance with ICH guidelines.

15.2 PUBLICATION

The Clinical Study Report (CSR) will be submitted to the Sponsor and REC within 1 year of the end of the study. Where acceptable, a published journal article may be submitted as the CSR. The Chief Investigator will provide the CSR to ACCORD, for review, prior to finalization. The clinical study report may be used for publication and presentation at scientific meetings. Investigators have the right to publish orally or in writing the results of the study. The results of the study, together with other mandated information, will be uploaded to the European clinical trials database within 1 year of the end of the study.

Summaries of results will also be made available to Investigators for dissemination within their clinics (where appropriate and according to their discretion).

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