Sugar or Salt (SOS) Trial: Hyperosmolar therapy in traumatic brain injury

Trial Protocol

V8.0 06/03/2024

SOS Trial Protocol

EudraCT Number:	2019-001688-66
ISRCTN Number:	ISRCTN16075091
Sponsor:	University Hospitals Birmingham NHS Foundation Trust and University of Warwick
Funding Body:	NIHR Health Technology Assessment Programme
Ethics Approval date:	NHS REC: 19/EE/0228
Version Number:	Version 8.0
Date:	6th March 2024
Stage:	Final

Protocol Amendments:

Amendment No.	Date of Amendment	Date of Approval
SA 04	02/04/2020	28/05/2020
NSA 01	16/07/2020	29/07/2020
SA 07	29/10/2021	14/12/2021
SA08	11/04/2022	11/05/2022
SA10	08/11/2022	04/01/2022
SA11	06/03/2023	27/04/2023
SA13		

This protocol has regard for current HRA guidance and content. This study is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment (HTA) Programme (Ref: 17/120/01). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

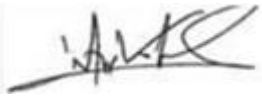
SIGNATURE PAGE

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 2006/199828) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's 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 study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

Chief Investigator:

Signature:  Date: 15 May 2024

Name (please print): MR ANGELOS KOLIAS

CONTACT NAMES AND NUMBERS

Role	Name, address, telephone
Sponsors:	Dr. Sarah Pountain Research and Development Directorate Office 18, Education Centre Queen Elizabeth Hospital Birmingham Mindelsohn Way Edgbaston Birmingham B15 2WB Tel: 0121 424 3631 Carole Harris Research and Impact Services University House University of Warwick Coventry CV4 8UW Tel: 02476 575 732
Chief Investigator:	Mr Angelos Kolias Addenbrooke's Hospital & University of Cambridge Hills Road Cambridge CB2 0QQ Warwick Clinical Trials Unit University of Warwick Gibbet Hill Campus Coventry CV4 7AL Tel: 01223 245151 Email: ak721@cam.ac.uk
Co-Chief Investigator:	Professor Peter Hutchinson Addenbrooke's Hospital & University of Cambridge Hills Road Cambridge CB2 0QQ Tel: 01223 245151 Email: pjah2@cam.ac.uk

Trial Manager:	Dr Hannah Noordali Warwick Clinical Trials Unit University of Warwick Gibbet Hill Campus Coventry CV4 7AL Tel: 02476 150478 Email: hannah.noordali@warwick.ac.uk SOStrial@warwick.ac.uk
Trial Manager:	Mrs Louisa Berridge Warwick Clinical Trials Unit University of Warwick Gibbet Hill Campus Coventry CV4 7AL Tel: 024765 73757 Email: louisa.berridge@warwick.ac.uk SOStrial@warwick.ac.uk
Co-investigators:	Professor Gavin Perkins, University of Warwick Professor Peter Andrews, University of Edinburgh Professor Paul Dark, University of Manchester Professor Danny McAuley, Queen's University Belfast Dr Matthew Rowland, University of Oxford Dr Tonny Veenith, University Hospitals Birmingham Professor Mark Wilson, St Mary's Hospital & Imperial College, London
Statistician:	Prof. Ranjit Lall Warwick Clinical Trials Unit University of Warwick Gibbet Hill Campus Coventry CV4 7AL Tel: 02476 574 649 Email: r.lall@warwick.ac.uk
Senior Project Manager	Mrs Kath Starr Warwick Clinical Trials Unit University of Warwick Gibbet Hill Campus Coventry CV4 7AL Email: kath.starr@warwick.ac.uk

Health Economist	Prof. James Mason Warwick Medical School University of Warwick Gibbet Hill Campus Coventry CV4 7AL Tel: 02476 151 853 Email: J.Mason@warwick.ac.uk
Data Monitoring and Ethics Committee (DMEC) and Trial Steering Committee (TSC)	A list of members and contact details can be found in the Trial Master File

For general queries and supply of trial materials please contact the coordinating centre:

SOS trial team, Warwick Clinical Trials Unit (WCTU)

The University of Warwick

Gibbet Hill Road

Coventry

CV4 7AL

Tel: 024765 73757 Email: SOStrial@warwick.ac.uk

TABLE OF CONTENTS PAGE

LIST OF TABLES PAGE

LIST OF FIGURES PAGE

TRIAL SUMMARY

Trial Title	"Sugar or Salt (SOS) Trial: Hyperosmolar Therapy in Traumatic Brain Injury"
Research Question	Does hyperosmolar therapy (mannitol or hypertonic saline) in traumatic brain injury (TBI) improve neurological function clinically and cost-effectively at 6 months?
Trial Design	Multi-centre, open label, randomised controlled clinical and cost effectiveness trial with an internal pilot
Setting	Intensive Care Units (ICUs) within NHS hospitals treating patients with TBI
Target Population	Adult patients (aged ≥16 years) with severe TBI and raised intracranial pressure (ICP)
Inclusion Criteria	1) Adult aged ≥16 years old 2) Admission to ICU following TBI 3) ICP >20mmHg for more than 5 mins despite stage 1 procedures 4) <10 days from initial primary head injury 5) Abnormal CT scan consistent with TBI
Exclusion Criteria	1) Devastating brain injury with withdrawal of treatment anticipated in the next 24 hours 2) Pregnancy 3) Severe hypernatraemia (serum Na > 155 mmol/L) 4) 2 or more prior doses of hyperosmolar therapy given on ICU
Planned sample size	234 per group (468 in total)
Health Technology being Assessed	Equi-osmolar dose of mannitol intravenous bolus Equi-osmolar dose of hypertonic saline intravenous bolus
Measurement of Outcomes and Costs	Primary outcome 1. Extended Glasgow Outcome Scale (GOS-E) measured at 6 months after randomisation Secondary outcomes 1. ICP control (during period of monitoring on ICU) 2. Progression to stage 3 therapies 3. Which stage 3 therapies were required 4. Organ support requirements during ICU 5. Critical care length of stay 6. Hospital length of stay 7. Modified Oxford Handicap Score (mOHS) at hospital discharge 8. GOS-E at 12 months 9. Survival at hospital discharge, 3 months, 6 months and 12 months 10. Quality of life (EQ-5D-5L) at hospital discharge, 3 months, 6 months and 12 months 11. Serious Adverse Events (SAEs) Health economic outcomes Costs and within-trial and lifetime cost-effectiveness from an NHS and Personal Social Services (PSS) perspective.
Follow-up Duration	Up to 12 months post-randomisation
Planned Trial Period	From 01/06/2019 to 28/02/2026 (total of 81 months)

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
ACCP	Advanced Critical Care Practitioner
AE	Adverse Event
AR	Adverse Reaction
AUC	Area Under the Curve
CCMDS	Critical Care Minimum Dataset
CI	Chief Investigator
Co-I	Co-Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CT	Computerised Tomography
CTA	Clinical Trials Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMEC	Data Monitoring and Ethics Committee
EudraCT	European Clinical Trials Database
EVD	Extra-Ventricular Drainage
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GDPR	General Data Protection Regulation
GOS-E	Glasgow Outcome Scale-Extended
HES	Hospital Episode Statistics
HTA	Health Technology Assessment
HTS	Hypertonic Saline (sodium chloride)
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICNARC	Intensive Care National Audit and Research Centre
ICP	Intracranial pressure
ICPM	Intracranial Pressure Monitor
ICU	Intensive Care Unit
IMP	Investigational Medicinal Product

IRAS	Integrated Research Application System
ISRCTN	International Standard Registered Clinical/soCial sTudy Number
IVR	Interactive Voice Response
MHRA	Medicines and Healthcare products Regulatory Agency
mOHS	Modified Oxford Handicap Score
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PerLR	Personal Legal Representative
PI	Principal Investigator
PPI	Patient & Public Involvement
ProfLR	Professional Legal Representative
PSS	Personal Social Services
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBI	Traumatic Brain Injury
TMG	Trial Management Group
TSC	Trial Steering Committee
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

1.1 Epidemiology and burden of the condition

Traumatic brain injury (TBI) is a major cause of death and severe disability throughout the world with an estimated global pooled incidence of 349 per 100,000 person years.[1] Across Europe it is estimated that each TBI related death results in on average 24 years of life lost, amounting to 1.3 million years of life lost annually across Europe due to TBI.[2]

In the United Kingdom, approximately 1.4 million people attend emergency departments in England and Wales annually following a head injury of which 3,500 patients have moderate to severe TBI requiring treatment in intensive care.[3] Resource use is high with an average length of stay in an ICU following TBI of 9 days.[3] Long term outcomes are also poor – the HTA Risk Adjustment In Neurocritical care (RAIN) study (n=3636)[4] reported 26% mortality in patients with TBI at 6 months, and amongst survivors 44% had severe disability, 30% had moderate disability, and only 26% had made a good recovery. 70% of patients with TBI reported problems performing usual activities, 60% reported problems with pain or discomfort and anxiety or depression. Furthermore, 50% of patients experienced problems with mobility and 35% reporting problems with self-care.[4]

1.2 Existing knowledge

1.2.1 Pathophysiology of raised ICP and mechanism of action for hyperosmolar therapies

A rise in intracranial pressure (ICP) is a secondary insult that can result from either the primary traumatic injury or other resulting pathologies such as cerebral oedema or obstruction to cerebrospinal fluid (CSF) flow. A number of studies have shown an association between raised ICP and poor neurological outcomes.[5,6] As a result, the treatment of elevated ICP has been a central focus of both the medical and surgical management of patients with severe TBI on the ICU.

ICP monitoring is undertaken in intensive care in the presence of an abnormal CT scan and Glasgow Coma Scale (GCS) <8 or if 2 or more of age >40 years, unilateral or bilateral motor posturing, or episodes of systolic blood pressure (BP) <90 mmHg.[7] A recent UK wide survey (Rowland et al., in preparation) indicates that most UK clinicians would initiate treatment for raised ICP if it increased to >20mmHg for at least 5 minutes with no reversible cause. This is consistent with the threshold used in previous trials (see Table 1) and similar to the Brain Trauma Foundation threshold (>22 mmHg)[7] and a recent consensus recommendation from the European Society of Intensive Care Medicine (>25mmHg).[8]

Table 1. Thresholds for ICP in previous trials

EUROTHERM[9]	>20mmHg for at least 5 minutes with no reversible cause
DECRA[10]	>20mmHg for more than 15 minutes (continuously or intermittently) within a 1-hour period
RESCUE-ICP[11]	>25mmHg for 1-12 hours [Note higher threshold as the trial aimed to assess craniectomy as a last-tier intervention]
POLAR[12]	>20mmHg for more than 5 minutes

The intensive care management of patients with severe TBI and raised ICP usually takes a stepwise approach. Initial treatment focuses on treatment of immediate surgical pathology (e.g. haematoma or hydrocephalus) and the optimisation of so called “stage 1” ICU interventions (e.g. sedation, ventilation, blood pressure, temperature and positioning). If ICP remains high following this, “stage 2” interventions normally include the use of neuromuscular blockade and hyperosmolar therapy. Finally, “stage 3” measures include surgical decompressive craniectomy, barbiturate coma or mild hypothermia.

Hyperosmolar therapies used to control ICP include mannitol and hypertonic saline. Mannitol is a sugar alcohol which exerts its ICP-lowering effects via two mechanisms—an immediate non-osmotic effect because of plasma expansion and a slightly delayed effect related to its osmotic action. The early plasma expansion reduces blood viscosity and this in turn improves regional cerebral microvascular flow and oxygenation. It also increases intravascular volume and therefore cardiac output. Together, these effects result in an increase in regional cerebral blood flow and compensatory cerebral vasoconstriction in brain regions where autoregulation is intact, resulting in a reduction in ICP. Mannitol also establishes an osmotic gradient between plasma and brain cells, drawing water from the cerebral extracellular space into the vasculature, thereby reducing cerebral oedema.

Hypertonic saline administration produces an osmotic gradient between the intravascular and intracellular/interstitial compartments, leading to shrinkage of brain tissue (where blood brain barrier is intact) and therefore a reduction in ICP. Hypertonic saline also augments volume resuscitation and increases circulating blood volume, mean arterial blood pressure and cerebral perfusion pressure. Other suggested beneficial effects of hypertonic saline include restoration of the neuronal membrane potential, maintenance of the blood brain barrier integrity, and modulation of the inflammatory response by reducing adhesion of leukocytes to endothelium.

1.2.2 Current evidence for the use of hyperosmolar therapy in the management of TBI

There have been three recently published systematic reviews based on 16 trials investigating the use of hyperosmolar therapy in patients with TBI.[13-15] Trial sample size ranged from 9 to 132, although only one trial had more than 100 participants. The index trials examined different interventions in mixed settings and were limited by moderate to high risk of bias, inconsistency, imprecision and indirectness. Furthermore, the majority of trials spanned over three decades during which time contemporary management of TBI has evolved significantly.

One of the reviews compared hypertonic saline with mannitol and found a reduced risk of treatment failure (and 95% CI) with hypertonic saline RR risk ratio 0.39 (0.18 to -0.81).[14] The review focusing primarily on hypertonic saline, concluded there was insufficient evidence to support its use in severe TBI.[13] Finally, the review of mannitol therapy for raised ICP reported it may have a beneficial effect on mortality when compared to pentobarbital treatment RR for death as 0.85 (95% CI:0.52 to 1.38) but may have a detrimental effect on mortality when compared to hypertonic saline RR for death as 1.25 (95% CI 0.47 to 3.33).[15]

In preparation for this trial, a further four systematic reviews of relevance were identified. Schwimmbeck shared their completed systematic review and trial sequential analysis comparing hypertonic saline and mannitol. Their analysis includes 2 small additional trials not reported in previous reviews.[16,17] A recent meta-analysis comparing hypertonic saline with mannitol reported a risk ratio of 0.67 (0.43-1.02) for mortality and 0.76 (0.22-2.63) for favourable outcome - although the index trials were small in size. The European Society of Intensive Care Medicine (March 2018)[8] review found low quality evidence that mannitol and hypertonic saline were effective, in a dose dependent manner, at reducing ICP. No meta-analysis was performed due to heterogeneity. The panel gave a weak recommendation in favour of the use of mannitol or hypertonic saline. The two further reviews drew similar conclusions about there being insufficient evidence to favour mannitol or hypertonic saline.[18,19]

Observational studies suggest continuous hyperosmolar therapy may be more effective than intermittent boluses. This hypothesis is being tested in the French COntinuous hyperosmolar therapy for traumatic Brain Injury (COBI) trial.[20] Continuous therapy is rarely used in the UK and the research question is different to the one identified in the HTA commissioning brief.

Survey of UK practice

We conducted a survey amongst 554 clinicians from around the UK (anaesthesia (22%), ICU (44%), emergency medicine (18%), neurosurgery (9%) and pre-hospital (7%)) involved in the treatment of patients with TBI. UK wide respondents prioritised a trial of osmotherapy in the ICU as the most important setting for a trial in the NHS (95% agreement across speciality background). Clinicians used both hypertonic saline and mannitol as first line therapy). A range of concentrations of hypertonic saline is used nationally on the intensive care as a stage 2 measure to manage raised ICP – ranging from 2.7% to 30% (see Table below).

Almost all clinicians (91%) currently use bolus treatment rather than an infusion. Clinicians had equipoise for a trial comparing mannitol versus hypertonic saline when ICP > 20mmHg despite stage 1 measures. Clinicians did not support a placebo trial.

Types of hypertonic saline used		**Treatment options in response to vignette with 36 year old male with severe TBI**
Concentration	**Response n (%)**	
5%	66 (40)	
2.7%	59 (35)	
30%	23 (13)	
7.5%	17 (10)	
15%	1 (1)	
23%	1 (1)	

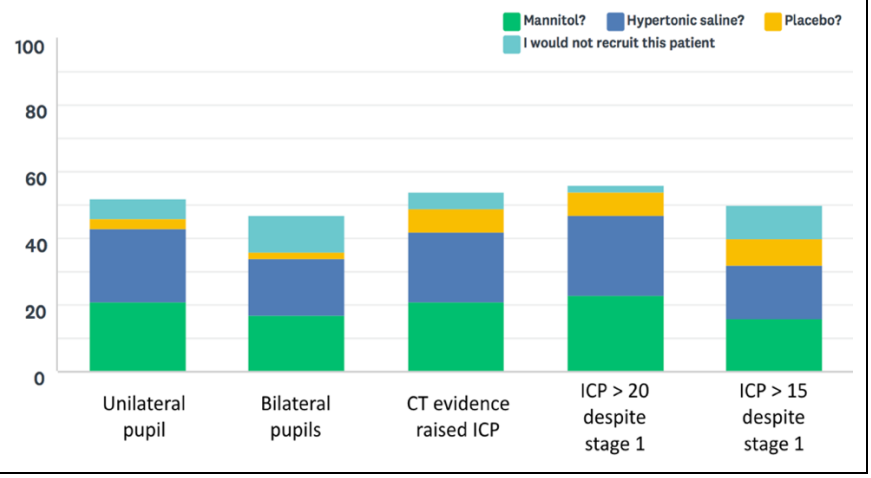


Figure 1. Results of survey of UK practice

Side effects of hyperosmolar treatment

The occurrence of adverse events are poorly reported in the published clinical trials. The main adverse events are electrolyte disturbance and acute kidney injury.

Hypernatraemia is common in patients with severe TBI. It may arise as a consequence of direct injury to the brain (diabetes insipidus) or hyperosmolar therapies. Observational studies have linked hypernatraemia with an independent risk of adverse outcome.[21,22] Meta-analysis of randomised trials noted higher serum sodium concentration (9 mmol L [95% CI 6-12]) in patients treated with hypertonic saline.[18] Whether this directly contributes to adverse outcomes is uncertain.[23]

Acute kidney injury occurs in approximately 5% of patients with severe TBI (EUROTHERM data). Un-published post-hoc analysis of their Erythropoietin in TBI (NCT00987454) suggested that mannitol may be associated with a greater chance of acute kidney injury (OR 1.27 [95% CI: 1.1-1.5]). Similar findings were observed in the EUROTHERM study (un-published).

1.3 Hypothesis

The primary hypothesis is that hypertonic saline is more effective than mannitol in the management of raised ICP after severe TBI through improving clinical outcomes and cost-effectiveness.

1.4 Need for a trial

As highlighted in section 1.2 above, it remains unclear whether there is a treatment benefit to using either mannitol or hypertonic saline in the management of raised ICP after severe TBI. The 2018 survey of UK clinical practice we conducted demonstrated that more UK centres are moving to the use of hypertonic saline as first line osmotherapy compared to mannitol (75% v 25%) with little empirical trial evidence to support this practice (Rowland et al., 2018). It also highlighted widespread variation in practice in both the timing and dosing of hyperosmolar therapy in general.

The importance of a trial directly comparing bolus mannitol with hypertonic saline was highlighted in the recent NIHR HTA Programme commissioning brief (17/20). The HTA prioritisation group and secretariat assessed this topic as an important uncertainty with significant equipoise about the most effective and safe treatments. This view is concordant with research gaps identified by the Brain Trauma Foundation and the European Society for Intensive Care Medicine and was recommended in the recent editorial accompanying the publication of the COBI trial protocol.[24]

1.5 Ethical considerations

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to International Conference on Harmonisation Good Clinical Practice (GCP) guidelines. It will also comply with the Medicines for Human Use (Clinical Trials) Act 2004, subsequent amendments and

Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with the Data Protection Act 2018.

Both treatments are currently used in the NHS and the trial protocol does not mandate any interventions outside of routine clinical practice. It is our assessment that the Medicines and Healthcare products Regulatory Agency (MHRA) trial category is a type A trial, which has no higher risk than that of standard medical care. The main additional burden of the trial protocol relates to the follow-up and completion of questionnaires about resource use and health related quality of life.

Conducting research in emergency situations where a patient lacks capacity is regulated by The Medicines for Human Use Act (UK Clinical Trial Regulations) and amendment 2006 which relates to Article 5 from the EU Directive 2001 and HRA Informed Consent Guidance. We have based our assessment of the ethical considerations for this trial on the template outlined at the Health Research Authority Workshop 2012 on conducting emergency research in patients who lack capacity.

Patients enrolled in this trial, due to the nature of their underlying condition, will lack capacity to consent. We will therefore seek informed consent from a personal or professional legal representative, if there is sufficient time available and it is appropriate to do so. If treatment needs to be provided urgently without delay, deferred consent from a personal or professional legal representative using the provisions within the EU Clinical Trials Directive and the Clinical Trials Regulations (2006, No 2984) on the basis that:

- The patient is incapacitated
- Treatment needs to be given urgently
- It is necessary to take urgent action to administer the drug for the purposes of the trial
- It is not reasonably practical to obtain consent from a legal representative
- The procedure is approved by a Research Ethics Committee
- Consent is sought from a legal representative as soon as possible

1.5.1 What happens to someone when they sustain a severe TBI?

Patients who sustain a severe TBI and develop raised intracranial pressure will be unconscious due to the severity of damage to the brain. Current best practice is to treat such patients with deep sedation to facilitate endotracheal intubation (protection of the airway), invasive mechanical ventilation to achieve satisfactory oxygenation and to “rest” the brain (induced coma to reduce oxygen demand).

1.5.2 Is this research needed and is there uncertainty about treatment?

It remains unclear whether there is a treatment benefit to using mannitol or hypertonic saline in the management of raised ICP after severe TBI, and the importance of a trial directly comparing the two treatments was highlighted in a NIHR HTA Programming commissioning brief (17/20).

1.5.3 Is there a need to recruit participants who lack capacity?

The clinical trial relates directly to the treatment of severe TBI, which is a life-threatening emergency. Patients that receive hyperosmolar therapy will be unconscious, require heavy sedation and therefore

lack capacity to consent. There are no alternative groups of patients amongst whom this research could be conducted.

1.5.4 In the context of the research is consent or consultation feasible?

The occurrence of TBI is unpredictable and the patient will be unconscious or sedated. It is therefore not possible to consult with or obtain prospective consent directly from the research participant.

1.5.5 Does treatment need to be given quickly and might delay change the effect of treatment or the results?

If a patient develops a sustained elevation in ICP >20mmHg treatment needs to be given urgently to reduce the risk of death and severe disability. A delay in providing treatment risks worsening of brain injury which may reduce the overall effectiveness of hyperosmolar therapy.

1.5.6 Will procedures accommodate variations in capacity?

All patients will lack capacity throughout the intervention period of the trial due to the nature of the underlying medical condition (TBI).

1.5.7 Is it practical to consult a personal or professional legal representative unconnected to the research?

It is our assessment that in many cases it will not be reasonably practical to obtain written informed consent from a legal representative prior to enrolment in the trial as the urgency with which treatment must be provided would not allow sufficient time to explain the nature, significant, implications and risks of the trial as is required by the Medicines for Human Use (Clinical Trials) Regulations. As enrolment will take place twenty four hours a day and seven days a week this will make it impractical to rely on timely access to a professional legal representative. However if a legal representative is available prior to enrolment, and there is sufficient time, then a personal or professional legal representative will be informed about the trial and informed consent will be sought. This will only be done after an assessment of whether it is appropriate to approach the legal representative at that time. The presence and willingness of a legal representative to provide informed consent will likely vary according to certain factors e.g. time of day, day of the week, age, health literacy, spoken language etc. If recruitment was limited to situations where a legal representative was present, it would introduce selection bias, which would potentially undermine the scientific value of the trial and generalisability of study results.

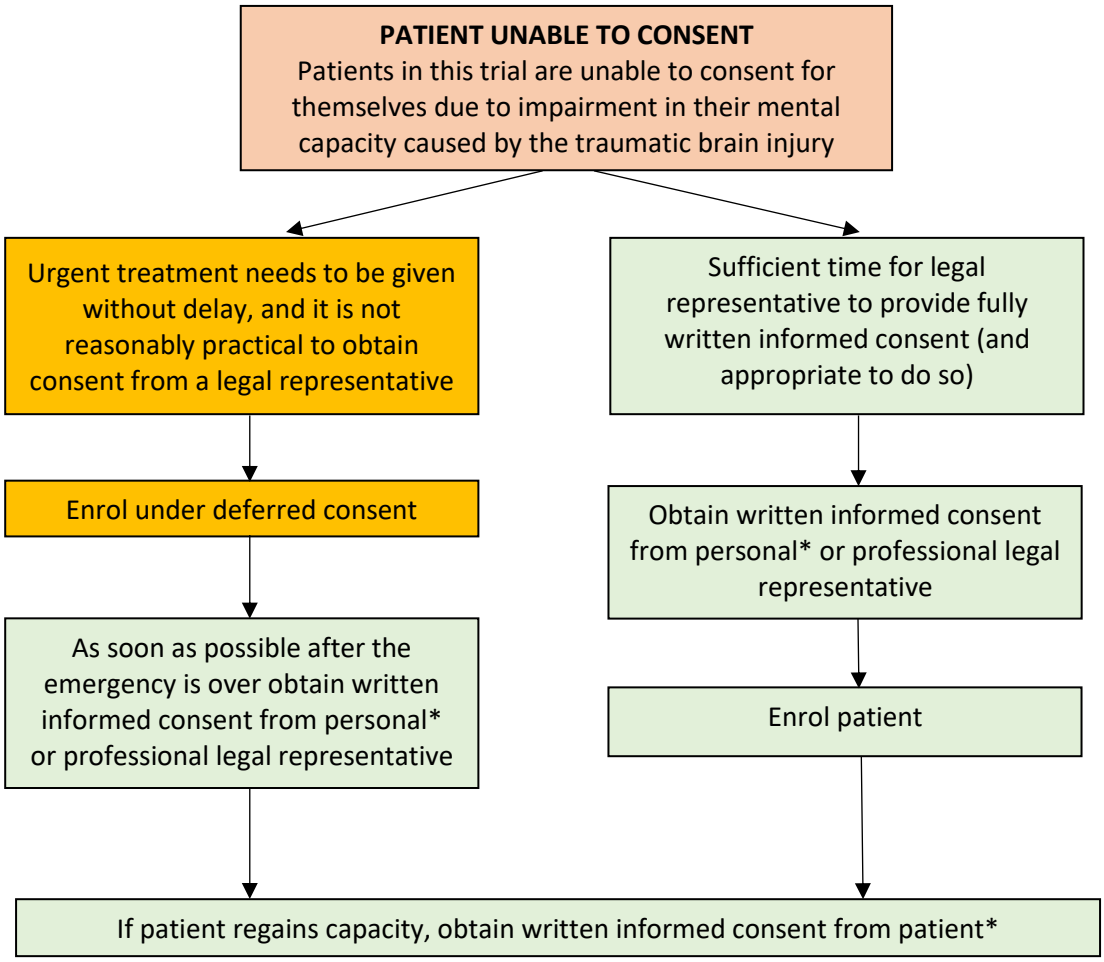
1.5.8 What should the patient or legal representative be asked later?

If a personal or professional legal representative has not provided consent prior to enrolment, once the initial emergency has passed they will be informed about the trial as soon as practicably possible and asked for consent for the patient to continue in the trial (see section 1.6).

1.5.9 Provision of general information about the trial

A poster about the trial will be displayed in hospital waiting areas and information leaflets about the trial will be made available. These will provide summary information about the trial and where people can find out more information.

1.6 Informed consent process



* Witnessed verbal consent may be obtained if it is not feasible to obtain written consent from personal legal representatives and patients.

Figure 2. Informed consent process

1.6.1 Personal legal representative consent

Definitions

The definition of a Personal Legal Representative (PerLR) for **England, Wales and Northern Ireland** is: "A person not connected with the conduct of the trial who is suitable to act as a legal representative by virtue of their relationship with the adult and available and willing to do so".

The definition of a PerLR for **Scotland** is: "Any guardian or welfare attorney who has power to consent to the adult's participation in research. If there is no such person, the adult's nearest relative as defined in section 87(1) of the Adults with Incapacity (Scotland) Act 2000".

Prior to enrolment

If there is a personal legal representative, and sufficient time, available prior to the patient being enrolled and randomised they will be given a patient information sheet by a member of the research team, if the nurse or doctor providing clinical care assesses it is appropriate to do so. They will then be asked to consider the patient's wishes regarding participation in the trial. If the PerLR decides that the patient would have no objection to participating in the trial, they will be asked to sign the PerLR consent form which will then be countersigned by the Investigator or their nominee.
If the PerLR is unable to attend the hospital to sign the consent form in person, for example due to the COVID-19 pandemic, witnessed verbal consent will be sought over the telephone. The PerLR will be sent a copy of the patient information sheet and will have the opportunity to discuss the trial and ask any questions over the phone. If the PerLR decides that the patient would have no objection to participating in the trial, the consent form will be read to the PerLR and their verbal consent will be documented on the consent form. Verbal consent should be obtained in the presence of an impartial witness i.e. a person who is independent of the study and who cannot be unfairly influenced by people involved with the study. Both the Investigator or nominee obtaining consent, and the witness will sign the consent form. Consent will be later re-confirmed with the PerLR at the next visit/contact and documented in the medical notes.

The PerLR will be provided with a copy of the signed consent form. A second copy will be placed in the patient's medical records whilst the original will be retained in the Investigator Site File. If the PerLR indicates that they believe the patient would not wish to take part in the trial then the patient will not be enrolled and standard care will be provided without prejudice.

After enrolment (deferred consent)

If it is not reasonably practical to obtain consent from a legal representative, relative to the urgency with which treatment needs to be given, the patient will be enrolled under emergency provisions. Consent to continue (deferred consent) will be sought as soon as is practicable. The PerLR will be approached to discuss the trial, provide them with the patient information sheet and answer any questions they may have. The PerLR will be given adequate time to consider the patient's wishes regarding participation in the trial. If the PerLR decides that the patient would have no objection to participating in the trial, they will be asked to sign the PerLR consent form which will then be countersigned by the Investigator or their nominee. If the PerLR is unable to attend the hospital to sign the consent form in person, for example due to the COVID-19 pandemic, witnessed verbal consent will be sought over the telephone. The PerLR will be sent a copy of the patient information sheet and will have the opportunity to discuss the trial and ask any questions over the phone. If the PerLR decides that the patient would have no objection to participating in the trial, the consent form will be read to the PerLR and their verbal consent will be documented on the consent form. Verbal consent should be obtained in the presence of an impartial witness i.e. a person who is independent of the study and who cannot be unfairly influenced by people involved with the study. Both the Investigator or nominee obtaining consent, and the witness will sign the consent form. Consent will be later re-confirmed with the PerLR at the next visit/contact and documented in the medical notes.

The PerLR will be provided with a copy of the signed consent form. A second copy will be placed in the patient's medical records whilst the original will be retained in the Investigator Site File.

1.6.2 Professional legal representative consent

Definition
The definition of a Professional Legal Representative (ProfLR) in **England, Wales, Northern Ireland and Scotland** is: "A person not connected with the conduct of the trial who is the doctor primarily responsible for the adult's medical treatment or a person nominated by the relevant health care provider".

Prior to enrolment
If no suitable PerLR is available or reasonably contactable, then a doctor who is not connected with the conduct of the trial may act as a ProfLR prior to the patient being enrolled providing there is someone available and there is sufficient time to obtain informed consent. The doctor will be informed about the trial by a member of the research team and given a copy of the patient information sheet. If the doctor decides the trial is in the best interests of the patient, taking into consideration any advanced statements, they will be asked to sign the ProfLR consent form. The doctor will retain one copy of the signed consent form. A second copy will be placed in the patient's medical records whilst the original will be retained in the Investigator Site File.

If the ProfLR indicates that they believe participating in the trial would not be in the best interests of the patient, then the patient will not be enrolled and standard care will be provided without prejudice.

After enrolment
If no suitable PerLR is available or reasonably contactable, then a doctor who is not connected with the conduct of the trial may act as a ProfLR. The doctor will be informed about the trial by a member of the research team and given a copy of the patient information sheet. If the doctor decides the trial is in the best interests of the patient, taking into consideration any advanced statements, they will be asked to sign the ProfLR consent form. The doctor will retain one copy of the signed consent form. A second copy will be placed in the patient's medical records whilst the original will be retained in the Investigator Site File.

If a PerLR should subsequently become available after enrolment and before the patient has regained capacity they should be informed about the patient's participation in the trial. They will be asked to consider the wishes of the patient regarding ongoing participation in the trial and the process in section 1.6.1 will be followed. Their consent or dissent will then override that provided by the ProfLR.

1.6.3 Patient consent

If the patient regains capacity while still in hospital, they will be informed about their participation in the trial and given a patient information sheet. If they agree, consent for ongoing trial participation will be sought. If it is not feasible to obtain written informed consent from the patient due to the COVID-19 pandemic, verbal consent will be obtained in the presence of an impartial witness i.e. a

person who is independent of the study and who cannot be unfairly influenced by people involved with the study. The patient will retain one copy of the signed consent form. A second copy will be placed in the patient's medical records whilst the original will be retained in the Investigator Site File.

After hospital discharge it will not be reasonable or practical to assess patient's capacity and obtain written consent in the event that the patient regains capacity. Questionnaires will therefore be sent to the patient's legal representative, and return of a completed questionnaire from either the legal representative or the patient will be considered implied consent.

1.6.4 Translations

If needed, local centres can use hospital interpreter and translator services, if available, to assist with the discussion of the study.

1.7 Assessment and management of risk

The risk associated with this trial is categorised as Type A i.e. no higher than the risk of standard medical care. The national survey conducted as part of this study (Rowland et al, in preparation) shows that patients receive both mannitol and hypertonic saline as part of routine standard clinical management of raised ICP following severe TBI.

1.7.1 Risk/benefit of study treatments

As discussed previously in section 1.2 and 1.4, current literature and clinical expertise demonstrates equipoise as to the benefit of hypertonic saline compared to mannitol in the management of raised ICP following severe TBI. These include large meta-analyses and systematic reviews of all currently available data. Furthermore, the UK survey of clinicians involved in the management of patients with severe TBI conducted in 2018 demonstrated that both mannitol and hypertonic are used for this indication with considerable regional variation in dose, timing and indication.

As with most treatment interventions there are some potential associated risks. Patients with severe TBI are at increased risk of hypernatraemia. This may arise as a consequence of endocrine disorders associated with direct brain injury (e.g. diabetes insipidus) or as a complication of fluid and hyperosmolar therapies. Observational studies have linked hypernatraemia with an independent risk of adverse outcome.[21,22] Meta-analysis of randomised trials noted higher serum sodium concentration (9 mmol/L [95% CI 6-12]) in patients treated with hypertonic saline.[18] Whether this directly contributes to adverse outcomes is uncertain. Whilst on the ICU, serum sodium is measured routinely on blood gas samples which are taken at regular intervals. Any abnormalities can be treated accordingly and patients will stop receiving hypertonic saline if serum sodium levels are > 155mmol/L.

Acute kidney injury occurs in approximately 5% of patients with severe TBI (EUROTHERM data). Un-published post-hoc analysis of the Erythropoietin in TBI (NCT00987454) suggested that mannitol may be associated with a greater chance of acute kidney injury (OR 1.27 (95% CI: 1.1-1.5)). Similar findings were observed in the EUROTHERM study (un-published). Study participants will routinely have

measurements of kidney function on a daily basis as part of routine clinical practice. Incidence of acute kidney injury (as defined by the requirement for renal replacement therapy) will be monitored and reported to the Trial Steering Committee (TSC).

2. TRIAL DESIGN

2.1 Trial summary and flow diagram

The SOS Trial is a UK multi-centre, open label, randomised controlled clinical and cost effectiveness trial with an internal pilot and blinded assessment of primary outcome at 6 months.

Adult patients (≥16 years old) will be eligible for recruitment if they have sustained a severe TBI with raised intracranial pressure requiring ICU admission.

Patients will be randomised to either hyperosmolar therapy with mannitol or hypertonic saline. Outcomes are Glasgow Outcome Scale – Extended (GOS-E) at 6 months post-randomisation (primary outcome) as well as mOHS at hospital discharge, GOS-E (12 months), mortality (hospital discharge, 3, 6 and 12 months), ICP control in ICU, time to discharge from hospital, resource use, quality of life, health economics and serious adverse events (secondary outcomes).

Figure 3 shows the flow diagram for the study.

2.2 Pilot study

The main SOS Trial will be preceded by an internal pilot to test that the components of the SOS Trial will work together. The internal pilot will run for 6 months and the progression of the pilot will be informed by the recently published best practice guidelines.[25]

We anticipate that by 6 months, approximately 50 patients will have been recruited which is in line with the guidelines for the sample size of pilot and main studies.[26] The pilot will take place in up to 8 sites chosen to reflect those sites that will take place in the main trial and will be used to confirm recruitment, randomisation, treatment and follow-up assessments.

The recruitment rate is anticipated to be one patient per centre, per month open to recruitment. Success criteria for recruitment will be based on the traffic light system:

(a) **Go:** 75-100% recruitment = progress to main trial following a review of screening logs and protocol. Any barriers to recruitment will be addressed.
(b) **Amend:** 50-75% recruitment = progress to main trial with additional sites being recruited as well as a screening log and protocol review.
(c) **Stop**: <50% recruitment = the decision to progress will be made by the TSC in association with the funder.

Protocol compliance and the completeness of follow-up data will be reviewed by the TSC noting that 6 month follow-up data will not be completed by the end of the pilot.

On reaching the pre-defined success criteria, the internal pilot will run seamlessly into the main SOS Trial. Results from the pilot study will be reported in the HTA Monograph in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines for pilot studies. We will continue monitoring processes to ensure the trial is delivered as planned.

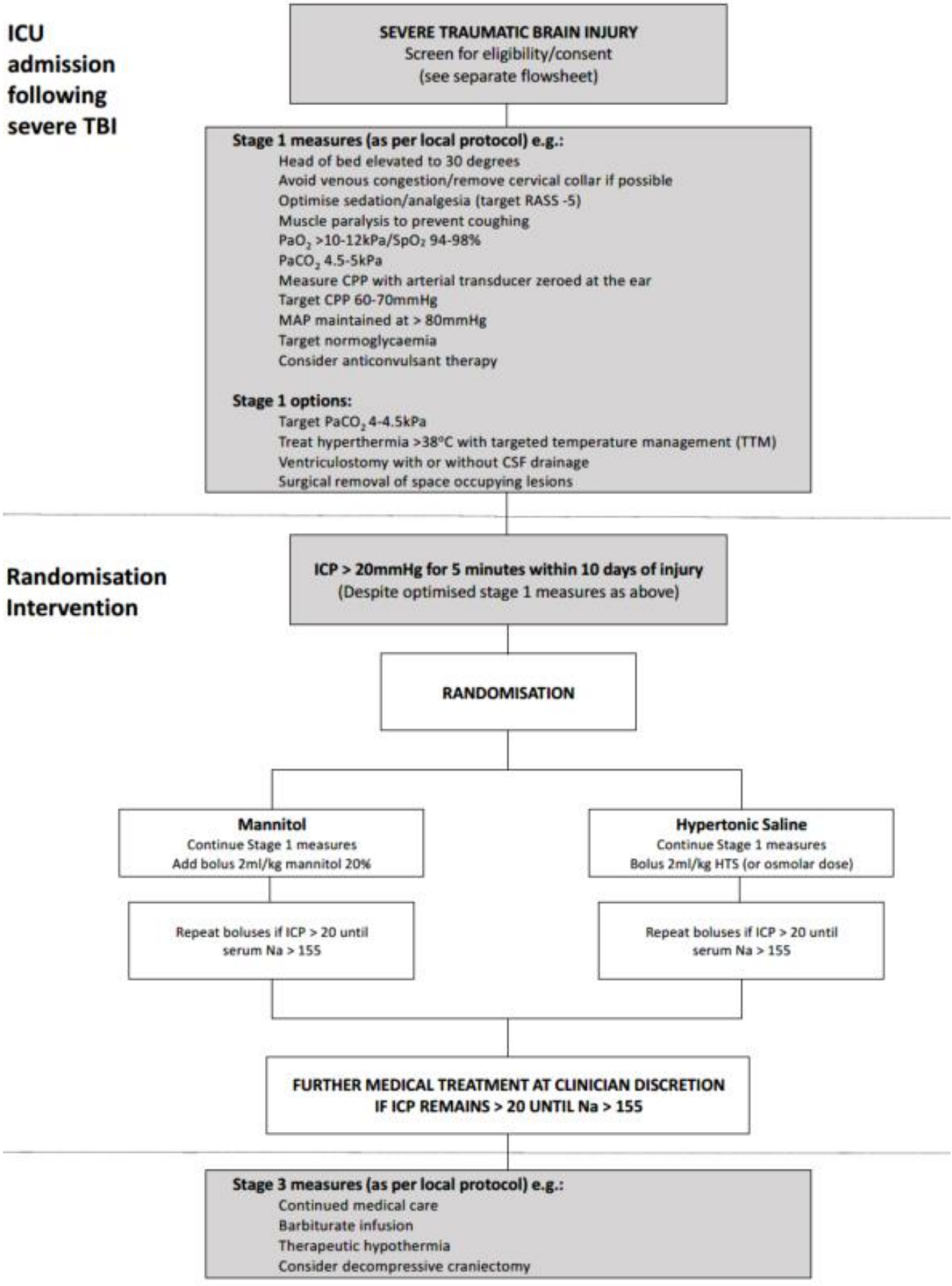


Figure 3: SOS trial flow diagram

2.3 Trial objectives

2.3.1 Primary objective

The primary objective of this trial is to compare the effectiveness of hypertonic saline versus mannitol (as measured by the GOS-E questionnaire at 6 months) following TBI with raised ICP.

2.3.2 Secondary objectives

Secondary objectives are to assess the effects of hyperosmolar therapy comprising hypertonic saline or mannitol on clinical, patient-centered and economic outcomes in the ICU, in hospital and up to 12 months follow-up post randomisation. These will provide a definitive assessment of the clinical and cost effectiveness of hyperosmolar treatments in the management of TBI.

2.4 Outcome measures

2.4.1 Clinical outcomes

Primary Outcome

The primary trial outcome will be the GOS-E at 6-months post-randomisation. The GOS-E questionnaire is a global functional outcome scale incorporating assessment of functional status, independence and role participation, and is recommended as the core global outcome for TBI research (http://comet-initiative.org/studies/details/562). This scale is the most commonly used global outcome measure in published research on TBI and can be reliably collected through a structured questionnaire/interview. Response rates at 6 months in previous large Randomised Controlled Trials RCTs have been excellent (up to 99%). The eight outcome categories are:

- **Death**
- **Vegetative state** (unable to obey commands)
- **Lower severe disability** (dependent on others for care)
- **Upper severe disability** (independent at home and outside the home but with some physical or mental disability)
- **Lower moderate disability**
- **Upper moderate disability**
- **Lower good recovery** (able to resume normal activities with some injury related problems)
- **Upper good recovery** (no problems)

Secondary Outcomes

Efficacy

1. ICP control (during period of monitoring in ICU)
2. Progression to stage 3 therapies
3. Which stage 3 therapies were required

Resource use

4. Organ support requirements during ICU
5. Critical care length of stay
6. Hospital length of stay

Patient outcomes

7. Longer term neurological outcomes: mOHS at discharge and GOS-E at 12 months
8. Survival: to hospital discharge (the time at which the patient is discharged from the hospital regardless of neurological status, outcome or destination) and at 3 months, 6 months and 12 months
9. Quality of life: EQ-5D-5L at hospital discharge, 3 months, 6 months and 12 months post-randomisation

Adverse events

10. Serious adverse events

Outcome measurements

- Neurological outcomes will be measured using the mOHS at hospital discharge, and the GOS-E at 6 and 12 months. The mOHS at discharge has been shown to be correlate highly with GOS-E scores at 6 months in a previous TBI study. [27]
- ICP will be recorded continuously or at regular intervals.
- Treatment failure will be defined as progression to stage 3 treatments (i.e. any use of additional treatments e.g. barbiturate coma, decompressive craniectomy and hypothermia).
- Need for other treatments will capture the frequency and individual components of stage 3 treatment described above.
- Resource use will comprise of daily organ support requirements according to the Critical Care Minimum Data Set definitions, critical care and hospital length of stay.

2.4.2 Safety

There will be a system for reporting serious adverse events in addition to the trial outcomes by participating centres (see Section 4). See section 6.2 for information relating to interim analyses and early stopping criteria.

2.4.3 Health Economics

Primary economic outcome

The primary health economic outcome will be incremental cost per Quality-Adjusted Life Year (QALY) gained from the perspective of the NHS and personal social services perspective.

Secondary economic outcomes

Cost of critical care stay (level 2/3 days); cost of hospital stay; utilisation of NHS and PSS resources after discharge; broader resource utilisation after discharge.

2.5 Sample size

The originally planned size of this trial is 638 patients. This is based on a superiority hypothesis of a difference between the two interventions, using 90% power, a significance level of 5% with a dropout/withdrawal rate of 6%. In order to detect a treatment reduction of 13% (63.5% to 50.5%) in

the proportion of patients having a unfavourable (worse) neurological outcome (GOS-E: dead, vegetative state, lower severe disability, upper severe disability) compared to better outcome (GOS-E: lower moderate disability, upper moderate disability, lower good recovery, upper good recovery) between mannitol and hypertonic saline, 319 patients would be required on each arm.

Details of the evidence for the sample size parameters can be found in the previous protocol versions (v1.0-6.0).

However, the dichotomisation leads to a reduction in statistical power and loss of information, which means that more patients are required in the study to detect a fixed clinically relevant difference.

The RESCUE-ICP study (Hutchinson, 2016)[11] and the RESCUE-ASDH study have adopted the approach of using the ordinal scale of the GOS-E as their primary outcome. The main advantage of this is that it yields substantial efficiency gains in comparison with the conventional dichotomous analysis and as such is the preferred method described by the TBI-IMPACT recommendations (Maas et al. 2010)[28]. It will assist to decrease the sample size, in the presence of challenges in recruitment with the SOS trial. Although ordinal regression, the commonly used method for ordinal data analysis, has a stringent assumption of proportional odds, it should not set precedence for rejecting the results from a proportional odds model (https://www.fharrell.com/post/po/). By adopting an ordinal outcome, we will be able to gain efficiency in power and carry out important comparisons of the refined outcome categorisation.

With the recommendations of the independent committees (TSC, DMEC) and TMG as well as the approval by the funder, we changed the primary outcome to the ordinal GOS-E score at 6 months.

The sample size calculation is still based on a superiority hypothesis of a difference between the two interventions, using 90% power, a significance level of 5%. We aim to detect an absolute reduction of 13% in the form of binary outcome (71.9% to 58.9% unfavourable neurological outcome, as opposed to 63.5% to 50.5%, based on the observed rate using SOS data up to 1st February 2023). The dropout/withdrawal rate was also updated from 6% to 16% based on the observed data. Hence, the new sample size is 468, using recently available statistical methods based on ordered data (White, 2023)[29].

2.6 Eligibility criteria

Patients are eligible to be included in the trial if they meet the following criteria:

2.6.1 Inclusion criteria

1. Adult aged $\geq$ 16 years old
2. Admission to ICU following TBI
3. ICP > 20mmHg for more than 5 mins despite stage 1 procedures
4. < 10 days from the initial primary head injury
5. Abnormal CT scan consistent with TBI

2.6.2 Exclusion criteria

1. Devastating brain injury with withdrawal of treatment anticipated in the next 24 hours
2. Pregnancy[¥]
3. Severe hypernatraemia (defined as serum Na > 155 mmol/L)
4. 2 or more prior doses of hyperosmolar therapy given on ICU

This is a pragmatic trial and therefore will not exclude patients that are given hyperosmolar therapy prior to ICU admission. The rationale is that this trial is addressing the use of hyperosmolar therapy in monitored patients in intensive care. Un-monitored hyperosmolar therapy occurs in practice currently and is likely to continue after this trial. Following ICU admission, patients who have received a single dose of hyperosmolar therapy as a rescue (providing serum Na <155) or a constant infusion of hypertonic saline to correct a low serum sodium level to normal (as the purpose is different to trial) will also not be excluded. The sub-set of patients (with clinical signs of raised ICP) frequently will go direct to theatre for surgical intervention, which may resolve the raised ICP or indicate that injuries are non-survivable.

[¥]Pregnancy is not a contraindication to hyperosmolar therapy, and TBI during pregnancy is relatively uncommon. However, for regulatory reasons, patients who are known or appear to be pregnant are required to be excluded from the trial.

2.7 Co-enrolment

Co-enrolment to other concurrent Clinical Trials of Investigational Medicinal Products (CTIMPs) and non-CTIMP studies will be considered on a case-by-case basis. Patients who are known to have participated in a CTIMP within the preceding 30 days are not permitted to be enrolled in this trial, unless co-enrolment has been agreed.

Co-enrolment to other studies will be allowed where the PIs and/or trial management teams have considered the scientific and practical implications of co-enrolment and agreed that co-enrolment is permitted, referring to UK guidance for critical care trials and/or local SOPs. The option for co-enrolment will only apply where agreement has been reached between the two studies prior to an individual participant being considered for inclusion, and this has been documented in the trial materials and site files.

2.8 Participant identification/screening

2.8.1 Sites

The main trial will take place in up to 28 UK NHS hospitals with ICUs with a proven track record of participating in critical care / neurosurgical research. We know that these centres have access to the TBI population and that consultants and staff managing the patients have clinical equipoise for the

use of protocolised hyperosmolar therapy (either mannitol or hypertonic saline) and agree to maintain trial allocation in randomised patients. To further improve recruitment and decision making regarding study enrolment, we have identified both neurosurgical and intensive care PIs for each site. This is because there is often local variation regarding which clinical team is responsible for the clinical management of patients with severe TBI requiring ICU admission. Local research staff must also demonstrate and document a willingness to comply with the protocol, the principles of GCP and regulatory requirements and be prepared to participate in training. Sites will need to establish experience with receiving and acting on protocolised advice on the management of TBI patients. This will be addressed with a "run-in" period while the pilot phase is ongoing with all sites having access to the educational package.

2.8.2 Patients

All patients admitted to ICU with severe TBI will be screened by hospital/research staff on the ICU. Screening should be a continuous process as patients could be admitted at any time of day and may become eligible for the trial very quickly. We will work with each recruitment centre (including those in Northern Ireland, Scotland and Wales) to adopt best practice for screening. Screening information will be entered on to a trial web application, hosted by Warwick Clinical Trials Unit (WCTU), and will include data on the numbers of patients meeting inclusion criteria for the trial but not entered into the trial along with the reasons for non-enrolment. Recording this information is required to establish an unbiased study population and for reporting according to the CONSORT statement. Screening of patients will involve reviewing personal identifiable information of patients, which may be undertaken by a member of the patient's existing clinical care team, or by a member of the hospital research team, depending on local arrangements.

All laboratory and diagnostic testing needed to confirm eligibility will be performed as part of routine care. Confirmation that all eligibility criteria are met will be entered on to the trial web application prior to the patient being randomised. Patient eligibility will be confirmed by the Principal Investigator (PI), or a nominee that the PI feels is clinically competent to perform this task. The PI nominee will include medical practitioners and advanced clinical practitioners (e.g. advanced critical care practitioners (ACCPs) who would typically assess the indications for and prescribe hyperosmolar therapy as part of their practice; these persons will be able to assess eligibility and enrol patients in SOS if trained in the trial protocol. In the event that an advanced clinical practitioner is assessing eligibility, access to a medically qualified doctor should be available.

2.8.3 Recruitment and retention

The UK TBI audit indicates that approximately 1000 patients have ICP monitored annually. This concords with our audit across 10 sites informing this application. Approximately 70% (700) patients receive hyperosmolar therapy, thus a population of 3500 patients are expected to be available during the 5 year recruitment window for this trial. We will aim to recruit 468 patients over a period of 63 months from approximately 25 sites. The trial will require 0.5 patient per month per centre during the duration of the trial, which will include the internal pilot. We have increased this to one patient per centre per month to account for a staggered site set up.

Recruitment and retention will be reviewed on a monthly basis in the Trial Management Group (TMG) meeting and will be closely reviewed by the independent monitoring committees as well as the representatives from HTA. A CONSORT flow diagram will display the recruitment and retention in the study.

2.9 Site Staff Training

The patient's direct clinical care team, or hospital research team, will be responsible for identifying potential patients and taking consent. The PI retains overall responsibility for informed consent at their site and must ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent.

Site staff will be trained in the trial protocol, data collection and the consent process prior to undertaking these trial activities.

2.10 Randomisation

2.10.1 Randomisation

A simple and secure, web-based and allocation concealed randomisation system will be established by the programming team. A computer-generated randomisation sequence will be generated by the minimisation method and patients will be randomised in a ratio of 1:1 to either mannitol or hypertonic saline. Patients will be stratified by site, and predicted probability of 6 month unfavourable outcome. This predicted probability will be calculated using age, pupillary response and documented GCS motor score at intubation using the IMPACT calculator.[30] Local PIs will be asked to document participation in the trial either in the paper notes or electronic patient records (as applicable locally). In the event that the web-based system cannot be used, an emergency Interactive Voice Response (IVR) randomisation system will also be in place, in addition to an emergency paper-based system at WCTU (available Monday-Friday 9am-5pm). To use this, site staff should call the WCTU on 024 7615 0402 and they will be informed of the participant's trial number and treatment allocation over the phone. This information will then be added to the trial database retrospectively.

2.10.1 Post-randomisation withdrawals, exclusions and moves out of region

Participants, or their legal representatives on their behalf, may request to be withdrawn from the trial at any time without prejudice. Previous ICU studies coordinated from WCTU have managed to achieve consistently >98% follow-up for their primary outcome (e.g. BALTI-2, HARP-2, BREATHE and OSCAR).

Patients who are later found to be ineligible but who have received the trial drug will be included in follow-up and in the final analysis. Patients or legal representatives who decline to be contacted will be logged on the database from the point that they communicate their intention to the trial team and no further contact will be made. Data already collected will be retained and included in the analysis unless otherwise indicated. The information sheet explains the trial and the data that will be collected. Patients and legal representatives will be informed that the research team will continue

to collect data remotely as per the protocol until the end of the trial, unless they explicitly withdraw their consent for this. In the rare situation where a patient or legal representative has neither consented nor declined, they will not be sent follow-up questionnaires, but remote data collection as per trial protocol will continue. This will be made explicit in the patient information sheet and consent forms.

Participants may be withdrawn from the trial intervention at the discretion of the investigator and/or TSC due to safety concerns.

2.11 Trial interventions

2.11.1 Trial intervention

Within 10 days of the estimated primary TBI and provided the patient satisfies the other inclusion criteria as specified in section 2.6.1 above, they will be randomly assigned to boluses of either mannitol or hypertonic saline using the concentration used locally by participating study centres.

Doses administered will be equi-osmolar as per the dosing table below (Table 2), which provides the volume (ml) of IMP to be administered according to the concentration of IMP used and the patient's weight. If the patient's weight exceeds 155kg, equi-osmolar doses will be calculated on a case-by-case basis.

IMP will be administered by clinical staff in accordance with local policy.

There may be instances where the dose or treatment given needs to be tailored to the individual characteristics of the patient or the TBI case based on clinical judgement for the best interest of the patient.

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.

Weight (Kg)	**<35-39**	**40-44**	**45-49**	**50-54**	**55-59**	**60-64**	**65-69**	**70-74**	**75-79**	**80-84**	**85-89**	**90-94**	**95-99**	**100-104**	**105-109**	**110-114**	**115-119**	**120-124**	**125-129**	**130-134**	**135-139**	**140-144**	**145-149**	**150-154**
Weight for calculation	**35**	**40**	**45**	**50**	**55**	**60**	**65**	**70**	**75**	**80**	**85**	**90**	**95**	**100**	**105**	**110**	**115**	**120**	**125**	**130**	**135**	**140**	**145**	**150**
Mannitol (ml)																								
20%	70	80	90	100	110	120	130	140	150	160	170	180	190	200	210	220	230	240	250	260	270	280	290	300
15%	105	120	135	150	165	180	195	210	225	240	255	270	285	300	315	330	345	360	375	390	405	420	435	450
10%	140	160	180	200	220	240	260	280	300	320	340	360	380	400	420	440	460	480	500	520	540	560	580	600
Hypertonic saline (ml)																								
30%	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
23%	11	12	13	15	17	18	20	21	23	24	26	27	29	30	32	33	35	36	38	39	41	42	44	45
7.50%	31	36	40	45	50	54	59	63	68	72	77	81	86	90	95	100	104	108	113	117	122	126	131	135
5%	46	52	59	65	72	78	85	91	98	104	111	117	124	130	137	143	150	156	163	169	176	182	189	195
2.70%	84	96	108	120	132	144	156	168	180	192	204	216	228	240	252	264	276	288	300	312	324	336	348	360

Table 2. Dosing table for equi-osmolar doses (ml/kg) of Mannitol (osmolarity = 1100 mOsm/L) and Hypertonic Saline (osmolarity = 1026 mOsm/L).

2.11.2 Drug storage, labelling and dispensing

As highlighted in the 2018 national survey, both mannitol and hypertonic saline are routinely used in the clinical management of patients with TBI. Sites selected for participation in the trial have been identified as routinely using both drugs in the management of raised ICP. The doses administered will be equi-osmolar. Storage and dispensing of mannitol and hypertonic saline will follow local protocols. There will be no trial specific labelling requirements as NHS clinical stock of both drugs will be used for the trial interventions. The name of the substance, strength, pharmaceutical form, route of administration, batch number and expiry date will be listed on the standard packaging for the mannitol and hypertonic saline. Sponsor and investigator contact details can be found within the trial protocol and on the trial web application.

2.11.3 Drug accountability

As the trial is a Type A trial there is no requirement for shipping receipt and destruction records, drug accountability and recording batch numbers/expiry dates (unless part of routine practice). Data on administration of the IMP will be captured in the trial Case Report Forms (CRFs).

2.11.4 Compliance/contamination

Compliance with the study protocol will be monitored centrally during the pilot study, and throughout the trial, to ensure the interventions in the trial and other routine clinical care are conducted consistently.

Crossover between arms and the requirement for other treatments (e.g. barbiturate coma, decompressive craniectomy) will be documented.

Contamination will be minimised through standardising and protocolising routine clinical management of TBI in both groups in line with Brain Trauma Foundation guidelines (see Trial flowsheet in Figure 3).

2.12 Blinding/Prevention of other bias

To ensure appropriate treatment, participants must be monitored closely and investigation results known to the treating clinical staff. As patient safety is paramount, and key patient clinical parameters (urine output and serum sodium levels) monitored in TBI patients will be influenced by the IMPs, it is not possible to blind clinical staff as to the patient's treatment allocation.
We will not specifically set out to inform patients or their legal representative of the treatment allocation. We recognise however that it may become evident during the course of the patient receiving the treatment.

2.12.1 Methods for protecting against bias

Patients will be stratified and randomised using a web-based randomisation sequence with the minimisation method. Patients will be randomised in an equal allocation ratio of 1:1 (hypertonic saline:mannitol) ensuring allocation concealment to reduce selection bias.

We will limit the effect of knowledge of treatment allocation through the use of clinical protocols of TBI treatments to reduce performance bias. Treatment allocation will not be intentionally revealed to the patient or their legal representative.

We will reduce detection bias by allocating all patients a unique study number during the randomisation process which will be used on all data collection forms and questionnaires. Treatment allocation will be stored in a secure part of the trial database which will only be accessible to a limited number of authorised trial staff. The primary outcome will be completed via a questionnaire posted to the patient or their legal representative. The main clinical and resource utilisation outcomes for this study and adverse events are recorded contemporaneously on patient clinical records or are collected by questionnaire. We will undertake source data verification (from clinical records) and hospital computer records as described in our data management plan.

Data completeness and withdrawal rates will be reviewed by the DMEC to monitor for any systematic differences between groups to limit attrition bias.

The trial outcomes are defined, *a priori,* in this protocol and will be entered in to the ISCRTN registry and EudraCT prior to recruitment of the first patient. The Statistical Analysis Plan (SAP) will be finalised prior to database lock. Any post-hoc analyses will be clearly identified as such in subsequent publications. These steps will minimise the risk of reporting bias.

2.13 Concomitant illness and medication

2.13.1 Concomitant illness

Significant past medical illness will be recorded by a member of the research team. There are no significant illnesses which represent contra-indications to the administration of either mannitol or hypertonic saline.

2.13.2 Concomitant medication

Concomitant treatments will be recorded by a member of the research team.

2.14 End of trial

After a 6 month set-up period, an internal pilot will run for 6 months. Assuming pre-defined milestones are achieved, the internal pilot will run seamlessly into the main trial.

We plan to accrue our target sample size in a further 57 months (with a total recruitment time of 63 months) and follow-up for 6 months. The end of trial is defined as the last trial data being received and queries resolved. Analysis and reporting will require a further 6 months. Therefore, the total project duration is 81 months and the planned project end date is 28/02/2026.

The trial will be stopped prematurely if:

- Mandated by the Ethics Committee

- Mandated by the MHRA
- Following recommendations from the DMEC
- Funding for the trial ceases

The Research Ethics Committee and MHRA will be notified in writing within 90 days when the trial has been concluded or within 15 days if terminated early.

3. METHODS AND ASSESSMENTS

3.1 Schedule of delivery of intervention and data collection

Table 3:

	1	2	3	4	5	6	7
	ICPM insertion	ICP > 20 for 5 minutes	Hospital	Hospital discharge	Month 3 (2 - 4)	Month 6 (5 - 10)	Month 12 (11-13)
Informed consent	X	X	✓	X	X	X	X
Inclusion/ exclusion criteria	✓	✓	X	X	X	X	X
Patient identifiers	✓	X	X	X	X	X	X
Demographics	✓	X	X	X	X	X	X
Medical history	✓	X	X	X	X	X	X
Best GCS score prior to intubation/ sedation	✓	X	X	X	X	X	X
CT scan	✓	X	X	X	X	X	X
Details of TBI	✓	X	X	X	X	X	X
Intervention	X	✓	X	X	X	X	X
ICP control	✓	✓	✓	X	X	X	X
Adverse event reporting, stage 3 therapies, treatment failure, organ failure	X	✓	✓	X	X	X	X
ICU/Hospital length of stay	X	✓	✓	✓	X	X	X
Survival status	X	X	X	✓	✓	✓	✓
Neurological outcome (mOHS)	X	X	X	✓	X	X	X
Neurological outcome (GOS-E)	X	X	X	X	X	✓	✓
Quality of Life (EQ-5D-5L)	X	X	X	✓	✓	✓	✓
Health Economics Questionnaire	X	X	X	X	✓	✓	✓

3.2 Laboratory assessments

Serum blood samples may be collected as part of a future sub-study, subject to funding. Further detail will be provided once funding is confirmed. Routine laboratory assessments will be captured in the trial database.

3.3 Radiological data

Data from computed tomography (CT) scans may be collected as part of a future sub-study. Further detail will be provided once funding is confirmed. Routine scan data will be captured in the trial database.

3.4 Follow-up

TBI patients who survive to hospital discharge will be followed up approximately 3, 6 and 12 months after their TBI as per **Table 2.** Outcome data (GOS-E and quality of life outcomes and resource use) will be collected by postal questionnaires or online Qualtrics questionnaires which will be sent to the patient or their legal representative by the WCTU trial team. If the patient regains capacity prior to hospital discharge, the questionnaire will be posted or a text message link sent to the patient and/or their legal representative. A text message or email will be sent when the questionnaire is posted to let them know it's on its way. Completed paper questionnaires will be returned to WCTU using a pre-paid envelope. If a response is received from both the patient and their legal representative, then the response from the patient will take precedence. If the patient is still in hospital, research staff will aim to obtain their data by visiting them and if required, assisting them with the completion of this questionnaire. If the patient has been discharged, then the status of the patient will be checked e.g. by the GP register route or Summary Care Record before a questionnaire is sent out or link texted. Participants will receive a £10 monetary voucher with their 3-, 6- and 12-month questionnaires as a compensation for their time spent completing the questionnaire. Vouchers will be provided regardless of whether questionnaires are completed or returned.

In the case of no response from the patient or legal representative within 2 weeks, a phone call, text message or email will act as a reminder. If necessary another questionnaire will be sent to act as a reminder. If there is still no response, then we will telephone the patient or legal representative in the view to collect the core information from the questionnaire. Alternatively the patient's carer, GP or professionals involved in their care will be contacted for this information. In some cases a telephone interview will need to be undertaken by a member of the research team, for example if there are practical difficulties with filling in or returning the questionnaire, or posting out the questionnaire due to the COVID-19 pandemic.

If no response is obtained from the patient's carer or GP for the 6 month and 12 month GOS-E score, the recruiting hospital site will be contacted to request this based on the most up to date patient medical notes. Where the site is unable to provide a GOS-E, use of a clinical adjudication panel will be an option to use the data that is available to assess whether the patient outcome at 6 months is favourable or unfavourable.

To ensure accurate, complete and reliable data are collected, the WCTU will provide training to site staff in the format of investigator meetings and site initiation visits. Quality assurance procedures and process evaluation will be put in place to ensure training is delivered in a standardised manner. The WCTU will provide the local PIs and research staff with training on the protocol, completion of the CRF and trial procedures including SOPs.

4. ADVERSE EVENT MANAGEMENT/PHARMACOVIGILANCE

4.1 Definitions

4.1.1 Adverse Events (AE)

An AE is defined as any untoward medical occurrence in a patient or clinical investigation participant taking part in health care research, which does not necessarily have a causal relationship with the research.

4.1.2 Adverse Reaction (AR)

An AR is defined as all untoward and unintended responses to either mannitol or HTS related to any dose administered.

4.1.3 Serious Adverse Events (SAEs), including Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARS)

An AE or AR is considered serious if it fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent/significant disability or incapacity
- Is a congenital abnormality or birth defect
- Requires medical intervention to prevent one of the above, or is otherwise considered medically significant by the investigator (e.g. participant safety is jeopardised).

Suspected Unexpected Serious Adverse Reactions (SUSARs) are SARs that are considered to be related to the administration of the trial drug and are also unexpected i.e. their nature or severity is not consistent with the current approved Reference Safety Information for the trial. There need only be an index of suspicion that the event is a previously unreported reaction to the IMP, or a previously reported but exaggerated or unexpectedly frequent adverse drug reaction.

4.2 Reporting SAEs and SUSARs

Events that do NOT need to be reported as SAEs

The trial is being conducted in a critical emergency condition using two drugs which are in common use. Events that are known to occur in TBI patients requiring ICU admission do not need to be reported as SAEs even though they may fulfil criteria for 'serious'. These exclusions from reporting are listed below:

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

The pre-specified outcomes of death, disability and organ failure will be recorded on the trial CRF and monitored by the independent DMEC.

Any SAEs/SARs/SUSARs that occur from the **time that the patient is randomised, through to and including 28 calendar days after the last administration of IMP** must be reported to WCTU. This timeframe may be extended to hospital discharge, but it will never be less than 28 days under any circumstances.

If the patient is discharged from hospital prior to the end of the 28 day reporting window, any SAEs/SARs/SUSARs that the site become aware of during the reporting timeframe must still be reported to WCTU. However, sites do not need to actively follow up with the patient to determine if any SAEs have occurred post-discharge.

SAEs/SARs/SUSARs must be reported to WCTU by email **within 24 hours of first becoming aware of the event or reaction to WCTUQA@warwick.ac.uk.**

For each SAE/SAR/SUSAR the following information will be collected:

- full details in medical terms and case description
- date site aware (Reporting of the SAE to WCTU will be expected to occur within 24 hours of this date)
- event duration (start and end dates, if applicable)
- action taken
- outcome
- date deemed serious
- seriousness criteria
- causality (i.e. relatedness to IMP / investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected (this assessment will be completed by WCTU).

Any change of condition or other follow-up information should be emailed to WCTU as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

All reports of SAEs or SARs will be reviewed on receipt by the Chief Investigator (CI) or a medically qualified delegate, and those that are considered to satisfy the criteria for being related to the drug and unexpected will be notified to the REC, MHRA and Sponsor as a SUSAR within 7 or 15 days of receipt in accordance with regulatory requirements. Reports of SAE/SAR/SUSAR will also be reviewed by the TMG and DMEC at their regular meetings, or more frequently if requested by the DMEC Chair.

The causality of SAEs (i.e. relationship to trial treatment) will be assessed by the investigator(s) on the SAE form.

Relationship to trial medication	**Description**
Unrelated	There is no evidence of any causal relationship
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication or device). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication or device). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

Responsibilities are as follows:

- **Principal investigator or medically qualified delegate**: Assess causal relationship to administration of IMP based on knowledge of drug and patient
- **CI or medically qualified delegate**: also assess causality based on knowledge of drug and protocol
- **Appropriately trained WCTU team members**: will assess expectedness against the Reference Safety Information if PI and/or CI deem there to be at least a possibility of causal relationship

4.2.1 Reference Safety Information

Section 4.8 of the SmPC for mannitol and hypertonic saline will be used as the reference safety information.

4.3 Procedures in case of overdose

Overdoses come under 'Patient Safety Incidents' and are defined as 'any unintended or unexpected incident which could have or did lead to harm for one or more patients' (also may be referred to as adverse incidents, clinical errors or near-miss). Although not a requirement of the CT regulations, the PI at each centre should ensure their NHS Trust is notified of any patient safety incidents, according to local policy and should inform WCTU within 24 hours of becoming aware of the incident.

4.4 Procedures in case of pregnancy

Known pregnancy at the time of TBI is an exclusion criterion for this trial.

The SmPC for mannitol reports "There are no adequate published data from the use of mannitol in pregnant women. There are no adequate published data, from animal studies, with respect to mannitol's effect on pregnancy and/or embryo/foetal development and/or parturition and/or postnatal development. Mannitol should not be used during pregnancy unless clearly needed. There is no information on excretion of mannitol in breast milk. Mannitol should not be used during lactation unless clearly necessary."

The SmPC for Hypertonic Saline reports "It is safe to use in pregnancy and lactation after risk assessment."

Should the patient later be known to have been pregnant at the time of TBI and trial intervention (e.g. positive B-HCG sample) then the following will apply:

- Discontinue trial interventions
- Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP under study may have interfered with the effectiveness of a contraceptive medication
- The outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth or congenital abnormality) must be followed up and documented even if the subject was discontinued from the study
- All reports of congenital abnormalities/birth defects must be reported and followed up as a SAE

4.5 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the MHRA and the relevant REC of the measures taken and the circumstances giving rise to those measures.

5. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with the Data Protection Act 2018 and Warwick SOPs.

5.1 Data collection and management

The data dictionary and bespoke CRFs will be designed by the Trial Manager in conjunction with the CI, Statistician and local PIs to ensure consistent data are captured through the trial. This will capture baseline characteristics (patient demographics, comorbidities, pre-admission function, inclusion/exclusion criteria, consent, GCS motor score, date/time and mechanism of TBI, , CT scan appearance (Marshall category 1-6), details of injury on head and other body systems). Daily data captured following randomisation will include ICP, blood pressure, ICU / hospital admission status, resource use (Critical Care Minimum Dataset (CCMDS)), AEs (treatment failure, need for other treatments, electrolytes, renal function, renal replacement therapy), survival status. After discharge, data will be collected on GOS-E, survival status, EQ-5D-5L, utilisation of community care resources after acute hospital discharge up to 12 months after randomisation.

Once consent has been obtained, personal identifiable information will be shared with WCTU, to allow future contact and follow-up. Handling of personal identifiable data will occur in accordance with Warwick SOPs. Where we have not been able to collect data about the patient's stay in hospital, such as length of stay on ICU, this will be collected from Intensive Care National Audit and Research Centre (ICNARC), or Hospital Episode Statistics from Patient Episodes Database for Wales (PEDW), or Information Services Division Scotland, or Health and Social Care Northern Ireland where feasible. Survival status and health outcomes will be tracked through linkage (NHS England), hospital and/or GP records.

Mortality will be reported from hospital records up until discharge and tracked after discharge using the NHS England tracking service, hospital records and GP records. ICU and hospital length of stay will be obtained from local centres.

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.
CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data).

5.2 Database

The database has been developed by the Programming Team at WCTU and all specifications (i.e. database variables, validation checks, screens) have been agreed between the programmer and appropriate trial staff. The database is accessible through an online web application.

5.3 Data storage

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel. Any paper data forms will be stored in a lockable filing cabinet in a secure room, to which access is restricted to authorised personnel. Electronic data will be stored in a secure area of the

computer with access restricted to staff working on the trial and the WCTU Quality Assurance team. All databases containing identifiable information will be password protected. Any data that are transferred out of the secure environment (for example for statistical analysis, ICNARC, NHS England) will adhere to our unit SOPs.
On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number, not by name.

5.4 Data access and quality assurance

Personal patient identifiable data from enrolled participants will be stored securely at WCTU in accordance with GCP, the General Data Protection Regulation (GDPR) and the Data Protection Act 2018. Participants will be identified by code only. Laboratory specimens and radiological data will be identified by the same code.

5.5 Data Shared with Third Parties

The trial statisticians and DMEC will have access to the dataset for the analysis of trial outcomes. Once the main analyses have been undertaken, deidentified individual participant data will be available to principal and other investigators subject to approval of data analysis plans by the TSC and compliance with the University of Warwick SOPs on Data Management and Sharing. We will comply with Data Sharing Policies that may be instituted by the NIHR during the lifetime of the project.

5.6 Archiving

Trial documentation and data will be archived for at least ten years by the coordinating centre and at sites after completion of the trial. Electronic data sets will be stored indefinitely.

6. STATISTICAL ANALYSIS

The main statistical analysis will be using intention-to-treat, which will include all randomly assigned patients, unless they have withdrawn their consent specifically with regards to using their data. We will carry out a complier average causal effect (CACE) analysis to address the issue of non-compliance.[31]

6.1 Analysis of primary/secondary outcomes

Primary outcome analyses

For the primary analysis, we will compare the ordinal outcome of the 6-month GOS-E questionnaire between the two intervention arms using the ordinal logistic regression model, based on the proportional odds (PO) assumption. The PO assumption will be tested using the score test. If the assumption is violated, we will report the results of both PO and non-PO models as the PO model provides a useful estimation of the average treatment effect over the ordinal categories. Odds ratio

with 95% confidence interval will be reported. Stacked bar charts will be used to display the observed GOS-E data. This analysis will be adjusted for key clinically important co-variates. Odds ratios and 95% confidence intervals will be presented.

As a secondary analysis, we will assess the binary GOS-E (i.e., unfavourable versus favourable) using binary logistic regression models.

A further exploratory analysis to assess the impact of missing outcome data on the GOS-E questionnaire will be examined using multiple imputation techniques. In addition to this, we will assess the unfavourable neurological outcome (GOS-E: 1-4) against the favourable neurological outcome (GOS-E: 5-8) using similar methods as stated above.

Secondary outcomes analyses

Survival status to hospital discharge will be examined in a similar way to the binary GOS-E questionnaire. In addition to this survival status over the course of the study (3, 6 and 12 months) and to time to discharge (ICU and hospital) will be assessed using Kaplan-Meier plots. The survival curves will be assessed using the log-rank test (unadjusted) and the Cox-proportional Hazards model (adjusted).

Continuous variables will be examined using linear regression models and summarised using mean, standard deviation, median and range values. Categorical data will be assessed using logistic regression models and summarised using the number of patients and proportions. Where appropriate, 95% confidence intervals will be presented with the appropriate point estimates.

In order to obtain more insight into the primary outcome, Bayesian methods will be used taking various informative from the literature.

6.2 Interim analyses

The timing and frequency of the interim analyses will be discussed and agreed with the DMEC members and a detailed SAP will be written by the trial statistician and approved by the DMEC prior to any interim analysis. It is anticipated that no more than one formal interim analysis will take place during the course of the study. We will formalise the statistical stopping criteria using the O'Brien and Fleming stopping rules[32]. In making a decision to terminate the clinical trial, the DMEC will use the statistical evidence as guidance to their decision making and will be also presented with a 95% confidence interval of the treatment difference.

6.3 Sub-group analyses

Exploratory analyses will be reported using 99% confidence intervals. Binary logistics regression (GOS-E at 6 months: unfavourable versus favourable) will be used with interaction terms (treatment group by sub-group) for the following sub-groups selected:

- Age (<45, ≥45 years)
- Time from TBI (<12 hours, ≥ 12 hours)
- Pupillary response at randomisation (both or one, none)

- Severe TBI v moderate TBI as illustrated by the GCS (3-8, 9-12)
- Bolus of hyperosmolar therapy prior to inclusion in the study
- Blood level of sodium before inclusion (<138 mmol/L, 138-145 mmol/L, >145 mmol/L)
- ICP level at randomisation
- Craniotomy or craniectomy before randomization (yes/no)
- Polytrauma (yes/no)
- Type of brain injury (diffuse or non-diffuse)

The statistical analyses will be formalised in a SAP and approved by the DMEC.

6.4 Health Economic Evaluation

A prospectively planned economic evaluation will be conducted from a NHS and personal social services perspective, in accordance with an agreed Health Economics Analysis Plan (HEAP). The methods will adhere to the recommendations of the National Institute for Health and Care Excellence (NICE) Reference Case.[33]

Resource use will include intervention, hospital (ICU, High Dependency Unit and ward days) and community costs (primary care and social care costs) in the first 12 months following intervention. Resources will be costed using national reference unit costs where available, reflated to current prices.

Health-related quality of life (EQ-5D-5L) responses will be used to generate QALYs using the UK time-trade-off (TTO) value set recommended by the EuroQol group and Area Under the Curve (AUC) method.[34] The baseline EQ-5D-5L values will be imputed to reflect the unconscious health state and applied to all patients, minimising potential bias in the QALY AUC calculation.

Within-trial analysis (to 12 months) using bivariate regression of costs and QALYs will inform a probabilistic assessment of incremental treatment cost- effectiveness.[35] Following best practice, missingness mechanisms will be explored and multiple imputation methods will be used where appropriate to avoid biases associated with complete case analysis.[36] Costs and outcomes arising during the trial will be undiscounted, reflecting the 12-month time horizon. Sensitivity analyses will be undertaken to explore uncertainty in the incremental cost-effectiveness and to consider issues of generalisability of the study.

Although not anticipated to be necessary, more extensive economic modelling using decision-analytic methods may be considered to extend the time horizon and decision context if costs and benefit profiles are non-convergent at 12 months. Such modelling will draw upon best available information from the literature and stakeholder consultations to supplement the trial data. Parameter uncertainty in the decision-analytic model will be explored using probabilistic sensitivity analysis. Longer term costs and consequences will be discounted to present values using discount rates recommended for health technology appraisal in the UK (current discount rate: 3.5%).

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Sponsor and governance arrangements

University Hospitals Birmingham and University of Warwick will act as co-sponsors for the trial. Warwick SOPs will be followed.

7.2 Regulatory authorities/ethical approval

All required ethical approval(s) for the trial will be sought using the UK Integrated Research Application System. Before enrolling patients into the trial, each trial site must ensure that the local conduct of the trial has the agreement of the relevant NHS/Health and Social Care Organisation's research management function (e.g. Research & Development (R&D) department). WCTU will only activate a site to recruitment once written confirmation of the NHS/Health and Social Care Organisation's agreement to participate in the study.

Substantial amendments to the protocol will be communicated to all relevant parties (i.e. investigators, NIHR, RECs, NHS Trusts, regulators, trial registries and journals).

Annual reports 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. Authorities (REC/MHRA) will be notified of the end of the trial (whether at planned time or prematurely).The CI will submit a final report to the required authorities with the results, including any publications within one year of the end of the trial.

7.3 Trial Registration

The trial will be registered on the EudraCT website and ISRCTN Registry prior to submission for approvals to commence the trial.

7.4 Notification of serious breaches to GCP and/or trial protocol

A "serious breach" is a breach which is likely to effect to a significant degree:

1. the safety or physical or mental integrity of the participants of the trial; or
2. the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase. Furthermore, the sponsor will notify the licensing authority in writing of any serious breach of

1. the conditions and principles of GCP in connection with that trial; or
2. the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

7.5 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for any harm caused to participants by the design of the research protocol.

7.6 Trial timetable and milestones

	Month	Recruitment
Set-up	1-6	n/a
Pilot study	7-12	50
Recruitment	13-69	418 (468 in total)
Follow up	70-75-	n/a
Analysis	76-81	n/a

7.7 Administration

The trial coordination will be based at WCTU, University of Warwick.

7.8 Trial Management Group (TMG)

A TMG consisting of the CI Mr Angelos Kolias (who will be its chair), clinical leads, the Clinical Trial Manager and WCTU study staff, and co-applicants will oversee the management of the trial. The TMG will meet face to face and/or by teleconference every 2-3 months. All day-to-day activity will be managed by the SOS trial team based at WCTU working under the direction of Mr Angelos Kolias. This ensures that there is a single point of contact for all enquiries and a single dissemination point for project communications.

7.9 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as at least one 'lay' representative. The TSC will have an independent Chairperson. Face to face meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The TSC, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMEC
- Informing and advising on all aspects of the trial

7.10 Data Monitoring and Ethics Committee (DMEC)

The DMEC will comprise of two independent clinicians with experience in clinical trials and an independent statistician. One of the independent clinicians will have experience in undertaking clinical trials in emergency or acute care. The DMEC charter will be based on the DAMOCLES study group template.[37] Its roles will include: monitoring the data and making recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue; considering the need for any interim analysis; advising the TSC regarding the release of data and/or information; considering data emerging from other related studies. If funding is required above the level originally requested, the DMEC may be asked by the CI, TSC, Sponsor or Funder to provide advice and, where appropriate, information on the data gathered to date in a way that will not compromise the trial.

DMEC meetings will also be attended by the CI and Trial Manager (for non-confidential parts of the meeting) and the trial statistician. Any publications relating to this trial or that may have an impact on the running of the trial will be reviewed by the DMEC and fed back to staff through training.

7.11 Essential Documentation

A Trial Master File will be set up according to Warwick SOP and held securely at the coordinating centre. The coordinating centre will provide Investigator Site Files to all recruiting centres involved in the trial.

8. MONITORING AND QUALITY ASSURANCE OF TRIAL PROCEDURES

8.1 Training

PIs, site teams and WCTU administration staff will be required to undergo GCP training. PIs will be required to provide a copy of their GCP certificate and a signed and dated CV to the WCTU. Site staff listed on the delegation log should ensure their CVs and evidence of GCP training is available to WCTU on request. The set up and training of staff at sites wishing to collaborate will be the responsibility of WCTU, with advice from the TMG experts in TBI.

Educational and training material will be developed by the WCTU to standardise the processes of administering the treatment and patient care. Material will be developed to support study staff at the site initiation visit. In addition to this the WCTU will provide advice and support to site PIs; provide instructional material to trial site; and instruction on protocol and training manual. Training materials including slide shows, videos, FAQs and written material will be provided.

Any new staff to the trial within the WCTU administration team will follow a thorough induction plan put together by the Trial Manager. Training will also be carried out for WCTU administration staff who may answer phone calls from patients or legal representatives and need to deal sensitively with their questions.

8.2 Data quality

Data entered into the trial database will be checked for accuracy in accordance with the Warwick SOPs and trial Data Management Plan. Quality assurance checks on eligibility, completion of data, follow up questionnaires and the consent process will ideally be carried out after the pilot period and each year of recruitment, but as this may pose logistical issues, the checks and any subsequent training will be carried out at least once during the recruitment period and as per the WCTU Data Management Plan.

8.3 Completeness of data

Local audits of routine clinical data will be performed at regular intervals, to identify patients with TBI and potentially eligible patients who were not reported to the trial.

8.4 Site visits

As per the WCTU monitoring plan, after the initial in-person or remote site initiation visit with each centre, the Trial Manager will have regular contact with the enrolled centres to identify any problems with compliance with the protocol, training, data collection, or other barriers to recruitment and progress, and to support sites with the day to day management of the trial. As well as regular telephone and email contact, monitoring activities will be conducted annually either remotely or on-site to meet with the trial team at each centre and discuss any issues and check for inconsistencies. The Trial Manager will check with each trial site that all Site File documents are up to date at least once during the trial. A monitoring report will be prepared following each visit and reviewed by the TMG. A copy of the report will be sent to the PIs and study coordinator at the site and will be filed in the site Investigator Site File.

9. PATIENT AND PUBLIC INVOLVEMENT (PPI)

This application is informed through a series of meetings with survivors and carers of patients with previous brain injury, facilitated through Headway West Midlands (https://www.headway.org.uk). The group are supportive of this trial. We discussed and decided together our joint position on the use of placebo, trial outcomes and how to optimise the process for approaching, informing and consenting relatives (including the use of professional legal representative) and optimising follow-up. Two members (Muzaffar and Malins) have committed to join the investigator team as co-applicants. Further PPI input will be provided through independent membership of the TSC.

We will follow INVOLVE best practice guidance in our approach. We will meet with the PPI group at the start of the study and regularly thereafter to enable full involvement through the trial and have included funds to support this. We will work with our PPI group to ensure that we are all clear about expectations and jointly agree a role description, terms of reference and organisational responsibilities including payments. We will provide training and support through informal mentorship with experienced PPI and formal training through our PI group. The group will help keep patients and public informed through the progress of the trial and lead the dissemination of the trial findings to lay persons.

10. DISSEMINATION AND PUBLICATION

The results of the trial will be reported first to trial collaborators. The main report will be drafted by the trial co-ordinating team, and the final version will be agreed by the TSC before submission for publication, on behalf of the collaboration.

The success of the trial depends on the collaboration of doctors, nurses and researchers from across the UK. The SOS investigators aim to ensure that all those who make a wholehearted contribution to the SOS trial are appropriately recognised in research outputs. We will comply with the ICMJE guidelines and any journal requirements when defining authors and collaborators. It is anticipated that there will be a minimum of two major outputs to the trial – the main trial publication (key study findings) and the NIHR Journals report. Investigators, research staff, principal investigators (and their staff) will be provided with the opportunity to co-author the paper based on their contributions. Centres recruiting >30 participants will be entitled to one name, >60 two names, >100 three names, >150 four names, >200 five names in the author list. Those who do not fulfil the criteria for authorship will be provided the opportunity to be formally listed in the paper as collaborators. The trial will be reported in accordance with the CONSORT guidelines (www.consort-statement.org).

Authorship of any additional papers (e.g. sub-group analyses, longer term outcomes) will be decided on a case by case basis by the trial management committee and will follow the principles described above.

We will continue to build links with key stakeholder groups (e.g. UK Intensive Care Society, Faculty of Intensive Care Medicine, Society of British Neurological Surgeons, Neuroanaesthesia and Critical Care Society of Great Britain and Ireland, PPI Groups etc.). We will continue to publish editorials and review articles related to hyperosmolar therapy use in TBI. The purpose of these activities are to highlight the uncertainty of current treatment with hyperosmolar therapy and to generate and sustain interest from the clinical community so that the trial results will be eagerly anticipated. We will publish the trial protocol and final trial results in high impact, open access peer reviewed journals. The results of the trial will be reported first to trial collaborators. The main report will be drafted by the WCTU team, and the final version will be agreed by the TSC before submission for publication, on behalf of the collaboration. The main publications will be the report to the funding body (HTA Monograph) and a journal publication. In addition, the results will be presented at national and international medical conferences as well as disseminated via social media (Twitter/Facebook) and blog postings. This will ensure that the results are communicated rapidly to clinicians who will then be able to put them into practice.

We will aim to incorporate the results into national and international TBI guidelines via existing guideline development groups, which include several of the applicants (Hutchinson/Kolias/Andrews). We will incorporate the findings of the trial into relevant review articles and ensure the findings of the trial are available through NHS Evidence. We will work with our Marketing and Communication team to develop a strategy for communication with the media (television, radio, newspaper, etc.) to enhance communication of the trial results to patients and participants. We will produce a lay summary of the trial results with our PPI partners. This will be disseminated through our press officer,

user groups, websites and INVOLVE database to participants of the trial who indicated they wanted to know the results.

We expect the output from this trial will impact international TBI practice and we will ensure that the results of this trial are fed into the Brain Trauma Foundation and European Society of Intensive Care Medicine evidence assessment and guideline process. Finally, a policy for authorship of trial publications will be drafted and agreed by the investigators early in the trial, in accordance with the Warwick SOPs.

11. REFERENCES

1. Nguyen R, Fiest KM, McChesney J, et al. The International Incidence of Traumatic Brain Injury: A Systematic Review and Meta-Analysis. Can J Neurol Sci 2016;43:774-85.

2. Majdan M, Plancikova D, Maas A, et al. Years of life lost due to traumatic brain injury in Europe: A cross-sectional analysis of 16 countries. PLoS Med 2017;14:e1002331.

3. Lawrence T, Helmy A, Bouamra O, Woodford M, Lecky F, Hutchinson PJ. Traumatic brain injury in England and Wales: prospective audit of epidemiology, complications and standardised mortality. BMJ open 2016;6:e012197.

4. Harrison DA, Prabhu G, Grieve R, et al. Risk Adjustment In Neurocritical care (RAIN)--prospective validation of risk prediction models for adult patients with acute traumatic brain injury to use to evaluate the optimum location and comparative costs of neurocritical care: a cohort study. Health Technol Assess 2013;17:vii-viii, 1-350.

5. Sorrentino E, Diedler J, Kasprowicz M, et al. Critical thresholds for cerebrovascular reactivity after traumatic brain injury. Neurocrit Care 2012;16:258-66.

6. Marmarou A, Anderson RL, Ward JD, et al. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. Special Supplements 1991;75:S59-S66.

7. Carney N, Totten AM, O'Reilly C, et al. Guidelines for the Management of Severe Traumatic Brain Injury, Fourth Edition. Neurosurgery 2017;80:6-15.

8. Oddo M, Poole D, Helbok R, et al. Fluid therapy in neurointensive care patients: ESICM consensus and clinical practice recommendations. Intensive Care Med 2018;44:449-63.

9. Andrews PJ, Sinclair HL, Rodriguez A, et al. Hypothermia for Intracranial Hypertension after Traumatic Brain Injury. N Engl J Med 2015;373:2403-12.

10. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. N Engl J Med 2011;364:1493-502.

11. Hutchinson PJ, Kolias AG, Timofeev IS, et al. Trial of Decompressive Craniectomy for Traumatic Intracranial Hypertension. N Engl J Med 2016;375:1119-30.

12. Cooper J, Nichol AD, Bailey M, et al. Effect of early sustained prophylactic hypothermia on neurologic outcomes among patients with severe traumatic brain injury The POLAR randomized controlled trial. JAMA 2018;320:2211-20.

13. Berger-Pelleiter E, Emond M, Lauzier F, Shields JF, Turgeon AF. Hypertonic saline in severe traumatic brain injury: a systematic review and meta-analysis of randomized controlled trials. CJEM 2016;18:112-20.

14. Burgess S, Abu-Laban RB, Slavik RS, Vu EN, Zed PJ. A Systematic Review of Randomized Controlled Trials Comparing Hypertonic Sodium Solutions and Mannitol for Traumatic Brain Injury: Implications for Emergency Department Management. Ann Pharmacother 2016;50:291-300.

15. Wakai A, McCabe A, Roberts I, Schierhout G. Mannitol for acute traumatic brain injury. Cochrane Database Syst Rev 2013:CD001049.

16. Jagannatha AT, Sriganesh K, Devi BI, Rao GS. An equiosmolar study on early intracranial physiology and long term outcome in severe traumatic brain injury comparing mannitol and hypertonic saline. J Clin Neurosci 2016;27:68-73.

17. Hendoui N, Beigmohammadi MT, Mahmoodpoor A, et al. Reliability of calcium-binding protein S100B measurement toward optimization of hyperosmolal therapy in traumatic brain injury. Eur Rev Med Pharmacol Sci 2013;17:477-85.

18. Zhang W, Neal J, Lin L, et al. Mannitol in Critical Care and Surgery Over 50+ Years: A Systematic Review of Randomized Controlled Trials and Complications With Meta-Analysis. J Neurosurg Anesthesiol 2018.

19. Gu J, Huang H, Huang Y, Sun H, Xu H. Hypertonic saline or mannitol for treating elevated intracranial pressure in traumatic brain injury: a meta-analysis of randomized controlled trials. Neurosurg Rev 2018.

20. Roquilly A, Lasocki S, Moyer JD, et al. COBI (COntinuous hyperosmolar therapy for traumatic Brain-Injured patients) trial protocol: a multicentre randomised open-label trial with blinded adjudication of primary outcome. BMJ open 2017;7:e018035.

21. Maggiore U, Picetti E, Antonucci E, et al. The relation between the incidence of hypernatremia and mortality in patients with severe traumatic brain injury. Crit Care 2009;13:R110.

22. Kolmodin L, Sekhon MS, Henderson WR, Turgeon AF, Griesdale DE. Hypernatremia in patients with severe traumatic brain injury: a systematic review. Ann Intensive Care 2013;3:35.

23. Tan SK, Kolmodin L, Sekhon MS, et al. The effect of continuous hypertonic saline infusion and hypernatremia on mortality in patients with severe traumatic brain injury: a retrospective cohort study. Canadian journal of anaesthesia = Journal canadien d'anesthesie 2016;63:664-73.

24. Mangat HS. Hypertonic saline infusion for treating intracranial hypertension after severe traumatic brain injury. Crit Care 2018;22:37.

25. Avery KNL, Williamson PR, Gamble C, et al. Informing efficient randomised controlled trials: exploration of challenges in developing progression criteria for internal pilot studies. BMJ open 2017;7.

26. Cocks K, Torgerson DJ. Sample size calculations for pilot randomized trials: a confidence interval approach. J Clin Epidemiol 2013;66:197-201.

27. Perel P, Edwards P, Shakur H, Roberts I. Use of the Oxford Handicap Scale at hospital discharge to predit Glasgow Outcome Scale at 6 months in patients with traumatic brain injury. BMC Medical Research Methodology 2008;8:72.

28. Maas AI, Roozenbeek B, Manley GT. Clinical trials in traumatic brain injury: past experience and current developments. Neurotherapeutics. 2010 Jan;7(1):115-26. doi: 10.1016/j.nurt.2009.10.022. PMID: 20129503; PMCID: PMC5084118.

29. White I, et al. Sample size for an ordered categorical outcome. The Stata Journal (2023); 23, No1, 3-23

30. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. PLoS Med 2008;5:e65.

31. Dunn G. The challenge of patient choice in nonadherance to treatment in randomised controlled trials of counselling and psychotherapy. Understanding Statistics 2002:19-29.

32. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics 1979,35:549-56.

33. National Institute for Health and Care Excellence. Guide to the methods of technology appaisal 2013. Process and methods [PMG9] 2013.

34. Devlin NS, Feng K, Mulhern B, van Hout B. Valuing health-related quality of life: An EQ-5D-5L value set for England. Office of Health Economics 2016.

35. Willan AR, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. Health Econ 2004;13:461-75.

36. Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. Pharmacoeconomics 2014:1157-70.

37. DAMOCES Study Group. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. Clinical Trials 2005;365:711-722.