EVIS: Information Sheet for Clinical Staff: INTERVENTION Arm

Study: **EVIS:** Early Vasopressors in Sepsis (**EudraCT No:** 2021-006886-39)

EVIS Participant No.:		Insert Patient ID/Addressograph label
Randomisation: This patient has been randomised to the **EARLY PERIPHERAL VASOPRESSOR / INTERVENTION arm** of the EVIS study.		
Participant randomised on: _____ *(insert date)* **at** _____ *(insert time hh:mm)*		

If you need more information:

- Contact the Research Team on _____
- The protocol and other current study documents can be found on the website www.evis.scot.nhs.uk or by scanning the QRS code opposite

SCAN ME

Key information for Clinicians for EARLY PERIPHERAL VASOPRESSOR / INTERVENTION arm

Intervention: Norepinephrine (noradrenaline) administered via peripheral intravenous route

Study treatment period: maximum 48 hours from the time of randomisation (see above).

The following tasks can ONLY be performed by trained research staff on the site delegation log:

- Prescription of norepinephrine for **peripheral** IV administration

Norepinephrine dose for peripheral administration

- All participants start with norepinephrine dose of 0.05 micrograms/kg/minute.
- Titrate the dose of norepinephrine to target MAP of 65 mm Hg. See over.
- **Maximum dose is 0.15 micrograms/kg/min**

Maintenance and rescue treatment that may be prescribed by the treating clinician

- **Rescue IV fluids:** If target MAP not reached at maximum norepinephrine dose of 0.15 micrograms/kg/min or clinician concerns of organ hypoperfusion, administer 250-1000ml balanced crystalloid via peripheral IV route.
- **Maintenance IV fluids:** At clinician discretion, maintenance rather than resuscitation IV fluid can be at a rate of no more than 125 ml/hour.
- **Rescue vasopressors:** If target MAP not reached using maximum permitted dose and use of rescue IV fluids/concerns of organ hypoperfusion, then rescue vasopressor can be administered via a **CENTRAL** route. STOP peripheral norepinephrine infusion.
- **Weaning peripheral norepinephrine:** Once MAP > 65 mmHg on a stable dose, wean as per usual practice This can be done by reducing the dose by ≥ 25% of the stabilising dose at intervals of ≤ 4 hours to maintain MAP ≥ 65mmHg. The infusion can be restarted if required within 48 hour post-randomisation study period.
- **Requirement for operative intervention:** Maintain treatment allocation where possible Anaesthetist discretion permitted for other fluids, blood product and vasopressor use.
- **End of study period** *(> 48 hours since randomisation)***:** The peripheral norepinephrine infusion may be continued if permitted locally once the EVIS study period is completed.

PERIPHERAL NOREPINEPRINE INFUSION STOPPING CRITERIA

The peripheral norepinephrine infusion **must be IMMEDIATELY AND PERMANENTLY STOPPED** and the participant returned to usual care treatment if one of the following occur.

- Systolic BP > 180 mmHg **OR** Diastolic BP > 110 mmHg that fails to resolve despite following local treatment protocols.
- Tachyarrhythmia (ventricular tachycardia or ventricular fibrillation) that is life-threatening
- Suspected local extravasation of IMP.
    - Disconnect the infusion line from the cannula.
    - Attempt to aspirate 3-5ml from the peripheral venous cannula
    - Remove the cannula and apply a dressing
    - Mark the extravasation area and elevate the limb if able to reduce swelling
    - Inform research team and continue to manage as per local policy

Guidance on preparation and administration of peripheral IV norepinephrine

Preparation

Dilute norepinephrine wither either 0.9% sodium chloride injection or 5% glucose to achieve **a final concentration of 16 micrograms/ml**.

Supplies

- **Norepinephrine (noradrenaline) 1 mg/ml Concentrate for solution for infusion**.
- **For 250ml infusion:** 1 x 250ml infusion bag and 1 x 4ml Norepinephrine 1mg/ml ampoule
- **For 500ml infusion:** 1 x 500ml infusion bag and 1 x 8ml Norepinephrine 1mg/ml ampoule

Method

1. Withdraw volume of diluent from infusion bag equal to the volume of norepinephrine solution that will be added (4 or 8ml) and then discard.
2. Draw up contents of one ampoule (4ml or 8ml) of norepinephrine 1 mg/ml concentrate for solution for infusion and add to the infusion bag.
3. Mix thoroughly and inspect. Do not use if solution it is discoloured or contains precipitate.
4. Label infusion bag as per standard practice. Apply EVIS study label (optional)

Peripheral IV catheter use for norepinephrine administration

- Choose at least a 20G (pink) or larger peripheral venous catheter

Administration

Table below provides the drug dose and flow rate per hour for starting and maximum dose for peripheral norepinephrine administration.

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	30.0	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

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

Worked Infusion rate calculation for peripheral norepinephrine infusion in patients > 120kg

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