

Training for Prescribing SOS Trial Interventions

This training should be completed by those who will be prescribing the trial interventions but have not completed full protocol or GCP training. Please document that you have completed this training by signing the Investigator Training Log.

Inclusion Criteria

- ✓ Adult >16
- ✓ Admission to ICU with TBI
- ✓ ICP > 20mmHg for more than 5 mins despite stage 1 measures
- ✓ < 10 days from initial TBI
- ✓ Abnormal CT scan consistent with TBI*

Exclusion Criteria

- ✗ Devastating brain injury with withdrawal of treatment anticipated in the next 24 hours
- ✗ Pregnancy**
- ✗ Severe hyponatraemia (serum Na < 135mmol/L)

*This relates to the initial CT scan at the first hospital that the patient was admitted to as part of routine care (not a separate scan for the purposes of the trial).

**Please note, pregnancy is not a contraindication to hyperosmolar therapy, but these patients must be excluded for ethical and regulatory reasons.

Prescribing Hypertonic Saline and Mannitol

Once eligibility has been confirmed by a medically qualified clinician, patients will be randomised to receive boluses of either:

- **2ml/kg 20% mannitol** intravenous bolus (osmolarity = 1100 mOsm/L) – or equivalent osmolar dose using the concentration used locally by participating study centres.
- **2ml/kg 3% hypertonic saline** intravenous bolus (osmolarity = 1026 mOsm/L) – or equivalent osmolar dose using the concentration used locally by participating study centres.

Please refer to the dosing table for guidance on equivalent osmolar doses for different concentrations of Mannitol and Hypertonic Saline.

- The trial interventions can be prescribed by anyone authorised to prescribe mannitol and hypertonic saline as part of routine clinical practice.
- Patients **must** be prescribed the allocated intervention at randomisation.
- Use local stock. Storage and dispensing will follow local protocols.
- The trial interventions become Investigational Medicinal Product (IMP) at the point of administration.
- IMP will be administered by clinical staff in accordance with local policy.
- If ICP remains >20mmHg, boluses of each IMP can be repeated until serum sodium is > 155 mmol/L.
- If there is a second spike in ICP to >20mmHg, allocated IMP should continue to be used.

Good Clinical Practice (GCP)

GCP is an internationally agreed **ethical and scientific quality standard** for designing, conducting, recording and reporting trials that involve the participation of human subjects.

Working to GCP principles provides assurance that the **rights, safety and well-being of trial subjects are protected**, we are working ethically and in accordance with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial **data is credible**.

13 PRINCIPLES

- 1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
- 2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
- 3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.
- 4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
- 5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
- 6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.
- 7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
- 8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
 - The reason for doing this training!
- 9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.
- 10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.
 - Details of prescribed and administered doses must be documented in the medical records.
- 11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).
- 12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
 - Hypertonic Saline and Mannitol should be used in accordance with the approved protocol.
- 13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.