SOS Randomisation

Sugar or Salt trial: Hyperosmolar therapy in traumatic brain injury

This training should be completed by site members who will be randomising eligible patients into the trial but have not completed full protocol or GCP training.

Please document that you have completed this training by signing the paper Investigator Training Log OR completing the online confirmation form: randomisation (warwick.ac.uk)

Contact details:

- Chief Investigator – Prof. Gavin Perkins
- Sponsor – University Hospitals Birmingham NHS Foundation Trust and University of Warwick
- Coordinating Centre – Warwick Clinical Trials Unit

If you have any questions, please do not hesitate to contact the trial team on:
Email: sostrial@warwick.ac.uk
Tel: 024 761 50478

Trial Summary:

- Design: Multi-centre, open label, phase III randomised controlled clinical and cost-effectiveness trial with internal pilot
- Population: Adult patient >16 with severe TBI and raised ICP requiring ICU
- Intervention: Mannitol or Hypertonic Saline
- Outcome: Extended Glasgow Outcome Scale (GOS-E) at 6 months post-TBI
- Sample size: 638 patients in 36 months

Eligibility Criteria

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

- X *Devastating brain injury with withdrawal of treatment anticipated in the next 24hours*
- X *Pregnancy***
- X *Severe hypernatraemia (serum Na> 155mmol/L)*
- X *2 or more prior doses of hyperosmolar therapy given on ICU*

**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.*

- Do not exclude patients that are given hyperosmolar therapy **prior to** ICU admission
- Do not exclude patients who once admitted to ICU have received **1 rescue dose** of hyperosmolar therapy or a constant infusion of hypertonic saline to correct a low Na
- Co-enrolment with other Clinical Trials of Investigational Medicinal Products (CTIMP) and non-CTIMPs is permitted (following discussion and agreement on a case-by-case basis)

Process for randomisation

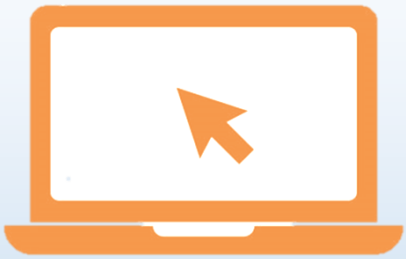
- Patient randomisation should only take place once eligibility has been confirmed.
- Once eligibility has been confirmed, if treatment is not urgent, consent from a Professional Legal Representative (a medical doctor not on the delegation log) or Personal Legal Representative (from the patient's family/friend/carer) can be obtained prior to randomisation
- However, if treatment is urgent, randomisation can proceed as soon as eligibility has been confirmed.
- In order to randomise, you will need to ensure you have the following information ready:
  - Confirmation that all eligibility criteria has been met
  - Name, date and time details for person who confirmed eligibility (not for IVR)
  - Patient's age
  - Best GCS motor score prior to intubation/sedation
  - Pupillary response prior to intubation
- Randomisation can be achieved either through the **online trial database** or by **phone**:

Randomising through the database:

Online database: https://ctu.warwick.ac.uk/SOS

You will need:

- A unique user login (provided by the Warwick trial team)
- Access to a computer
  - If not a site computer, you need to be connected to VPN



If you need guidance on how to use the online database, please refer to the SOS trial Data Collection guide located in your sites Investigator Site File folder 11.4 or on our webpage: Training Resources (warwick.ac.uk)

Randomising via phone:

Automated IVR phone number: 024 7610 0792

You will need:

- The phone pin code for your site (provided by the Warwick trial team)

You will not require a database login or computer access

If you need guidance on how to use the IVR phone line, please refer to the SOS trial IVR guide located in your sites Investigator Site File folder 11.4 or on our webpage: Training Resources (warwick.ac.uk)

If you are having difficulties accessing either the online database or IVR phone line, you can call the emergency randomisation line (Mon-Fri, 9am-5pm) where a member of the clinical trials unit will assist with randomising. If using this method, please ensure you have the required randomisation form details ready.

Emergency backup phone line: 024 7615 0402

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.
   - Ensure a TBI diagnosis and SOS eligibility have been confirmed before randomising the patient.
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.
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.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Principle 3: What is a Serious Adverse Event (SAE)?

An adverse event is considered to be serious if it fulfils one of the following criteria:

- **Results in death**
- **Is life-threatening**
- **Requires hospitalisation or prolongation of existing inpatients' hospitalisation**
- **Results in disability/incapacity**
- **Congenital abnormality/birth defect**
- **Requires important medical event/medical intervention**

Please inform your research team of any possible SAEs as these need to be reported to the trial coordinating centre **within 24 hours** of becoming aware of the event.

- **Serious Adverse Reaction (SAR) -** Serious, and at least possibly related to IMP
- **Suspected Unexpected Serious Adverse Reaction (SUSAR) -** A SAR which is unexpected in nature, severity or frequency as documented in section 4.8 of Reference Safety Information (RSI)/Summary of Product Characteristics (SmPC) .

What is causality?

A medical assessment by a doctor of whether a SAE has a possible causal relationship to the administration of the Investigational Medicinal Product.

What should not be reported as a SAE for SOS?

- **Death**
- **Persistent or significant disability/incapacity**
- **Organ failure**
- **Any other events relating to the underlying illness/injury**