EARLY VASOPRESSORS IN SEPSIS

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Sponsor:	Greater Glasgow and Clyde Health Board
Funder:	NIHR

This protocol has regard for the HRA guidance and order of content

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: 

Date: 07/11/2022 ~~15 March 2022~~

Name: Joanne McGarryy ~~Pamela Sandu~~

Position: R&I Coordinatorr

Chief Investigator:

Signature: 

Date: 08/11/2022 ~~15 March 2022~~

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Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
CTU	Clinical Trials Unit
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
ED	Emergency Department
EMEA	European Medicines Agency
EQ-5D-5L	Quality of Life Questionnaire
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Clinical Trials Database
EudraVIGILANCE	European database for Pharmacovigilance
GCP	Good Clinical Practice
GGC	Greater Glasgow & Clyde Health Board
GP	General Practitioner
GMP	Good Manufacturing Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.

ICU	Intensive Care Unit
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISF	Investigator Site File
ISRCTN	International Standard Randomised Controlled Trials Number
MA	Marketing Authorisation
MAP	Mean Arterial Pressure
MHRA	Medicines and Healthcare products Regulatory Agency
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health & Care Excellence
NIMP	Non-Investigational Medicinal Product
NE	Norepinephrine (IRNN)
PAG	Patient Advisory Group
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient & Public Involvement
PPS	Personal Social Services
PV	Pharmacovigilance
PVI	Peripheral Vasopressor Infusion
QA	Quality Assurance
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event

SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SBP	Systolic Blood Pressure
SDP	Source Data Plan
SDV	Source Data Verification
SMG	Study Management Group
SOFA	Sequential Organ Failure Assessment
SOP	Standard Operating Procedure
SmPC	Summary of Product Characteristics
SSC	Surviving Sepsis Campaign
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIDieR	Template for Intervention Description and Replication
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
WoCBP	Women of Child Bearing Potential

TRIAL SUMMARY

Trial Title	EARLY VASOPRESSORS IN SEPSIS
Internal ref. no. (or short title)	EVIS
Clinical Phase	Phase III
Trial Design	Open label, two-arm, multicentre, pragmatic parallel group randomised trial with an internal pilot
Trial Participants	Adult patients with septic shock recruited from the Emergency Department and Acute Assessment Units.
Planned Sample Size	3286 patients
Treatment duration	48 hours
Follow up duration	90 days
Planned Trial Period	45 months
	Objectives
Primary	To determine whether early peripheral vasopressor infusion (PVI) targeted to MAP>65 improves clinical effectiveness (30 day mortality) in hospitalised adult patients with septic shock compared with usual care, in the first 48 hours.
Secondary	Secondary objectives are to assess the effects of PVI, compared with usual care, on clinical, patient centred, health service and economic outcomes in the acute hospital setting and during three months follow-up post randomisation. These will include protocol adherence and safety outcomes.
Investigational Medicinal Product(s)	Norepinephrine

Formulation, Dose, Route of Administration	Continuous intravenous infusion (16 micrograms per ml) delivered via peripheral cannula at a titrated rate of up to 0.15 micrograms / kg / min

1.1 ROLE OF TRIAL SPONSOR

NHS Greater Glasgow & Clyde is the Sponsor for this trial. The study sponsor takes on overall responsibility for proportionate, effective arrangements being in place to set up, run and report the research project.

The Sponsor will delegate specific roles to the Chief Investigator, Edinburgh CTU and other third parties. These arrangements will be clearly documented in a collaboration agreement.

The Sponsor will publicly register the study on the Clinicaltrials.gov website before the first patient is enrolled. https://clinicaltrials.gov

1.2 ROLE OF FUNDER

This is an investigator-initiated clinical trial. National Institute for Health Research (NIHR) have commissioned this research and provided support in terms of funding. NIHR does not have a designated role or responsibility in trial design, conduct, data analysis and interpretation, manuscript writing and dissemination of results. A representative from NIHR will be invited to attend TSC meetings as an observer. Support from NIHR will be acknowledged in any publications relating to the study.

1.3 ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT GROUPS

1.3.1 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of Good Clinical Practice (GCP) and the relevant regulations. The TSC will be convened by the Sponsor with approval from NIHR to:

- Agree any substantial protocol amendments
- Provide advice to the investigators on all aspects of the trial

The TSC will meet at the start of the study, and annually or more frequently thereafter. The TSC will have its own charter outlining the role and responsibilities of its members. The TSC may invite other attendees from the trial team to present or participate in discussions on particular topics. These attendees will be non-voting members.

1.3.2 Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to review study data to ensure the safety of the trial and will review study data with respect to stopping rules outlined in Section 1212. The IDMC will meet at the start of the study, or as soon as possible thereafter, and annually or more frequently thereafter. The IDMC may invite other

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attendees from the trial team to present or participate in discussions on particular topics. These attendees will be non-voting members. The IDMC will report to and advise the TSC and Sponsor if it is safe an appropriate to continue the trial.

1.3.3 Study ~~Trial~~ Management Group (S~~T~~MG)

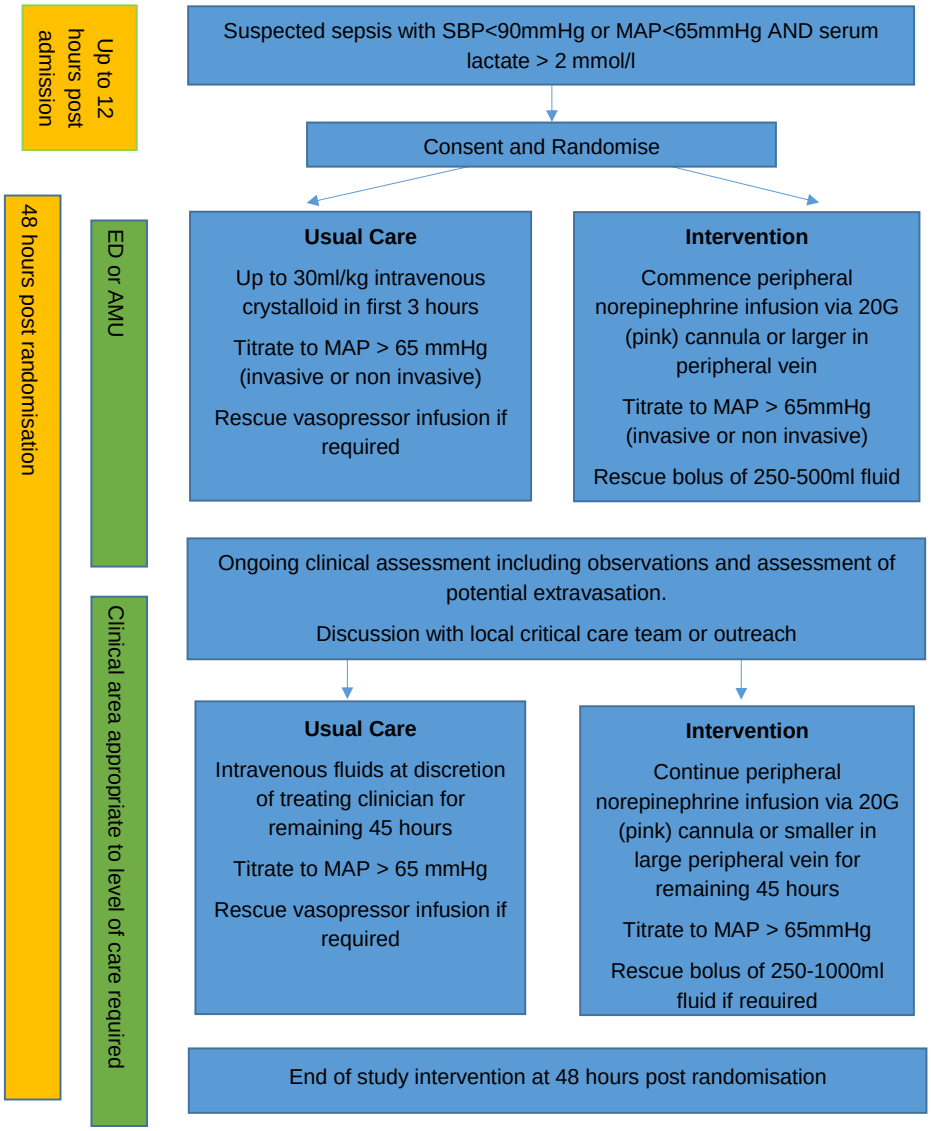
The trial will be coordinated from NHS Greater Glasgow & Clyde Project Management Unit. The S~~T~~MG will minimally consist of the Chief Investigator, project manager, R&I coordinator, Sponsor pharmacy representative, trial monitor, representatives from the Edinburgh Clinical Trials Unit (ECTU) and additional representatives where required. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

1.3.4 Protocol contributors

The protocol has been develped by a group with extensive clinical and research experience relevant to this trial including the design and conduct of multicentre clinical trials in acute and critical care. This includes specialists in emergency medicine, critical care, anaesthetics, health economics and clinical trials.

KEY WORDS: sepsis
resuscitation
norepinephrine
intravenous fluids
emergency medicine
critical care

PATIENT PATHWAY



SCHEDULE OF ASSESSMENTS

Trial Activity	Screening	Baseline	6 hours (+/- 1 hour)	12 hours (+/- 4 hours)	24 hours (+/-6 hours)	48 hours (+/-12 hours)	72 hours (+/-12 hours)	+/- 7 days	Hospital Discharge	30 days	90 days
Eligibility – Inclusion/Exclusion*	X	X						X			
Written Informed Consent	X										
Demographics/Medical History/estimated weight/ Frailty score		X									
Vital signs		X	X	X	X	X	X				
Blood results (routine) incl lactate		X	X**	X**	X**	X**	X**				
~~Blood results (research)~~		~~X~~			~~X**~~	~~X**~~					
IMP administration		X	X	X	X	X					
IMP adherence		X			X	X					
Total intravenous fluid volume delivered		X	X	X	X	X	X				
Total dose of norepinephrine delivered		X	X	X	X	X	X				
Total dose of other vasopressors delivered		X	X	X	X	X	X				
Safety outcomes (pulmonary oedema/extravasation)							X		X		
Mortality/interventions/length of stay/readmissions									X	X	X

Adverse Events ***		X	X	X	X	X	X**	X			
EQ-5D-5L ****		X								X	X

*All women of childbearing potential must have a negative urine or serum pregnancy test completed as part of study eligibility checks.

** Daily (+/- 12 hours) for any routine bloods collected up to 72 hours. If bloods (or individual parameters) are not requested by the clinical team, this will not be recorded as a deviation.

*** Adverse Event reporting is a continuous process

**** EQ-5D-5L should only be completed ~~at baseline~~ if the patient has capacity.

1. BACKGROUND

Sepsis results from overwhelming reactions to microbial infections where the immune system initiates dysregulated responses that lead to remote organ dysfunction, shock and ultimately death [1]. Sepsis remains a significant global issue [2] – as well as direct mortality, survivors suffer long term reductions in patient centred outcomes, with reduced quality of life and functional status [3]. Patients with hypotension and organ hypoperfusion as a result of sepsis have poorer outcomes by dysregulated inflammation, endothelial dysfunction, immune suppression, and organ dysfunction. Current guidelines [4, 5] highlight the importance of early fluid resuscitation, but the association of early fluid therapy with improved outcomes is unclear [6, 7]. In the resuscitation phase, current practice is to give intravenous (IV) fluid and intermittent vasopressor boluses if required, before, for some patients, continuous vasopressor infusion via a central venous line in Intensive Care (ICU). An alternative, early continuous peripheral vasopressor infusion (PVI) is not routine practice in the UK [4].

Negative effect of liberal intravenous fluids in sepsis

Liberal IV fluids with positive fluid balance in sepsis is associated with increased organ failure, ICU length of stay and mortality [7, 8]. Two recent randomised controlled trials comparing liberal versus conservative intravenous fluid resuscitation in children [9] and adults [10] with sepsis in Africa showed increased mortality in the treatment arms receiving higher IV fluid volumes. In line with this, recent experimental data suggested that fluid resuscitation preceding the start of vasopressors is associated with higher lactate levels and a paradoxical increase in vasopressor requirements when compared with an immediate start of vasopressor therapy without previous fluid administration [11, 12]. Likewise, a number of observational studies suggest that increased volume of resuscitation fluids and net positive fluid balance is associated with mortality in sepsis [12, 13].

Intravenous fluid restriction in sepsis

Patient observational data and laboratory experimental medicine support the hypothesis that restriction of IV fluid during the resuscitation phase for septic shock patients, and maintenance of organ perfusion with vasopressors may improve outcomes via an altered host inflammatory response [14 - 16]. The reduction in host inflammatory response may be mediated by several mechanisms:

- Increased cardiac output by vasoconstriction mediated increased preload, moving fluid from unstressed to stressed circulation [16] and by improving myocardial contractility [16].

- Increased microcirculatory perfusion in septic shock [18, 19], especially when the baseline microcirculatory blood flow is abnormal [20]
- Improved regional distribution of blood flow [20].

Intravenous fluid restriction in sepsis achieved via vasopressor infusion

Ospina-Tascon et al [21] investigated a propensity matched cohort of early (<1 hour) versus delayed (>1 hour) vasopressor initiation for patients with septic shock. In 186 patients their data showed separation of total IV fluids delivered at 6 hours (900 vs. 2000ml, p <0.001) which continued to separation in net fluid balance at 24 hours (3905 vs. 5400, p <0.001).

Laboratory experimental models of sepsis have shown improved mortality in early administration of norepinephrine (norepinephrine) in septic shock [14]. In patients with sepsis, Bai et al [45] showed increased mortality if norepinephrine commenced >3h after septic shock onset (OR 2.16, 95%CI 1.23-3.81, P=0.0007). Ospina-Tason et al [21] reported decreased mortality in patients where vasopressor therapy was initiated early (<1h) (HR 0.31, 95%CI 0.17-0.57, p<0.001). These studies were conducted in ICUs with vasopressors delivered via a central venous route.

Peripheral use of norepinephrine

A systematic review recommends norepinephrine as the first line vasopressor for septic shock [46]. Potential safety concerns exist around peripheral venous infusion (PVI), in particular, extravasation with skin and/or tissue necrosis [24]. However, multiple recent studies challenge this including two recent systematic reviews and meta-analysis. Pancaro et al [25] showed very low complication rates (0.01 – 0.07%) for norepinephrine PVI during elective operations. In emergency and critical care settings, a meta-analysis [26] of PVI in sepsis reported complications in 3.4% (47/1382) of all patients. Complications were all graded objectively as minor (skin blanching or local pain). Norepinephrine [27-29] was the most commonly used PVI with a complication rate of 3.1% (22/702). Mean duration of norepinephrine infusion was 13 to 60 hours, with peak infusion rates of between 0.13 to 0.70 micrograms/kg/min. A second systematic review and meta-analysis [30] of a wider group of patients receiving PVI found a complication rate of 3% when a clear protocol was in use for the delivery of PVI. This study also showed that PVI in cardiogenic shock was associated with much higher incidence of complications than other shock aetiologies. Overall the risk of PVI is low and the benefits of peripheral administration (ease, speed, minimal training requirements, no central venous catheter risks, ability to provide with ward level care) are likely to outweigh the traditional central venous route [30].

Efficacy of early peripheral vasopressor infusion

Two recently published interventional studies investigated a similar patient population to our proposal comparing PVI to standard care. The REFRESH trial [31] recruited 99 patients in a multicentre Australian study and demonstrated separation in the median fluid volume administered in the first 6 hours between the PVI and standard arm of 550ml (IQR 0, 1150) and 1535ml (IQR 1000, 2200) respectively. Protocol deviations occurred in 6/50 (12%) in PVI and 11/49 (22%) in the usual care group. Overall mortality in this cohort was significantly lower than expected at 7%, and the study was not powered to detect a difference in this outcome. A specific vasopressor was not specified in this protocol.

The CENSER trial was a single centre case study conducted in Thailand [11]. 310 patients were randomised to early norepinephrine or usual care. The dose of norepinephrine was a fixed dose of 0.05 micrograms/kg/minute, with no titration. The primary outcome of MAP >65mmHg with correction of organ hypoperfusion at 6 hours was significantly better in the early norepinephrine group (76.1% vs. 48.4%, p<0.001). The early norepinephrine group had a signal to lower 28-day mortality (15.5% vs. 21.9%, p+0.15). Half of patients in the norepinephrine arm have the infusion through a peripheral intravenous catheter with no reported complications. In CENSER, median fluid volume administration prior to study inclusion was 800ml in both arms, showing recruitment of this patient group was feasible.

2. RATIONALE

Current practice in the UK is guided by NICE Sepsis guidance [4] and the international Surviving Sepsis Campaign (SSC) consensus recommendations [5]. Both specify intravenous fluid administration as a central tenet of early resuscitation of patients with septic shock, with intravenous vasopressor administration recommended after intravenous fluid resuscitation. NICE recommend boluses of 500ml of crystalloid and *"refer to critical care for review of management including need for central venous access and initiation of vasopressors"*. SSC recommend 30ml/kg crystalloid in first hour, followed by vasopressors to maintain MAP>65.

The current NICE fluid resuscitation guideline, November 2020, continues to emphasise 500ml boluses of crystalloid as usual care. A recent international survey of 100 critical care and EM physicians [32] regarding intravenous fluid resuscitation practice, confirmed that an initial bolus of 1000ml of crystalloid, followed by 500ml boluses of crystalloid remained the most common management strategy for the initial treatment of septic shock. This persisted despite the lack of benefit demonstrated in three landmark trials of protocolised sepsis management.

In recent years, there has been increasing acceptance of peripheral administration of norepinephrine, based on evidence of safety and efficacy. The Intensive Care Society published guidance on peripheral

vasopressor infusion in November 2020 [33]. We have recently conducted a survey amongst ED and ICU clinicians in the UK regarding attitudes and current practice related to the use of intravenous peripheral vasopressors. Eighty two respondents provided the following answers 1. Experience of use of any intravenous vasopressor in ED was high (81%); 2. Exclusive PVI made up 23% of all vasopressor use in ED; 3. Norepinephrine (norepinephrine) was the most common vasopressor (54%); 4. Barriers to PVI were local protocols and an appropriate level of care in the destination ward for a patient on vasopressor infusion.

Dosing regimen for peripheral norepinephrine infusion

The dosing regimen for peripheral norepinephrine infusion used in this protocol is based on the current UK guidance for peripheral vasopressors from the Intensive Care Society [33]. The initial dosing in this protocol is the same as the initial dosing recommended in the ICS guidance (0.05mcg/kg/min).There is no upper dosing in the ICS guidance. For our study we have adopted a cautious approach and listed the upper does of peripheral norepinephrine infusion as 0.15mcg/kg/min. This is well below the upper dosing given in the meta analysis of vasopressor infusions [30].

Overall there is limited good quality evidence on the dosing for peripheral norepinephrine. We have used the information above, along with clinical consensus from a range of specialties and disciplines, to agree a conservative dose range for the peripheral norepinephrine infusion used in the study.

Appendix A gives a weight based starting and maximum dosing schedule for peripheral norepinephrine, along with specific advice about how to adjust dosing for the patient during the study. Treatment duration is based on clinical effect (up to 48 hours). There is guidance in section 10.3.1.8 about weaning from treatment at the end of the study period, or before, if treatment is successful

3. ASSESSMENT AND MANAGEMENT OF RISK

This study involves randomisation to early vasopressors versus standard care for hospitalised, adult patients with septic shock during the first 48 hours post randomisation.

3.1. Risk of Fluid Administration

Patients in both arms of the study will receive intravenous fluids. This carries the potential risk of fluid overload, including acute congestive heart failure, breathing difficulties, and increased peripheral oedema. Incidence of pulmonary oedema in trial participants will be reported as an outcome measure.

3.2. Risk of peripheral vasopressor administration

The potential risk of peripheral vasopressors utilisation is extravasation and soft-tissue toxicity/injury if extravasation occurs. As detailed in section 2, there is established guidance around safe governance for the use of peripheral vasopressor infusion. Patients receiving vasopressors will be cared for in an appropriate clinical environment where any complications can be appropriately acted upon. Specific advice is contained within the protocol for managing extravasation of norepinephrine. There is an extravasation action list for treating clinicians to use if an extravasation is suspected to have occurred (Section 10.3.1.7)

3.3. Risk of Vasopressor Administration

The potential risks of vasopressors include cardiac ischemia, cardiac dysrhythmias, bowel ischemia, or limb ischemia. Patients receiving vasopressors in either arm will be cared for in an appropriate clinical environment where any complications can be appropriately acted upon. Specific advice is contained within the protocol for managing extravasation of norepinephrine.

3.4. Risks of Blood Samples

~~The protocol includes provision for additional research blood samples to be taken, subject to specific consent being obtained.~~ All patients will have routine blood samples taken as part of routine care. ~~Where possible, any additional research blood samples will be obtained at the same time as routine blood samples.~~ In cases where an invasive line is not present, the risks of drawing blood are uncommon and include bleeding and bruising. Commonly, drawing blood is painful, and rarely, drawing blood can lead to infections at the site of the blood draw. Any blood sampling undertaken will be done so by clinical

staff with appropriate training. Where possible, existing cannula will be used for blood sampling where this is normal practice for clinical staff.

3.5. Risk of Line Placement

Patients admitted to hospital with septic shock will often have central venous access placed to increase venous access in the anticipation of the need for reliable and increased access for fluid, medication, and vasopressor administration. However, if restoration of blood pressure occurs without needing vasopressor medications, clinicians may decide to not place central venous access. The early vasopressor arm is intended to facilitate an increase in the utilisation of vasopressors delivered via a peripheral cannula; thus, this practice may lead to a reduction in the placement of central venous catheters. The decision to place a central venous line is part of standard care and is not a study intervention and will be left to the treating and/or study clinician. The risks of central venous access include infection, pneumothorax (punctured lung), vessel injury, haemorrhage and inclusive of inadvertent arterial cannulation. Placement of a central line will be undertaken by an appropriately trained individual after consideration of individual patient risk/benefit for the procedure as per standard care.

3.6. Risk of Death

It is possible that one treatment arm may lead to more deaths; mortality will be monitored lregulalry during the course of the study by the TMG and Data Monitoring Committee.

This trial is categorised as:

- Type B= somewhat higher than the risk of standard medical care

4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

4.1. Primary objective

To determine whether early PVI (within 12 hours of admission) targeted to MAP>65 improves clinical effectiveness (30 day mortality) in hospitalised adult patients with septic shock compared with usual care, in the first 48 hours.

4.2. Secondary objectives

Secondary objectives are to assess the effects of PVI, compared with usual care, on clinical, patient centred, health service and economic outcomes in the acute hospital setting and during the six months after participant randomisation. These will include protocol adherence and safety outcomes.

4.3. Primary endpoint/outcome

The primary outcome is all-cause mortality at 30 days following randomisation.

4.4. Exploratory endpoints/outcomes

See Appendix B for full description of data definitions

4.4.1. Clinical outcomes during first 72 hours following randomisation comprise:

- accumulated volume of iv fluid delivered in each arm in the first 6,12, 24, 48, 72 hours;
- blood lactate at 0, 6, 12, 24 hours;
- Organ dysfunction score (SOFA) at 0, 24, 48, 72 hours;
- Total dose of Norepinephrine delivered in first 6, 12, 24, 48, 72 hours.
- Total dose of other vasopressor delivered at 0, 6,12,24,48, 72 hours.
- Proportion of patients who receive vasopressors in the first 6, 12, 24, 48hrs after recruitment to control arm.
- Proportion of patients who require central venous access at 24 and 48 hours;
- Proportion of patients developing acute kidney injury during first 72 hours;
- Proportion of patients receiving parenteral corticosteroids at 24 and 48 hours

4.4.2. Outcomes during 6 month follow-up comprise:

- All-cause mortality during index hospital admission and at 90 days,
- Length of hospital stay for index admission; Proportion of patients admitted to and length of stay in critical care (level 2 or 3) during index hospital admission;
- Proportion of participants needing renal replacement therapy during index hospital admission;
- Proportion of participants needing non-invasive ventilation during index hospital admission;
- Proportion of participants needing advanced respiratory support (ICNARC definition) during index hospital admission;
- Readmission in first 30 days after discharge;

4.4.3. Patient centred outcome:

- organ support free days at 30 days;

4.4.4. Protocol Adherence**:**

- Proportion of patients who have PVI discontinued for non-clinical reasons after recruitment to intervention arm;

4.4.5. Safety:

- Proportion of patients developing vasopressor extravasation during first 72 hours
- Proportion of patients developing pulmonary oedema during index hospital admission;

4.4.6. Process evaluation: embedded qualitative research to: (a) establish the extent to which the intervention is implemented as intended; (b) ascertain how feasible and acceptable the intervention is to clinical staff and patients; and (c) identify any facilitators and barriers to recruitment. This will consist of a rapid ethnographic assessment [65] involving a 6-month observation of EDs and AMUs, review of key documentary data, and semi-structured interviews with clinical and trial staff;

4.4.7. Longer term follow-up: Questionnaire HRQoL using EQ5D-5L– HRQoL at 30-days and 90 -days;

4.4.8. Health Economic evaluation: This will be conducted from the perspective of the NHS and Personal and Social Security (PSS) in line with NICE guidance. Data on healthcare resource use will include inpatient and community care health services, and will be collected alongside the trial and through data linkage. Unit costs will be obtained from standard sources. HRQoL will be assessed at baseline (7 days before admission), 30 days and 90 days using EQ5D-5L. Patient-level costs and quality adjusted life years (QALYs) will be estimated. Within trial and a model-based analyses will be undertaken based on six-month and lifetime horizon, respectively.

4.5. Table of endpoints/outcomes

Objective	Outcome measure	Time point of evaluation
Primary Objective	All-cause mortality	30 day
Clinical outcomes	Accumulated volume of iv fluid delivered in each arm	Frist 6,12,24,48, 72 hours
	All-cause mortality	During index hospital admission and at 90 days
	Lactate	0, 6, 12, 24, 48 hours
	SOFA score	0, 24, 48, 72 hours
	Total dose of Norepinephrine	6,12,24,48, 72 hours
	Total does of other vasopressors (epinephrine, metaraminol, vasopressin)	6,12,24,48, 72 hours
	patients who require central venous access	24, 48 hours
	patients developing Acute Kidney Injury	72 hours
	Patients receiving new parenteral corticosteroids	24 and 48 hours
Health outcomes	Length of hospital stay of index admission;	During index hospital admission
	patients admitted to critical care (level 2 or 3);	
	length of stay in critical care (level 2 or 3);	
	participants needing new renal replacement therapy	
	participants needing initiation of non-invasive ventilation;	
	patients needing advanced respiratory support	
	participants readmitted in first 30-days after discharge;	Linkage: SMR01/HES
Patient centred outcomes	Organ support free days (alive and without mechanical ventilation, new renal replacement or vasopressors)	30 days

Protocol Adherence	patients who have PVI discontinued for non-clinical reasons after recruitment to intervention arm;	At 24 and 48 hours
Safety	vasopressor extravasation (NIH graded)	At 72 hours
	patients developing pulmonary oedema	During index hospital admission
Longer term outcomes	Health economic outcomes	
	HRQoL derived from EQ-5D-5L index values.	30 and 90 days

5. TRIAL DESIGN & SETTING

This trial will be an open label, two-arm multicentre pragmatic parallel group randomised trial of adult patients with sepsis recruited from the Emergency Department and Acute Medical/Surgical Assessment Units across 60 UK NHS sites, including an internal pilot.

6. PARTICIPANT ELIGIBILITY CRITERIA

There will be no trial specific screening tests performed. The patient will receive routine acute clinical assessment including severity of illness assessment and be treated in accordance with current UK guidelines (Sepsis 6). The results of these will inform trial eligibility and the patient will be approached as soon as these are available.

6.1. Inclusion criteria

- Age ≥18 years
- Clinically suspected or proven infection resulting in principal reason for acute illness
- SBP <90 mmHg or MAP < 65 mmHg and measured serum lactate of > 2 mmol/L at the time of eligibility assessment
- Hospital presentation within last 12 hours

6.2. Exclusion criteria

- >1500ml of intravenous fluid prior to screening
- Clinically judged to require immediate surgery (within one hour of eligibility

- assessment);
- Immediate (< 1hour) requirement for central venous access
- Chronic renal replacement therapy
- Known allergy/adverse reaction to norepinephrine
- Palliation / end of life care (explicit decision by patient/family/carer in conjunction with clinical team that active treatment beyond symptomatic relief is not appropriate)
- Previous recruitment in the trial
- Patients with permanent incapacity
- Pregnancy. Women of childbearing potential (WoCBP) must have a negative urine or serum pregnancy test result completed as part of screening requirements.
  WoCBP are defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
- Other primary causes of shock (e.g. suspected cardiogenic shock, haemorrhagic shock, etc)
- History or evidence of any other medical, neurological or psychological condition that would expose the subject to an undue risk of a significant Adverse Effect as determined by the clinical judgement of the investigator
- Participation in other clinical trials of investigational medicinal products

7. CO-ENROLMENT

7.1. 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).

7.2. CTIMP-CTIMP Co-enrolment

This is not permitted.

7.3. CTIMP-Non-CTIMP Co-enrolment

Participants who are active in the interventional phase of a non-CTIMP may be co-enrolled to the EVIS study – please contact the Sponsor in advance of recruitment to EVIS to discuss. In addition, when considering permitting co-enrolment, investigators should be mindful of the potential burden upon participants, their families and research staff.

7.4. 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 so they can determine the appropriate course of action.

8. TRIAL PROCEDURES

8.1. Recruitment

Patients will be recruited from the Emergency Department, Medical or Surgical assessment units or any other area used for acute assessment in the recruiting sites.

The Clinicians and clinical research staff have an essential role to support enrolment to the trial. The research team will then coordinate all other trial procedures.

All study data will be entered either directly into an electronic case report from, or onto a paper CRF then transferred onto the eCRF, whichever is normal practice at the recruiting institution.

8.2. Screening

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 that 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 this way.

Where researchers are not 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.

A screening log will record consecutive patients but without any identifiable data. Baseline characteristics and the reason for not being included according to the inclusion and exclusion criteria

will be recorded in the screening log but no follow-up information will be recorded in this database. The reasons for not enrolling in the study or not having eligibility criteria (e.g. presence of exclusion criteria, absence of inclusion criteria) will be prospectively recorded.

8.3. INFORMED CONSENT

8.3.1 Patient Consent

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 required.

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 GCP trained members of the clinical team, or members of the research team who have been delegated this responsibility. A record of eligibility will be made recorded in the participant's clinical notes.

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 nature of the study the treatment will start ideally within one hour and 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 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. The witness should be someone who is impartial to the research team and who is not on the research delegation log.

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.

Should the consent form not be fully completed or completed incorrectly at the time of consent process then as soon as feasibly possible and at least prior to the date of discharge responsible parties should complete or amend the form as appropriate as per the intention on the day of consent. Any additions or changes to the consent form should be initialed and dated by the responsible party. Where this is not possible, for reasons other than incapacity of the patient, the reason for incomplete consent should be fully documented within the patients' medical records.

Due to the emergency nature of the clinical trial and the need for assessment and decisions to be made under pressure and within tight timescales it is an anticipated that this may, on occasion, result in some unintentional issues during the consent process. Should the consent form not be fully completed or completed incorrectly at the time of the consent process then as soon as feasibly possibly and at least prior to the date of the discharge responsible parties should complete or amend the form as appropriate as per the intention on the day of consent. Any additions or changes to the consent form should be initialed and dated by the responsible party. Where this is not possible, for reasons other than incapacity of the patient, the reason for incomplete consent should be fully documented within the patients' medical records.

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. If patients lack capacity and it is not categorised as permanent incapacity, then the following processes will be followed.

8.3.1. Personal/Professional Representative consent

Laws governing consent procedures, and in particular those governing incapacitated adults and their involvement in research, must be followed. Written informed consent from the patient should always be sought where possible. If this is not possible because the patient cannot read or write, the randomising investigator or nurse can gain witnessed verbal consent.

If a patient lacks capacity to consent for themselves then a legal representative may consent on the patient's behalf. The table below specifies the hierarchy which should be applied in England, Wales and Northern Ireland and Scotland where the laws differ slightly.

Hierarchy of Informed Consent for Incapacitated Adults	
England, Wales and Northern Ireland	**Scotland**
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.	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.

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.

8.3.2. 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, before any contact is made by the research team; in some circumstances the research team will be part of the clinical care team. However, 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, or can be sent via email. 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 another member of clinical ~~or research~~ staff not involved in the research.

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.

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 email.

All methods of patient consent must be documented in the patient's notes.

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 Professional legal representative is 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. A Personal Representative should be approached for consent to continue as soon as they are available, and it is feasible to do so.

8.3.3. Deferred Consent (only allowed in England/Wales)

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 a doctor at training level ST4 or above or an associate PI or consultant who has appropriate trial training and this should be clearly documented in the medical notes.

The following statement should be written in the medical notes:

This patient has life threatening features of septic shock and has been enrolled into the EVIS study with a deferral of consent. I have discussed this with Dr [insert name] who agrees this is in the patient's best interest at this time.

This statement should be signed and dated by the enrolling doctor.

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 8.4 will be followed.

8.3.4. Recovered Capacity

If and when the participant recovers capacity to consent 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.

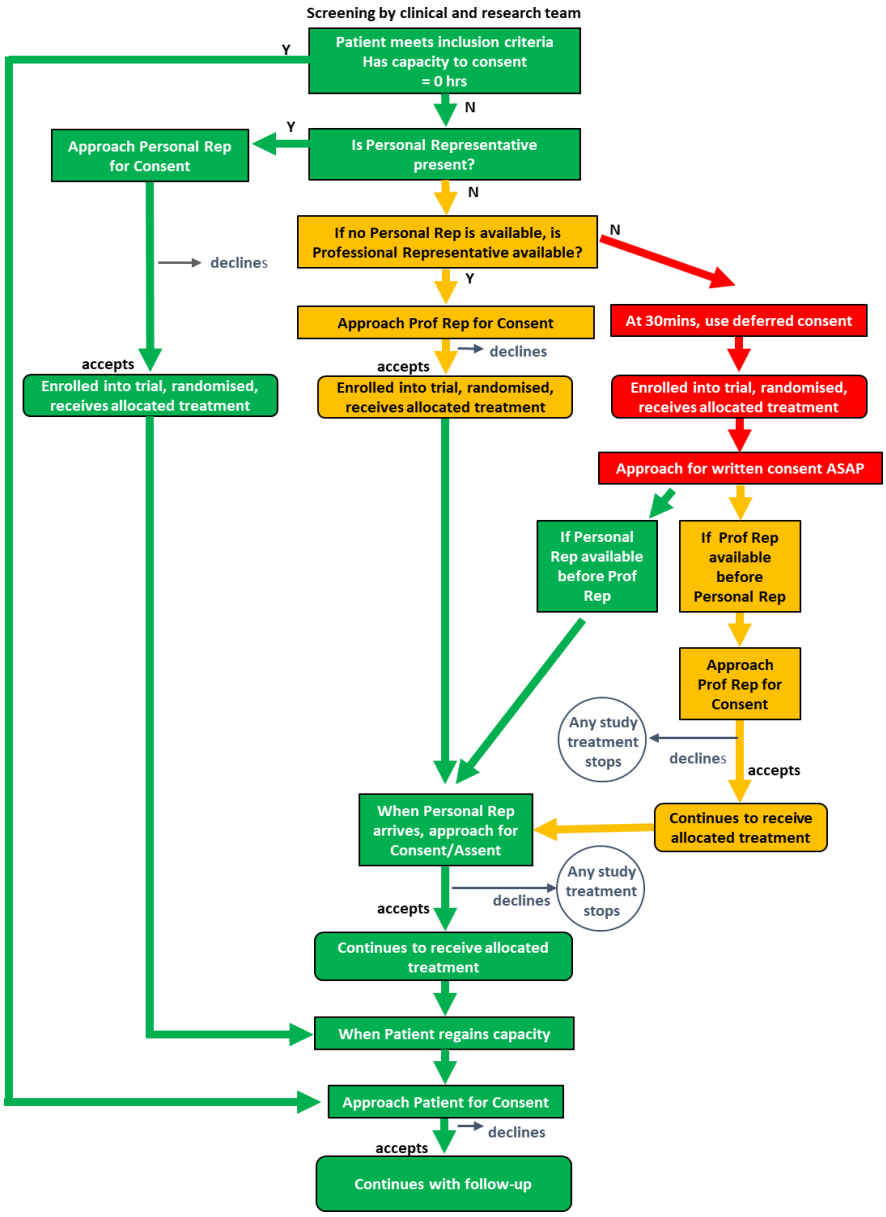
In the event that a patient is not able to be approached for consent to remain in the trial prior to hospital discharge, the local research team will send a letter to the participant informing them of their involvement in the trial. This letter will have details of the local trial team so if the participant has any questions or wishes to withdraw from the trial then can get in touch with the local trial team. If the local team do not get a response then on-going 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 8.4 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 data will be retained and analysed.

Patients with permanent incapacity will not be recruited and this is an exclusion criteria.

Fig 1. Hierarchical consent process



8.3.5. Witnessed Methods of Obtaining Consent

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, or an appropriate electronic capture of consent if a local process is available for this.

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.

8.4. Withdrawal

The participant can decide to withdraw from the trial at any time for no reason. The CI or principal investigator also has the right to withdraw patients from the trial if deemed in the best interests of the patient or in the event of protocol deviations, administrative or other reasons. 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:

- Study treatment with continuation of the collection of clinical and safety data

OR

- 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.

Where no consent is given by any legal representative, i.e. deferred consent is used and a participant dies before any consent is obtained, we will retain the patient in the study. To safeguard rights, the minimum personal information possible will be collected.

8.5. RANDOMISATION

8.5.1. Randomisation procedures

After participant 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 previous, 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 where recruitment occurs 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 study 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 PVI or standard care and will be stratified by age (<70 and ≥70) and study site.

8.5.2. Treatment Allocation

Peripheral vasopressor Infusion will be compared to standard care. This is an open label study.

A. Peripheral Vasopressor Infusion arm

Participants will receive peripheral vasopressor infusion of norepinephrine (16 micrograms /ml). See section 10.1 for further information. All other care will be as per local protocol.

B. Standard care arm

Participants will receive standard care as per UK national guidelines on sepsis. See section 2. All other care will be as per local protocol.

8.5.3. Emergency Unblinding procedures

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

9. STUDY VISITS

9.1.1. Screening

- Confirm eligibility
- Written Informed Consent

9.1.2. Baseline

- Randomisation
- Demographics

- Routine Blood results – haematology full blood count (FBC), biochemistry urea and electrolytes (U&E), liver function tests (LFT), Glucose, C-reactive protein (CRP), blood lactate
- IMP administration
- IMP Adherence
- Adverse Events
- EQ-5D-5L
- ~~Research bloods (optional)~~

9.1.3. 6hours (+/- 1 hour)

- Routine bloods - blood lactate (optional)
- Total iv fluid volume delivered
- Clinical observations (pulse, blood pressure, respiratory rate, oxygen saturations, oxygen therapy, concious level – Glasgow Coma Scale (GCS))

9.1.4. 12 hours (+/- 4 hours)

- Routine bloods - blood lactate (optional)
- Total iv fluid volume delivered
- Clinical observations (pulse, blood pressure, respiratory rate, oxygen saturations, oxygen therapy, concious level – Glasgow Coma Scale (GCS))

9.1.5. 24 hours (+/- 6hours)

- Routine bloods - FBC, U&E, LFT, Glucose, CRP, blood lactate (optional)
- ~~Research bloods (optional)~~
- Total IV fluid volume delivered
- Clinical observations (pulse, blood pressure, respiratory rate, oxygen saturations, oxygen therapy, concious level – Glasgow Coma Scale (GCS))
- Parenteral corticosteroid administration
- IMP administration
- IMP Adherence

9.1.6. 48 hours (+/- 12 hours)

- Routine bloods - FBC, U&E, LFT, Glucose, CRP, blood lactate (optional)
- ~~Research bloods (optional)~~
- Total IV fluid volume delivered
- Clinical observations (pulse, blood pressure, respiratory rate, oxygen saturations, oxygen therapy, concious level – Glasgow Coma Scale (GCS))
- Parenteral corticosteroid administration
- IMP administration
- IMP Adherence

9.1.7. 72 hours (+/- 12 hours)

- Routine bloods - FBC, U&E, LFT, Glucose, CRP, blood lactate (optional)
- ~~Research bloods (optional)~~
- Total IV fluid volume delivered
- Clinical observations (pulse, blood pressure, respiratory rate, oxygen saturations, oxygen therapy, concious level – Glasgow Coma Scale (GCS))
- Incidence of safety outcomes (extravasation NIH score)

9.1.8. 7 days (+/- 1 day)

- Routine bloods (optional)

9.1.9. Hospital discharge

- Length of stay
- Length of critical care stay

9.1.10. 30 days

- Mortality – via data linkage

9.1.11. 30 days (+/- 7 days)

- EQ-5D-5L

9.1.12. 90 days (+/- 14 days)

- Mortality – data linkage
- EQ-5D-5L

~~9.2. STORAGE AND ANALYSIS OF RESEARCH BLOODS~~

~~9.2.1. Blood Sampling~~

~~There will be an integrated sub-study active in a subset of recruiting sites.~~

~~Subject to consent, participants in the EVIS trial will have two blood samples taken at three points:~~

- ~~Baseline (0 hrs): this sample will be taken at the point of enrolment into the sub-study, with the aim of characterising the inflammatory response to sepsis before, or at, the point of administration of the trial intervention.~~
- ~~Second (24 ± 6 hrs) after enrolment~~
- ~~Third sample (48 +- 6 hours) after enrolment~~

~~In each case, two samples will be taken sequentially, from the same point of access. In order to minimise burden to the participants, the study team will work with the clinical team to identify opportunities to take blood simultaneously with routine sampling, as well as identifying sampling options which use existing points of access. Examples of this include:~~

- Taking research samples at the same time that venepuncture is being performed for routine clinical samples (e.g. taking the research samples with the routine samples from the same 'needle')
- Taking research samples at the same time that a new, or re-sited, point of vascular access is inserted (e.g. taking the research samples when a new peripheral cannula is inserted)
- Taking research samples from an existing port of vascular access which allows sampling (e.g. taking research samples from an arterial line, a central line or a PICC).

9.2.2. Storage and analysis of Research Blood Samples

The addition of the research blood sampling phase is dependent on securing additional funding. Please see lab manual for full details of sample storage and analysis.

At each sampling point during this study, two research blood samples will be taken - a 9mL EDTA tube, and a 2.5mL PAXgene tube.

From the EDTA tube of blood, we will aliquot one millilitre into cytodelics cell preservation medium for cellular phenotyping (referred to as "cells") and the remaining blood in EDTA tube will be spun down to isolate), which will be stored in aliquots for measuring cytokines. They will be labelled using pseudonymous study identifiers and stored locally at -80ºC and then shipped to the central laboratory (at the University of Edinburgh) for analysis.

We propose to measure pro- and anti-inflammatory cytokines (GM-CSF; IFN-gamma; IL-1 beta; IL-2; IL-4; IL-5; IL-6; IL-8 (CXCL8); IL-10 (CXCL10); IL-12p70; IL-13; IL-17A (CTLA-8); MCP-3 (CCL7); and TNF alpha).

In the case of the PAXgene tube, will undertake CAGE RNA sequencing. Because these tests include genetic analysis, explicit consent will be sought from patients. Genome-wide genotyping will be performed using an efficient, cost-effective microarray (Illumina Global Screening Array) followed by genome-wide imputation to > 5M variants.

There will be an SOP for sample tracking-collection, transfer, storage, analysis and to data collection forms (CRF/ e-CRF). That will be included in the lab manual.

Consent will be sought for long term storage at the University of Edinburgh for all samples (i.e. PAXgene, cells and plasma), anticipated to be a period of up to 10 years. Access to or use of these samples will be overseen by TSC in short/medium term. A replacement committee following this study will be put in place for this purpose. Subsequent disposal will compliant with the Human Tissues Act 2004.

~~9.3.~~9.2. END OF TRIAL

For the purposes of regulatory requirements the end of trial is defined as 12 months after last patient last visit.

For trials requiring MHRA approval the end of the trial should be clearly defined in the protocol. The sponsor must notify the MHRA of the end of a clinical trial within 90 days of its completion. It is usually the date of the last visit/data item of the last patient undergoing the trial. For the purpose of informing the MHRA "database lock" is not appropriate as a definition as it does not allow for early termination (section 10.6) to be reported within 15 days.

~~9.4.~~9.3. COVID-19 PANDEMIC

Safety of patients is of the primary concern and during the current COVID-19 pandemic we will comply with Government, health board, MHRA and Health Research Authority (HRA) guideline on clinical research participation. Sites are requested to communicate any issues relating to COVID-19 and conduct of the trial at their location to the Sponsor. Any risk to trial participants and trial team members will be addressed with via local risk mitigation measures in place at the time. A positive COVID status is not an exclusion to participation, dependent on meeting all other inclusion/exclusion criteria and clinical need for treatment of sepsis.

Based on the risk assessment concomitant use of COVID-19 vaccines are permitted with no minimum time period between any dose of trial IMP and deployed vaccine. No direct drug-drug interaction between the COVID-19 vaccines and the trial IMP(s) is anticipated. COVID-19 vaccinations or boosters that may become available must be recorded in the patient notes as a concomitant medicine (name, date of vaccination).

10. INVESTIGATIONAL MEDICINAL PRODUCT AND COMPARATOR

10.1 STUDY DRUG

10.1.1 Study Drug Identification

Noradrenaline (Norepinephrine) 1 mg/ml Concentrate for Solution for Infusion

10.1.2 Study Drug Manufacturer

Any preparation of Norepinephrine 1mg/ml which has marketing authorisation in the UK may be used for this trial. All supplies for use in the trial will be sourced from routine hospital stocks and will not be reimbursed. There is no requirement to 'ring-fence' supplies for use in the EVIS trial or to apply study

specific labelling. Norepinephrine reconstitution and preparation of the infusion will be performed in near-patient clinical areas as is current standard of practice. Records of administration will be retained for traceability purposes.

10.1.3 Storage

Norepinephrine 1mg/ml must be stored in accordance with the current SmPC. There is no requirement by sponsor for sites to temperature monitor storage conditions of the IMP. Norepinephrine Storage must be secure in the clinical areas as per local medicines policies.

10.1.4 Destruction of Trial Drug

No IMP destruction required.

10.1.5 Summary of Product Characteristics (SmPC)

There is no specified brand of Norepinephrine 1mg/1ml for this trial. Each hospital pharmacy may stock several brands and these may change over the course of the trial. Supplies of any brand of Norepinephrine 1mg/1ml currently in stock may be used in the trial. A representative Summary of Product Characteristics is provided for the purposes of Reference Safety Information. See section 11.3.

10.2 COMPARATOR

10.2.1 Study Drug Identification

Intravenous “balanced” crystalloids.

10.2.2 Study Drug Manufacturer

Any preparation of intravenous “balanced” crystalloid which has marketing authorisation in the UK may be used in this trial, all supplies for use in the trial will be sourced from routine hospital stocks and will not be reimbursed. There is no requirement to ‘ring-fence’ supplies for use in the EVIS trial or to apply study specific labelling. Records of administration will be retained for traceability purposes

10.2.3 Storage

The balanced Crystalloid must be stored in accordance with the manufacturer’s labelling. There is no requirement by sponsor for sites to temperature monitor storage conditions of the crystalloids. Storage must be secure in the clinical areas as per local medicines policies.

10.2.4 Destruction of Trial Drug

No crystalloid destruction required

10.2.5 Summary of Product Characteristics (SmPC)

There is no specified brand of balanced crystalloid for this trial. Each hospital may stock several brands and these may change over the course of the trial. Supplies of any brand of Balanced Crystalloid currently in stock may be used in the trial. A representative Summary of Product Characteristics is provided for the purposes of Reference Safety Information. See section 11.3

10.3 DOSING REGIMEN

10.3.1 INTERVENTION ARM

Participants allocated to the intervention arm will receive peripheral vasopressor infusion during the initial 48 hour study period. For the purposes of dosing, patient weight should be rounded to the nearest 10kg, based on either estimated weight or recent weight recorded in medical notes. Dosing is not capped for weight and dosing tables are in appendix A up to 120kg. For weights higher than this the dose must be calculated manually as detailed below.,

10.3.1.1 Dilution

Norepinephrine should be prepared by dilution in either 0.9% sodium chloride injection or 5% glucose to provide a final concentration of 16 microgram / mL. Please see trial specific IMP Management Document for Sites for details. Preparation may be undertaken by any staff in the clinical area if this forms part of their usual duties and does not require those staff to undertake study-specific training to do so, nor do they require to be on the delegation log for this activity.

10.3.1.2 Method of Administration & Dose

Norepinephrine must be administered via an infusion pump attached to a peripheral intravenous catheter. Clinicians should choose a site in which they are confident and consider the use of ultrasound in their assessment.

- Choose at least a 20G PVC size

- Peripheral long lines can be used if this is normal practice for the treating clinician / institution
- Locate in a site according to standard practice
- If possible, avoid sites of flexion in awake patients due to the risk of occlusion
- Avoid sites requiring more than 1 venepuncture
- Ensure there is a return of blood following insertion of the PVC and that the PVC flushes easily with 5-10mL of 0.9% sodium chloride
- Site a second PVC in case of failure of the primary site (if possible)

Commence infusion at a starting dose of 0.05 microgram /kg /min. For example for a 70kg patient this will be calculated as follows:

- 0.05*70 = 3.5 micrograms per min
- 3.5*60 = 210 micrograms per hour
- Infusion rate =210/16 = 13.1ml per hour

See Appendix A for dosing and infusion rates for alternative weights.

10.3.1.3 Dose titration

The clinical team must titrate the dose of norepinephrine delivered to target MAP of 65 mmHg. The maximum dose permitted to be delivered peripherally in this trial is 0.15 micrograms / kg / min. Further detail of up titration and down titration of dose is given in Appendix A.

Invasive blood pressure monitoring is recommended but it is acknowledged that it might not be considered appropriate in all cases. Regular interval non-invasive blood pressure monitoring must be ensured in these cases as appropriate for their clinical environment.

10.3.1.4 Administration of rescue intravenous fluids

If target MAP not reached once maximum titrated dose of 0.15 micrograms / kg / min has been reached, or clinician concerns of organ hypo perfusion based on heart rate, skin perfusion, mentation or urine output or other imaging if part of treating clinicians normal practice, then the treating clinicians can administer IV 250-1000ml boluses of balanced crystalloid. These must be documented in the eCRF. See control arm section for details of balanced crystalloid.

10.3.1.5 Administration of maintenance intravenous fluids

If the treating clinician wishes to administer maintenance rather than resuscitation IV 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. **Additional maintenance fluids are not considered IMP for the purpose of the EVIS trial.**

10.3.1.6 Administration of rescue vasopressors

If target MAP not reached following protocol to reach the maximum dose of peripheral vasopressor infusion and the use of rescue intravenous fluids and / or clinician concerns of organ hypo perfusion based on heart rate, skin perfusion, mentation or urine output or other imaging if part of treating clinicians normal practice, then the treating clinicians can administer rescue vasopressor via a central venous route. Rescue vasopressor can be an increased dose of norepinephrine or alternative vasopressor if this is the clinician's normal practice. The rescue vasopressor use will be captured on the CRF.

In this situation, the peripheral vasopressor infusion must be discontinued.

10.3.1.7 Suspected extravasation

Extravasation describes the leakage of any drug into surrounding tissues and is a rare complication of peripheral vasopressor infusion (see Section 3.2). Regular monitoring of the infusion site is essential to enable early recognition and management of extravasation events. Extravasation should be suspected if there is

- Patient reports pain or itching at infusion site
- Pallor, oedema or erythema of skin at intravenous cannula site

If extravasation is suspected the following actions are recommended

1. Stop the infusion immediately and disconnect the line from the PVC.
2. Attempt to aspirate 3-5mL from the PVC if able.
3. Remove the cannula and apply a dressing to the removal site.
4. Mark the extravasation area if possible, in order to allow monitoring of any developing injury.
5. Elevate the affected limb if able to do so to reduce swelling.

6. Consider application of a topical vasoactive agent to encourage local blood flow (for example nitroglycerin paste).
7. Administer analgesia if required.
8. Seek advice from a surgeon or your local tissue viability service if concerned.

Participating sites may follow any local extravasation treatment policy as an alternative to above.

10.3.1.8 Conclusion (weaning) of peripheral vasopressor infusion

Patients allocated to the intervention arm (peripheral vasopressor infusion) may require the peripheral infusion to stop within the study period of 48 hours, following clinical assessment. This must involve assessment by the treating clinician and gradual weaning of the dose of norepinephrine administered. When MAP > 65 mmHg on a stable dose of vasopressor, the treating clinicians can begin reduction of the vasopressor, as per their normal practice.

This can be done by reducing the dose by greater than or equal to 25% of the stabilizing dose at intervals of less than or equal to 4 hours to maintain MAP greater than or equal to 65 mmHg, or at the clinicians discretion.

The time of conclusion of the peripheral vasopressor infusion should be clearly documented.

After discontinuation, flush the peripheral cannula with sodium chloride 0.9% at the same rate the medicine was infused to avoid adverse haemodynamic effects. The concomitant administration of noradrenaline and other medicines via a Y-site should be avoided to prevent inadvertent bolus administration of noradrenaline.

If following conclusion of peripheral vasopressor infusion, the treating clinicians' wishes to restart the peripheral vasopressor infusion, this can be done and the time of commencement should be clearly documented.

10.3.1.9 End of study period

At the conclusion of the 48 hour post randomisation period, the treating clinician can continue the peripheral vasopressor infusion at their discretion based on clinical need of the participant.

10.3.1.10 Operative intervention

For any participants requiring operative intervention during the 48 hours post randomisation period, treatment allocation should be maintained where possible in theatre and in critical care after but allow for anaesthetic discretion/judgement around other fluid, blood product and vasopressor use.

10.3.2 CONTROL ARM

Participants allocated to the control arm will receive standard care as defined by the UK NICE guidelines and the Surviving Sepsis Campaign guidelines during the 48 hour study period post randomisation.

10.3.2.1 Method of administration and dose titration

Initial treatment with intravenous fluid must be by peripheral venous cannula

10.3.2.2 Choice of balanced Crystalloid

Any of the following may be used as the balanced crystalloid for fluid resuscitation:

- Compound sodium lactate (Ringers Lactate or Hartmanns solution)
- Plasma-lyte 148

Any brand available at site may be used and any others not listed should be discussed with Sponsor during set-up processes for the site.

10.3.2.3 Dose titration

Intravenous fluid administration should be targeted to MAP of 65mmHg. 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 48 hours will be at the discretion of the clinical team and targeted to MAP of 65mmHg and will be documented in the eCRF.

Invasive blood pressure monitoring is recommended but it is acknowledged that it might not be considered appropriate in all cases. Regular interval non-invasive blood pressure monitoring must be ensured in these cases.

10.3.2.4 Administration of rescue vasopressors

Participants in the balanced crystalloid arm must not receive peripheral vasopressor infusion during the 48 hour study period (see Sectio)

If target MAP not reached following protocol for the control arm or clinician concerns of organ hypo perfusion based on heart rate, skin perfusion, mentation or urine output or other imaging if part of treating clinicians normal practice, then the treating clinicians can administer rescue vasopressor. This should be delivered via a central venous route.

10.3.2.5 Administration of additional intravenous fluids

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.

10.3.2.6 End of study period

At the conclusion of the 48 hour post randomisation period, the treating clinician can continue the allocation to standard care at their discretion at their discretion and based on clinical need of the participant.

10.3.2.7 Operative intervention

For any participants requiring operative intervention during the 48 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.

10.4 DIFFERENCE BETWEEN CURRENT / PLANNED PATHWAY

There will be no difference between treatment arms other than allocation to peripheral vasopressor infusion the first 48 hours of care after recruitment. Other care will follow national sepsis guidelines.

10.5 PARTICIPANT ADHERENCE

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

10.6 CROSSOVER OF TREATMENT ARMS

If a participant receives the intervention from the arm they were not allocated to within 48 hours 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.

10.7 OVERDOSE

Over dosage of norepinephrine may result in severe hypertension, reflex bradycardia, marked increase in peripheral resistance and decreased cardiac output. These may be accompanied by violent headache, photophobia, retrosternal pain, pallor, intense sweating and vomiting. In the event of over dosage:

1. Stop the infusion immediately and disconnect the line from the PVC.
2. Attempt to aspirate 3-5mL from the PVC if able.
3. Remove the cannula and apply a dressing to the removal site.

Other care should be supportive, and directed by the patient's condition. There is no specific antidote.

Excess fluid administration will be handled in line with standard practice.

10.8 OTHER MEDICATIONS

10.8.1 Non-Investigational Medicinal Products (NIMP)

There are no NIMPs for this study.

10.8.2 Permitted Medications

Participants may continue on their current medicines as appropriate to their care during this trial. If the patient's clinical condition requires that all routine medication they were taking prior to admission is stopped and reintroduced during the study period this is permitted.

Caution is recommended for any patient receiving peripheral norpeinephrine infusion with the following medication:

- volatile halogenated anaesthetic agents,
- monoamine oxidase inhibitors,
- linezolid,
- tricyclic antidepressants,
- adrenergic-serotoninergic drugs or
- any other cardiac sensitising agents

Co administration with norepinephrine is not recommended as severe, prolonged hypertension and possible arrhythmias may result

10.8.3 Prohibited Medications

No medicines that are appropriate to the care of a participant are prohibited.

10.8.4 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.

10.9 Withdrawal of peripheral vasopressor infusion: Stopping criteria

In the event of any serious adverse reaction(s) suspected to be attributable to IMP (peripheral vasopressor infusion) then the PVI must be withdrawn immediately.

The following events are the principle anticipated serious adverse reactions requiring cessation of infusion but this list is not exhaustive.

- Sustained hypertension (Systolic blood pressure greater than 180 mmHg or diastolic blood pressure greater than 110 mmHg that fails to resolve despite implementation of local protocols for management of vasopressor induced hypertension
- Tachyarrhythmia (ventricular tachycardia or ventricular fibrillation) determined to be life threatening by the treating clinician
- Suspected local extravasation of IMP

11. PHARMACOVIGILANCE

11.1. Definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. It is important to note that this is entirely separate to the known side effects listed in the SmPC. It is specifically a temporal relationship between taking the drug, the half-life, and the time of the event or any valid alternative etiology that would explain the event.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which 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.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	~~A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information.:~~ ~~• in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken.~~ ~~in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question~~ A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the reference safety information: • in the case of a product with a marketing authorisation, this could be in the summary of product characteristics (SmPC) for that product, so long as it is being used within its licence. If it is being used off label an assessment of the SmPCs suitability will need to be undertaken. • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question

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11.2. Operational definitions for (S)AEs

Adverse events (AEs) will be recorded, notified, assessed, reported, analysed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) and this protocol.

EVIS is an emergency medicine trial in a population that is acutely ill at the point of entry to the study. Under these circumstances participants are subject to multiple adverse events and serious adverse

events and it may be difficult for investigators to distinguish AEs and SAEs that are a consequence of sepsis from those that have a causative relationship with the IMP(s). As such adverse event reporting will focus specifically on events that may have a causative relationship with the IMP(s) and require more extensive monitoring to ensure that safety can be assessed between arms. See section 11.5 for more detail.

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 present at the time of entry to the trial and throughout their hospitalisation. These events will be recorded in the medical records and assessed in the same way as AE/SAEs. Generally these events will not be recorded in the eCRF unless they develop following treatment with IMP or are exacerbated following treatment with IMP- see section 11.3 for further detail~~see section 11.3 for further detail~~. Examples of such events are as follows:

- 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

There are specific events that are required for the assessment of safety endpoints that do not ordinarily have a causative relationship with the IMP. These events are not subject to expedited reporting as SAEs but will be collected as per section 11.4.~~4~~5.

11.3. Reference Safety Information

For the purposes of the EVIS trial section 4.8 of the following SmPCs will be used as the Reference Safety Information:

- Noradrenaline (Norepinephrine) 1 mg / ml Concentrate for solution for infusion (Manufacturer: Aguettant Ltd)
  - https://www.medicines.org.uk/emc/product/5353/smpc
- Balanced Crystalloids Plasma-Lyte® 148 (pH 7.4) solution for infusion:
  - https://www.medicines.org.uk/emc/product/1795

11.4. Recording and reporting of Adverse Events

All AEs at the time of trial entry that are observed by the Investigator or reported by the participant will be recorded in the participant's medical records. Following consent and randomisation to the trial AEs

occurring during or following administration of the IMP that are observed by the Investigator or reported by the participant will be recorded in the participants medical records and assess relatedness to study treatment and seriousness.

Where an event is considered related to the trial IMP (that is, an adverse reaction) and was not present at baseline assessment or has worsened since baseline then it should be recorded within the eCRF.

For each Adverse Reaction the following information will be recorded within the eCRF:

- nature of the event
- event duration (start and end dates, if applicable)
- if related, whether the reaction would be considered expected or unexpected
- action taken
- outcome (if applicable)

Adverse events are collected from the time of randomisation until 24 hours post administration of the final dose of IMP

11.5. Recording of safety endpoints not subject to expedited reporting as SAEs

The following events are subject to recording within the eCRF from the date of randomisation until 7 days post IMP administration. These are safety outcome events that are anticipated to occur in this participant group and will are therefore from excluded from expedited reporting as SAEs. These events will be subject to monitoring by the trial data monitoring and ethical committee.

- Death related to infection (including multi-organ failure)
- Critical care (HDU/ICU) admission
- Acute kidney injury
- Pulmonary oedema
- Extravasation
- ~~Pulmonary oedema~~
- ,

~~Extravasation~~

These events will be summarised and presented to the DMC to ensure that trial safety is suitably monitored.

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11.6. Recording and Reporting of Serious Adverse Events (SAE)

As per AEs any event presenting at baseline and prior to receiving trial IMP meeting the seriousness criteria of an SAE should be fully recorded within the patient notes including start and stop dates, causal relationship with IMP, seriousness, and outcome

All SAEs that occur following the administration of IMP, or SAEs present prior to administration that are exacerbated following IMP administration must be recorded within the study eCRF from the time of randomisation until 24 hours post administration of the last dose of trial IMP.

~~**Note: Any incidence of extravasation that occurs a participant following IMP administration must be reported as an SAE.**~~

All Serious Adverse Events must be recorded within the eCRF within 24 hours of investigator awareness of the event.

Full details of SAEs will be recorded in the electronic Case Report Form. The following information will be collected at a minimum:

- nature of the event
- event duration (start and end dates, if applicable)
- relationship to trial medication in the opinion of the investigator
- if related, whether the reaction would be considered expected or unexpected
- action taken
- outcome (if applicable)
- Seriousness criteria

~~**Note: Where extravasation is recorded as an SAE, additional information will be requested via the eCRF form.**~~

Any change of condition or other follow-up information should be added to the eCRF as soon as it is available or at least within 24 hours of the information becoming available.

All Serious Adverse Events will be followed up until the event has resolved or a final outcome has been reached.

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11.7. Assessment of Serious Adverse Events

All SAEs must be assessed for severity, causality and expectedness with reference to this protocol and the Reference Safety Information (RSI).

Assessment of seriousness

An adverse event will be considered serious if it:

- Results in death
- Is life threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is otherwise considered medically significant by the investigator

Assessment of severity

This should be assessed and described using the following categories:

- Mild-awareness of event but easily tolerated
- Moderate-discomfort enough to cause some interference with usual activity.
- Severe-inability to carry out usual activity.

NB: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

Assessment of causality

i.e. does the event have a “reasonable causal relationship” with trial medication. A binary Yes/No decision will be used for the assessment of causality.

SAEs will be submitted with a provisional assessment of causality by the reporting investigator. Following this initial submission SAEs must be reviewed for causality by the Principal Investigator, or their medically qualified designee(s) as soon as possible and within 5 days of the

site becoming aware of the event for fatal or life-threatening SAEs and 10 days for all other SAEs. In addition the CI will carry out an assessment of causality secondary to that of the local investigator. Where the CI and local investigator disagree regarding the causality of an event both opinions will be captured within the eCRF. The CI may upgrade events but cannot downgrade the local clinicians assessment of causality

Assessment of expectedness

If the SAE is considered to be related to IMP, an assessment should be made of the expectedness of the reaction i.e. is the reaction a recognised adverse effect of the medication. The Chief Investigator and the Sponsor PV Manager (or their delegates) are responsible for the assessment of expectedness of all SAEs deemed to be related to the IMP.

The expectedness of an adverse reaction is assessed against the Reference Safety Information (RSI) i.e. the information regarding expected reactions approved by the MHRA.

Expected events are those consistent with the relevant product information documented in the RSI i.e. a Serious Adverse Reaction
Unexpected are those not consistent with the relevant product information documented in the RSI i.e. a Serious Unexpected Serious Adverse Reaction.

COVID-19 Vaccination and Reporting

Where a deployed COVID-19 vaccine is suspected to be involved in the onset of a reported event it should be recorded as a concomitant medication. A causal relationship between the vaccine and the event, including potential drug interactions should be assigned by the reporting investigator.

If a reported event is suspected to be due to a deployed COVID-19 vaccine alone reporting investigators should ensure that standard Yellow Card reporting procedures for medicines used in the treatment/prevention of COVID-19 are followed.

11.8. Recording and reporting of SAEs where eCRF access is not possible

If recording in the eCRF is not possible e.g. website problem, then a paper SAE form should be completed.

The SAE form is downloaded from www.glasgowctu.org, printed off, completed and signed. The form is then ~~faxed to the Glasgow Clinical Trials Unit Pharmacovigilance (PV) Office on +44(0)141 357~~emailed to the Glasgow CTU PV office: pharmacoig@glasgowctu.org ~~5588~~. If faxing is not possible a copy of the SAE form should be scanned and emailed to: pharmacovig@glasgowctu.org. If this website is unavailable a paper copy of the SAE form is filed in the Investigator Site File at each site.

If necessary, a verbal report can be given by contacting the PV Office on +44(0)141 330 4744. This must be followed up as soon as possible with an electronic or written report.

11.9. Expedited Reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs)

Any SAE assigned by the PI or delegate as related to IMP and by the CI or Sponsor PV Manager as unexpected (i.e. not documented as an expected reaction to the trial medication in the RSI), will be classified as a SUSAR and subject to expedited reporting to the Medicines and Healthcare products Regulatory Agency (MHRA) and the Research Ethics Committee (REC). If the CI disagrees with the PI's causality assessment both opinions will be provided on the report.

The Sponsor will inform the MHRA and the REC of SUSARs within the required expedited reporting timescales:

Fatal or life threatening SUSARs: not later than 7 days after the sponsor had information that the case fulfilled the criteria for a fatal or life threatening SUSAR, and any follow up information within a further 8 days.

All other SUSARs: not later than 15 days after the sponsor had information that the case fulfilled the criteria for a SUSAR

11.10. Pregnancy

~~If p~~Patients included in this study are hospitalised and critically ill therefore extremely unlikely to become pregnant during the period of exposure to the IMP (48 hours maximum) particularly given the short half-life of noradrenaline which would be considered cleared shortly after cessation of the infusion.

However, should a participant become pregnant following their participation in the trial, or was pregnant at the time of entry to the trial, and the investigators believe the IMP to be implicated in the termination of that pregnancy or the occurrence of a congenital anomaly or birth defect within their child this should be reported as an SAE even if outside the protocol defined reporting period.

11.11. Reporting urgent safety measures

If any urgent safety measures arise the CI/Sponsor will phone the MHRA's Clinical Trial Unit, ideally within 24 hours. This will be followed up no later than 3 days from the date the measures are taken, giving written notice to the MHRA (who will advise the format required) and the relevant REC of the measures taken and the circumstances giving rise to those measures. A substantial amendment to the protocol must also be submitted to the MHRA and ethics committee.

11.12. Responsibilities for Safety Reporting and Review

This section details the responsibilities for reporting and reviewing safety information arising within the trial.

Data Centre

- Provide an eCRF for central data collection of ARs and SAEs;
- Provide the Sponsor PV Office with read-only access to relevant data and reporting facilities in the study database;
- Provide reports, including safety information, to the independent oversight committees identified for the trial (Independent Data Monitoring Committee (IDMC), Trial Steering Committee (TSC)) and the Sponsor

Principal Investigator (PI)

- Checking for AEs and ARs when participants attend for treatment / follow-up.
- Ensuring that AEs are recorded in line with the requirements of the protocol.
- Ensuring that all SAEs are recorded in the eCRF within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.

- Using medical judgement in assigning seriousness, causality, and severity with reference to the trial protocol

Chief Investigator (CI)

- Clinical oversight of the safety of patients participating in the trial, including involvement in the ongoing review of the benefit-risk ratio and mitigation strategies for adverse reactions
- Using medical judgement, confirm seriousness and causality and assess expectedness of SAEs
- Clinical review and final sign off of the reference safety information
- Immediate review of all SUSARs and life threatening or fatal SARs
- Preparing the clinical sections and final sign off of the Development Safety Update Report (DSUR)

Sponsor

- Verification of data collection, AEs, SAEs, SARs and SUSARs according to the trial protocol
- Reporting safety information to the CI or delegate for the ongoing assessment of the risk / benefit
- Ongoing review of the benefit-risk ratio and mitigation strategies for adverse reactions with the CI and trial pharmacist
- Preparation of the reference safety information in liaison with the CI and trial pharmacist
- Review of reported SAEs and assessing the expectedness of any reported SARs in accordance with the RSI for the trial
- Expedited reporting of SUSARs to the Competent Authority (MHRA in UK) and REC within required timelines
- Notifying Investigators of SUSARs that occur within the trial
- Checking for (annually) and notifying PIs of updates to the Reference Safety Information for the trial
- Preparing standard tables and other relevant information for the DSUR in collaboration with the CI and ensuring timely submission to the MHRA and REC
- Provide SAE Line Listings of the trial medication if required

11.13. Developmental Safety Update Report (DSUR)

A study specific DSUR will be submitted once a year, or on request, to the MHRA and REC until submission of the end of trial notification. The report will be submitted within 60 days of the anniversary of the issue of the Clinical Trials Authorisation for the Trial. The DSUR will be prepared by the Sponsor PV Manager in liaison with the CI and submitted by the sponsor (PV Office).

11.14. Notification of deaths

Deaths related to IMP

All deaths that are assessed by the local investigator to be causally related to IMP administration must be reported to the Sponsor as an SAE within 24 hours as per section 11.6.

Deaths unrelated to IMP

Deaths **not** attributable to IMP must be recorded as per section 11.5

12. STATISTICS AND DATA ANALYSIS

12.1. Sample size calculation

The sample size is based on clinical consensus of a minimal clinically important difference, likely economic benefit and the findings of previous studies (See section 4), we have chosen a difference in 30-day all-cause mortality of 5% for the primary outcome. The study would require 2928 randomised participants to detect this 5% difference (control 25% vs. intervention 20%) at 90% power and 5% level of significance (Stata 15.1 'power twoproportions'). This is increased to a maximum 3187 participants to allow for up to four interim analyses under a non-binding Hwang-Shih-DeCani spending function group sequential design (R 3.4.1 gsDesign module), which allows for early stopping for either overwhelming evidence of benefit, or for futility; and then further adjusted upwards to 3286 to allow 3% randomised missing data for 30-day mortality.

The Data Monitoring Committee (DMC) will consider advising the Trial Steering Committee (TSC) on re-estimation of the sample size based on aggregated, blinded data on the first 200 participants with complete 30-day mortality data available at around 1 month from the end of the 6-month internal pilot. Any other new relevant trial data will also be considered to inform discussions. The final decision on re-estimation of the sample size will be taken by the Chief Investigator and Trial Management Group.

12.2. Planned recruitment rate

We aim to recruit a maximum of 3286 patients over a period of 33 months. This includes an internal pilot recruiting the first 200 patients from ~30 sites over 6 months, reaching the full complement of 60 sites after 12 months, and recruiting for a further 21 months at full capacity from these sites, equating to a total recruitment rate of 2.1 patient /centre/month. We aim to have all approvals for the pilot sites in place prior to start of the study. Based on several data sources we estimate incidence of sepsis meeting the inclusion criteria to be 0.1% of all ED attendances [29, 34, 36, and 37]. For 60 UK sites with extra challenges of recruitment to emergency care studies [38] we anticipate recruitment of 2.1 patients per centre per month. The ProMISe trial [35] recruited at a similar rate.

For a stop-go guideline we will use a Green-Amber-Red approach [39]. 'Green' will be if we have randomised 160 or more we will continue unchanged. 'Amber' will be if we have recruited 100-160 we will consider adding new centres and/or extending the recruitment window. 'Red' will be triggered with <100 randomisations and serious consideration, in conjunction with HTA, around stopping the study.

We have 'front loaded' the clinical trial unit resource to achieve these targets, and will undertake substantial preparatory and approvals work before the official grant start date. During the internal pilot we will audit screening logs, recruitment, reasons for exclusion and protocol compliance. We will also

measure the completeness of datasets, and the completeness of the primary outcome, which we anticipate should be >95%. Process evaluation data during this phase will be important and will establish protocol fidelity, inform clarifications/modifications, and facilitate efficient set-up in other sites. We will also optimise the educational materials for use in the wider site recruitment and set-up.

12.3. Statistical analysis plan

All statistical procedures will be fully specified in a comprehensive Statistical Analysis Plan authored by the study statistician and approved by the independent oversight commitments (the iDMC and the TSC).

12.3.1. Summary of baseline data and flow of patients

List variables to be used to assess baseline comparability of the randomised groups including for each factor: a definition, any rules, references or programmes for calculation of derived values, what form it will take for analysis (e.g. continuous, categorical, ordinal) and how it will be reported (e.g. means, standard deviations, medians, proportions)

Produce a consort flow diagram http://www.consort-statement.org/

12.3.2. Primary outcome analysis

The main analysis will be according to the intention to treat principle and use a logistic regression model for the primary outcome of 30-day mortality, adjusting for centre as a random effect (or e.g. centres combined at a regional level if there are many small centres) and any pre-specified baseline covariates strongly predictive of outcome. We will run sensitivity type analyses that investigate the robustness of the findings to any patterns of missing data (expected to be negligible for the primary mortality outcome).

12.3.3. Secondary outcome analysis

We will investigate the influence of compliance (cumulative dose received) on the primary outcome using causal models (for example, using an instrumental variables approach).
The secondary outcomes will be analysed in a similar way to the primary analysis, using statistical models appropriate to the distribution of the outcome (mainly linear or logistic mixed effects models).
Likewise, safety outcomes will be analysed in similar ways appropriate to their distribution, and the findings presented descriptively.

We will conduct a secondary Bayesian analysis of

1. Primary outcome

2. Causal model

We will analyse the primary outcome using Bayesian methods, which allows quantification of probabilities of all effect sizes. We will explore the presence of heterogeneity of treatment effects using Bayesian hierarchical models in subgroups based on baseline parameters:

(a) Severity of illness (baseline NEWS/SOFA score)

(b) Amount of IV fluid given pre-randomisation, and

(c) Plasma lactate concentration (latest prior to randomisation).

12.4. Subgroup analyses

Predefined sub-group analyses (primary outcome) include: community versus hospital acquired infection, illness severity (baseline NEWS / SOFA / lactate), age, and co-morbidities along with time to randomisation, pre-randomisation IV fluid volume and frailty. We will adjust the level of significance and the confidence intervals to allow for the multiple pre-specified subgroup analyses undertaken.

12.5. Adjusted analysis

We will perform adjusted analyses as described in section 12.3.2 and 12.3.3

12.6. Interim analysis and criteria for the premature termination of the trial

We are using a group sequential design that allows for early stopping of the study due to either overwhelming evidence of benefit (stopping for benefit) or it being pointless continuing (very low chance of achieving a statistically significant result, conditional on what has been observed up to the scheduled interim analysis, in what remains to be observed after the scheduled interim analysis). We have scheduled 4 interim analyses, which will consider the primary outcome of all causes mortality, and be equally spaced at approximately 25%, 50%, 75% and then 100% (no early stopping, this would be a final analysis at the maximum sample size). These interim analyses will be presented by the unblinded statistician at the Edinburgh Clinical Trials Unit (ECTU) to the independent Data Monitoring Committee (iDMC), who will include an independent statistician who is knowledgeable about group sequential designs. The unblinded ECTU statistician would have no other role in the study while it was ongoing. The stopping rules are statistically non-binding (both for efficacy and futility). The iDMC may recommend early stopping of the study if the boundaries are crossed. They would make a recommendation to the independent Trial Steering Committee (TSC) who may or may not endorse that recommendation. Note also that the trial can stop at any time for safety, if there is an excess of mortality in the intervention

group that is considered to generate avoidable harm – and this would be a decision not based on any statistical criterion and taken by the iDMC and endorsed by the TSC.

In terms of timing of the looks, at this stage we intend equally spaced looks driven by the amount of information observed. This is the number of deaths at 30 days. We used the 'gsDesign' routine in R 4.0.1 for Mac for the estimation of the group sequential design. From Stata 15.1, for 90% power at a 5% level of significance using 'power twoproportions' for a 5% reduction from 25% to 20% in 30-day mortality requires 2928 participants (with evaluable data i.e. no loss to follow up). The group sequential design increases this to 3187 participants required. The operating characteristics for this asymmetric two-sided group sequential design using a Hwang-Shih-DeCani spending function [lower bounds (futility) with gamma=-2; upper bound (efficacy) with gamma=-4] are lower bounds [at interim analyses 1, 2, 3, and 4] of z=-0.63, 0.36, 1.20, and 2.01 with nominal p-values of 0.2644, 0.6393, 0.8855 and 0.9780 and lower bound spending of 0.0102, 0.0167, 0.0276, and 0.0455 (total 0.1000); and upper bounds of 3.16, 2.82, 2.44, and 2.01 with nominal p-values of 0.0008, 0.0024, 0.0074, and 0.0220 and upper bound spending of 0.0008, 0.0022, 0.0059 and 0.0161 (total 0.035 1-sided). The R-code generating these thresholds was gsDesign (k=4, test.type=4, alpha=0.025, beta=0.1, n.fix=2928, sfu=sfHSD, sfl= sfHSD). These thresholds are derived for the required number of participants with evaluable 30-day mortality. We allow a 3% rate of missing death status at 30 days, making the overall maximum target sample size 3286.

As indicated, the interim analyses will be scheduled in information time, and we are assuming a 25% and a 20% event rate, so the aggregate event rate is 22.5%. The four equally spaced interim analyses, assuming a maximum sample size of 3187, would be expected to occur at 797, 1594, 2390, and 3187 participants with mature 30-day mortality status – or 179, 359, 538 and 718 deaths. There are two practical issues in the scheduling of the formal interim analyses for the EVIS iDMC to address. First, it takes time to schedule these meetings and it is difficult to orchestrate them to exactly coincide with e.g. the first meeting having exactly 179 deaths, unless they meet sufficiently late that there are more than 179 deaths observed. So, we will fine tune the operating thresholds to adjust to what is actually observed. Second, it is our assumption that the event rates are 20% and 25%, averaging 22.5%. We have included a sample size re-estimation stage after the first 200 have mature 30-day mortality (estimated at 45 deaths; comfortably before the anticipated 1st formal interim analysis estimated at 797 patients with mature 30 day outcome), and if we have cause to re-estimate the sample size because the blinded death rate is substantially different from 22.5%, then we will of course adjust the group sequential operating characteristics as well, in sympathy with this change.

12.7. Participant population

We will recruit a broad range of hospitalised adult patients who have been commenced on emergency intravenous antibiotic treatments for moderate to severe sepsis, ensuring equity of access to participation in research. We will analyse on an intention to treat basis.

12.8. Procedure(s) to account for missing or spurious data

We will run sensitivity type analyses that investigate the robustness of the findings to any patterns of missing data (expected to be negligible for the primary mortality outcome).

12.9. Economic evaluation

We will conduct an economic evaluation to determine the cost-effectiveness of early peripheral vasopressor infusion of norepinephrine compared with usual care, in patients with septic shock. Cost-effectiveness will be estimated, as incremental costs per life year gained and incremental costs per quality-adjusted life year (QALY) gained, over the within-trial and lifetime horizons, from the perspective of the NHS and Personal Social Services (PSS). We will collect data on healthcare resource use (inpatient, outpatients and community care) alongside the trial and through data linkage. Resource use items will be valued using national unit cost schedules. We will also collect data on HRQoL at baseline, 30 days and 6 months using EQ-5D-5L. Health utility scores will be derived from the responses to the EQ-5D using valuations obtained from a general population. This will be used to estimate QALYs using the area-under-curve approach.

For the within trial analysis, we will estimate mean total costs and QALYs by fitting generalised linear models (GLM) to the data and adjusting for potential effect modifiers. The appropriate family for the GLM will be selected based on the results of the modified Park's test. We will explore uncertainty in our estimates using non-parametric bootstrapping and estimate the 95% confidence intervals for mean costs and QALYs for each arm. The resultant distribution of mean costs and QALYs will be presented graphically on the cost-effectiveness plane. Where appropriate, cost-effectiveness will be expressed as incremental cost-effectiveness ratio (ICER) and net monetary benefit (based on a willingness to pay threshold of £20,000). We will use cost-effectiveness acceptability curves to present the uncertainty in the decision regarding the most cost-effective option over a range of willingness to pay thresholds. For the lifetime analysis, we will develop a de novo or adapt an existing decision analytic model that will take into account related long-term health issues such as increased risk of cardiovascular events, renal failures and infection. The model will be informed by data from both the trial and the wider literature, to

estimate costs and QALYs. The final choice of modelling approach will be guided by consultation with the clinical team and PPI representatives, and a full review of existing economic models in this context [69]. All appropriate deterministic and probabilistic sensitivity analyses will be carried out. In particular, we will conduct sensitivity analysis according to the pre-planned subgroups detailed in 12.4 above. We will also conduct sensitivity analysis to explore the impact of missing data in our estimates by using appropriate imputation methods according to the pattern of missingness.

We will develop detailed health economic analysis plan and health economic modelling protocol during the first six months of the trial. The former will focus on the within trial analysis and the latter, on the full economic analysis of the lifetime perspective and will include a conceptual model to guide the analysis.

12.10. Process Evaluation

Implementation fidelity, that is, the degree to which an intervention is delivered as intended, is crucial for accurately interpreting findings of explanatory trials, but is a particular concern for pragmatic complex intervention trials, where intervention adherence is, by design, less tightly controlled by the research team. Drawing on data collected during the internal pilot (e.g. screening logs, case report forms), we will classify sites based on their intervention adherence and, using a deviant case sampling strategy, we will select the two with the highest adherence rates and the two with the lowest. We will employ a rapid ethnographic approach to document how the intervention works 'in the field' and better understand reasons for variance. We will use a range of methods for collecting data: intensive, multi-day observations (~200 hours, including observations of training events), shadowing of respective trial 'champions', and semi-structured interviews with approximately 15-20 clinical and trial staff. Ethnographic data will be captured in the form of in situ field notes and audio-recorded debrief reflections of researchers at the end of each day's observations. To facilitate reflexivity, regular team debriefs will also be held. All audio-recorded material (i.e. interviews, observer debriefs, and team debriefs) will be fully transcribed, anonymised, and imported into the NVivo software for coding and analysis. Data analysis will be based on the constant comparative method and informed by 'sensitising concepts' from the literature (e.g. concepts from organisational theory and implementation science), as well as discussions within the wider trial team.

13. DATA MANAGEMENT

13.1. Data collection

13.1.1. Source Data

ICH GCP defines source data as: “All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial” [80]. In this trial, the location of the majority of the source data will be the hospital’s medical records including subject case notes, laboratory records and ECGs. The source data transcribed into the eCRF from the medical records must be accurate and verifiable. For questionnaires completed by trial participants, the completed questionnaires will be regarded as source data location. In cases where the data is transcribed directly into the eCRF and no other paper or electronic source exists, then the eCRF will be considered the source record. In these cases, the data should be prospectively documented in the medical records to ensure a full record of the trial is available at site.

13.1.2. Completion of eCRF

An eCRF, developed by Edinburgh Clinical Trials Unit (ECTU) will capture all data required to me this protocols requirements. Access to the eCRF will be restricted, via a study specific web portal and only authorised site-specific personnel will be able to make entries to their patient’s data via the web portal. Only those that have been trained and approved will be able to enter or view any data via the web portal. Each site can only see their own patient’s data. Patient consent forms will be stored at the study site in a secure location accessible only to the study team. The Investigator, or his/her designee will be responsible for all entries into the eCRF and will confirm that the data are accurate, complete and verifiable.

13.1.3. Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections- in line with participant consent.

13.1.4. Data Validation

Where it is practical, data will be validated at the point of entry into the eCRF. Any additional data discrepancies will be flagged to the investigator and any data changes will be recorded to maintain a complete audit trail (reason for change, date change made, who made change).

13.1.5. Data Security

The Edinburgh Clinical Trials Unit systems are fully validated and compliant with regulatory requirements and the applicable sponsor related standard operating procedures (SOPs). High volume serves are firewall protected and preventative system maintenance policies are in place to ensure no loss of service or data. Web servers are secured by digital certificates. Data integrity is assured by strictly controlled procedures, including secure data transfer procedures. Data are stored on University of Edinburgh servers with backup performed nightly.

13.1.6. Record Retention

All biological samples from the trial will be retained by the Investigator for 10 years after the end of the trial.

All study documentation will be kept for 20 years from the end of trial.

13.1.7. Archiving

The Trial Master File will be archived by the Sponsor at the end of the trial for a minimum of 15 years.

Archiving of Investigator Site Files will also be for a minimum of 20 years from completion of the trial, and this action will be delegated to the sites in the Clinical Trial Site Agreement that will be put in place between Sponsor and the participating site. Sites will be notified by the Sponsors when the Site File can be archived.

Destruction of site files can only take place with the approval of the Sponsor.

14. MONITORING, AUDIT & INSPECTION

Monitoring will be conducted by NHS Greater Glasgow & Clyde (GG&C) Monitor(s) in accordance with local Standard Operating Procedures. The level, frequency and priorities of monitoring will be based on the outcome of the completed risk assessment, and will be clearly documented in the monitoring plan which will be approved by the NHS GG&C Research Governance Manager or Lead Clinical Trial Monitor. As standard, monitoring visit(s) will cover site file review, review of informed consent forms (ICFs), Source Data Verification (SDV) and Serious Adverse Event (SAE) review as per monitoring plan objectives.

14.1. Protocol Compliance

Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol. Accidental protocol deviations can happen at any time. They must be adequately documented on the relevant forms and reported to the Chief Investigator, Sponsor and GCTU immediately. Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

14.2. Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to affect to a significant degree –

- the safety or physical or mental integrity of the subjects of the trial; or
- the scientific value of the trial

If any of the above occurs then the CI and Sponsor will be notified. The sponsor will notify the appropriate authorities in writing of any serious breach in accordance with their standard operating procedures.

14.3. Data Protection and Patient Confidentiality

All investigators and trial site staff must comply with the requirements of applicable data protection legislation with regards to the collection, storage, processing and disclosure of personal information and will uphold the core principles of such legislation.

Personal information will be collected via the eCRF to enable record linkage to be carried out and to provide electronic access to study monitors to a copy of the signed informed consent document. These data items will be encrypted and only those individuals who require to see these data i.e. the person performing the record linkage and site research team staff or the study monitor, as appropriate, will be able to view them. All electronic data will be held securely in accordance with ISO 27001:2013 at the Edinburgh Clinical Trials Unit. All Centre staff are required to sign confidentiality agreements and to follow Standard Operating Procedures in accordance with Good Clinical Practice and ISO certification.

The trial data managers, statisticians, or any other staff who will perform data related tasks will only be able to access depersonalised data where the participant's identifying information is replaced by a unique study identifier.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1. Research Ethics Committee (REC) review & reports

Before the start of the trial, approval will be sought from a RECs for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters.

Substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the study (it is noted that amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites).

All correspondence with the REC will be retained in the Trial Master File/Investigator Site File.

An annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended (this is the Chief Investigator's responsibility).

The Chief Investigator will notify the REC of the end of the study.

If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination.

Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC

15.2. Peer review

The research plan was reviewed by eight expert reviewers as part of the NIHR grant process.

15.3. Public and Patient Involvement

Our patient and public collaborators have been involved through the development of this trial. The primary research question was identified in partnership with the James Lind Alliance as part of a priority setting exercise [54]. We have partnered with two large organisations – Sepsis Research (FEAT) and UK Sepsis Trust, in addition to working with our previous Sepsis PPI group. These groups, which, include patients and relatives who have experienced sepsis and acute hospital care, provide crucial insights for this trial and its acceptability for NHS patients.

Specifically, PPI members have actively reviewed and co-produced the plain English summary and outcome measures in this study. We have discussed and refined the inclusion criteria and recruitment window in line with their suggestions. Our consent processes have been developed and refined in conjunction with our Sepsis PPI group. Out team also has extensive experience in the design and delivery of interventional studies in Emergency Medicine, Acute Medicine and Critical care [ref] and the consent processes for this study will be based on tried and tested consent processes, developed and accepted by patient groups.

Overall our PPI has five key aims of active involvement in this trial:

1. To contribute to developing the highest quality clinical trial in a challenging acute care environment for patients often lacking capacity;
2. To provide patient, relative and public opinions to help refine and deliver our trial to time and target that will be acceptable to patients and provide the best potential for patient and public benefits;

3. To contribute to developing clear understandable trial documents, materials and results outputs for patients and their relatives (e.g. information sheets for patients and relatives and consent forms);
4. To guide public engagement and understanding of the key aims, objectives and results of this trial and to promote key understanding of sepsis and fluid resuscitation;
5. To develop inclusive clinical and research pathways for patients

The sepsis PPI group will be asked to form a Patient Advisory Group (PAG) for the trial and will be chaired by Mr Craig Stobbo, founding chair of Sepsis Research. The PAG will be established during trial set up and continue throughout the trial period that will ensure active input from patients and public throughout. The PAG will co-ordinate a number of different activities, review patient documentation and provide input to the ethics application and trial design. In addition to the PAG, two PPI representatives will sit as independent members of the TSC. As part of engagement and dissemination, our patient advisory group will work with team members to develop and implement a communication strategy (including multi-media and social networks) for the key aims, objectives and results from the trial. The EVIS trial will be registered with the INVOLVE open-access database which registers research health care projects involving members of the public as partners in the research process. Representatives from our PAG will attend an INVOLVE conference and work towards a PPI-led output/publication from the trial.

15.4. Regulatory Compliance

The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

Before any site can enrol patients into the trial, the Chief Investigator/Principal Investigator or designee will apply for NHS permission from the site's Research & Development (R&D) department.

For any amendment that will potentially affect a site's NHS permission the Chief Investigator/Principal Investigator or designee will confirm with that site's R&D department that NHS permission is ongoing (note that bot substantial amendments and amendments considered to be non-substantial for the purposes of REC may still need to be notified to NHS R&D.

15.5. Indemnity

The Sponsor NHS Greater Glasgow & Clyde is a member of the Clinical Negligence and Other Risks Indemnity Scheme (CNORIS), which provides a range of cover for NHS Boards in Scotland, including for Boards undertaking sponsor responsibility for clinical trials. CNORIS and equivalent schemes in the UK also provide clinical negligence cover for staff. Confirmation of cover can be obtained from

https://clo.scot.nhs.uk/media/16436/cnoris_confirmation_of_cover_2021-22.pdf

15.6. Amendments

Any change in the trial protocol will require an amendment. Any proposed protocol amendments will be initiated by the CI following discussion with the TSC and any required amendment forms will be submitted to the regulatory authority, REC and Sponsor.

The CI and TSC will liaise with the study sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and sponsor representative.

Before the amended protocol can be implemented (or sent to other participating sites) favourable opinion/approval must from the original reviewing REC, MHRA and Sponsor. All protocol versions and their amendments must be notified to the study team and to the data centre.

16. DISSEMINATION POLICY

16.1. Dissemination policy

Our dissemination plan will ensure the findings from this trial influence health services policy to deliver public benefit. Trial progress will be communication through appropriate social media and regular updates to NIHR networks and stakeholder networks. Our team contains expertise in dissemination (Horner) who will lead this aspect. We will publish our trial protocol and statistical analysis plan to ensure transparency in our methodology.

The study will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines and the template for intervention description and replication (TIDieR) checklist

and guide. The study findings will be presented to collaborators/investigators, and subsequently at national and international meetings. Out broad co-applicant group will ensure rapid comprehensive dissemination. We anticipate publishing the main trial results in a major international journal. The Health Economic evaluation will either be published with this report, or in a separate detailed evaluation. We will publish in Open Access journals wherever possible. The process evaluation will be published to ensure the fullest understanding of the trial findings, and provide Open Access data to support translation of findings into practice. These publications will supplement the final report published in the NIHR HTA journal. We will promote the study findings to ensure they are widely dissemination and are included in future guidelines and via professional societies.

With the help of our PPI group, a lay person's summary will be sent to local and national patient support and liaison groups. A report of the study findings will be sent to the INVOLVE registry (an open-access database which registers research health care projects involving members of the public. We will also communicate through press releases to ensure dissemination to the broader public and research participants.

16.2. Authorship eligibility guidelines and any intended use of professional writers

The main results of the study will be compiled, written up and published by the study investigators and others taking responsibility for the study results (e.g. the statistician conducting the final analysis) on behalf of the study investigators.

Authorship should align with the definition for authors and contributors as laid out by the International Committee of medical Journal Editors

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Appendix A – Dosing guidance for peripheral vasopressor infusion

As per guidance in Section 10.3.1~~10.3.1~~, norepinephrine should be prepared and delivered at a concentration of 16 micrograms/ml

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Patient weight*	**Starting dose of 0.05 micrograms / kg / min**			**Dose of 0.10 micrograms / kg / min**			**Maximum dose of 0.15 micrograms / kg / min**	
	Total drug dose per hour (micrograms / hour)	Flow rate per hour ** (ml / hr)		Total drug dose per hour (micrograms / hour)	Flow rate per hour ** (ml / hr)		Total drug dose per hour (micrograms / hour)	Flow rate per hour ** (ml / hr)
40kg	120	7.5		240	15.0		360	22.5
50kg	150	9.4		300	18.8		450	28.1
60kg	180	11.3		360	22.5		540	33.8
70kg	210	13.1		420	26.3		630	39.4
80kg	240	15.0		480	30		720	45.0
90kg	270	16.9		540	33.8		810	50.6
100kg	300	18.8		600	37.5		900	56.3
110kg	330	20.6		660	41.3		990	61.9
120kg***	360	22.5		720	45.0		1080	67.5

* Round to nearest 10 kg for dosing purposes

**Round to nearest whole ml if pumps cannot accommodate 1 decimal place

*** Calculate to exact kg for weights above 120kg using formula in section 10.1.3.2

Dose Up-Titration for PVI

Use local policy if available. The following guide is suggested for sites with no local policy in place.

1. Commence Norepinephrine at 0.05 micrograms/kg/min based on rounded weight in Table above. Aim for MAP of 65mmHg.
2. If MAP remains below 65mmHg within 15 minutes of commencement, increase infusion rate up to a maximum of 0.10 micrograms/kg/min, titrated to MAP of 65mHg
3. Reassess after 15 minutes. If MAP remains below 65mmHg, then increase infusion rate incrementally to a maximum of 0.15 micrograms/kg/min.
4. If MAP remains below 65mmHg after 30 minutes at 0.15 micrograms/kg/min, consider rescue intravenous fluids and discuss with senior medical staff regarding further escalation of treatment

Dose Down-Titration for PVI

If MAP is greater than 80mmHg for a sustained period of greater than 1 hour, consider down titration of PVI. This is the reverse of the up titration process above where the infusion is decreased in increments of 0.05 micrograms / kg/ min with reassessment. For example:

1. If MAP remains above 80mmHg for >1h at 0.15 micrograms/kg/min, decrease infusion rate to 0.1 micrograms/kg/min.
2. Reassess after 30 minutes. If MAP remains above 80mmHg, then decrease infusion rate to 0.05 micrograms/kg/min.
3. Reassess after further 30 minutes. If MAP remains greater than 80mmHg, then titrate infusion rate down incrementally and stop infusion when infusion rate reaches zero
4. If MAP remains above 65 mmHg and below 80 mmHg, adjust the infusion rate based on clinical judgement, if desired.

Appendix B - Definitions of outcome datapoints

1. Clinical outcomes during first 72 hours following randomisation comprise:

Accumulated volume of iv fluid delivered in each arm in the first 6, 12, 24, 48, 72 hours;
Total volume of intravenous fluid delivered intravenously to patient at each time point. This includes any intravenous fluid, including maintenance and medication preparation, prescribed over 100ml volume

Blood lactate at 0, 6, 12, 24 hours;
Blood lactate value taken at timepoints and can include arterial or venous sampling

Organ dysfunction score (SOFA) at 0, 24, 48, 72 hours;
SOFA score calculated at each timepoint

Total dose of Norepinephrine delivered in first 6, 12, 24, 48, 72 hours.
Total dose of intravenous norepinephrine delivered by any route (peripheral or central) at each timepoint

Total dose of other vasopressor delivered at 0, 6,12,24,48, 72 hours.
Total dose of intravenous vasopressor (vasopressin, metaraminol, epinephrine) delivered by any route (peripheral or central) at each timepoint

Proportion of patients who receive vasopressors in the first 6, 12, 24, 48hrs after recruitment to control arm. Proportion of patients recruited to control arm who receive any vasopressor (norepinephrine, vasopressin, metaraminol, epinephrine) at each timepoint

Proportion of patients who require central venous access at 24 and 48 hours - decision to treat based on treating clinician judgement; central venous access is defined as vascular device used to access large, central vein such as internal jugular, subclavian or femoral vein. Insertion of a peripheral long line or midline does not count as central venous access

Proportion of patients developing acute kidney injury during first 72 hours – Acute kidney injury in line with the (p)RIFLE (paediatric Risk, Injury, Failure, Loss, End stage renal disease), AKIN (Acute Kidney Injury Network) or KDIGO (Kidney Disease: Improving Global Outcomes) definitions, by using any of the following criteria:

- a rise in serum creatinine of 26 micromol/litre or greater within 48 hours
- a 50% or greater rise in serum creatinine known or presumed to have occurred within the past 7 days
- a fall in urine output to less than 0.5 ml/kg/hour for more than 6 hours in adults

Proportion of patients receiving parenteral corticosteroid at 24 and 48 hours; defined as new prescription of parenteral corticosteroid

2. Outcomes during 6 month follow-up comprise:

All-cause mortality during index hospital admission and at 90 days,

Length of hospital stay for index admission; index hospital admission ends when the patient is discharged from the facility providing definitive treatment for the episode of sepsis leading to inclusion in the study

Proportion of patients admitted to and length of stay in critical care (level 2 or 3) during index admission; level 2 care is for patients requiring more detailed observation or intervention including support for a single failing organ system or post-operative care and those 'stepping down' from higher levels of care; level 3 care is for patients requiring advanced respiratory support alone or monitoring and support for two or more organ systems. This level includes all complex patients requiring support for multi-organ failure.

Proportion of participants needing renal replacement therapy during index hospital admission - decision to treat based on treating clinician judgement; participants who receive new renal replacement therapy; participants with chronic renal replacement initiated prior to the index admission will not be eligible to meet this endpoint

Proportion of participants needing non-invasive ventilation during index hospital admission – decision to treat based on treating clinician judgement; defined as admissions receiving mask/hood CPAP or mask/hood BiPAP or non-invasive ventilation; admissions receiving CPAP via a tracheostomy

Proportion of participants needing advanced respiratory support (ICNARC definition) – decision to treat based on treating clinician judgement; Patients who receive one or more of the following:

A. Patients who receive invasive mechanical ventilation via endotracheal or tracheostomy tube, except those intubated solely for a procedure and extubated within 24 hours

B. BiPAP (bilevel positive airway pressure) applied via a trans-laryngeal tracheal tube or applied via a tracheostomy

C. CPAP (continuous positive airway pressure) via a translaryngeal tune of applied via a tracheostomy

D. extracorporeal respiratory support

Readmission in first 30 days after discharge;

3. Patient centred outcome:

organ support free days at 30 days; defined as the number of ventilator, renal replacement and vasopressor-free days up to day 30, defined as days from study drug initiation to 30 days thereafter, during which the patient was alive, free of mechanical ventilation, free of treatment with intravenous vasopressors including study drug, and free of renal replacement therapy. Any patient who died within 30 days was assigned zero days. After mechanical ventilation, renal replacement therapy and vasopressors were weaned, if either were restarted before day 30 for more than 60 minutes within a 24-hour period, the intervening days were not counted as being free of ventilator or vasopressor support. Use of mechanical ventilation or vasopressors during and up to 3 hours after surgery was exempt.

4. Protocol Adherence:

Proportion of patients who have PVI discontinued for non-clinical reasons after recruitment to intervention arm;

Non clinical reasons comprise:

- Patient withdrawal from treatment
- Representative withdrawal from treatment
- Treating clinician withdrawal from treatment
- Norepinephrine not available
- Infusion device not available
- Adverse event

- Staff too busy
- Other - specify

5. Safety

Proportion of patients developing vasopressor extravasation during first 72 hours – recorded on CRF and graded using the ordinal NIH scale. Values are from 0 to 4. The highest grade achieved in any category during the 72 hours should be recorded. If no signs of extravasation at 72 hours, the extravasation grade should be recorded as zero.

Grade	0	1	2	3	4
Colour of skin	Normal	Pink	Red	Blanched	Blackened
Integrity of skin	Intact	Blistered	Superficial skin loss	Tissue loss exposing subcutaneous tissue	Tissue loss exposing muscle / bone with a deep crater or necrosis
Oedema	Absent	Non-pitting	Pitting		
Mobility of limb	Full	Slightly limited	Very limited	Immobile	

Proportion of patients developing pulmonary oedema during index admission; defined as any new prescription of intravenous diuretic therapy or radiological diagnosis

HRQoL – baseline. Patient recall of status 7 days prior to admission

Appendix E – SOFA score

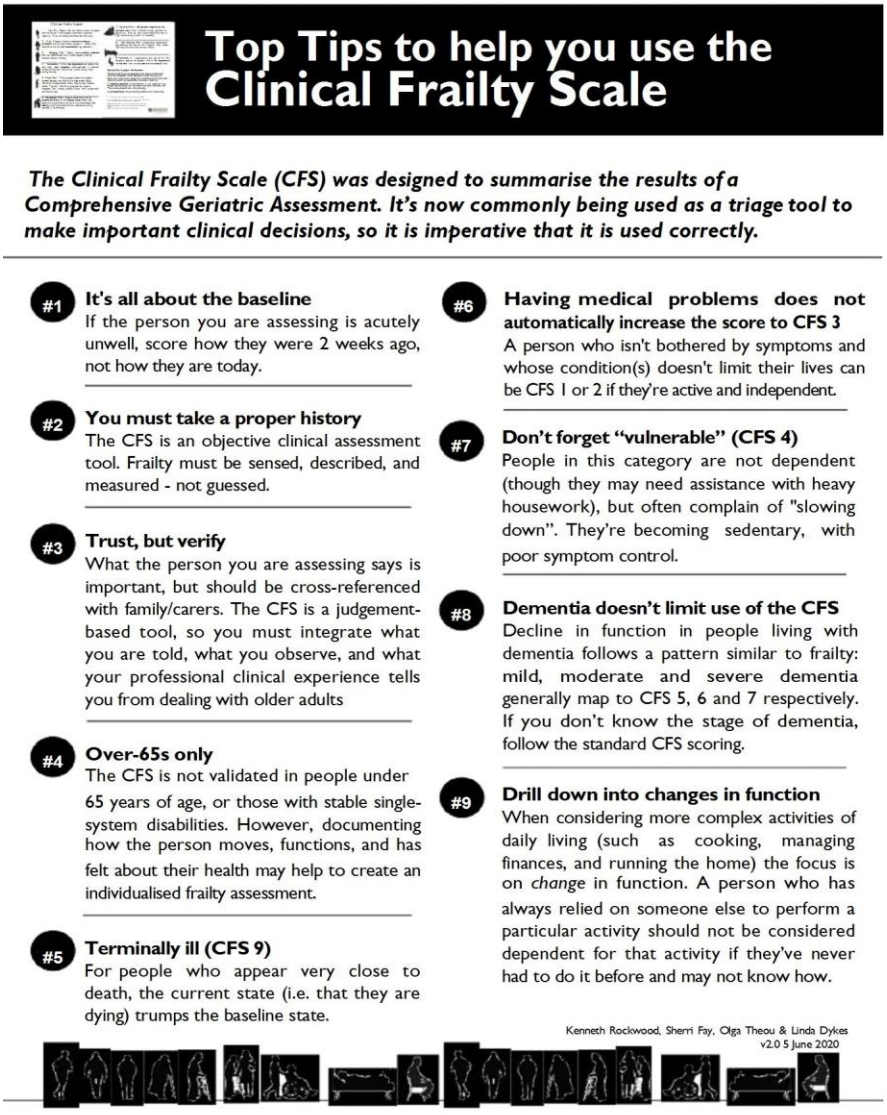
Table 1. Sequential Organ Failure Assessment Score

Variables	SOFA Score				
	0	1	2	3	4
Respiratory	PaO_2/FiO_2: > 400 SpO_2/FiO_2: > 302	PaO_2/FiO_2: < 400 SpO_2/FiO_2: < 302	PaO_2/FiO_2: < 300 SpO_2/FiO_2: < 221	PaO_2/FiO_2: < 200 SpO_2/FiO_2: < 142	PaO_2/FiO_2: < 100 SpO_2/FiO_2: < 67
Cardiovascular (doses in mcg/kg/min)	MAP ≥ 70 mm Hg	MAP ≥ 70 mm Hg	Dopamine ≤ 5 or ANY dobutamine	Dopamine > 5 Norepinephrine ≤ 0.1 Phenylephrine ≤ 0.8	Dopamine >15 or Norepinephrine > 0.1 Phenylephrine > 0.8
Liver (bilirubin, mg/dL)	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12
Renal (creatinine, mg/dL)	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9	> 5.0
Coagulation (platelets x $10^3/mm^3$)	≥ 150	< 150	< 100	< 50	< 20
Neurologic (GCS score)	15	13-14	10-12	6-9	< 6

According to Sepsis-3, a new (or presumed new) increase in SOFA score above baseline in the presence of infection makes the diagnosis of sepsis. Increasing SOFA scores are associated with incremental increases in mortality.

Abbreviations: GCS, Glasgow coma scale; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; PaO_2, arterial oxygen pressure; SOFA, sequential organ failure assessment (score); SpO_2, oxygen saturation.

Appendix G – Clinical Frailty Score



Top Tips to help you use the Clinical Frailty Scale

The Clinical Frailty Scale (CFS) was designed to summarise the results of a Comprehensive Geriatric Assessment. It's now commonly being used as a triage tool to make important clinical decisions, so it is imperative that it is used correctly.

#1 It's all about the baseline
If the person you are assessing is acutely unwell, score how they were 2 weeks ago, not how they are today.

#2 You must take a proper history
The CFS is an objective clinical assessment tool. Frailty must be sensed, described, and measured - not guessed.

#3 Trust, but verify
What the person you are assessing says is important, but should be cross-referenced with family/carers. The CFS is a judgement-based tool, so you must integrate what you are told, what you observe, and what your professional clinical experience tells you from dealing with older adults

#4 Over-65s only
The CFS is not validated in people under 65 years of age, or those with stable single-system disabilities. However, documenting how the person moves, functions, and has felt about their health may help to create an individualised frailty assessment.

#5 Terminally ill (CFS 9)
For people who appear very close to death, the current state (i.e. that they are dying) trumps the baseline state.

#6 Having medical problems does not automatically increase the score to CFS 3
A person who isn't bothered by symptoms and whose condition(s) doesn't limit their lives can be CFS 1 or 2 if they're active and independent.

#7 Don't forget "vulnerable" (CFS 4)
People in this category are not dependent (though they may need assistance with heavy housework), but often complain of "slowing down". They're becoming sedentary, with poor symptom control.

#8 Dementia doesn't limit use of the CFS
Decline in function in people living with dementia follows a pattern similar to frailty: mild, moderate and severe dementia generally map to CFS 5, 6 and 7 respectively. If you don't know the stage of dementia, follow the standard CFS scoring.

#9 Drill down into changes in function
When considering more complex activities of daily living (such as cooking, managing finances, and running the home) the focus is on *change* in function. A person who has always relied on someone else to perform a particular activity should not be considered dependent for that activity if they've never had to do it before and may not know how.

Kenneth Rockwood, Sherri Fay, Olga Theou & Linda Dykes
v2.0 5 June 2020

Clinical Frailty Scale*

1 Very Fit – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2 Well – People who have **no active disease symptoms** but are less fit than category 1. Often, they exercise or are very **active occasionally**, e.g. seasonally.

3 Managing Well – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 Vulnerable – While **not dependent** on others for daily help, often **symptoms limit activities.** A common complaint is being "slowed up", and/or being tired during the day.

5 Mildly Frail – These people often have **more evident slowing,** and need help in **high order IADLs** (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.

6 Moderately Frail – People need help with **all outside activities** and with **keeping house**. Inside, they often have problems with stairs and need **help with bathing** and might need minimal assistance (cuing, standby) with dressing.

7 Severely Frail – **Completely dependent for personal care**, from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8 Very Severely Frail – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. Terminally Ill - Approaching the end of life. This category applies to people with **a life expectancy <6 months**, who are **not otherwise evidently frail.**

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

* 1. Canadian Study on Health & Aging, Revised 2008.
2. K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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Appendix H – Amendment History

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
NSA04	V1.3	08/11/2022	Emma Moody Hannah Greenwood	Updates to sponsor and PMU contact Removal of research bloods. Clarifications on consent.

List details of all protocol amendments here whenever a new version of the protocol is produced. Protocol amendments must be submitted to the Sponsor for approval prior to submission to the REC committee or MHRA.