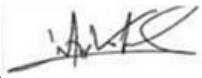
Sugar or Salt trial:
Hyperosmolar therapy in traumatic brain injury

ISRCTN:	ISRCTN16075091
Funding Body:	NIHR, Health Technology Assessment (HTA) programme
Ethics Approval:	19/EE/0228
HEAP version number:	1.0
Date:	29/05/2026
Stage:	Final

Junior Health economist signature: ____  _____ date: _13/07/2026___

Junior Health economist signature: _____  _____ date:_13/07/2026___

Senior Health economist signature:  _____ ___ date: _13/07/2026__

Chief Investigator signature: __  _____date: _10 July 2026__

WARWICK
CLINICAL TRIALS UNIT

The SoS Health Economics Analysis Plan

Table of contents

Administrative information

This document describes the planned analysis of economic data within the SoS trial. This Health Economics Analysis Plan (HEAP) should be read in conjunction with the SoS Trial Statistical Analysis Plan and Trial Protocol which provide in detail: trial design and methods, amendments, documentation, oversight, roles and responsibilities, and the statistical plan of analysis of clinical and patient outcome measures.

The objective of the health economics analysis is to inform decision makers regarding the cost-effectiveness of the use of hypertonic saline compared to mannitol in traumatic brain injury patients. This entails a systematic analysis of both the costs and consequences of both treatment options. The purpose of the HEAP is to outline a framework of methods that will be used to analyse the health economic components of the trial ensuring the integrity of the cost-effectiveness analysis.

1. Background

Traumatic brain Injury (TBI) is a major cause of death and severe disability throughout the world with a global pooled incidence of 349 per 100,000 person years (Nguyen et al., 2016). In England and Wales approximately 3500 patients require intensive care following moderate to severe traumatic brain injury (Lawrence et al., 2016). The average length of stay in an ICU following TBI is 9 days (Lawrence et al., 2016), a significant resource burden to the National Health Service. Long term outcomes are also poor with high levels of mortality (26%) and disability (74% in survivors) at 6 months (Harrison et al., 2013). This manifests itself with impacts upon quality of life with survivors reporting difficulties across different health dimensions over the long term. 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 flow. Studies have shown an association between raised ICP and poor neurological outcomes (Marmarou et al., 1991; Sorrentino et al., 2012). Consequently, the treatment of elevated ICP has been a central focus of both the medical and surgical management of patients with severe TBI in the intensive care unit.

Hyperosmolar therapies are used to control ICP. These 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. Hypertonic saline is a salt-based solution that 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. Both mannitol and hypertonic saline

have secondary benefits and adverse effects (e.g. kidney damage) that may further influence outcomes for the patients. Evidence on the relative effectiveness of the two hyperosmolar treatments is limited. This trial aims to address this gap in the medical literature by directly comparing mannitol and hyperosmolar therapy in severe TBI patients.

Participants are allocated to one of the two trial arms. Within 10 days of the estimated primary TBI and provided the patient satisfies the other inclusion criteria as specified in the published protocol (Rowland et al., 2020), they will be randomly assigned to boluses of either:

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

For both arms, 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.

The aim of the economic evaluation is therefore to answer the following question “What is the cost-effectiveness of hypertonic saline compared with mannitol following TBI with raised ICP?”.

1.1 General Principles of Economic Evaluation

Given the trial is funded by the National Institute for Health Research, we will adopt principles that best meet the requirements of local decision makers. The methods of economic evaluation will therefore be guided by the National Institute for Health and Care Excellence (NICE) guide to the methods of technology appraisal (NICE, 2022).

1.1.1 Type of economic evaluation

As recommended, the primary health economic analysis will be a cost-utility analysis with incremental quality adjusted life years (QALYs) as the primary health economic outcome (NICE, 2022). Following NICE guidance, the EQ-5D-5L will be used for the construction of QALYs (see section 2.1.1) (NICE, 2022).

1.1.2 Perspective

A healthcare and personal social services (PSS) will be adopted in the primary analysis as recommended by NICE (NICE, 2022).

1.1.3 Time Horizon

The health economic analysis will run concurrently to the effectiveness analysis. The EQ-5D-5L will be collected at discharge, three, six and 12-months post-randomisation. The primary time horizon will therefore be the 12-month period post-randomisation. Given the frequency of long-term impacts of TBI we will consider developing a decision analytic model to extrapolate the trial-based cost-effectiveness results over a lifetime horizon (see section 6).

1.1.4 Discounting

The trial-based analysis follows up participants for only 12 months and thus discounting will not be required. If a long term decision model is used, we will discount all costs and benefits beyond the first year of the trial using a 3.5% annual discount rate as recommended by NICE (NICE, 2022).

1.1.5 Intention to treat

We will adopt the 'intention to treat' principle whereby we will analyse individuals according to the arms which they are randomised.

1.1.6 Missing data

Missing data is a common occurrence in randomised controlled trials (RCT) and given the severe cognitive impacts associated with TBI missing data is likely to be prevalent within this RCT. Consequently, we will need to ensure appropriate methods are used to address missingness. We will therefore examine missing data and if nontrivial (5% or more in costs or QALYs) the primary analysis will use multiple imputation (MI) as the preferred method for estimating results in the presence of missing data. MI uses the observed data and samples from the predictive distribution to create multiple datasets (Sterne et al., 2009). Under the assumption of missing at random, this provides unbiased estimates; this allows uncertainty surrounding estimates to be maintained whilst allowing full use of the available data (see 5.2 for further details). Patterns of missingness will be examined to identify relationships with observed covariates, outcomes, or treatment allocation, providing insight into the likely missing data mechanism and the plausibility of the missing at random assumption.

2. Outcomes

2.1 Primary health economic outcome

Quality adjusted life years (QALYs) will be the primary measure of health consequence within the health economic analysis as recommended by NICE (NICE, 2022).

2.1.1 Quality adjusted life years (QALYs)

We will use QALYs as the primary health economic outcome. QALYs combine both mortality and morbidity into a single measure that can be compared across contexts within the healthcare service. To calculate QALYs, it is necessary to combine a preference-based health-related quality of life outcomes with survival benefits. In this study, we are collecting the EQ-5D-5L (Herdman et al., 2011) at four time points (discharge, 3 months, 6 months, 12 months). Baseline EQ-5D-5L will be imputed to reflect the unconscious health state and applied to all patients. Health-related quality-of-life at discharge will be captured as part of the index admission whilst participants will be contacted by telephone at 3 months, 6 months and 12 months post-intervention by site research staff to capture these time points. The EQ-5D-5L is a preference-based measure of health-related quality of life and is recommended by NICE for use in economic evaluation (NICE, 2022). The measure contains a descriptive system with five dimensions of health, each containing five levels. There exist value-sets (Devlin et al., 2016; Rowen et al., 2026; van Hout et al., 2012) that allow the calculation of *utility* scores for any given set of responses to the EQ-5D-5L descriptive system. A utility score is a score on a cardinal scale indexed at zero and one, where zero represents death, and one represents full health (negative states are possible). These utility values can be combined with survival benefits to derive QALYs. We will use the newest and most comprehensive available value set (Rowen et al., 2026) to calculate utility values at each time point. QALYs for each patient will be calculated using the EQ-5D-5L utility values at baseline, discharge, 3 months, 6 months and 12 months. QALYs accrued for each patient will be calculated by linearly interpolating the time points and calculating the area under the curve using the trapezium rule (Manca et al., 2005).

3. Resource use and costs

To calculate costs for use in cost-utility analysis it is necessary to capture information on resources used for both the control and intervention arm. Costs within this trial have the following components:

- Direct intervention costs (e.g. mannitol/hypertonic saline solution)
- Direct healthcare and PSS costs (e.g. intensive care stay)
- Other societal costs (e.g. absence from work)

NICE's guide to methods of technology appraisal recommend costing from an NHS and personal social services (PSS) perspective (NICE, 2022). The primary analysis will only consider the first two items; broader societal costs will be included within sensitivity analysis. To calculate costs, it is first necessary to capture resource use and then apply unit costs. The price year for the analysis will be informed by the latest available base year for common costing resources at time of analysis.

3.1. Direct intervention resource use and costs

Resource use during the index admission will be recorded on case report forms (CRFs). Thereafter, resource use relating to further health care following discharge will be recorded on CRFs at each follow-up time point (3, 6 and 12 months). The methods for capturing the direct intervention resource use and example sources of unit costs are presented in Table 1 below. We will also confirm with clinicians as to whether mannitol and hypertonic saline differ meaningfully in terms of administration, delivery time or monitoring implications, and if meaningful differences are found include these.

Table 1: Direct intervention resource use and cost sources

Intervention arm			
Resource type	**Resource use**	**How collected**	**Unit costs source examples**
Hypertonic saline	2ml/kg 3% hypertonic saline intravenous bolus (osmolarity = 1026 mOsm/L)	Trial CRF	BNF (BNF, 2021b) & NHS hypertonic saline guidelines (NHS, 2018a)
Mannitol Infusion	2ml/kg 20% mannitol intravenous bolus	Trial CRF	BNF (BNF, 2021a)
Initial ICU/HDU stay	Number of organs supported/number of days	Trial CRF	NHS reference costs (CCMDS) (NHS, 2025)
Other concomitant TBI treatments	Examples include interventions such as decompressive craniectomy	Trial CRF	NHS reference costs (HRGs including: AA52-AA57) (NHS, 2025)
Other hospital stays as part of index admission	Inpatient care following discharge from ICU/HDU	Trial CRF. HRG4+ 'Code to Group' (*HRG4+ 2020/21 Local Payment Grouper*, n.d.) used to allocate inpatient care to HRG groups for costing.	NHS Reference Costs (NHS, 2025)

3.2. Healthcare and social care resource use following index admission

In accordance with NICE guidance, we will capture healthcare and PSS costs for both arms of the trial (NICE, 2022) for the duration of follow up. This will include inpatient care, outpatient care, community care, accident and emergency admission, residential nursing, and equipment and adaptions. The methods for capturing the resource use and example sources for unit costs are

outlined in Table 2 below. These resource use items will be captured with the CRFs at 3, 6 and 12 months.

Table 2: Health care resource use

Resource type	Resource use	How collected	Unit cost source examples
Inpatient care	Specified within CRFs	CRFs at 3m, 6m and 12m HRG4+ 'Code to Group' (*HRG4+ 2020/21 Local Payment Grouper*, n.d.) used to allocate inpatient care to HRG groups for costing.	NHS Reference Costs (NHS, 2021) and PSSRU (Jones et al., 2025)
Hospital outpatient care	Specified within CRFs	CRFs at 3m, 6m and 12m	NHS Reference Costs (NICE, 2022) and PSSRU (Jones et al., 2025)
Accident and emergency care	Specified within CRFs	CRFs at 3m, 6m and 12m	NHS Reference Costs (NICE, 2022) and PSSRU (Jones et al., 2025)
Other hospital care	Specified within CRFs	CRFs at 3m, 6m and 12m	NHS Reference Costs (NICE, 2022) and PSSRU (Jones et al., 2025)
Residential nursing	Specified within CRFs	CRFs at 3m, 6m and 12m	NHS Reference Costs (NICE, 2022) and PSSRU (Jones et al., 2025)
Community care	Specified within CRFs	CRFs at 3m, 6m and 12m	NHS Reference Costs (NICE, 2022) and PSSRU (Jones et al., 2025)
Equipment and adaptations	Specified within CRFs	CRFs at 3m, 6m and 12m	NHS Supply chain (NHS, 2018b)

3.3. Wider costs

Within an additional sensitivity analysis, we will also be collecting information related to days lost from work and out of pocket expenses. Collection method and example of unit cost sources are shown in Table 3.

Table 3: Wider costs

Resource type	Resource use	How collected	Unit cost source examples
Absence from work and out of pocket expenses	Specified within CRFs	CRFs at 3m, 6m and 12m	Office of National Statistics (ONS, 2018)

4. Data integrity

On arrival in the trial office, data will be examined by trial staff to ensure its integrity. Blinded descriptive data will be routinely reported and presented to the data monitoring committee (DMC); this includes proportion of missingness of the health economic variables. Any questionable data (e.g. outliers/high missingness) will be queried and followed up if necessary. The DMCs will provide an opportunity to reflect whether the processes being used to collect data need refining or whether current methods are performing as desired. All data will be stored on secure University of Warwick servers in encrypted folders and access will be limited to only those approved to use it.

5. Statistical analysis

5.1. Descriptive analysis

Resource use, costs and EQ-5D-5L utility scores will be presented descriptively to inform parameters for future health economic studies.

5.2. Addressing missing data with multiple imputation

If the proportion of missing data for either costs or QALYs is more than 5% we will use multiple imputation to impute data within the base-case analysis. This data will then be used in the incremental analysis of costs, QALYs and the joint cost-effectiveness analysis. Meanwhile a complete case analysis will be included as a sensitivity analysis. Stata (StataCorp, 2025) will be used to conduct both the multiple imputation and the analysis of imputed data. The 'mi impute chained' command which uses chained equations to generate imputed datasets will be used for each treatment group. Within the imputation regression framework, we will include both costs and EQ-5D-5L at each timepoint as both imputed and predictor variables. We will also include any auxiliary variables that are found to be highly correlated ($r>0.4$) (UCLA IDRE, 2020) with costs or EQ-5D-5L, or are believed to be associated with missingness. We will use predictive mean matching drawing from the 5 nearest 'neighbours', this is necessary for the avoidance of drawing implausible values, e.g., utility values over 1, and 'negative costs'. The number of iterations will be guided by the fraction of missing information (Madley-Dowd et al., 2019). We will then use the 'mi estimate' functionality within Stata to run the analyses (specified in subsequent sections) within each dataset and to combine results using Rubin's combination rule to allow inferential statistics. Imputations will be added until estimates stabilise. We will examine the validity of the imputed data by comparing the distribution of the imputations and observed data both visually and statistically.

5.3. Single end point analysis: incremental costs and incremental QALYs

Before conducting the joint cost-effectiveness analysis, we will examine the impact of the intervention on incremental costs and incremental QALYs in isolation to assess the robustness of findings to model specification. Differences between the two arms will be assessed using a regression framework. The exact specification will depend upon the nature of the data. Costs will be estimated by combining resource use data with unit costs. Costs for each patient within the trial will be calculated and incremental costs between the two arms will be estimated. Again, a regression framework will be used, and its exact specification will be informed by the nature and distribution of the data.

5.4. Cost-effectiveness analysis and characterising uncertainty

The base case analysis will present the within trial incremental cost and QALY gained, adjusted for trial stratification covariates if necessary. We will use bivariate regression analysis in the form of seemingly unrelated regressions (with bootstrapping) for the joint analysis of costs and QALYs. This framework offers several benefits: first of all it accounts for the existence of correlation between costs and outcomes for patients; second it allows the inclusion of covariates within the analysis, this is particularly relevant for the adjustment of baseline utility with respect to QALYs accrued; third it is generally robust to non-normal distributions; fourth, it can account for clustering either by including clusters as a fixed effect or by running the seemingly unrelated regressions in a multi-level framework. Non-parametric bootstrapping will be used to examine the level of uncertainty by presenting the bootstrapped results on a cost-effectiveness plane, and by generating cost-effectiveness acceptability curves (CEACs). Should there be distributional or computational concerns (e.g. difficulty in fitting a multi-level seemingly unrelated regression model with imputed data in Stata) then we will consider combining costs and outcomes within a univariate net-benefit regression framework.

5.4.1 Characterizing uncertainty for decision makers

CEACs will be used to characterise uncertainty. CEACs show the probability that the intervention is cost-effective compared to the control at different levels of willingness to pay for QALYs and explicitly highlight the uncertainty within the decision problem. To avoid the issues related to uncertainty around cost-effectiveness ratios we will calculate net-monetary benefit for each of the bootstrapped iterations:

$$\Delta NB = \Delta e\gamma - \Delta c$$

In this instance, ΔNB refers to the incremental net monetary benefit, Δe reflects the incremental outcome of interest, incremental QALYs, whilst Δc refers to the incremental costs. The symbol γ refers to the decision maker's willingness to pay per QALY. For each of the bootstrapped cost-effectiveness samples we will calculate the associated net-monetary benefit across a range of levels of willingness to pay (γ). For each γ the proportion of iterations where net-benefit is greater than zero can be used estimate the probability that the intervention is more cost-effective at that willingness to pay. This will be conducted for a range of γ including £25,000 and £35,000 per QALY as specified by NICE and plotted to derive a CEAC (NICE, 2022).

5.4.2. Sensitivity analyses

In addition to the probabilistic sensitivity analysis outlined above we will also consider sensitivity analyses, these will include:

- Costing from a societal perspective
- Complete case analysis (if imputation is used for the base case analysis)
- Subgroup analyses of the trial stratification variables

6. Decision modelling

To validate within trial analysis without the need for further modelling one of three conditions should be true.

1. The group mean costs and QALYs converge during the trial
2. The ICER is robustly dominated (i.e. net costs increase, net QALYs decrease)
3. The ICER is robustly dominant (i.e. net costs decrease, net QALYs increase)

Should none of these conditions be observed, more extensive economic modelling using decision-analytic methods may be considered to extend the target population, time horizon and decision context, drawing 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. If longer term decision modelling is undertaken, then costs and outcomes will be discounted at 3.5% after the first year of randomisation in line with NICE reference case (NICE, 2022).

7. Dummy tables

Completeness of data by follow-up visit

	Control	*Intervention*	*Total*
	n (%, N)	**n (%, N)**	**n (%, N)**
Health status[1]			
EQ-5D Discharge			
EQ-5D 3 months			
EQ-5D 6 months			
EQ-5D 12 months			
EQ-5D All visits			
Resource use[2]			
Inpatient			
Outpatient			
Residential			
Community			
Equipment and adaptions			
Work absence			

1.EQ-5D-5L index score
2. Range shown (3M-12M)

Health Status, resource use and cost (complete cases)

	Control		*Intervention*		*Total*	
	mean	**(SD)**	**mean**	**(SD)**	**mean**	**(SD)**
Health status[1]						
EQ-5D-5L Discharge						
EQ-5D-5L 3 months						
EQ-5D-5L 6 months						
EQ-5D-5L 12 months						
QALYs						
Resource use *(all visits)*						
Inpatient days						
Outpatient visits						
A&E Visits						
Other hospital visit						
Residential nursing care						
Community ward						
Rehabilitation ward						
Nursing home						
Other residential nursing care						
Community						
GP surgery visits						
GP home visits						
GP telephone contacts						
Practice nurse contacts						
District nurse contacts						
Community Physiotherapy contacts						
NHS Direct contacts						
Calls for ambulance/paramedic						
Occupational therapy contacts						
Social worker						
Counsellor						
Home help/care worker						
Day centre						
Lunch or social club (NHS/Social Care)						
Food, medicine or laundry services						
Patient/Family support groups						
Other community contacts						
Special equipment and aids						
Cost[2]						
A: Cost (study procedures)						
B: Cost (NHS and social care)						
Cost (Total, A+B)						

1 EQ-5D-5L index score

2 Time from work is not included in the analytic perspective, which includes health service and personal social services costs

Cost-effectiveness results

	Incremental cost (95%CI)	Incremental QALYs (95%CI)	ICER (95%CI)	p[1]	p[2]	NMB[1]	NMB[2]
Base case							
Primary analysis							
Sensitivity analyses							
1 Inclusion of wider costs							
2 Complete case analysis							
3 Sub-group analyses							

[1] probability cost-effective or net monetary benefit if willing to pay £25,000/QALY. [2] probability cost-effective or net monetary benefit if willing to pay £35,000/QALY

References

BNF. (2021a). *BNF: Mannitol* [CorporatePage]. NICE. https://bnf.nice.org.uk/medicinal-forms/mannitol.html

BNF. (2021b). *BNF: Sodium Chloride* [CorporatePage]. NICE. https://bnf.nice.org.uk/medicinal-forms/sodium-chloride.html

Devlin, N., Shah, K., Feng, Y., Mulhern, B., & van Hout, B. (2016). Valuing health-related quality of life: An EQ-5D-5L value set for England. *OHE Research Paper*, *January*(January). https://www.ohe.org/publications/valuing-health-related-quality-life-eq-5d-5l-value-set-england

Harrison, D. A., Prabhu, G., Grieve, R., Harvey, S. E., Sadique, M. Z., Gomes, M., Griggs, K. A., Walmsley, E., Smith, M., Yeoman, P., Lecky, F. E., Hutchinson, P. J. A., Menon, D. K., & Rowan, K. M. (2013). 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 Technology Assessment (Winchester, England)*, *17*(23), vii–viii, 1–350. https://doi.org/10.3310/hta17230

Herdman, M., Gudex, C., Lloyd, A., Janssen, MF., Kind, P., Parkin, D., Bonsel, G., & Badia, X. (2011). Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Quality of Life Research*, *20*(10), 1727–1736. https://doi.org/10.1007/s11136-011-9903-x

HRG4+ 2020/21 Local Payment Grouper. (n.d.). NHS Digital. Retrieved 14 May 2020, from https://digital.nhs.uk/services/national-casemix-office/downloads-groupers-and-tools/local-payment-2020-21

Jones, K. C., Weatherly, H., Birch, S., Castelli, A., Chalkley, M., Dargan, A., Findlay, D., Gao, M., Hinde, S., Markham, S., Smith, D., & Teo, H. (2025). *Unit Costs of Health and Social Care 2024 Manual*. Personal Social Services Research Unit (University of Kent) & Centre for Health Economics (University of York). https://doi.org/10.22024/UNIKENT/01.02.109563

Lawrence, T., Helmy, A., Bouamra, O., Woodford, M., Lecky, F., & Hutchinson, P. J. (2016). Traumatic brain injury in England and Wales: Prospective audit of epidemiology, complications and standardised mortality. *BMJ Open*, *6*(11), e012197. https://doi.org/10.1136/bmjopen-2016-012197

Madley-Dowd, P., Hughes, R., Tilling, K., & Heron, J. (2019). The proportion of missing data should not be used to guide decisions on multiple imputation. *Journal of Clinical Epidemiology*, *110*, 63–73. https://doi.org/10.1016/j.jclinepi.2019.02.016

Manca, A., Hawkins, N., & Sculpher, M. J. (2005). Estimating mean QALYs in trial-based cost-effectiveness analysis: The importance of controlling for baseline utility. *Health Economics*, *14*(5), 487–496. https://doi.org/10.1002/hec.944

Marmarou, A., Anderson, R. L., Ward, J. D., Choi, S. C., Young, H. F., Eisenberg, H. M., Foulkes, M. A., Marshall, L. F., & Jane, J. A. (1991). Impact of ICP instability and hypotension on outcome in patients with severe head trauma. *Journal of Neurosurgery*, *75*(Supplement), S59–S66. https://doi.org/10.3171/sup.1991.75.1s.0s59

Nguyen, R., Fiest, K. M., McChesney, J., Kwon, C.-S., Jette, N., Frolkis, A. D., Atta, C., Mah, S., Dhaliwal, H., Reid, A., Pringsheim, T., Dykeman, J., & Gallagher, C. (2016). The International Incidence of Traumatic Brain Injury: A Systematic Review and Meta-Analysis. *The Canadian Journal of Neurological Sciences. Le Journal Canadien Des Sciences Neurologiques*, *43*(6), 774–785. https://doi.org/10.1017/cjn.2016.290

NHS. (2018a). *Guideline to make up hypertonic saline (3% NaCl)*. https://www.sort.nhs.uk/Media/Guidelines/Hypertonicsaline3sodiumchlorideguideline.pdf

NHS. (2018b). *NHS Supply Chain 2018*.

NHS. (2021). *National Schedule of NHS costs 2019-2020*. https://www.england.nhs.uk/national-cost-collection/#ncc1819

NHS. (2025). *National Cost Collection for the NHS* [Data set]. https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/

NICE. (2022). *NICE technology appraisal and highly specialised technologies guidance: The manual (2026 Update)*. NICE. https://www.nice.org.uk/process/pmg36/chapter/economic-evaluation-2

ONS. (2018). *Annual Survey of Hours and Earnings—Office for National Statistics*. https://www.ons.gov.uk/employmentandlabourmarket/peopleinwork/earningsandworkinghours/bulletins/annualsurveyofhoursandearnings/2014-11-19

Rowen, D., Mukuria, C., Bray, N., Carlton, J., Longworth, L., Meads, D., Oluboyede, Y., O'Neill, C., & Yang, Y. (2026). A United Kingdom Value Set for the EQ-5D-5L. *Value in Health*, *29*(5), 858–869. https://doi.org/10.1016/j.jval.2026.03.008

Rowland, M. J., Veenith, T., Scomparin, C., Wilson, M. H., Hutchinson, P. J., Kolias, A. G., Lall, R., Regan, S., Mason, J., Andrews, P. J. D., Horner, D., Naisbitt, J., Devrell, A., Malins, A., Dark, P., McAuley, D. F., & Perkins, G. D. (2020). Sugar or salt ("SOS"): A protocol for a UK multicentre randomised trial of mannitol and hypertonic saline in severe traumatic brain injury and intracranial hypertension: *Journal of the Intensive Care Society*. (Sage UK: London, England). https://doi.org/10.1177/1751143720901690

Sorrentino, E., Diedler, J., Kasprowicz, M., Budohoski, K. P., Haubrich, C., Smielewski, P., Outtrim, J. G., Manktelow, A., Hutchinson, P. J., Pickard, J. D., Menon, D. K., & Czosnyka, M. (2012). Critical thresholds for cerebrovascular reactivity after traumatic brain injury. *Neurocritical Care*, *16*(2), 258–266. https://doi.org/10.1007/s12028-011-9630-8

StataCorp. (2025). *Stata statistical software: Release 19.5*. College Station, TX: StataCorp LLC.

Sterne, J. A. C., White, I. R., Carlin, J. B., Spratt, M., Royston, P., Kenward, M. G., Wood, A. M., & Carpenter, J. R. (2009). Multiple imputation for missing data in epidemiological and clinical research: Potential and pitfalls. *BMJ (Clinical Research Ed.)*, *338*(jun29_1), b2393. https://doi.org/10.1136/bmj.b2393

UCLA IDRE. (2020). *Multiple Imputation in Stata*. https://stats.idre.ucla.edu/stata/seminars/mi_in_stata_pt1_new/

van Hout, B., Janssen, M. F., Feng, Y.-S., Kohlmann, T., Busschbach, J., Golicki, D., Lloyd, A., Scalone, L., Kind, P., Pickard, A. S., B., V. H., M.F., J., Y.-S., F., T., K., J., B., D., G., A., L., L., S., P., K., … P., K. (2012). Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value in Health*, *15*(5), 708–715.