EVIS IMP Manual for Sites

Study Website
www.evis.scot.nhs.uk
For Healthcare Professional Use Only

SCAN ME

Study title: EVIS - EARLY VASOPRESSORS IN SEPSIS

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Sponsor: NHS Greater Glasgow & Clyde

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ABBREVIATIONS

CI	Chief Investigator
CTU	Clinical Trials Unit
GCP	Good Clinical Practice
IMPs	Investigational Medicinal Products
IV	Intravenous
MAP	Mean Arterial Pressure
NHS GG&C	NHS Greater Glasgow & Clyde
PM	Project Manager
PVI	Peripheral Vasopressor Infusion
PVC	Peripheral Venous Catheter
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure

Section 1:Study background and summary

1.1 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. Those patients that survive often suffer long term reductions in patient centred outcomes, with reduced quality of life and functional status.

Current guidelines highlight the importance of early fluid resuscitation, but the association of early fluid therapy with improved outcomes is unclear. In the resuscitation phase, current practice is to give intravenous (IV) fluid and intermittent vasopressor boluses if required, before, commencing continuous vasopressor infusion via a central venous line in Intensive Care (ICU) if necessary. Early continuous peripheral vasopressor infusion (PVI) is not routine practice in the UK.

1.2 Study summary

The EVIS study is a phase 3, open label, two-arm multi-centre, pragmatic parallel group randomised trial. The aim is to recruit a maximum of 1005 participants from Emergency Departments and Acute Assessment Units across approximately 30 UK sites. Participants will be randomised 1:1 to:

- **Intervention arm: Peripheral Vasopressor Infusion (PVI) arm**
  Participants will receive early peripheral vasopressor infusion (within 12 hours of admission) with norepinephrine targeted to MAP ≥ 65 mmHg

OR

- **Standard Care (Control) arm**
  Participants will receive standard care as per current UK national guidelines on sepsis with fluid resuscitation using balanced crystalloids.

The primary objective of the EVIS study is to determine whether early PVI (within 12 hours of admission) targeted to achieve a MAP ≥ 65 mmHg improves clinical effectiveness (Days Alive and Out of Hospital at 90 days) in hospitalised adult patients with septic shock compared with usual care, in the first 48 hours.

See current protocol for full details.

1.3 Investigational medicinal products

The following are IMPs for the purposes of the EVIS study:

- **Intervention arm:** Norepinephrine 1mg/ml Concentrate for solution for infusion
- **Standard care (Control) arm:**
  - Compound sodium lactate solution for infusion (also known as Ringers Lactate Solution and Hartmann's Solution for Infusion)
  - Plasma-lyte® 148 (pH 7.4) solution for infusion

  Note: When the above fluids are administered in the intervention arm for fluid maintenance purposes rather than resuscitation they are not considered as IMPs.

Section 2:Overview of IMP related roles and responsibilities

2.1 Site pharmacy responsibilities

Pharmacy staff will be responsible for ensuring:

- IMPs are procured as per usual NHS supply mechanisms and are available in clinical areas which will care for patients recruited to the EVIS study. It is anticipated the IMPs will already be routinely available
- Liaise with sponsor if necessary regarding potential quality issues such as temperature deviations, defects, and recall which may impact on patient safety
- Provide at a minimum, pharmacist oversight for the EVIS study at site

2.2 Research team responsibilities

- Participant consent and randomisation
- Prescribe study IMP
- Through completion of the current version of the Source Data Plan, agree with the Project Manager (PM) and Study Monitor how IMP and other medicines related administration data will be collected at site. Any changes must be agreed with the Sponsor team prior to implementation
- Support treating clinician and staff who will prepare and administer study IMPs

Section 3:EVIS study information for pharmacy site staff

3.1 Pharmacy oversight, and training for pharmacy staff

From a sponsor perspective, there is no requirement for pharmacy clinical trial services to provide routine services such as IMP receipt, dispensing or supply as it is expected that all IMPs will be sourced via routine NHS supply routes and routinely held as stock items in clinical areas where EVIS participants will be managed.

As part of the risk mitigations associated with the EVIS study the sponsor will require at a minimum, an appropriate pharmacist to be included in the site delegation log from the purpose of pharmacy oversight of the EVIS study at the local site. It is at site discretion as to the pharmacist's speciality e.g. clinical trials or clinical pharmacist. Mandatory training requirements are detailed on the EVIS Training Matrix which can found on the EVIS website. The site pharmacist(s) and technician(s) who will be included on the delegation log will be invited to the site initiation meeting. Thereafter training may be cascaded locally as per local arrangements. Pharmacy staff on the site delegation log will be included in sponsor communications such as the opening of the site to recruitment and other updates in line with the sponsor SOPs. Circulation of approved protocol amendments is a local site responsibility.

Formal site initiation training for other pharmacy staff who will not be on the delegation log will not be provided but a training module for awareness purposes can be found on the EVIS website www.evis.scot.nhs.uk.

3.2 Provision and maintenance of an EVIS pharmacy site file

A pharmacy site file will not be provided by sponsor but sites should follow their own local SOP requirements as to preparation and maintenance of a pharmacy site file for the EVIS study. The current versions of documents such as the protocol and training videos for the EVIS study may be accessed from the study website at www.evis.scot.nhs.uk.

3.3 Monitoring arrangements for pharmacy sites

Study Monitors are not expected to perform any pharmacy site visits for the duration of the EVIS study.

3.4 Intervention arm: Supplies of norepinephrine for peripheral administration

There are no study specific supplies of norepinephrine. Usual hospital stocks of Norepinephrine 1mg/ml Concentrate for Solution for Infusion should be used. There is no requirement for pharmacy to ring-fence study stock for use in the EVIS study and supplies from any GB/UK licensed brand/manufacturer can be used interchangeably during the study. No reimbursement will be provided. It is expected that supplies of norepinephrine 1mg/ml concentrate for solution for infusion will be routinely held in areas where EVIS participants will be managed but pharmacy staff should confirm this with the relevant clinical areas.

IMPORTANT INFORMATION
Only **Norepinephrine 1mg/ml Concentrate for solution for infusion** can be used to prepare norepinephrine infusions for peripheral administration in participants randomised to the intervention arm (early peripheral vasopressor administration) of the EVIS study.

3.5 Standard care (Control) arm: Supplies of balanced crystalloids

The following balanced crystalloids are permitted for use in the study:

- Compound sodium lactate solution for infusion (also known as Ringers Lactate Solution and Hartmann's Solution for Infusion)
- Plasma-Lyte® 148 (pH 7.4) solution for infusion

There are no study specific supplies of balanced crystalloids for use in the study. Usual hospital stocks should be used. There is no requirement for pharmacy to ring-fence supplies for use in the EVIS study. Supplies from any UK/GB licensed brand/manufacturer can be used interchangeably during the study. No reimbursement will be provided.

Other balanced crystalloids are **not** permitted for use as IMPs in the EVIS study. Please contact the sponsor/PM if further clarification is required.

3.6 IMP labelling requirements

There are no mandated/trial specific labelling requirements. Sites must label prepared IMPs in accordance with local requirements. Labels are available for use in the intervention and control groups (figures 2 and 5 respectively) to help raise awareness that the participant is participating in the EVIS study, but use is not mandated.

3.7 Temperature monitoring requirements

All IMPs in the EVIS study will come from usual hospital stock and should be stored in accordance with the relevant Summary of Product Characteristics (SmPC). The sponsor has completed a risk assessment and does not require evidence of on-going temperature monitoring for any of the IMPs, but sites should comply with any local temperature monitoring requirements.

3.8 Storage of IMPs in clinical areas

Treatment of sepsis is a clinical emergency and EVIS IMPs should be immediately accessible within clinical areas where EVIS patients will be managed. We anticipate that IMPs will be routinely held in these clinical areas. Sites should consider stock requirements and also consider if any additional mitigations are necessary if clinical areas would not routinely hold either the permitted balanced crystalloids (standard care arm) or norepinephrine 1mg/ml concentrate for solution for infusion required for the intervention arm. Please inform the PM if IMPs are not routinely held in the relevant clinical areas.

3.9 Randomisation

Participants will be randomised via the study web-based randomisation service. Treatment allocation will not be routinely communicated to pharmacy site staff unless required as part of other delegated duties.

3.10 EVIS prescribing requirements

Intervention arm: Norepinephrine infusion must be prescribed by those delegated the responsibility by the local principal investigator on the site delegation log. Further information is provided in section 5 below.

Control arm: The initial prescription for balanced crystalloid fluids must be prescribed by staff delegated this responsibility by the local principal investigator on the site delegation log.

Pharmacy staff are asked as part of study set-up to consider how hospital electronic prescribing systems can be utilised to support prescribing in EVIS. See also sections 5 and 6.

3.11 IMP accountability requirements

There are no additional traceability requirements for EVIS IMP beyond usual processes in place at site. Batch and expiry information for the study IMPs will only be recorded where these are routinely recorded on local site documentation.

Further information on documentation requirements is provided in section 4.4.

3.12 Temperature deviations, product defects, complaints and recall

Any temperature deviations, defects or recall should be dealt with via standard local site SOPs. Any recall or drug alert initiated by the Marketing Authorisation Holder (MAH) or Medicines and Healthcare product Regulatory Agency (MHRA) for any of the study IMPs must be complied with in full. The sponsor must be promptly informed where a reported temperature deviation, defect or recall that has the potential to impact on patient safety.

3.13 Disposal of IMPs

All IMPs should be disposed of in line with routine arrangements at site for disposal of pharmaceuticals.

Section 4:Site support for EVIS study

4.1 Review of local protocols for noradrenaline administration

Around the UK, norepinephrine is routinely administered via a central venous line however the typical norepinephrine concentrations for infusion via a central line are higher than would be tolerated for peripheral administration. Therefore as recommended by the Intensive Care Society, the infusion rate for central and peripheral administration are likely to differ to deliver the same dose. The expectation is that sites will review their local processes around administration of norepinephrine as part of site set-up and risk assess the potential impact of the EVIS study particularly given the potential for norepinephrine to be administered for similar clinical indications but via different routes (central versus peripheral IV infusion). The Principal Investigator and wider research team should work together to consider what risk mitigations/additional training might be required locally including for treating clinicians (see section 6) and staff preparing and administering norepinephrine peripherally.

4.2 EVIS resources for sites

The following resources have been prepared with a view to supporting site staff who will perform activities which although unique to EVIS are limited and within their normal remit and clinical responsibility of staff:

- **Clinical information sheets:** These contain key information for treating clinicians on permitted rescue and maintenance treatments and also for nursing staff on preparation and administration of peripheral norepinephrine
- **Template Peripheral Norepinephrine Preparation and Administration record (optional):** this document is intended to be used near patient to highlight that a patient is enrolled in EVIS and to provide summary information on preparation and administration It is intended to facilitate the recording of dose changes and hourly PVC checks as well as routine infusion checks performed as part of usual practice.
- **Training modules:** A number of IMP related training modules are provided on the EVIS website covering areas such as awareness of GCP, IMP Prescribing and IMP Preparation and Administration. Other training modules cover topics such as monitoring and consent.

- **Training Matrix:** A training matrix is provided covering the mandatory training for staff delegated study specific responsibilities and recommended training for other staff by staff group.
- **Labels (optional):** For use on paper infusion charts and/or prepared infusions to highlight to those involved in their care EVIS participants and their randomisation.

4.3 EVIS website

The EVIS study website contains multiple resources including study documentation and training modules. To facilitate access, the QRS code is included on many of the study documents. Please note, the website is intended for healthcare professional use and the address must not be shared with study participants.

Study Website: www.evis.scot.nhs.uk

4.4 Sponsor requirements for local set-up for EVIS study

In additional to meeting usual site initiation requirements the sponsor will also require the following:

- **EVIS Local Risk Awareness form:** The Principal Investigator must complete this form as part of the site initiation process. It details potential risks and variations to usual clinical care that could occur in practice with the EVIS study. Whilst Sponsor/CI will review and provide advice/suggestions where they can, ultimately the site need to consider the potential risk implications of EVIS at their site.
- **Pharmacist oversight:** The Sponsor requires that a pharmacist(s) is included in the site delegation log – this may be for example a clinical trials pharmacist or a clinical pharmacist.

4.5 Source documentation for IMP related data

As part of site set-up/initiation the Study Monitor will review the Source Data Plan which includes the site's preference for IMP related data collection. EVIS is a pragmatic study and much of the IMP related data may be captured from the infusion chart and fluid balance chart(s) used at site particularly for control arm patients. A template **Peripheral Norepinephrine Preparation and Administration Record** is available that sites can amend to reflect local site requirements and incorporates EVIS specific information such as the requirement for hourly PVC checks. More detailed information is provided in the EVIS Source Data Plan.

When completing the Source Data Plan for site, please consider how collection of data may differ depending on the area of care. For example documentation to record the fluid balance and medicine administration records may be collected differently in the Emergency Department compared to a High Dependency Area. Furthermore data may be collected using paper or electronic systems. The final site EVIS Source Data Plan must be comprehensive and cover the origins of source data for all the expected clinical areas that will routinely care for EVIS participants.

Once the initial Source Data Plan is agreed by the Study Monitor, a copy will be returned to site for retention in the investigator site file. The Source Data Plan is a living document. Please contact the Study Monitor to discuss any proposed/planned changes in source.

Section 5:Prescribing EVIS IMPs

5.1 Training requirement for EVIS prescribers

Mandatory training requirements for EVIS prescribers are detailed in the **EVIS Training Matrix** which can be found on the EVIS study website. Mandatory module training must be documented on the **EVIS Module Training Log**.

5.2 Initial prescription of EVIS IMPs (Intervention & Control Arm)

Only medically qualified or non-medical prescribers who have completed the relevant training and delegated this responsibility by the Principal Investigator on the site delegation log may initiate treatment and write the prescription for the intervention (peripheral norepinephrine) and control (permitted balanced crystalloid) IMPs.

5.3 Detailed information on peripheral norepinephrine prescribing

Peripheral norepinephrine must be prescribed by investigators who are trained and delegated this responsibility on the site delegation log. Guidance on dose-up and down titrations for peripheral norepinephrine is provided in protocol Appendix A but sites may use local practice if they choose.

Patients in the intervention arm should not receive any other peripheral vasopressor infusion during the 48 hours study period. In the event a central line is required, it is acknowledged that participants may receive additional bolus or short infusion of peripheral vasopressor at a higher dose as clinically required until the central line can be sited. Peripheral vasopressor administration after the decision is made to place a central line is considered 'off-trial'. Data on vasopressor administration must still be recorded for the remainder of the 48 hour treatment period. See the current protocol for further information.

At a practical level it is recognised that due to the emergency nature of the EVIS trial a delegated prescriber may not always be available. In order to minimise the potential for treatment delays and prescribing errors that may occur with untrained staff, sites must consider how this will be managed. As permitted by local processes, the norepinephrine prescription should be written so as to allow dosing as per protocol requirements taking into consideration that norepinephrine treatment may be temporarily stopped and restarted at any point within the 48 hour treatment. Where possible, the prescription should not be discontinued or 'scored off' until either the end of the study treatment period or if permanent discontinuation is required for another reason. Treatment can be reinstated as per the study protocol in the following situations:

- If the target MAP ≥ 65 mmHg is achieved immediately post-randomisation, the norepinephrine infusion should still be prescribed, but the rate set initially at zero with rate increased at any point during the subsequent 48 hour study period to maintain target MAP ≥ 65 mmHg.
- Should the target MAP be achieved within the 48 hour treatment period and the participant weaned off norepinephrine the rate should be reduced to zero with the potential for the rate to be increased as necessary to achieve target MAP.

5.4 Subsequent prescription of permitted balanced crystalloids

It is recognised that due to the emergency nature of the EVIS trial and the potential training burden, a delegated prescriber may not always be available. In the control arm balanced crystalloids are used in accordance with standard care and therefore subsequent prescriptions for the permitted balanced crystalloid IMPs may be prescribed by treating clinicians as per usual practice.

5.5 Prescribing EVIS IMPs across different clinical areas

The rapidly changing clinical nature of sepsis means that participants may be treated in a more than one clinical area during the 48 hour study period. Based on experience, prescribing of EVIS IMPs can be overlooked when participants are transferred from one setting to another particularly when prescribing systems differ between clinical areas eg. paper prescription versus electronic prescribing system. Taking into consideration the caveats above around need to ensure that only trained staff prescribe EVIS study medicines, if patients are transferred from one clinical area to another with different prescribing systems then it is acceptable for IMP prescription to be transcribed by someone other than a trained investigator. However, this should be clearly documented and performed in accordance with local procedures. It is important that supporting

documents such as the relevant EVIS Clinical Information Sheets are always transferred with the patient so that receiving sites have access to relevant information.

5.6 Good practice when prescribing EVIS IMPs

IMPs must be prescribed in accordance with local requirements and it must be clear on the prescription the IMPs are being prescribed for use in the EVIS study. Good prescribing habits are particularly important for peripheral norepinephrine infusion and should include information such as:

- **IMP** use local nomenclature for norepinephrine (see 5.7 below)
- **Route of administration:** must be clearly prescribed as peripheral IV
- **Drug concentration**
- **Diluent**
- **Dose:** this may be a range/flow rate depending on local requirement
- **Study identifiers:** For example, short study title, EudraCT Number
- **EVIS participant number**

The choice of diluent (5% glucose or 0.9% sodium chloride) used for peripheral norepinephrine is at local discretion.

Stickers are available that may be applied to the infusion chart to highlight that participants are enrolled in the EVIS study where these are permitted locally (see figures 2 and 5 below)

IMPORTANT INFORMATION
The research team and prescribers must ensure there are clear communication pathways at site so that participants in the EVIS study can be clearly identified to all relevant staff involved in their care regardless of their treatment allocation.

5.7 Access to clinical information on IMPs

Site staff should refer to the relevant Summary of Product Characteristics (SmPC) for preparations used at site for up-to-date clinical information on study IMPs. These are often available from emc (https://www.medicines.org.uk/emc/).

5.8 Norepinephrine nomenclature

The EVIS protocol and supporting documents refers principally to norepinephrine which is the approved INN (International Non-proprietary Name). Noradrenaline and norepinephrine and both recognised as British Approved Names (BAN); that is the non-proprietary or generic name for an active pharmaceutical ingredient for use in the UK. The BNF uses both terms. Individual sites should consider which BAN/drug name will be routinely used at site.

Noradrenaline preparations on the UK market may be described as either noradrenaline base or noradrenaline acid tartrate. 1mg noradrenaline (base) is equivalent to 2mg noradrenaline acid tartrate. All dose and administration information in the EVIS protocol and associated documentation is expressed solely in terms of norepinephrine (noradrenaline) base.

Section 6: Treating clinicians in EVIS

6.1 Training requirements for EVIS Treating Clinicians

The clinical decisions made by treating clinicians are within the usual remit/practice. Whilst training is not mandated, recommendations for training modules are listed in the current EVIS Training Matrix which can be found on the training tab of the EVIS website. Training should be documented on the **EVIS Module Training Log**.

6.2 Prescribing of maintenance and rescue interventions for EVIS participants

The EVIS protocol details use of maintenance and rescue treatments which may be implemented by a treating clinician. These are medical staff who will be responsible for providing clinical care to EVIS participants as part of their routine practice but who are not specifically trained in the protocol nor are they delegated specific responsibilities on the EVIS site delegation log. The clinical decisions/treatment interventions by treating clinicians are essentially in line with usual management of patients with sepsis. Detailed information is provided in the protocol on permitted maintenance and rescue interventions and these are also summarised in the Current Information Sheets for Clinical Staff which are provided for the standard care and intervention arms.

6.3 EVIS prescribing support materials

Treatment of sepsis is a clinical emergency and a pragmatic approach is necessary. **EVIS: Clinical Information Sheets** have been prepared for the control and intervention groups which contain key summary information prescribing of maintenance and rescue treatments permitted by the EVIS protocol. These will be inserted into the participant's care record at the time of randomisation by the research team and are also available to download from the EVIS study website.

Section 7: Peripheral norepinephrine: preparation & administration

7.1 Training requirements for preparation and administration of peripheral norepinephrine

As per the protocol, preparation of norepinephrine for peripheral administration may be undertaken by any staff in the clinical area provided they are recognised/accredited as IV trained by their local Trust/Board and are routinely involved in the preparation and administration of vasopressors such as norepinephrine as part of their usual duties. There is no sponsor dictated minimum training requirements for those staff whose role is limited to preparation and administration. However recommended training is detailed in the current version of the **EVIS Training Matrix** which is available on the EVIS website. Whilst staff are not required to undertake study-specific training, we would encourage staff to complete the relevant training modules on the EVIS website. Training should be documented on the **EVIS Module Training Log**.

Local requirements for a second preparation check of the prepared infusion should be followed.

7.2 Preparation of norepinephrine 16 microgram/ml infusion for peripheral administration

Sites should adhere to local policies/practices regarding best practice for a near patient preparation of an infusion for peripheral administration. The following preparation method is recommended.

IMPORTANT INFORMATION
With Sponsor approval, sites may use a norepinephrine solution with a different concentration where this is their usual policy. Sites affected must use local guidance/documentation for information on preparation and flow rates. Please contact the local research team in the first instance if there are any queries.

Supplies

To prepare a 250ml infusion containing norepinephrine 16 micrograms/ml

- 1 x **4ml** ampoule norepinephrine 1mg/ml concentrate for solution for infusion
- 1 x 250ml infusion bag of 5% glucose or 0.9% sodium chloride

To prepare a 500ml infusion containing norepinephrine 16 micrograms/ml

- 1 x 8ml ampoule norepinephrine 1mg/ml concentrate for solution for infusion
- 1 x 500ml infusion bag of 5% glucose or 0.9% sodium chloride

PLUS

- Other equipment such as needles, alcohol swabs and filter needles (for withdrawal from glass ampoules) as per local practice

Personal protective equipment (PPE)

- standard PPE for preparation of parenteral medicine

Example calculation

Each 4ml ampoule contains 4mg of norepinephrine.
When added to 246ml diluent, the resulting solution contains 4mg norepinephrine in 250ml. This is equivalent to 4000 micrograms of norepinephrine in 250ml
= 16 micrograms/1ml

Method

Using appropriate aseptic technique throughout:

To prepare a 250ml infusion containing norepinephrine 16 micrograms/ml

1. Withdraw 4ml from a 250ml infusion bag and discard.
2. Withdraw the contents of one ampoule (4ml) of norepinephrine 1mg/1ml concentrate for solution for infusion into a suitable syringe.
3. Add the contents of the syringe (4ml) to the infusion bag

To prepare a 500ml infusion containing norepinephrine 16 micrograms/ml

1. Withdraw 8ml from a 500ml infusion bag and discard.
2. Withdraw the contents of one ampoule (8ml) of norepinephrine 1mg/1ml concentrate for solution for infusion into a suitable syringe.
3. Add the contents of the syringe (8ml) to the infusion bag

THEN

4. Mix thoroughly and inspect. Do not use the solution for infusion if it is discoloured (eg. pink, dark yellow or brown or contains a precipitate.
5. Label infusion bag as per standard practice.
   See figure 1 for an example additive label.
6. Add an EVIS study sticker (Optional - Figure 2)
7. Obtain a second check as per local procedures

Figure 1: Example additive label for 250ml infusion containing norepinephrine 16 micrograms/ml in glucose 5%

<table>
<tr><th colspan="4">DRUGS ADDED TO THIS INFUSION</th></tr>
<tr><td colspan="2">PATIENT: Patient Evis</td><td colspan="2">Hospital No: 0512741111</td></tr>
<tr><td colspan="2">WARD: 4</td><td colspan="2">ROUTE: Peripheral IV Infusion</td></tr>
<tr><td>DRUG
Norepinephrine
DILUENT
5% Glucose</td><td>AMOUNT
4mg

250ml</td><td>BATCH No.
CXY1083

INF00789</td><td>PREP'D BY
A. Person
CHECKED BY
B. Person</td></tr>
<tr><td colspan="2">DATE/TIME PREP'D
14/May/2022
10:30</td><td colspan="2">EXP. DATE/TIME
14/May/2022
22:30</td></tr>
<tr><td colspan="4">DISCONTINUE IF CLOUDINESS OR PRECIPITATE DEVELOPS.</td></tr>
</table>

Figure 2: EVIS sticker for INTEVENTION arm

Notes:

- EVIS stickers are available from sponsor and are intended to raise awareness that a patient/medicine is being administered as part of a clinical trial. Use of EVIS sticker on the infusion and/or infusion chart is at discretion of each study site.
- The expiry date assigned to the prepared infusion should be in line with the relevant SmPC and local site requirements.

IMPORTANT INFORMATION
1. Norepinephrine solutions for peripheral administration in EVIS participants must be prepared by dilution of one 4ml or 8ml vial containing **Norepinephrine (Noradrenaline) 1 mg/ml concentrate for solution for infusion** in 0.9% sodium chloride injection or 5% glucose to provide a final concentration of norepinephrine 16 microgram/ml. Do not use any other norepinephrine presentation such as ready-diluted solutions. 2. Norepinephrine peripheral infusions for peripheral administration **should** be prepared as a 16 microgram/ml infusion.

7.3 Peripheral norepinephrine dose and infusion rates for participants ≤ 120kg

Norepinephrine infusion will commence at a dose of 0.05 micrograms/kg/minute with a maximum dose of 0.15 micrograms/kg/minute. Figure 2 details the minimum and maximum dose and flow rate per hour for a norepinephrine peripheral administration based on an infusion concentration of norepinephrine of 16 micrograms/ml for participants weighing less than or equal to 120kg.

Figure 3: Starting and maximum dose and flow rate per hour for peripheral infusion of norepinephrine 16 micrograms/ml

Patient weight*	Starting dose of 0.05 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)
40kg	120	7.5	360	22.5
50kg	150	9.4	450	28.1
60kg	180	11.3	540	33.8
70kg	210	13.1	630	39.4
80kg	240	15.0	720	45.0
90kg	270	16.9	810	50.6
100kg	300	18.8	900	56.3
110kg	330	20.6	990	61.9
120kg***	360	22.5	1080	67.5

Key *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 (see section 7.4)

7.4 Peripheral norepinephrine dose and infusion rate calculation for participants >120kg

The infusion rate calculation for participants weighing greater than 120kg and a worked example are given in figures 3 and 4 respectively.

When calculating the peripheral noradrenaline infusion rate for patients over 120kg please remember the following points:

- Calculate using the kilogram body weight. Do not round or use IBW etc. Estimated weights are acceptable as per the protocol
- It's recommended that both the starting and maximum infusion rate are calculated for individual patients and documented by the delegated prescriber.

Figure 4: Infusion rate calculation for peripheral norepinephrine administration for participants over 120kg

Calculation
Step 1: Calculate the dose (micrograms/minute) = Starting dose (microgram/kg/min) x Patient Weight (kg) **Step 2: Convert dose from microgram/minute) to micrograms/<u>hour</u>** = Dose (micrograms/minute) x 60 **Step 3: Calculate the infusion rate (ml/hour)** $= \frac{\text{Dose (micrograms/hour)}}{\text{Concentration of norephinepherine solution (16 micrograms/ml)}}$

Figure 5: Worked example for 123kg patient dosed at norepinephrine starting dose of 0.05 micrograms/kg/min

Step 1: Calculate the dose (micrograms/minute) = 0.05 micrograms/kg/min x 123 kg

= 6.15 micrograms/minute

Step 2: Convert dose from microgram/minute to micrograms/hour

= 6.15 micrograms/minute x 60

= 369 micrograms/hour

Step 3: Calculate the infusion rate (ml/hour)

$$= \frac{=369 \text{ micrograms/hour}}{16 \text{ micrograms/ml}}$$

= 23.1 ml/hour

Note: If the infusion pump cannot accept volumes to 1 decimal place round to 23ml/hour.

7.5 Detailed information on peripheral norepinephrine administration

Peripheral norepinephrine infusions must be administered via an infusion pump attached to a peripheral venous catheter (PVC). Guidance on siting of IV catheters for peripheral norepinephrine administration is provided in the protocol and the intervention clinical information sheet. Norepinephrine dose administration to achieve target MAP must be performed in accordance with the written prescription.

The protocol and clinical information sheet contain guidance on weaning the peripheral norepinephrine infusion when MAP > 65 mmHg on a stable dose is achieved. After discontinuation the peripheral cannula should be flushed with sodium chloride 0.9% at the same infusion rate to avoid adverse haemodynamic effects. As with administration of norepinephrine administered via a central line, staff should ensure that the hung norepinephrine infusion is not allowed to completely run through and end. Due to the very short half-live of norepinephrine (1-2 minutes) abrupt discontinuation without appropriate weaning is likely to have deleterious effects on the patient.

Treatment with peripheral norepinephrine infusion as part of the EVIS study may continue for up to 48 hours from the time of randomisation. The EVIS Intervention Clinical Information Sheet completed by the research team and inserted into the participant's medical records details the time of randomisation. After the completion of the EVIS treatment period, peripheral norepinephrine treatment may continue at the discretion of the treating physician provided this is in line with any local requirements/restrictions but treatment will no longer be under the auspices of the EVIS study protocol.

The concomitant administration of peripheral norepinephrine with other medicines using the same infusion line should be avoided even where compatibility is demonstrated in order to prevent inadvertent bolus administration of norepinephrine.

Information is provided in the protocol on action in the event of overdose.

7.6 Infusion stopping criteria

The protocol and intervention clinical information sheets detail infusion stopping criteria. In the event that a listed infusion stopping criteria is met then the peripheral norepinephrine infusion **must be immediately and permanently stopped**. The participant will remain in the study (providing consent is still valid and in place) but protocol directed treatment with the IMPs will stop and the participant should be managed in line with standard practice at site. See also section 7.7 below on extravasation

7.7 PVC check requirements and extravasation

Extravasation is the inadvertent leakage of any drug or fluid into the surrounding tissues. The protocol requires that PVC checks are performed approximately **hourly** for the duration of the peripheral norepinephrine infusion as early recognition and management should help mitigate against severe extravasation events occurring. At each PVC check

the grade of extravasation should be assessed and the score ranging from 0 to 4 documented. Where signs span more than one grade the highest grade score should be assigned.

Example: Participants skin is pink and blistered (signs of grade 1 extravasation) but there is very limited limb mobility (grade 2) the PVC grade should be recorded as grade 2.

The full extravasation grading table is located in Appendix B of the study protocol with a summary of key clinical signs included on the **Template Intervention Arm Peripheral Norepinephrine Preparation and Administration Record**. Sites using their own documentation should consider how they will disseminate the PVC grading scheme.

Patients with minor extravasation (grades 1 or 2) may continue to receive peripheral norepinephrine infusion at a new/different peripheral infusion site. In the event that grade 3 or 4 extravasation is occurs, the peripheral norepinephrine infusion must be immediately and permanently stopped.

The protocol contains recommended actions in the event extravasation occurs but sites may also follow their own local extravasation policy. Instances of extravasation must be reported to the research team in a timely manner. For further information on pharmacovigilance reporting requirements see the current protocol.

7.8 Documentation of norepinephrine administration

As per section 4.4 above, the documentation that will be used for documenting norepinephrine administration will be agreed at site initiation and this must be used for all EVIS participants unless otherwise agreed.

It is critical that all norepinephrine infusion rate changes and the times they occurred are fully documented on the agreed documentation chart. The time the infusion is temporarily or permanently stopped must also be accurately documented as well as the participant's weight.

Section 8: Balanced crystalloid administration and rescue interventions

8.1 Training requirements for administration of balance crystalloid fluids

As per the protocol, administration of balanced crystalloid fluids may be undertaken by any staff in the clinical area provided they are recognised/accredited as IV trained by their local Trust/Board. Whilst staff are not required to undertake study-specific training, the Sponsor would encourage staff to complete the relevant training modules as detailed on the **EVIS Training Matrix** which can be accessed on the study website. Training should be recorded on the **EVIS Module Training Log**.

8.2 Balanced crystalloids for control arm fluid resuscitation

Only the following balanced crystalloids are permitted for fluid resuscitation in participants randomised to the EVIS control (standard care) arm.

- Compound sodium lactate solution for infusion (also known as Ringers Lactate Solution and Hartmann's Solution for Infusion)
- Plasma-lyte® 148 (pH 7.4) solution for infusion

Any local requirements for a second check prior to hanging the infusion should be followed.

8.3 Administration of protocol directed balanced crystalloids

As per section 4.4 above, the documentation that will be used for documenting IMP administration will be agreed at site initiation and this must be used for all EVIS participants unless otherwise agreed.

It is critical that all infusion rate changes and the times they occurred are fully documented on the agreed documentation chart. The time the infusion is temporarily or permanently stopped must also be accurately documented as well as the participant's weight.

An EVIS sticker is available from the sponsor for participants randomised to the control arm (Figure 5) and are intended to raise awareness that a patient/medicine is being administered as part of a clinical trial. Use of EVIS sticker on the infusion and/or infusion chart is at discretion of each study site.

Figure 6: EVIS sticker for Standard care (Control) Group

8.4 Administration of rescue vasopressors and additional IV fluids

Participants in the standard care arm treated with balanced crystalloids should not receive peripheral vasopressor infusion during the 48 hour study period even at sites where norepinephrine is routinely administered peripherally. The 48 hour study period starts at the time of randomisation which is listed on the Clinical Information Sheet that will be inserted into each participant's medical records.

Section 9:Concomitant medicines and fluids

9.1 Concomitant medicines including those for COVID-19

The protocol provides detailed information on concomitant medicines including those requiring caution. There are no medicines that are specifically prohibited. Due to the fast moving nature of developments in COVID-19 vaccination and treatments, only broad guidance is provided in the protocol and treatment will be at the treating physician's discretion. Patients already enrolled on another clinical trial of an investigational medicinal product (CTIMP) including those for COVID-19 treatments cannot be co-enrolled on EVIS. See protocol for further details on co-enrolment.

9.2 Administration of fluids other than balanced crystalloids

Other fluids including colloids such as albumin or plasma, may contribute towards the overall fluid resuscitation effect, but the indication for their use will be primarily to meet other clinical needs the patient and for the purposes of the EVIS study they are not considered to be IMPs. These must be recorded in the eCRF.

9.3 Documentation of other fluids and medicines

Other medicines such as alternative rescue vasopressors are permitted by the protocol. It is important that route of administration is clearly documented and that times of any rate changes etc are fully documented on the standard care records.

Participants are also likely to be commenced on other medicines such as IV antibiotics which are most likely be prepared in fluids such as 0.9% sodium chloride or 5% glucose which again may contribute to the overall fluid resuscitation effect so accurate documentation is required. IV medicines with volume greater than 100ml must be recorded in the eCRF as maintenance fluids.

Section 10:History of Changes

Version 1.0– Released to sites 27.06.2022

Version 2.0 - The following changes have been made

- **Section 2.2 Research team responsibilities:** Reference added to Source Data Plan and its use.
- **Section 3.5: Standard care (Control) arm: Supplies of balanced crystalloids:** Clarification that only those balanced crystalloids detailed in the protocol can be used as IMP in the Standard Care arm
- **Section 3.10: EVIS prescribing requirements:** Additional detail on prescribing requirements.
- **Section 4.2: EVIS resources for sites:** Text revised in line with change to Sponsor provision of Template record sheet only for norepinephrine administration and to reflect current version of template record form. Also splitting of EVIS IMP module into separate Prescribing and Preparation/Administration modules.
- **Section 4.3 EVIS Website:** New section added
- **Section 4.5 Source documentation for IMP related data:** Content revised based on experience with initial sites
- **Section 5: Prescribing EVIS IMPs:** Section extensively revised to clarify prescribing arrangements for norepinephrine and balanced crystalloids taking into account practical considerations and experience from initial EVIS sites.
- **Section 6.1 Training requirement for EVIS Treating Clinicians:** New section added
- **Figure 2:** Revised protocol table inserted with starting and maximum dose
- **Section 7.5 Detailed information on peripheral norepinephrine administration:** Reminder added that norepinephrine dose administration to achieve target MAP must be performed in accordance with the written prescription
- **Section 7.7 PVC check requirements and extravasation:** Text revised in line with current protocol
- **Section 9.1 Concomitant medicines including those for COVID-19:** Addition of information on medicines for COVID and co-enrolment

Other changes include:

- Addition of EVIS Training Matrix and EVIS Module Training Log to training information
- Change from descriptor of Usual Care to Standard Care
- Minor typographical changes

Version 3.0 - The following changes have been made

- **Section 1.2 Study summary:** Section revised to reflect changes in anticipated study duration
- **Section 3.1 Pharmacy oversight, and training for pharmacy staff:** Additional information on location of mandatory training requirements for pharmacist/pharmacy technicians delegated responsibilities on site delegation log.
- **Section 7.2 Preparation of norepinephrine 16 microgram/ml infusion for peripheral administration:** Box added to highlight that with sponsor permission, sites may use a norepinephrine solution containing a concentration other than 16 micrograms/ml where this is local policy. Text also updated to indicate that Norepinephrine peripheral infusions for peripheral administration **should** be prepared as a 16 microgram/ml infusion (previously 'must').

Version 3.1 - The following changes have been made

- **Section 10 History of changes:** Correction made to versioning. Version 2.1 changed to version 3.0. No other changes made.

Version 4.0 - The following changes have been made

- **Section1.2 Study summary:** In line with the substantial protocol amendment, number of participants to be recruited reduced to a maximum of 1005. The number of expected recruiting sites has been reduced from 60 to 30. The target MAP clarified as ≥ 65 mmHg and the primary outcome is revised from all-cause mortality at day 30 to Days Alive and Out of hospital at 90 days
- **Section 5.3 Detailed information on peripheral norepinephrine prescribing:** Target MAP clarified as ≥ 65 mmHg