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Extended Research Article

Decompressive craniectomy versus craniotomy for patients undergoing surgical evacuation of an acute subdural hematoma: RESCUE-ASDH RCT and cost effectiveness

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Abstract

Background: Traumatic acute subdural haematomas often require surgical evacuation via craniotomy or decompressive craniectomy. Decompressive craniectomy may prevent intracranial hypertension; however, it is unclear whether it is associated with better outcomes.

Objective: Multicentre, pragmatic, parallel-group randomised trial to compare the clinical and cost-effectiveness of decompressive craniectomy versus craniotomy for evacuation of acute subdural haematomas.

Design: International, multicentre, pragmatic, parallel-group randomised trial with additional observational arm.

Setting: Hospitals with neurosurgical services in the UK and internationally.

Participants: Patients aged ≥ 16 years, with a diagnosis of acute subdural haematomas on a computed tomography scan that required evacuation with a large bone flap either by craniotomy or decompressive craniectomy according to the opinion of the admitting neurosurgeon.

Interventions: The enrolled patients underwent acute subdural haematoma evacuation in the operating room under general anaesthesia. A large bone flap ipsilateral to the haematoma was raised, the dura opened and the haematoma evacuated. Other haematomas, such as contusions, were evacuated at the discretion of the surgeon. If clinically appropriate randomisation occurred, the bone flap was either replaced (craniotomy) or not replaced (decompressive craniectomy). Patients who could not be randomised were followed up in the observational arm.

Main outcome measures: Primary outcome measure was the extended Glasgow Outcome Scale assessed 12 months post injury. An economic evaluation (based on UK participants) was undertaken to estimate the cost-effectiveness of craniotomy compared to decompressive craniectomy.

Results: Four hundred and fifty patients were randomised: 228 to craniotomy and 222 to craniectomy – with the common odds ratio for the differences across the Glasgow Outcome Scale scores of 0.85 [95% confidence interval (0.6 to 1.18; p = 0.324)]. The results were similar at 6 months. At 12 months, death occurred in 30.2% of the craniotomy group versus 32.2% of the decompressive craniectomy group, vegetative state occurred in 2.3% versus 2.8%, and good recovery occurred in 25.6% and 19.9%, respectively. In the observed cohort, those who had a decompressive craniectomy had significantly worse outcomes at 6 and 12 months, but their baseline characteristics were different.

Limitations: Clinicians were not blinded to the trial groups. Decompressive craniectomy was performed in 8.8% of patients allocated to the craniotomy group, and 5.4% of patients allocated to the decompressive craniectomy group underwent craniotomy. Intraoperative non-adherence with allocation did not influence the primary analysis, which was based on the intention-to-treat principle.

Conclusions: Among patients undergoing evacuation of acute subdural haematomas, the outcomes were similar in both groups. Additional surgery was required in a higher proportion of patients in the craniotomy group, but more wound complications occurred in the decompressive craniectomy group.

Future work: Long-term outcomes of patients following decompressive craniectomy, timing and impact of cranial reconstruction on a patient's rehabilitation.

Trial registration: This trial is registered as ISRCTN87370545.

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Contents

List of tables

List of figures

List of supplementary material

Supplementary material can be found on the NIHR Journals Library article page (https://doi.org/10.3310/GJPH0512).

Supplementary material has been provided by the authors to support the article and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

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Glossary

Missing at random Any systematic difference between the missing values and the observed values can be explained by differences in observed data.

Multiple imputation An approach to the problem of missing data. It aims to replace the missing data by creating several different plausible imputed data sets and combining the results from each of these appropriately.

MICE A multiple imputation method used to replace missing data values in a data set under certain assumptions about the mechanism of missingness.

List of abbreviations

AE	adverse event
ASDH	acute subdural haematoma
AWI Act 2000	The Adults with Incapacity (Scotland) Act 2000
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CRF	case report form
CT	computed tomography
CUA	cost–utility analysis
DC	decompressive craniectomy
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
EVD	external ventricular drain
GCS	Glasgow Coma Scale
GOSE	Glasgow Outcome Scale-Extended
HCP	healthcare professional
HE	haematoma evacuation
HEAP	Health Economic Analysis Plan
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
ICP	intracranial pressure
ICU	intensive care unit
IMPACT-TBI	International Mission for Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury
ITT	intention to treat
LOS	length of stay
MAR	missing at random
MI	multiple imputation
MRI	magnetic resonance imaging
NCCU	neurocritical care unit
NHSCII	NHS Cost Inflation Index
NICE	National Institute for Health and Care Excellence
NNT	number needed to treat
NSU	neurosurgical unit
PSA	probabilistic sensitivity analysis
PSS	Personal Social Services
QALY	quality-adjusted life-year
RESCUE	randomised evaluation of surgery with craniectomy for patients undergoing evacuation of acute subdural haematoma
SA	sensitivity analysis
SAP	statistical analysis plan
SBNS	Society of British Neurological Surgeons
TBI	traumatic brain injury
TIL	therapy intensity level

Plain language summary

Background

Approximately 4000 head-injured patients undergo emergency brain surgery each year in the UK, of whom two-thirds have a blood clot between the outer lining of the brain and the brain itself, known as an acute subdural haematoma, and if not removed, it can be life-threatening. When an acute subdural haematoma is evacuated, a piece of skull can be left out, known as a decompressive craniectomy, or replaced prior to closing the skin, known as a craniotomy.

Methods

This study was a head-to-head comparison of craniotomy and decompressive craniectomy as to whether one is better for the management of acute subdural haematoma. Following consent, the patients were randomly allocated to receive either craniotomy or decompressive craniectomy. Patients unsuitable for inclusion had the operation deemed to be in their best interest by the operating neurosurgeon, and all participants were followed up for 1 year. To assess the value for money, data from UK patients were collected in relation to both health and social service usage and health-related quality of life.

Results

The analysis of the randomised patients showed no significant difference in the functional outcomes of the two arms at 12 months, but there were differences in functional outcomes between the groups in the observed cohort; however, patients undergoing decompressive craniectomy were worse before the operation. UK craniotomy patients were estimated to have lower costs and a higher quality of life than decompressive craniectomy patients.

Discussion

This study showed no significant difference in the overall functional outcomes at 12 months between the operations. Craniotomy was estimated to offer better value for money than craniectomy, with no reduction in activities of daily living.

Conclusion

Among patients undergoing evacuation of a traumatic acute subdural haematoma, decompressive craniectomy did not result in better outcomes than craniotomy and was not considered to represent value for money.

Scientific summary

Background

Acute subdural haematoma (ASDH) is a common consequence of traumatic brain injury (TBI) and is associated with a high mortality rate. These haematomas are commonly treated with surgical evacuation using two different surgical procedures: craniotomy or decompressive craniectomy (DC). In a craniotomy, the skin is opened, a piece of skull is removed, the haematoma evacuated, the piece of skull replaced and the skin closed. DC is a similar procedure, but the piece of skull is not replaced prior to closing the skin. The advantage of a DC is that it is thought to be superior in controlling brain swelling, but the patient will require a further operation to rebuild their skull usually weeks or months later, known as cranioplasty. The advantage of a craniotomy is the patient will not require a second operation to rebuild their skull, but it is believed to be inferior at controlling life-threatening brain swelling that can occur after the operation. Both procedures are commonly performed worldwide, but there is no level-one evidence comparing them. Thus, we conducted the RESCUE (randomised evaluation of surgery with craniectomy for patients undergoing evacuation of acute subdural haematoma)-ASDH trial to compare the effectiveness and cost-effectiveness of craniotomy versus DC in patients with ASDH.

Objectives

Primary

Compare the long-term clinical effectiveness of DC versus craniotomy.

Secondary

1. Compare the adverse events (AEs) and surgical complications between the two arms.
2. Undertake a detailed economic evaluation.

Methods

Trial design

An international multicentre, pragmatic, parallel-group randomised trial to compare the effectiveness of craniotomy versus DC for the management of adult head-injured patients undergoing evacuation of an ASDH. In addition, an observational cohort included eligible patients enrolled into the study who could not be randomised after evacuation of haematoma due to significant swelling of the brain, or patients who had a traumatic ASDH removed as part of their standard care and who were enrolled postoperatively.

Health technologies being assessed

Approximately two-thirds of head-injured patients undergoing emergency brain surgery have an ASDH evacuated. When an ASDH is evacuated, the bone flap can be left out or replaced prior to closing the skin. The RESCUE-ASDH trial compared these two specific components of the operation to remove an ASDH. Enrolled patients underwent evacuation of the ASDH in the operating room under general anaesthesia. A large bone flap ipsilateral to the haematoma (recommended size ≥ 11 cm in anteroposterior diameter) was raised, the dura opened and the haematoma evacuated. Other haematomas, such as contusions, could be evacuated at the surgeon's discretion.

Eligibility criteria

Inclusion criteria

- Adult head-injured patients (aged > 16 years).
- ASDH on computed tomography (CT).
- The admitting neurosurgeon felt that the haematoma needed to be evacuated with a large bone flap (recommended size ≥ 11 cm anteroposterior diameter) either by a craniotomy or by DC [*patients with additional lesions (such as intracerebral haemorrhage/contusions) could also be included*].

Exclusion criteria

- Bilateral ASDHs, both requiring evacuation.
- Previous enrolment in RESCUE-ASDH study.
- Severe pre-existing physical or mental disability or severe comorbidity, which would lead to a poor outcome even if the patient made a full recovery from the head injury.

Recruitment

The study focused on adult head-injured patients who require an operation to evacuate an ASDH. Patient enrolment (including screening for eligibility and consent) occurred in hospitals with neurosurgical services in the UK and internationally.

Patients from 40 sites in 11 countries were randomised between 8 September 2014 and 29 April 2019. Sites included: UK 23, India 4, Canada 3, USA 2, Spain 2, Malaysia 1, Singapore 1, Germany 1, Australia 1, Pakistan 1, Hungary 1.

Outcomes

Primary end point

The Glasgow Outcome Scale-Extended (GOSE) at 12 months post injury. The use of the GOSE as a core global outcome measure is recommended by the interagency TBI Outcomes Workgroup and the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT-TBI) group. The GOSE is an ordinal outcome scale assessing functional independence, work, social and leisure activities, and personal relationships. There are eight outcomes, namely death, vegetative state (unable to obey commands), lower severe disability (dependent on others for care), upper severe disability (independent at home), lower moderate disability (independent at home and outside the home but with some physical or mental disability), upper moderate disability (independent at home and outside the home but with some physical or mental disability, with less disruption than lower moderate disability), lower good recovery (able to resume normal activities with some injury-related problems) and upper good recovery (no problems).

Secondary end points:

- GOSE at 6 months post injury.
- Health-related quality of life at discharge from neurosurgical unit (NSU), 6 and 12 months post injury.
- Glasgow Coma Scale (GCS) on discharge from the intensive care unit (ICU) and from NSU.
- Length of stay (LOS) in ICU, neurosurgical and rehabilitation unit.
- Therapy intensity level in the ICU.
- Discharge destination from NSU.
- Mortality.
- Serious AEs and surgical complications during index admission.
- Cranial surgery within 2 weeks after randomisation.
- Subsequent re-admissions to the NSU within the 12-month follow-up period.

- Hydrocephalus requiring shunt insertion within the 12-month follow-up period.
- Healthcare service utilisation over 12 months.
- Detailed economic evaluation.

Sample size

The sample size was 440, which had more than 90% power to detect a between-group difference of 14 percentage points in an ordinal analysis and more than 80% power to detect a difference of 14 percentage points in a binary analysis.

Randomisation

Following enrolment in the study, suitability for randomisation was assessed in the operating room by the operating neurosurgeon (see Trial Flow chart). A secure web-based or telephone randomisation service was used for the randomisation of suitable patients. Blocked randomisation was used, with a block size of four and allocation ratio of 1 : 1; subjects were allocated randomly within each block. Allocation was stratified by geographical region, age group, severity of injury and CT findings. Patients who could not be randomised were followed up in the observation arm.

Blinding

Patients, relatives and treating doctors could not be blinded due to the nature of the intervention (after a craniectomy, a skull defect is noticeable until a cranioplasty is undertaken). The follow-up questionnaires were collected centrally (Cambridge Clinical Trials Unit) and outcome scored by two outcome adjudicators independently. The outcome adjudicators were blinded to the allocation of patients. Any disagreements in scoring were presented and discussed in the outcome's adjudication committee. The members of this committee were also blinded to the allocation of patients.

Analysis

Outcome in this study was measured using the GOSE. Conventionally, scales such as this are analysed by dichotomising the ordinal scale into a binary scale: 'unfavourable' versus 'favourable' and an odds ratio (OR) calculated. A significant number of patients will not have a realistic chance of crossing the threshold between 'unfavourable' and 'favourable' outcome and will not contribute data to the analysis. The crude OR is, therefore, not a meaningful effect measure for many patients. It discards much relevant information, reducing both the clinical relevance of the results and the statistical efficiency of the analysis. We, therefore, consider it more appropriate to quantify prognostic effects across the full range of the GOSE.

Based on IMPACT recommendations (NIH-funded IMPACT-TBI project), our statistical analysis used an ordinal approach, based on proportional odds methodology. The IMPACT recommendations have been endorsed by the American Brain Injury Consortium, European Brain Injury Consortium, International Neurotrauma Society and National Neurotrauma Society (USA).

Analysis was performed on an intention-to-treat (ITT) basis. Ordinal analysis methodology (as described) was undertaken, but dichotomised outcome (alive/dead; favourable/unfavourable) was also reported as sensitivity analyses (SAs).

To estimate the cost-effectiveness of craniotomy compared to craniectomy, a within-trial economic evaluation was undertaken based on UK participants, where costs were estimated from an NHS and Personal Social Services (PSS) perspective and EuroQol-5 Dimensions, five-level version data were used to estimate quality-adjusted life-year (QALY)

scores. To examine the potential for long-run effects to influence estimates of cost-effectiveness, a long-run health economic model was also constructed.

Results

Primary outcome (randomised)

In the modified ITT analysis (ordinal analysis based on the proportional odds model), there was no significant difference between the two groups with regard to GOSE scores at 12 months [common OR 0.845; 95% confidence interval (CI), 0.6 to 1.18; $p = 0.324$]. The distribution of GOSE scoring across the two groups was: death, 30.2% among 215 patients in the craniotomy group versus 32.2% among 211 patients in the DC group; vegetative state, 2.3% versus 2.8%; lower severe disability (dependent on others for care), 17.7% versus 19.4%; upper severe disability (independent at home), 13.0% versus 12.8%; moderate disability, 11.2% versus 12.8%; and good recovery, 25.6% versus 19.9%.

Secondary outcomes (randomised)

At 6 months, there was no difference in the GOSE scores between the two groups in the ordinal analysis (common OR 0.836, 95% CI 0.59 to 1.18; $p = 0.307$). There was no between-group difference with regard to the 30-day ($p = 0.710$), 6-month ($p = 0.623$) or 12-month ($p = 0.657$) mortality. A time-to-event analysis of LOS, with follow-up data censored at death for patients who died in the ICU, showed that the median LOS in ICU was 10 days in both groups. In the economic evaluation, the mean difference in cost for craniotomy compared with DC was estimated to be −£5520 (95% CI −£18,060 to £7020), with a mean QALY difference of 0.093 (95% CI 0.029 to 0.156). Results from the long-run health economic model were broadly consistent with the within-trial results.

Observational data results

At 12 months, there were significant differences in the GOSE scores between the two groups in the ordinal analysis ($p = 0.0002$), but these patients had significantly different baselines, with the DC group being younger, with more extracranial injuries, lower GCS and more likely to have had parenchymal lesions and traumatic subarachnoid haemorrhages.

Conclusions

Among adult patients undergoing evacuation of a traumatic ASDH, a DC did not result in better outcomes than craniotomy in the randomised cohort. Secondary craniectomies were most frequently performed in the craniotomy group, but wound-related complications and surgical site infections occurred more frequently in the craniectomy group. Craniotomy was estimated to be cost-effective compared to craniectomy.

Implications for health care

Although the present trial found no significant difference in mortality or GOSE outcomes between the DC and the craniotomy groups, the trial may well have practical implications. If the bone flap can be replaced without compressing the brain, surgeons should consider doing so, as opposed to performing a pre-emptive DC. This will also have an impact when considering the rehabilitation for this cohort of patients, as further neurosurgical procedures, such as cranioplasty, can impact this process. These findings may not be relevant for resource-limited or military settings, where an upfront craniectomy is often used due to absence of sophisticated ICU facilities for postoperative care.

Recommendations for research (numbered in priority order)

1. Evaluation of the timing of cranial reconstruction on functional recovery.
2. Long-term outcome following DC.

Trial registration

This trial is registered as ISRCTN87370545.

Funding

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Chapter 1 Introduction

Scientific background

Head injury is common with approximately 900,000 people attending emergency departments per year in the UK,[2] of which most patients sustain a mild traumatic brain injury (TBI). However, most fatal and unfavourable outcomes occur in patients with moderate or severe TBI, which account for approximately 10% of attenders. An estimated 1.2 million people live with some level of TBI-related disability in the UK, which has profound socioeconomic consequences, as the prevalence is particularly high among children and young to middle-aged adults.

By far, the most important early consequence of TBI is the development of an intracranial haematoma.[3] Intracranial haematomas can be extradural, subdural, intraparenchymal or a combination thereof. Without effective surgical management, an intracranial haematoma may transform an otherwise benign clinical course with the expectation of recovery, to a situation where death or severe disability will occur.

Studies conducted after the introduction of computed tomography (CT) scanning report an incidence of acute subdural haematoma (ASDH) between 12% and 29% in patients admitted with severe TBI.[4] Studies looking at patients with ASDH requiring surgery quote mortality rates between 40% and 60%. The decision to operate on an ASDH is usually based on the patient's GCS score, pupillary exam, comorbidities, CT findings, age and, in delayed decisions, intracranial pressure (ICP). Neurological deterioration over time is also an important factor influencing the decision to operate. Different surgical techniques have been advocated for the evacuation of an ASDH. Patients with an ASDH that require an operation to remove the clot are currently treated either with a craniotomy or a decompressive craniectomy (DC). The choice of operative technique is influenced by the surgeon's expertise, training and evaluation of the situation. Some centres treat all ASDH with DCs, whereas other centres used solely craniotomies.[4]

Head-injured patients with ASDHs that require an operation to remove the clot are currently treated either with a craniotomy or a DC.[3] The steps of a craniotomy are: opening of the skin, removal of a piece of skull, removal of the clot, replacement of the piece of skull and closure of the skin. A DC is a similar procedure, but the piece of skull is left out prior to closing the skin. The advantage of a DC is that it is very effective in controlling brain swelling, which is often a problem in the days after the operation. When the swelling goes down, the patient has another operation to reconstruct their skull. The advantage of a craniotomy is that the patient will not need a later operation to rebuild the skull. However, this type of operation may fail to control the brain swelling in some patients.[3] Both approaches are widely used among neurological surgeons (although the indications may differ); therefore, there is sufficient experience in the centres to set up a randomised trial.

Both procedures are carried out regularly in the NHS and worldwide. All neurosurgeons can perform both types of operation. With the objective of examining current practice patterns of surgical treatment for ASDH, we undertook a survey of members of the European Association of Neurosurgical Societies (EANS), Neurocritical Care Society, NeuroCritical Care Network, full members of the Society of British Neurological Surgeons (SBNS) and members of the British Neurosurgical Trainees Association during October and November 2011.[5] The questionnaire survey was approved by the Academic Committee of the SBNS (project no. NE0026). From the survey,[1] the question 'When evacuating a traumatic ASDH, how often do you perform a primary DC (i.e. leave the bone flap out)?' was answered by 283 neurosurgeons (201 board-certified consultants or equivalent; 82 trainees).

There were 138 from UK/Irish countries, 110 from other European countries, 13 North Americans and 22 respondents from various other countries. We decided to group together the responses of neurosurgeons working in countries with national representation to the EANS in order to have two similar-sized groups (UK/Irish and other European). We also think that these two groups have a degree of intrinsic homogeneity with respect to clinical neurosurgical

practice. Although 41% of the respondents use primary DC < 25% of the time, almost one-third use DC in more than 50% of such cases. We found that a higher proportion of neurosurgeons from other European countries (48/110; 44%) as compared with UK/Irish neurosurgeons (29/138; 21%) use primary DC in more than half of ASDH cases ($p < 0.001$). Another interesting finding was that of the 23 UK/Irish neurosurgical units (NSUs) with at least 2 consultant respondents, only 6 units (26%) showed intradepartmental agreement regarding the use of primary DC for ASDH. We do not think that the observed variation in practice can be fully explained by regional/national differences in trauma care systems or the epidemiology of TBI within Europe. Rather, we believe that the variation in practice reflects the lack of high-quality evidence regarding the use of primary DC for ASDH evacuation.

A systematic review published by the Brain Trauma Foundation in 2006 concluded that research on the role of DC versus craniotomy is the top key issue for future investigation likely to improve the care of patients with ASDH.[3]

The Brain Trauma Foundation systematic review (literature search from 1975 to 2001) demonstrated the dearth of high-quality evidence addressing the effectiveness of the two main surgical procedures (craniotomy and DC) used for treating patients with ASDH.[3] The available evidence consists of retrospective studies only, which do not usually address the effectiveness of the procedure.

We performed a systematic literature search from 2001 to April 2013 using the same search terms/methodology as the Brain Trauma Foundation investigators. We identified 16 published studies which present the outcome from ASDH. No prospective randomised studies comparing DC with craniotomy for patients with ASDH were found. Only five retrospective cohort comparison studies addressing the effect of the operative technique on outcome from ASDH were identified (3, 5–8). A finding that was universal across these five studies was that patients undergoing DC had significantly more severe injuries compared to patients treated with a craniotomy.

All these studies have methodological weaknesses because of their observational designs, with limited details regarding patient selection, outcome assessment and small sample sizes. It is not possible to draw meaningful conclusions from the available non-randomised studies, and the evidence base for the use of one approach over the other is weak. A well-designed and conducted randomised trial comparing the effectiveness and cost-effectiveness of craniotomy and DC is needed to inform current NHS practice, health policy and individual surgeon and patient clinical decision-making.

Following a DC, patients require reconstruction of their skull. However, a number of currently unknown parameters could render DC more cost-effectively than craniotomy. These parameters include: functional outcome, health-related quality of life (HRQoL), length of stay (LOS) in the intensive care unit (ICU) and length of rehabilitation. An economic analysis, embedded within a pragmatic randomised trial, is required to establish the relative cost-effectiveness of the different procedures when adopted into routine clinical practice.

Currently, there is only class III evidence with retrospective studies investigating the role of DC as a primary procedure for ASDH.

Explanation of rationale

There is currently no high-quality evidence guiding surgeons as to which operation they should be offering as first-line treatment to patients with ASDH. The results of a high-quality study will be used to inform future National Institute for Health and Care Excellence (NICE) head-injury guidelines and the practice of neurosurgeons in the NHS and worldwide.

Five-year pilot data from an NHS NSU (Cambridge) showed that 56% of patients with ASDH were treated with a DC.[3] In this retrospective cohort comparison study, 91 patients had an operation for an ASDH. The standardised morbidity ratio was lower in individuals who received DC [0.75, 95% confidence interval (CI) 0.51 to 1.07] than in those treated with a craniotomy (0.90, 95% CI 0.57 to 1.35). Although the standardised morbidity ratio 95% CIs overlap, this study lends support to the hypothesis that DC may lead to better functional outcomes in comparison to craniotomy for adult head-injured patients with ASDH.

Health technologies being assessed

The two health technologies we wish to assess are the two most widely used surgical techniques for the evacuation of an ASDH: craniotomy and DC. When an ASDH is evacuated, the bone flap can be left out or replaced prior to closing the skin. The RESCUE (randomised evaluation of surgery with craniectomy for patients undergoing evacuation of acute subdural haematoma)-ASDH trial will compare these two specific components of the operation to remove an ASDH (i.e. bone flap left out prior to closing the skin vs. bone flap replaced prior to closing the skin). Both options are widely practised and accepted, but they have never been compared head-to-head in a randomised trial. When the bone flap is replaced prior to closing the skin, the operation is named craniotomy. On the other hand, when the bone flap is left out, the operation is named DC. The advantage of a DC is that it is effective in controlling brain swelling, which is often a problem in the days after the operation. When the swelling goes down, the patient has another operation to reconstruct the skull (cranioplasty). The advantage of a craniotomy is that the patient will not need a later operation to rebuild the skull. However, it may fail to control brain swelling in some patients.

Chapter 2 Methods

Trial design

The RESCUE-ASDH was an international, multicentre, pragmatic, parallel-group randomised trial that compared the effectiveness of craniotomy versus DC for the management of adult head-injured patients undergoing evacuation of an ASDH. There was an additional observational cohort which included eligible patients enrolled into the study who could not be randomised after evacuation of haematoma due to significant swelling of the brain or who were enrolled following surgery.

Full ethical approval was obtained from each participating site. An internal pilot randomised trial was undertaken to confirm operational feasibility. Patients with an ASDH present in an incapacitated state, and due to its life-threatening nature, an operation is undertaken as soon as possible. Thus, a written agreement was obtained from the next of kin whenever feasible. If the next of kin was not available, the operation was undertaken in the patient's best interest and agreement from the next of kin retrospectively obtained. An independent steering committee and an independent Data Monitoring and Ethics Committee reviewed the trial at regular intervals to assess conduct, progress and safety. The trial protocol was designed in a collaborative fashion by clinicians and researchers from the Academic Division of Neurosurgery and Anaesthesia at the University of Cambridge in conjunction with the SBNS and the European Brain Injury Consortium. The trial protocol was published previously and available with the full text of this article at NEJM.org.[6] The trial investigators vouch for the accuracy and completeness of the data and the analyses and for the fidelity of this report to the trial protocol and the statistical analysis plan (SAP).

Participants

For enrolment in the study, patients had to be 16 years or older and have had an ASDH on a CT scan of the brain that required surgical evacuation with a large bone flap either by a craniotomy or by CT according to the opinion of the admitting neurosurgeon. Patients with additional lesions (such as intracerebral haematoma or contusions) could be included. Patients with bilateral ASDHs both requiring evacuation, previous enrolment in the trial, severe pre-existing disability or severe comorbidity which would lead to a poor outcome even if the patient made a full recovery from the head injury were excluded from trial participation. Trial sites were hospitals with acute neurosurgical services for patients with TBI.

Patients were enrolled into the trial from September 2014 through April 2019 in 40 centres in 11 countries. A total of 3566 patients were screened for eligibility, and 462 were randomised. Twelve patients were withdrawn due to lack of valid informed consent or withdrawal of consent. This resulted in a total of 228 in the craniotomy arm and 222 in the DC arm. There were 386 patients in the observational cohort: 141 received a craniotomy, and 245 received a DC.

Interventions

This trial compared two surgical procedures – craniotomy and DC. For the craniotomy arm, a large bone flap (recommended size ≥ 11 cm) anteroposterior diameter was raised and the ASDH evacuated. Other haematomas could be evacuated at the surgeon's discretion. The bone was replaced and fixed to the surrounding skull with an appropriate fixation system. Hinge or floating flaps were not allowed. The size and location of the initial incision; method used to close the dura, galea and skin; use of drains and ICP monitors were left to the surgeon's discretion. The DC arm followed the same procedure as the craniotomy arm, except the dura was left open or in a non-constricting manner

and the bone flap was not replaced. Operations were undertaken by consultant neurosurgeons or trainees according to local practice. Medical management of these patients, pre, intra and postoperatively, were undertaken according to the centre's standard practice for head-injured patients. The operating neurosurgeon assessed the suitability of randomisation in the operating theatre. Blocked randomisation was used, with a block size of four and allocation ratio of 1 : 1, and subjects were allocated randomly within each block. Allocation was stratified by country, geographical region, age, severity of injury and CT findings (see protocol and SAP for further details).[6] Patients in the craniotomy arm could undergo a DC at a later stage if their condition deteriorated after their index procedure at the discretion of their treating physician. It was not possible to blind patients, relatives and treating doctors due to the nature of the operation (after a DC, a skull defect is noticeable until a cranioplasty is undertaken). However, the researchers assessing the outcome via follow-up questionnaires were blind to the operation undertaken.

Aims and objectives

Aim

The aim was to perform a multicentre, pragmatic, parallel-group randomised trial to compare the clinical and cost-effectiveness of DC versus craniotomy for the management of adult head-injured patients undergoing evacuation of an ASDH with an additional observational cohort for those patients' undergoing surgery but who were unable to be randomised.

Primary objective

To compare the long-term clinical effectiveness of DC versus craniotomy (1-year follow-up period).

Secondary objectives

Compare the adverse events (AEs) and surgical complications between the two arms.

Undertake a detailed economic evaluation.

Outcomes

Primary end point

The Glasgow Outcome Scale-Extended (GOSE) at 12 months post injury. The use of the GOSE as a core global outcome measure is recommended by the interagency TBI Outcomes Workgroup and the International Mission for Prognosis and Analysis of Clinical Trials in TBI (IMPACT-TBI) group.

Secondary end points:

- GOSE at 6 months post injury
- HRQoL [EuroQol-5 Dimensions, five-level version (EQ-5D-5L)] at discharge from NSU, 6 and 12 months post injury
- Glasgow Coma Scale (GCS) on discharge from the ICU and from NSU
- LOS in ICU, neurosurgical and rehabilitation unit
- therapy intensity level (TIL) in the ICU
- discharge destination from NSU
- mortality
- serious AEs and surgical complications during index admission
- cranial surgery within 2 weeks after randomisation
- subsequent re-admissions to the NSU within the 12-month follow-up period
- hydrocephalus requiring shunt insertion within the 12-month follow-up period
- healthcare service utilisation over 12 months
- detailed economic evaluation.

Sample size

At the outset of the trial in 2014, the group of co-applicants deemed an 8% treatment effect as a clinically important difference. Subsequently, a formal sample size calculation was performed with the nQuery Advisor Version 7.0 (Statistical Solutions, Saugus, MA, USA) using a Mann–Whitney–Wilcoxon rank-sum test for ordered categories. We estimated that a sample of 990 patients would allow us to detect the equivalent of an absolute difference of 8% in the proportion of participants at 12 months after randomisation, with a favourable outcome [90% power and two-sided significance 0.05 (35% vs. 43%), 10% dropout rate] with ordinal analysis. Mortality is recorded as part of the GOSE (death – GOSE score 1), so it will not impact on loss to follow-up. In addition, a simulation study was undertaken to look at the impact on statistical power of covariate (age, GCS motor score and pupillary reaction) adjustment over and above the ordinal analysis. The simulation study confirmed that the planned sample size of 990 patients would give over 90% power to detect an 8% treatment effect.

However, it was clear by 2017 that the sample of 990 at the outset of the trial might not be appropriate given discussions in the neurosurgical community that evidence of a larger treatment effect is required to encourage surgeons to change their practice, especially when the intervention in question (i.e. craniectomy) will necessarily lead to a second operation (i.e. cranial reconstruction). A survey among an international pool of neurosurgeons who have expertise in neurotrauma and are interested in the study question was undertaken. The results showed that the mean number needed to treat (NNT) that would lead these surgeons to change their practice was seven. We believe that surgeons who do not have expertise or interest in neurotrauma are likely to suggest that an even lower NNT would be necessary in order to lead to a practice change. A NNT of seven is equivalent to a 14% treatment effect, and the sample size was re-estimated [using WinPepi version 11.65 (Joe Abramson, Hebrew University of Jerusalem, Jerusalem, Israel)] in 2018 using this treatment effect, giving a sample size of 440, allowing for a 10% dropout rate. The new sample size of 440 will have more than 80% power for a 14% treatment effect with binary analysis (corresponding to NNT of 7) and more than 90% power for a 14% treatment effect with ordinal analysis. The results of the survey and the implication for sample size adjustment were discussed at the HTA and Trial Steering Committee meetings, both unanimously agreed that reducing the sample size to 440 randomised patients was valid, based on these results.

If the target sample size of 440 is reached before 30 April 2019 (end of study recruitment date), we will continue recruiting patients until the end of the recruitment period.

Randomisation

Following enrolment in the study, suitability for randomisation was assessed in the operating room by the operating neurosurgeon. A secure web-based or telephone randomisation service was used for the randomisation of suitable patients. To randomise a patient, the following information was required: age, best pre-intubation GCS, pre-operative pupillary reactivity, CT findings.

Sequence generation

Blocked randomisation was used, with a block size of four and allocation ratio of 1 : 1. Subjects were allocated randomly within each block. Allocation was stratified by country/geographical region (UK/other European countries/North America/Australia/other), age group (< 40, 40–65, > 65 years), severity of injury (GCS 3–8, GCS 9–15) and CT findings (parenchymal injury, no parenchymal injury).

Implementation

The system provided an immediate allocation along with the patient identifier number for the trial. A confirmatory e-mail was sent to the e-mail addresses of the members of the study team at the site randomising the patient. The 24-hour randomisation service was also backed by 24-hour availability of trial investigators who could advise on patient eligibility.

Eligible non-randomised participants who had the operation (i.e. craniotomy or DC) deemed to be in their best interests by the operating surgeon were followed up in a similar manner to randomised patients in the observational arm of the study.

Blinding

Patients, relatives and treating doctors were unable to be blinded due to the nature of the intervention (after a craniectomy, a skull defect is noticeable until a cranioplasty is undertaken). The follow-up questionnaires were collected centrally (Cambridge), and outcome scores determined by two outcome adjudicators independently. The outcome adjudicators were blinded to patient allocation. Any disagreements were discussed in the outcome's adjudication committee.

In the international sites, the same procedure was followed, with the difference that local staff were responsible for sending postal questionnaires to patients. If a telephone or face-to-face interview needed to be undertaken to complete the questionnaires, a standard operating procedure ensured strict separation between staff conducting these interviews and staff that are involved in the acute care of recruited patients. Questionnaires from international sites were returned to the Cambridge Clinical Trials Unit and outcome scores determined as described above.

Statistical methods

Primary outcome in this study will be measured using the GOSE. Conventionally, scales such as this are analysed by dichotomising the ordinal scale into a binary scale: 'unfavourable' versus 'favourable' and an odds ratio (OR) calculated. A significant number of patients will not have a realistic chance of crossing the threshold between 'unfavourable' and 'favourable' outcome and will not contribute data to the analysis. The crude OR is, therefore, not a meaningful effect measure for many patients. It discards much relevant information, reducing both the clinical relevance of the results and the statistical efficiency of the analysis. We, therefore, consider it more appropriate to quantify prognostic effects across the full range of the GOSE, and previous work by the IMPACT-TBI project has recommended that the primary analysis of the GOSE should use an ordinal approach, based on proportional odds methodology.[7]

Outcome analyses were performed in the modified intention-to-treat (ITT) population, which included all randomly assigned patients, except those who withdrew consent for participation in the trial and those lost to follow-up. Patients were retained in the group to which they were originally allocated, regardless of protocol adherence. The primary analysis was undertaken as an ordinal analysis using the proportional odds model, with the results presented as the estimated common OR with its corresponding 95% CI and *p*-value. The goodness of fit of the unadjusted proportional odds model was tested, and if rejected at 5% significance level, then that would mean that the model's assumptions are not met.

The choice of ordinal logistic regression is based on the results of statistical research and trials, which showed that ordinal methods can increase statistical power substantially, equivalent to allowing a reduction of over 40% in the sample size without loss of statistical power. Ordinal logistic regression analysis is similar to logistic regression analysis, but it simultaneously estimates multiple ORs instead of just one. The number of ORs it estimates is equivalent to the number of ordered categories minus one. The ordinal regression model assumes that the OR for each potential split of the GOSE is constant no matter which cutpoint is taken, that is, it follows a proportional odds model; this assumption can be tested with a formal test of goodness of fit. The final estimated effect size is the common OR.

Further pre-specified secondary analyses were planned, including a fixed dichotomy analysis and a sliding dichotomy. The former compared the proportion of patients achieving a 'favourable' outcome (defined as upper severe disability or better on GOSE) between the two arms using the chi-squared test. The latter used a sliding dichotomy to define favourable outcome; if the randomisation GCS was between 3 and 8, a favourable GOSE outcome was defined as upper severe disability or better, but if the randomisation GCS was between 9 and 15, a favourable GOSE outcome was defined as lower moderate disability or better.

Analyses of secondary outcomes used proportional odds models for ordinal outcomes and chi-squared tests and logistic regression to estimate for binary outcomes. Chi-squared tests were used for categorical outcomes with categories combined, where necessary, due to low frequency, and Fisher's exact tests were used for binary outcomes with low frequency in one category. Mann–Whitney U-tests were used for non-normally distributed continuous data

and medians and interquartile ranges reported as the lower (Q1) and upper (Q3) quartiles. For LOS and survival data, Kaplan–Meier plots were produced and log-rank tests and Cox regression undertaken. Full details of the analysis are provided in the SAP (reference). Statistical analysis was undertaken using SPSS version 27 (IBM Corporation, Armonk, NY, USA).

Summary of any changes to the project protocol

The sample size was adjusted to 440, which had more than 80% power for a 14% treatment effect with binary analysis (corresponding to NNT of 7) and more than 90% power for a 14% treatment effect with ordinal analysis.

Chapter 3 Results: randomised

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Study flow chart

Please see *Appendix 4*.

Recruitment

Trial enrolment started in September 2014 through to April 2019 in 40 centres across 11 countries. A total of 3566 patients were screened for eligibility, and 462 were randomised. Twelve patients were withdrawn due to lack of valid informed consent or withdrawal of consent. This resulted in a total of 228 in the craniotomy arm and 222 in the DC arm.

Numbers analysed

From the 228 patients in the craniotomy arm, 208 received the allocated intervention and 20 received a DC. Regarding the 222 patients in the DC arm, 210 received the allocated intervention and 12 received a craniotomy. The primary outcome was reported in 426 patients (215 in the craniotomy arm and 211 in the DC arm) (*Table 1*).

Baseline demographics

TABLE 1 Randomised arm: characteristics of the patients at baseline

Characteristics of the patients at baseline[a]		
Characteristic	**Craniotomy (*N* = 228)**	**DC (*N* = 222)**
Age – year	48.3 ± 16.5	48.8 ± 16.6
Male sex – number/total number (%)	178/228 (78.1)	179/222 (80.6)
Any antithrombotic medication – number/total number (%)[b]	30/209 (14.4)	31/202 (15.3)
Presence of major extracranial injury requiring admission – number/total number (%)	90/225 (40.0)	83/220 (37.7)
GCS 3–8[c]	148/228 (64.9)	146/222 (65.8)
Initial CT brain findings		
Presence of midline shift > 5 mm – number/total number (%)	195/226 (86.3)	189/221 (85.5)
Compression/absence of basal cisterns – number/total number (%)	197/226 (87.2)	192/221 (86.9)
Presence of parenchymal contusions < 25 cc – number/total number (%)	109/227 (48.0)	104/221 (47.1)

a Plus–minus values are means ± standard deviation (SD). Total number of patients that are < 228 in the craniotomy group and < 222 in the DC group indicate that data were missing/unknown for some patients.
b Includes antiplatelets and anticoagulants.
c Scores on the GCS range from 3 to 15, with lower scores indicating a worse injury.

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Injury and pre-hospital data

Almost all injuries were closed-head injuries (96%). The distribution of the mechanism of injury and presence of major extracranial injury was similar in the two treatment groups. The presence of pre-hospital hypoxia, hypotension and hypothermia and of cardiac arrest, seizures or clinical deterioration in the two patient groups was similar (*Table 2*).

TABLE 2 Randomised arm: baseline data; injury details and pre-hospital data

		Randomised craniotomy (*n* = 228)	Randomised DC (*n* = 222)
Injury mechanism	Motor vehicle occupant	28 (12%)	33 (15%)
	Cyclist	6 (3%)	7 (3%)
	Incidental fall	100 (44%)	93 (42%)
	Motor bike	26 (12%)	27 (12%)
	Suicide attempt	1 (–%)	1 (–%)
	Other non-intentional	3 (1%)	4 (2%)
	Pedestrian	17 (8%)	15 (7%)
	Violence/assault	22 (10%)	19 (9%)
	Other	22 (10%)	20 (9%)
	Not available	3	3
Pre-hospital hypoxia (PO_2 < 8 kPa or 60 mmHg/SpO_2 < 90%)	Yes	7 (3%)	7 (3%)
	Suspected	26 (12%)	20 (9%)
	No	110 (49%)	122 (55%)
	Unknown	81 (36%)	71 (32%)
	Not available	4	2
Pre-hospital hypotension (SBP < 90 mmHg)	Yes	6 (3%)	5 (2%)
	Suspected	14 (6%)	9 (4%)
	No	133 (59%)	142 (65%)
	Unknown	71 (32%)	64 (29%)
	Not available	4	2
Pre-hospital hypothermia (temp < 35 °C)	Yes	11 (5%)	16 (7%)
	Suspected	8 (4%)	3 (1%)
	No	129 (58%)	131 (60%)
	Unknown	76 (34%)	70 (32%)
	Not available	4	2
Pre-hospital cardiac arrest	Yes	7 (3%)	2 (1%)
	No	202 (94%)	210 (99%)

TABLE 2 Randomised arm: baseline data; injury details and pre-hospital data (*continued*)

		Randomised craniotomy (*n* = 228)	Randomised DC (*n* = 222)
	Unknown	7 (3%)	1 (–%)
	Not available	12	9
Pre-hospital seizures	Yes	18 (8%)	24 (11%)
	No	172 (77%)	172 (79%)
	Unknown	34 (15%)	22 (10%)
	Not available	4	4
Pre-hospital clinical deterioration	Yes	64 (29%)	67 (30%)
	No	119 (53%)	132 (60%)
	Unknown	41 (18%)	21 (10%)
	Not available	4	2
Pre-intubation GCS	3–8	148 (65%)	146 (66%)
	9–15	80 (35%)	76 (34%)
Pupil reactivity	Neither pupil reactive	31 (14%)	36 (16%)
	At least one reactive	182 (80%)	176 (79%)
	Both untestable	2 (1%)	3 (1%)
	Unknown	13 (6%)	7 (3%)

SBP, systolic blood pressure.

Medical history

There were no major differences in medical history between the two treatment groups (*Table 3*).

TABLE 3 Randomised arm: baseline data; medical history

		Randomised craniotomy (*n* = 228)	Randomised DC (*n* = 222)
Any medical history	No	101 (44%)	88 (40%)
	Yes	111 (49%)	109 (50%)
	Unknown	16 (7%)	21 (10%)
	Missing		4
Conditions	Cardiovascular	53	48
	Endocrinological	25	23

continued

TABLE 3 Randomised arm: baseline data; medical history (*continued*)

		Randomised craniotomy (*n* = 228)	Randomised DC (*n* = 222)
	Hearing/vision	6	3
	Gastrointestinal	11	11
	Haematological	4	4
	Liver	7	8
	Musculoskeletal	5	5
	Respiratory	13	18
	Neurological	25	28
	Oncological	17	9
	Psychiatric	29	31
	Renal	12	7
	Other	41	51

Note
Vital signs on admission were recorded, including blood pressure, pulse, respiratory rate and temperature. These were similar in both treatment groups (see *Appendix 2*).

Primary outcome: Glasgow Outcome Scale-Extended

Death occurred in 30.2% in the craniotomy group versus 32.2% in the craniectomy group; vegetative state occurred in 2.3% versus 2.8%, and good recovery occurred in 25.6% versus 19.9%, respectively. Non-statistically significant better outcomes were seen in patients undergoing craniotomy initially than in those undergoing DC, with a common OR across the GOSE scores of 0.85 [95% CI (0.6 to 1.18, p = 0.324)] (*Figure 1* and *Table 4*).

TABLE 4 Randomised data, primary outcome summary

Variable	Craniotomy	DC	Measure of effect	Difference or OR (95% CI)	*p*-value
Primary outcome					
GOSE at 12 months – number/total number (%)					
Ordinal outcomes					
Dead	65/215 (30.2)	68/211 (32.2)	Common OR	0.85 (0.6 to 1.18)	0.324
Vegetative state (VS)	5/215 (2.3)	6/211 (2.8)			
Lower severe disability (LSD)	38/215 (17.7)	41/211 (19.4)			
Upper severe disability (USD)	28/215 (13.0)	27/211 (12.8)			
Lower moderate disability (LMD)	12/215 (5.6)	11/211 (5.2)			
Upper moderate disability (UMD)	12/215 (5.6)	16/211 (7.6)			
Lower good recovery (LGR)	17/215 (7.9)	13/211 (6.2)			
Upper good recovery (UGR)	38/215 (17.7)	29/211 (13.7)			

TABLE 4 Randomised data, primary outcome summary (*continued*)

Variable	Craniotomy	DC	Measure of effect	Difference or OR (95% CI)	*p*-value
Dichotomous outcomes					
Unfavourable outcome (dead, VS, LSD)	108/215 (50.2)	115/211 (54.5)	OR	0.84 (0.58 to 1.23)	–
Favourable outcome (USD, LMD, UMD, LGR, UGR)	107/215 (49.8)	96/211 (45.5)			–

Source
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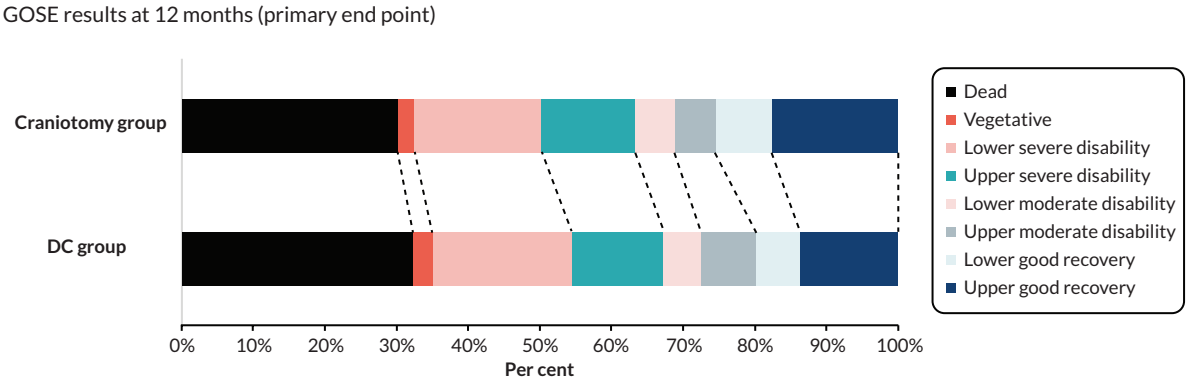

FIGURE 1 Primary end point: stacked bar chart of GOSE results at 12 months. Reproduced with permission from Hutchinson *et al.*[6] © 2023 Massachusetts Medical Society.

Secondary outcomes: Glasgow Outcome Scale-Extended, efficacy and safety

TABLE 5 Randomised arm: secondary outcomes efficacy and safety

GOSE evaluated at 6 months – number/total number (%)					
Dead	63/206 (30.6)	57/201 (28.4)	Common OR	0.84 (0.59–1.18)	–
Vegetative	7/206 (3.4)	14/201 (7.0)			
Lower severe disability	34/206 (16.5)	45/201 (22.4)			
Upper severe disability	28/206 (13.6)	29/201 (14.4)			
Lower moderate disability	16/206 (7.8)	9/201 (4.5)			
Upper moderate disability	17/206 (8.3)	16/201 (8.0)			
Lower good recovery	16/206 (7.8)	15/201 (7.5)			
Upper good recovery	25/206 (12.1)	16/201 (8.0)			
Mortality at 30 days – number/total number (%)	48/225 (21.3)	44/220 (20.0)	OR	1.09 (0.69–1.72)	–

continued

TABLE 5 Randomised arm: secondary outcomes efficacy and safety (*continued*)

AEs					
Extracranial – number/ total number (%)[a]	113/228 (49.6)	104/222 (46.8)	Percentage-point difference	2.7 (−0.07 to 0.12)	0.282
Procedure-related	60/228 (26.3)	57/222 (25.7)	Percentage-point difference	0.64 (−0.07 to 0.08)	0.438
Further cranial surgery within 2 weeks after randomisation – number/ total number (%)[b]	28/192 (14.6)	13/188 (6.9)	Percentage-point difference	7.6 (0.01–0.14)	–
Mean EQ-5D-5L utility index score					
At discharge (no)	0.247 (179)	0.271 (185)	Difference (95% CI)	−0.024 (−0.098 to 0.049)	–
At 6 months (no)	0.434 (193)	0.386 (188)		0.048 (−0.031 to 0.126)	–
At 12 months (no)	0.455 (197)	0.397 (199)		0.058 (−0.024 to 0.141)	–

a Two hundred and seventy extracranial AEs were reported for 113/228 patients in the craniotomy group, whereas 289 AEs were reported for 104/222 patients in the DC group. There were no differences in the types of AEs experienced between the two groups.
b A total of 49 cranial operations within 2 weeks after randomisation were reported in 41 patients across both groups; 5/28 patients in the craniotomy group and 2/13 patients in the craniectomy group had more than one cranial operation within 2 weeks after randomisation. Of the 49 operations, 19 were DCs (38.8%); 18 of those occurred in the craniotomy group.
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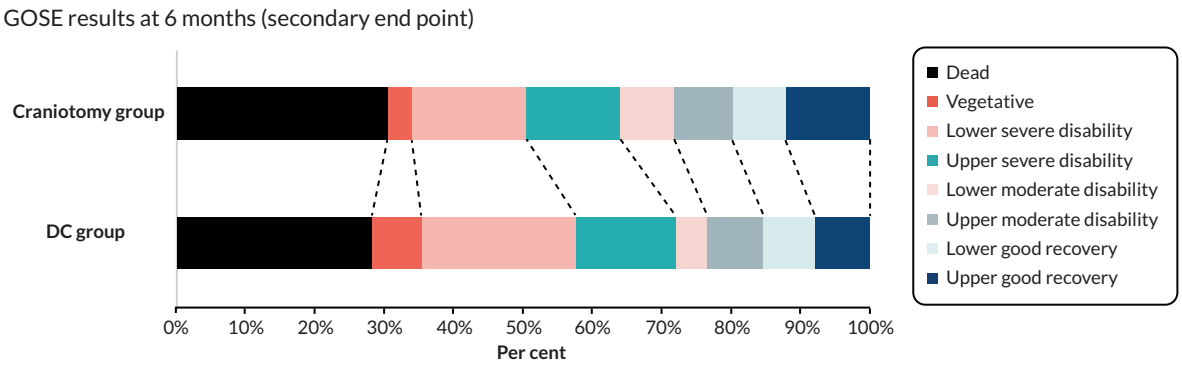

FIGURE 2 Stacked bar chart of GOSE results at 6 months. Reproduced with permission from Hutchinson *et al.*[6] © 2023 Massachusetts Medical Society.

Additional data randomised arm

Computed tomography scan results

The characteristics of the CT scans were very similar in the two treatment groups.

TABLE 6 Randomised arm: stage 1 case report form CT scan results

		Randomised craniotomy (*n* = 228)	Randomised craniectomy (*n* = 222)	Total randomised (*n* = 450)
Midline shift	None	3 (1%)	9 (4%)	12 (3%)
	≤ 5 mm	28 (12%)	23 (10%)	51 (11%)
	5.1–10 mm	97 (43%)	95 (43%)	192 (43%)
	> 10 mm	98 (43%)	94 (43%)	192 (43%)

TABLE 6 Randomised arm: stage 1 case report form CT scan results (*continued*)

		Randomised craniotomy (*n* = 228)	Randomised craniectomy (*n* = 222)	Total randomised (*n* = 450)
	Not available	2	1	3
Obliteration of basal cisterns	Normal	29 (13%)	29 (13%)	58 (13%)
	Compressed	160 (71%)	130 (69%)	313 (70%)
	Absent	37 (16%)	39 (18%)	76 (17%)
	Not available	2	1	3
Parenchymal lesions	No	118 (52%)	117 (53%)	235 (52%)
	Yes	109 (48%)	104 (47%)	213 (48%)
	Not available	1	1	2
Intraventricular blood	No	216 (95%)	202 (91%)	418 (93%)
	Yes	11 (5%)	19 (9%)	30 (7%)
	Missing	1	1	2
Traumatic SAH	No	117 (52%)	102 (46%)	219 (49%)
	Yes	110 (48%)	119 (54%)	229 (51%)
	Missing	1	1	2
Extradural haematoma	Absent	212 (93%)	206 (93%)	418 (93%)
	≤ 25 cc	11 (5%)	11 (5%)	22 (5%)
	> 25 cc	4 (2%)	4 (2%)	8 (2%)
	Missing	1	1	2
Subdural haematoma	Absent	171 (75%)	172 (78%)	343 (77%)
	≤ 25cc	301(14%)	25 (11%)	56 (13%)
	> 25cc	25 (11%)	24 (11%)	49 (11%)
	Missing	1	1	2
Intracerebral haematoma	Absent	182 (80%)	178 (81%)	360 (80%)
	≤ 25 cc	38 (17%)	34 (15%)	72 (16%)
	> 25 cc	7 (3%)	9 (4%)	16 (4%)
	Missing	1	1	2
Posterior fossa haematoma	No	223 (98%)	219 (99%)	442 (99%)
	Yes	4 (2%)	2 (1%)	6 (1%)
	Missing	1	1	2
Depressed skull fracture	No	211 (94%)	211 (95%)	422 (95%)
	Yes	14 (6%)	10 (5%)	24 (5%)
	Missing	3	1	4

SAH, subarachnoid haemorrhage.

The distribution of pre-intubation GCS and the pupil reactivity was similar in the two treatment groups (see *Appendix 3*).

Surgery details and postoperative destination

There was a small difference in the location of the ASDH between the treatment groups. Patients in the craniotomy group were more likely to have the ASDH located on the right, while those in the DC group were more likely to have the ASDH located on the left.

There were no differences between the treatment groups in terms of the type of skin incision, with 84% reverse question mark, or in the size of the bone flap [with a mean of 12.9 cm (± 1.7 cm)].

A drain was used in 85% of patients and was usually subgaleal 70% rather than subdural (15%). Intracranial monitoring devices were used in 51% of patients, with the majority being parenchymal and most (69%) being located ipsilateral to the ASDH.

For the patients who underwent DC, the bone flap was either stored inside the body (40%) or disposed (340).

TABLE 7 Randomisation arm: stage 1 case report form: surgery details and postoperative destination

		Randomised craniotomy (*n* = 228)	Randomised DC (*n* = 222)
Type of skin incision	Reverse question mark	190 (83%)	186 (84%)
	T-shaped	6 (3%)	5 (2%)
	Other	32 (14%)	31 (14%)
Drain used	Subdural	30 (13%)	36 (16%)
	Subgaleal	170 (75%)	145 (66%)
	None	27 (12%)	39 (18%)
	Not available	1	2
Length of bone flap (cm)	Mean (SD)	12.9 (1.7)	12.8 (1.8)
	Median	13	13
	IQR	2	2
	Not available	10	7
Location of ASDH	Left convexity	100 (44%)	119 (54%)
	Right convexity	128 (56%)	103 (46%)
Other haematoma evacuated[a]	No	181 (78%)	177 (81%)
	Intracerebral	22 (6%)	6 (2%)
	Extradural	9 (4%)	11 (5%)
	Contusions	29 (14%)	29 (12%)
	Other	1 (–%)	3 (1%)
Intracranial monitoring device	No	102 (45%)	119 (54%)
	Yes, EVD	4 (2%)	7 (3%)
	Yes, epidural	32 (14%)	29 (13%)

TABLE 7 Randomisation arm: stage 1 case report form: surgery details and postoperative destination (*continued*)

		Randomised craniotomy (*n* = 228)	Randomised DC (*n* = 222)
	Yes, subdural/subarachnoid	2 (1%)	2 (1%)
	Yes, parenchymal	81 (36%)	61 (28%)
	Other	7 (3%)	3 (1%)
	Not available	–	1
Transfer destination after operation	ICU	171 (75%)	166 (75%)
	NSU/ward	56 (25%)	52 (25%)
	Other	1 (–%)	0

EVD, external ventricular drain; IQR, interquartile range; SD, standard deviation.
a Patients can have more than one other haematoma type evacuated.

There was no difference in the occurrence of intraoperative complications (χ^2 p = 0.82) or the destination from the operating theatre (χ^2 p = 0.89).

Treatment received

Most patients received the treatment they were allocated to. The main reason given for patients crossing over from the craniotomy group was due to intraoperative swelling. The main reason given for patients crossing over from the DC group was because the brain was relaxed (see *Appendix 4*).

Discharge from the intensive care unit

There was no difference in mortality in ICU (χ^2 p = 0.789), and survivors were no more likely go to anywhere other than the NSU (χ^2 p = 0.207).

For those that died in ICU, there was no difference by treatment group in the length of time they spent in ICU (Mann–Whitney U-test p = 0.823). For those that were discharged from ICU, there was no difference in their GCS score at discharge (Mann–Whitney U-test p = 0.884), in whether their pupil reactivity was positive or negative in either eye (right χ^2 p = 0.484, left χ^2 p = 0.492) or in their LOS (Mann–Whitney U-test p = 0.680).

Please see *Appendix 5* for table.

Neurosurgical interventions within 14 days

These are recorded on the discharge from NSU case report form (CRF). The information is not recorded for the patient who did not go from the operating theatre into the ICU or NSU or for a further 69 patients (35 craniotomy and 34 DC) who initially went into ICU (including most of the patients who died in ICU or were discharged to a different hospital). Please see *Appendix 6* for table.

Discharge from neurosurgical unit

Patients were admitted to the NSU either directly from operating theatre (56 craniotomy, 56 DC) or after a stay in the ICU (126 craniotomy, 128 DC) but excludes cases who died in the ICU or were discharged directly from the ICU (*Table 8*).

TABLE 8 Randomisation arm: stage 3 CRF: discharge from NSU

		Randomised craniotomy (*n* = 182)	Randomised DC (*n* = 184)
Discharge destination from NSU	Died	15 (8%)	14 (8%)
	Home	43 (24%)	35 (19%)
	Rehabilitation	36 (20%)	43 (24%)
	Different hospital	72 (40%)	77 (42%)
	Nursing home	11 (6%)	7 (4%)
	Other	2 (1%)	5 (3%)
	Unknown	1 (1%)	1 (1%)
	Missing	2	2
Patients discharged alive from NSU		Randomised craniotomy (*n* = 165)	Randomised DC (*n* = 168)
GCS total score of patients discharged alive from NSU	Score 3	1 (1%)	0
	Score 4	0	0
	Score 5	0	1 (1%)
	Score 6	0	0
	Score 7	1 (1%)	2 (1%)
	Score 8	1 (1%)	2 (1%)
	Score 9	2 (1%)	3 (2%)
	Score 10	12 (9%)	9 (6%)
	Score 11	4 (3%)	2 (1%)
	Score 12	5 (4%)	12 (8%)
	Score 13	7 (5%)	14 (10%)
	Score 14	37 (287%)	45 (31%)
	Score 15	62 (47%)	57 (39%)
	Untestable	24	21
	Missing	9	0

Length of stay in intensive care unit and neurosurgical unit

Figure 3 is a survival plot of LOS in ICU (deaths are censored). The mean LOS for craniotomy is 12.8 days (95% CI 10.8 to 14.9), and for craniectomy, 13.0 days (95% CI 11.2 to 14.9). The median LOS for craniotomy is 10 days (95% CI 8.6 to 11.4), and for DC, 10 days (95% CI 9.0 to 11.0). Log-rank $p = 0.681$.

Figure 4 demonstrates that the median LOS in the NSU is 18 days and does not differ by treatment group (craniotomy 17 days, DC 18 days). Log-rank $p = 0.51$.

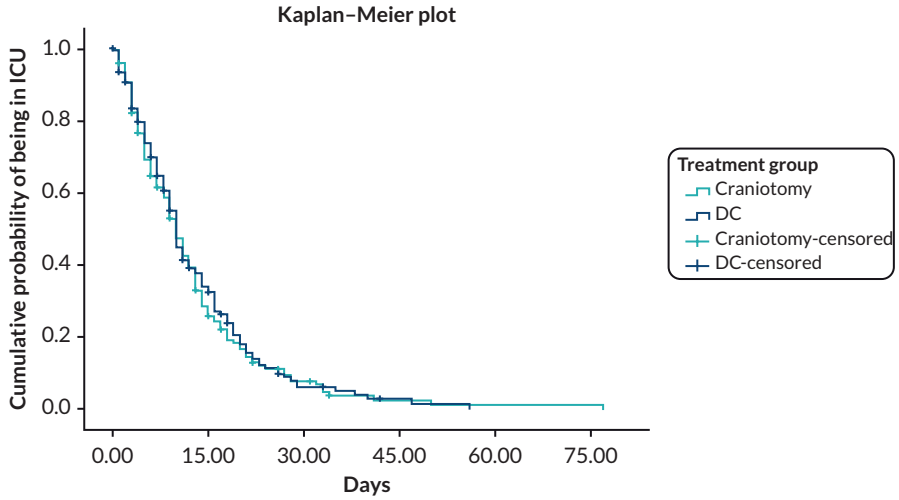

FIGURE 3 Randomised data: survival plot of LOS in ICU. Reproduced with permission from Hutchinson *et al.*[6] © 2023 Massachusetts Medical Society.

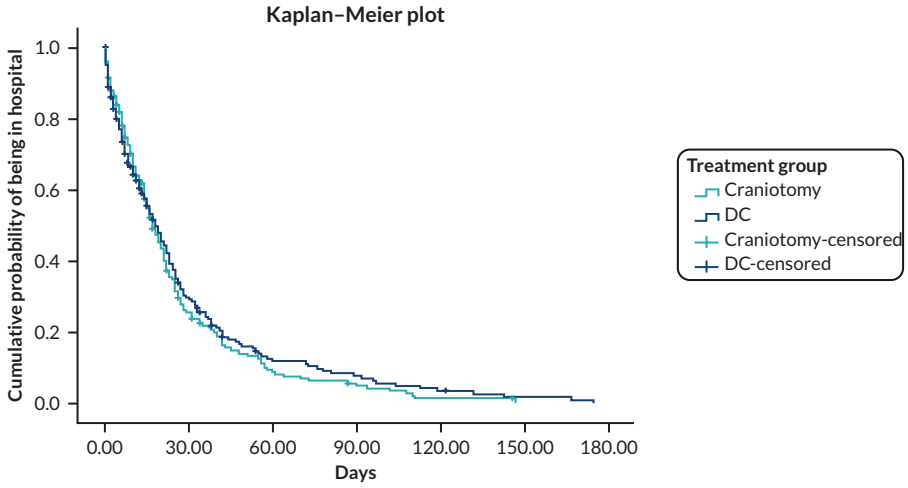

FIGURE 4 Randomised data: survival plot of median LOS in NSU. Reproduced with permission from Hutchinson *et al.*[6] © 2023 Massachusetts Medical Society,

Patients who died in hospital are censored for this analysis.

Eighty-two patients died in hospital after a mean of 14.8 days (median 8.5 days). No difference in time to death in hospital (Mann–Whitney U-test $p = 0.831$) (note – this will be further described using Kaplan–Meier). The median LOS for patients who were discharged from this hospital alive (to other hospitals, rehab, home nursing homes, etc.) was 15 days. There was no difference in LOS (Mann–Whitney U-test $p = 0.831$).

TABLE 9 Randomised data: LOS

		Randomised craniotomy (*n* = 228)	Randomised DC (*n* = 222)	Total randomised (*n* = 450)
Discharge destination from NSU	Died in hospital	41	41	82
	Discharged from NSU	185	179	364
	Missing (still on ward at 12 months)	2	2	4
Patients discharged alive		Randomised craniotomy (*n* = 185)	Randomised DC (*n* = 179)	Total randomised (*n* = 364)
LOS[a]	Mean	22.0	24.3	23.3
	SD	24.3	31.0	27.8
	Median	15	15	15
	IQR	21	24	22.25
	Minimum, maximum	0, 147	0, 175	0, 175
	Number missing	2	0	2
Patients died in hospital		Randomised craniotomy (*n* = 41)	Randomised DC (*n* = 41)	Total randomised (*n* = 82)
LOS[b]	Mean	14.9	14.7	14.8
	SD	25.5	21.1	23.2
	Median	9	8	8.5
	IQR	11.5	11	11
	Minimum, maximum	0, 146	0, 122	0, 146

IQR, interquartile range; SD, standard deviation.
a This is the LOS for all patients prior to their discharge to another hospital/unit/home.
b Total includes those who died in ICU (53) as well as those who died in NSU (29).

Therapy intensity level

The median number of days of ICP-directed therapy was 8 days in the craniotomy group and 10 days in the DC group (p = 0.128, Mann–Whitney U-test).

Please see *Appendix 7* for table.

Cranioplasty and shunts for hydrocephalus

TABLE 10 Randomised data: stage 4 CRF cranioplasty and shunts for hydrocephalus

		Randomised craniotomy (*n* = 228)	Randomised DC (*n* = 222)	*p*
Had DC before 12 months	Yes at index surgery	20 (8.8%)	210 (94.6%)	
	Yes, later	22 (10.1%)	1 (0.5%)	
	No	185 (81.1%)	11 (5.0%)	
	Missing	1		

TABLE 10 Randomised data: stage 4 CRF cranioplasty and shunts for hydrocephalus (*continued*)

		Randomised craniotomy (*n* = 228)	Randomised DC (*n* = 222)	*p*
Had cranioplasty by 12 months		**(n = 42)**	**(n = 211)**	0.271
	Yes	26 (63%)	113 (54%)	
	No	15 (36%)	96 (46%)	
	Missing	1	2	
Had a cranioplasty material		**(n = 26)**	**(n = 113)**	
	Autograft	9 (35%)	61 (57%)	0.027
	Non-metallic	10 (38%)	17 (16%)	
	Metallic	7 (27%)	29 (27%) 6	
		(n = 228)	**(n = 222)**	
Did patient develop hydrocephalus	Yes	11 (5%)	13 (6%)	0.586
	No	216 (95%)	203 (94%)	
	Missing	1	6	
Did the patient have a shunt	Yes	6	8	
	No	5	5	

Adverse events: randomised

Extracranial adverse events

Two hundred and seventy AEs are reported for 113 (50%) of the 228 patients randomised to craniotomy. The maximum number of events reported for a single patient was 9, and the average number of events reported by those randomised to craniotomy was 1.18. Two hundred and eighty-nine AEs were reported for 104 (47%) of the 222 patients randomised to DC. The maximum number of events reported for a single patient in this group was 6, and the average number of events reported by a patient randomised to DC was 1.30. The types of AEs experienced between the two treatment groups were similar.

Please see *Appendix 8* for AEs and procedure-related complications tables.

Chapter 4 Results: observational study

Study flow chart

Please see *Report Supplementary Material 2*.

Recruitment

A total of 386 patients from 37 sites in 10 countries were recruited to the observation data set between 8 September 2014 and 29 April 2019 (UK 22, India 4, Canada 3, USA 2, Spain 1 Malaysia 1, Greece 1, Germany 1, Australia 1, Hungary 1).

Numbers analysed

A total of 3566 patients were screened for eligibility, with 386 enrolled in the observed arm. There were 141 in the craniotomy arm and 245 in the DC arm.

Baseline data

Behavioural history, demography and coagulation history

Patients having DC were 17 years younger on average, less likely to have insurance, less likely to have been on anticoagulants or aspirin and more likely to have had a GCS between 3 and 8 (*Table 11*).

TABLE 11 Observational: characteristics of the observation cohort patients at baseline

Characteristics of the observation cohort patients at baseline[a]			
Characteristic	**Observed craniotomy (*N* = 141)**	**Observed DC (*N* = 245)**	**χ^2, *p*-values (age = Mann–Whitney U-test)**
Age – year	59.2 ± 15.9	42.4 ± 15.5	< 0.0001
Male sex – number/total number (%)	101/140 (72.1)	195/244 (79.9)	0.081
Any antithrombotic medication – number/total number (%)[b]	41/122 (33.6)	14/225 (6.2)	< 0.0001
Presence of major extracranial injury requiring admission — number/total number (%)	54/140 (38.6)	127/245 (51.8)	0.012
GCS 3–8[c]	57/128 (44.5)	156/231 (67.5)	< 0.0001
Initial CT brain findings			
Presence of midline shift > 5 mm – number/total number (%)	120/139 (86.3)	206/244 (84.4)	0.615
Compression/absence of basal cisterns – number/total number (%)	107/139 (77.0)	212/243 (87.2)	0.009
Presence of parenchymal contusions < 25 cc – number/total number (%)	50/139 (36.0)	166/242 (68.6)	< 0.0001

a Plus–minus values are means ± SD. Total number of patients that are < 141 in the craniotomy group and < 245 in the DC group indicate that data were missing/unknown for some patients.
b Includes antiplatelets and anticoagulants.
c Scores on the GCS range from 3 to 15, with lower scores indicating a worse injury.

Accident details and pre-hospital events

Almost all injuries were closed-head injuries (96%). Patients undergoing DC were more likely to have extracranial injury requiring admission. They were more likely to have been injured as a motorcyclist and less likely to have been injured in an incidental fall. Their experience of pre-hospital events was similar. (Combining suicide, other non-intentional injuries with other gives $p < 0.0001$ *Table 12*.)

Medical history

Patients treated by craniotomy had more medical history (*Table 13*).

TABLE 12 Observational: accident details and pre-hospital events

		Observed craniotomy ($n = 141$)	Observed DC ($n = 245$)	χ^2 – p-values
Injury mechanism	Motor vehicle occupant	9 (6%)	23 (9%)	
	Cyclist	2 (1%)	12 (5%)	
	Incidental fall	90 (64%)	93 (38%)	
	Motor bike	0	39 (16%)	
	Suicide attempt	0	3 (1%)	
	Other non-intentional	2 (1%)	1 (–%)	
	Pedestrian	9 (6%)	27 (11%)	
	Violence/assault	10 (7%)	27 (11%)	
	Other	18 (13%)	20 (8%)	
	Not available	1		
Pre-hospital event hypoxia (PO_2 < 8 kPa/SpO_2 < 90%)	Yes	11 (8%)	17 (7%)	0.575
	Suspected	14 (10%)	25 (10%)	
	No	91 (65%)	145 (60%)	
	Unknown	24 (17%)	56 (23%)	
	Not available	1	2	
Pre-hospital event hypotension (SBP < 90 mmHg)	Yes	7 (5%)	18 (7%)	0.091
	Suspected	9 (6%)	13 (5%)	
	No	106 (76%)	159 (65%)	
	Unknown	18 (13%)	54 (22%)	
	Not available	1	1	
Pre-hospital event hypothermia (temp < 35 C)	Yes	9 (6%)	17 (7%)	0.383
	Suspected	3 (2%)	2 (1%)	
	No	96 (69%)	152 (63%)	
	Unknown	32 (23%)	71 (29%)	
	Not available	1	3	

continued

TABLE 12 Observational: accident details and pre-hospital events (*continued*)

		Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	χ^2 – *p*-values
Pre-hospital event cardiac arrest	Yes	6 (4%)	3 (1%)	0.074
	No	127 (95%)	234 (96%)	
	Unknown	1 (1%)	6 (2%)	
	Not available	7	2	
Pre-hospital event seizures	Yes	21 (15%)	19 (8%)	0.072
	No	101 (72%)	187 (76%)	
	Unknown	18 (13%)	39 (16%)	
	Not available	1		
Pre-hospital event clinical deterioration	Yes	50 (36%)	66 (27%)	0.197
	No	79 (56%)	154 (63%)	
	Unknown	11 (8%)	24 (10%)	
	Not available	1	1	
Pre-intubation GCS	3–8	57 (45%)	156 (68%)	< 0.0001
	9–15	71 (55%)	75 (32%)	
	Not available	13	14	
Pupil reactivity	Neither pupil reactive	15 (11%)	51 (21%)	0.014
	At least one reactive	115 (82%)	173 (71%)	
	Both untestable	0 ()	6 (2%)	
	Unknown	11 (8%)	15 (6%)	

TABLE 13 Observational: medical history

		Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	χ^2 – *p*-values
Any medical history	No	19 (14%)	136 (57%)	< 0.0001
	Yes	116 (84%)	89 (37%)	
	Unknown	3 (2%)	15 (6%)	
	Missing	3	5	
		n = 135	*n* = 225	
Conditions	Cardiovascular	60 (44%)	21 (9%)	< 0.0001
	Endocrinological	28 (21%)	16 (7%)	< 0.0001
	Hearing/vision	5 (4%)	5 (2%)	0.408
	Gastrointestinal	16 (12%)	10 (4%)	0.009

TABLE 13 Observational: medical history (*continued*)

		Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	χ^2 – *p*-values
	Haematological	3 (2%)	1 (–%)	0.119
	Liver	7 (5%)	5 (2%)	0.129
	Musculoskeletal	5 (4%)	6 (3%)	0.580
	Respiratory	20 (15%)	9 (4%)	< 0.0001
	Neurological	29 (21%)	22 (10%)	0.002
	Oncological	16 (12%)	7 (3%)	0.001
	Psychiatric	27 (20%)	25 (11%)	0.020
	Renal	14 (10%)	5 (2%)	0.001
	Other	59 (44%)	39 (17%)	< 0.0001

Please see *Appendix 10* for admission vital signs table.

Glasgow Outcome Scale-Extended outcomes

Six-month Glasgow Outcome Scale-Extended scores

TABLE 14 Observational: 6-month GOSE scores

		Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	Total observed (*n* = 386)
GOSE at 6 months	Dead	27 (22%)	80 (38%)	107 (32%)
	Vegetative	1 (1%)	10 (5%)	11 (3%)
	Lower severely disabled	34 (28%)	57 (27%)	91 (27%)
	Upper severely disabled	21 (17%)	19 (9%)	40 (12%)
	Lower moderately disabled	10 (8%)	17 (8%)	27 (8%)
	Upper moderately disabled	8 (7%)	17 (8%)	25 (7%)
	Lower good recovery	8 (7%)	5(2%)	13 (4%)
	Upper good recovery	15 (12%)	6 (3%)	21 (6%)
	Missing	17	34	51
Outcome	***OR***	***95% CI***	***p-value***	***Number of cases in analysis***
6 months, ordinal	0.430	0.287 to 0.642	< 0.0001	335
6 months, dichotomy	0.435	0.275 to 0.689	0.0003	335

Twelve-month Glasgow Outcome Scale-Extended scores

TABLE 15 Observational; 12-month GOSE scores

		Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	Total observed (*n* = 386)
GOSE at 12 months	Dead	29 (22%)	86 (38%)	115 (32%)
	Vegetative	3 (2%)	9 (4%)	12 (3%)
	Lower severely disabled	25 (29%)	47 (21%)	72 (20%)
	Upper severely disabled	20 (16%)	25 (11%)	45 (13%)
	Lower moderately disabled	7 (5%)	12 (5%)	19 (5%)
	Upper moderately disabled	15 (12%)	22 (10%)	37 (10%)
	Lower good recovery	13 (10%)	5 (2%)	18 (5%)
	Upper good recovery	17 (13%)	20 (9%)	37 (10%)
	No follow-up possible	3	3	6
	Known alive but lost to follow-up	9	16	25
Outcome	***OR***	***95% CI***	***p-value***	***Number of cases in analysis***
12 months, ordinal	0.476	0.323 to 0.702	0.0002	356
12 months, ordinal adjusted[a]	0.387	0.237 to 0.632	0.0001	332
12 months, dichotomy	0.465	0.300 to 0.722	0.0006	356
12 months, dichotomy adjusted[a]	0.329	0.178 to 0.608	0.0004	332

a For the adjusted analysis, the variables used were age group, GCS (< 9, > 8) and whether centre is in UK or not.

Case report form stage 1 results

Treatment received

Of the craniotomy patients, three mention use of floating brain flap, and one of the DC patients mention bifrontal DC. There were seven 'Other' reasons for not randomising in the craniotomy group: age (1), system failure (2), family refuse randomisation (2), recovered from stroke (1), infection of scalp (1) (*Table 16*).

There were three 'Other' reasons for not randomising in those that had DC: skull fracture (2), not expected to survive (1).

TABLE 16 Observational: stage 1 CRF: treatment received

		Observed craniotomy	Observed DC	Total
Number of patients		141	245	386
		N = 139	*N* = 244	*N* = 383
Reason not randomised	Intraoperative brain swelling	6 (4%)	201 (82%)	207 (54%)
	Brain relaxed	89 (64%)	7 (3%)	96 (25%)
	Anticipated swelling	1 (1%)	18 (7%)	19 (5%)

TABLE 16 Observational: stage 1 CRF: treatment received (*continued*)

		Observed craniotomy	Observed DC	Total
	Trial staff not available	15 (11%)	5 (2%)	20 (5%)
	Other	28 (20%)	13 (5%)	41 (11%)
	Not considered for trial	6 (4%)	4 (2%)	10 (3%)
	No equipoise/surgeon decision	15 (11%)	6 (2%)	21 (5%)
	Other	7 (5%)	3 (1%)	10 (3%)
	Not recorded	2	1	3

Computed tomography scan results

Patients with parenchymal lesions or traumatic subarachnoid haemorrhage (SAH) were more likely to have DC. Please see *Appendix 10* for full table.

Pre-intubation Glasgow Coma Scale and pupil reactivity

Patients receiving DC have lower GCS scores (Mann–Whitney U-test $p < 0.0001$) and are more likely to have neither pupil reactive (than at least one reactive) ($p = 0.009$). Please see *Appendix 10* for full table.

Surgery details and postoperative destination

There was no difference in the location of the ASDH between the treatment groups ($p = 0.630$).

There were no differences between the treatment groups in terms of the type of skin incision, with 89% reverse question mark ($p = 0.695$), or in the size of the bone flap [with a mean of cm (± cm)].

A drain was used in 78% of patients and was usually subgaleal (55%) rather than subdural (23%) [no difference between treatments ($p = 0.718$)]. Intracranial monitoring devices were used in 67% of patients, and most (78%) being located ipsilateral to the ASDH. They were more likely to be ipsilateral in craniotomy ($p = 0.004$). For the patients who underwent DC, the bone flap was either stored inside the body (34%) or disposed of (35%) (*Table 17*).

There were more likely to be intraoperative complications in DC (χ^2 $p = 0.010$). There were no differences between treatment groups in the destination from the operating theatre (χ^2 $p = 0.984$).

TABLE 17 Observational; stage 1 CRF: surgery details and postoperative destination

		Observed craniotomy ($n = 141$)	Observed DC ($n = 245$)	χ^2 – p-values
Type of skin incision	Reverse question mark	127 (90%)	215 (88%)	0.695
	T-shaped	1 (1%)	4 (2%)	
	Other	13 (9%)	25 (10%)	
	Not available		1	
Drain used	Subdural	34 (24%)	52 (21%)	0.718
	Subgaleal	74 (53%)	138 (57%)	
	None	32 (23%)	52 (21%)	
	Not available	1	3	

continued

TABLE 17 Observational; stage 1 CRF: surgery details and postoperative destination (*continued*)

		Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	χ^2 – *p*-values
Size of bone flap	Mean (SD)	12.1(1.8)	13.2 (2.0)	
	Median	12	13	
	IQR	2	3	
	Minimum, maximum	7, 20.3	1.2, 20.0	
	Not available	11	6	
Location of ASDH	Left	65 (46%)	120 (49%)	0.630
	Right	75 (54%)	125 (51%)	
	Not available	1		
Dura closure	Open	43 (31%)	108 (44%)	
	Closed	76 (54%)	20 (8%)	
	Duraplasty	18 (13%)	107 (44%)	
	Other	3 (2%)	9 (4%)	
	Not available	1	1	
Other haematoma evacuated[a]	No	121 (86%)	187 (77%)	
	Yes	20 (14%)	57 (23%)	
	Not available	5 (4%)	1	
	Intracerebral	5 (4%)	15 (6%)	
	Extradural	12 (9%)	10 (4%)	
	Contusions	2 (1%)	32 (13%)	
	Other		4 (2%)	
Intracranial monitoring device	No	43 (30%)	86 (35%)	
	Yes, EVD	2 (2%)	8 (3%)	
	Yes, epidural	41 (29%)	35 (14%)	
	Yes, subdural/subarachnoid	4 (3%)	3 (1%)	
	Yes, parenchymal	44 (31%)	104 (42%)	
	Other	7 (5%)	9 (4%)	
Location of the monitoring device	Ipsilateral to ASDH	83 (87%)	112 (72%)	
	Contralateral to ASDH	12 (13%)	44 (28%)	
	Not available	3	3	
	Not applicable	43	86	
Transfer destination after operation	ICU/neurocritical care unit (NCCU)	129 (91%)	224 (91%)	0.984
	NSU/ward	12 (9%)	21 (9%)	
	Other	0	0	

EVD, external ventricular drain; IQR, interquartile range; SD, standard deviation.
a Patients can have more than one other haematoma type evacuated.

Stage 2 case report form results

Glasgow Coma Scale and discharge details

Stage 2 GCS and discharge details for first stay of any patient in ITU. *Table 18* includes all those who were admitted to neurocritical care unit (NCCU) from the operating theatre.

Stage 3 case report form results

Neurosurgical interventions within 14 days of index surgery

These are recorded on the discharge from NSU CRF. The information is not recorded for 84 patients (24 craniotomy and 60 DC) (including most of the patients who died in ICU or were discharged from there to a different hospital) (*Table 19*).

TABLE 18 Observational; discharge from ICU/NCCU and status (stage 2 CRF)

		Observed craniotomy (*n* = 129)	Observed DC (*n* = 224)	
Discharge destination from ICU/NCCU	Died[a]	15 (12%)	47 (21%)	χ^2 – *p*-value 0.109
	NSU	99 (77%)	160 (71%)	
	Different hospital	12 (9%)	16 (7%)	
	Other	2 (2%)	1 (1%)	
	Missing data	1		
Number discharged from ICU/NCCU		**(*n* = 113)**	**(*n* = 177)**	
GCS total score (discharge from ICU/NCCU)	Scoring 3	2 (2%)	3 (3%)	Mann–Whitney U-test
	Scoring 4	1 (1%)	3 (3%)	*p*-value 0.004
	Scoring 5	0	0	
	Scoring 6	0	2 (2%)	
	Scoring 7	0	1 (1%)	
	Scoring 8	3 (3%)	3 (3%)	
	Scoring 9	2 (2%)	8 (7%)	
	Scoring 10	4 (4%)	9 (8%)	
	Scoring 11	6 (6%)	11 (9%)	
	Scoring 12	8 (8%)	7 (6%)	
	Scoring 13	7 (7%)	13 (11%)	
	Scoring 14	32 (33%)	38 (32%)	
	Scoring 15	31 (31%)	21 (18%)	
	Number unknown	16	1	
	Number untestable	1	51	
	Number missing		6	

a Patients treated by DC and going to ICU were more likely to die there (χ^2 p = 0.028).

TABLE 19 Observational: stage 3 CRF: neurosurgical interventions within 14 days of index surgery

		Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	Total observed (*n* = 386)
Neurosurgical interventions after index surgery	Yes	17 (15%)	15 (8%)	32 (11%)
	No	100 (85%)	170 (92%)	270 (89%)
	Missing	24	60	84
Number of interventions	1	16	13	29
	2	0	2	2
	3	1	0	1
	4	0	0	0
Total number of interventions		*N* = 19	*N* = 17	*N* = 36
Intervention	Craniectomy	5 (26%)	0	5 (14%)
	Cranioplasty	0	0	0
	SDH evacuation	3 (16%)	3 (18%)	6 (17%)
	EDH evacuation	4 (21%)	2 (12%)	6 (17%)
	ICH evacuation	0	1 (6%)	2 (3%)
	EVD inserted	1 (5%)	3 (18%)	4 (11%)
	Shunt placement	0	0	0
	ICP monitor	2 (11%)	3 (18%)	5 (14%)
	Wound revision	2 (11%)	3 (18%)	5 (14%)
	Other	2 (11%)	2 (12%)	4 (11%)

EVD, external ventricular drain.

Length of stay of all patients discharged from neurosurgical unit or intensive care unit

Among patients who were discharged alive, those who had had DC as initial surgery had a longer stay (Mann–Whitney U-test $p = 0.007$). There was no difference in time to death for those who died in hospital (Mann–Whitney U-test $p = 0.449$) (*Table 20*).

TABLE 20 Observational; stage 3 CRF: LOS of all patients discharged from NSU or ICU

		Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	Total observed (*n* = 386)
Discharge destination from NSU	Died in hospital	21	61	82
	Discharged from NSU	118	184	302
	Missing (still on ward at 12 months)	2	0	2

TABLE 20 Observational; stage 3 CRF: LOS of all patients discharged from NSU or ICU (*continued*)

Patients discharged alive		Observed craniotomy (*n* = 118)	Observed DC (*n* = 184)	Total observed (*n* = 363024)
LOS[a]	Mean	23.8	37.6	32.2
	SD	18.9	45.4	37.9
	Median	18.5	27	22
	IQR	20.6	35	28
	Minimum, maximum	0, 91	0, 321	0, 321
	Number missing		1	1
Patients died in hospital		**Observed craniotomy (*n* = 21)**	**Observed DC (*n* = 61)**	**Total observed (*n* = 82)**
LOS[b]	Mean	9.4	8.6	8.8
	SD	7.0	7.8	7.6
	Median	7	5	6.5
	IQR	9.5	11.5	11
	Minimum, maximum	0, 26	0, 30	0, 30

IQR, interquartile range; SD, standard deviation.
a This is the LOS for all patients prior to their discharge to another hospital/unit/home.
b Total includes those who died in ICU (62) as well as those who died in NSU (20).

Status and destination at discharge from any part of the neurosurgical unit

Discharge destination (combining nursing home, unknown and other) (p = 0.014). GCS total χ^2 = 0.056 (3 category) (Mann–Whitney U-test on full score p = 0.048). Please see *Appendix 10* for full table.

Stage 4 case report form results

Stage 4 cranioplasty and shunt use

Details about cranioplasty are recorded at 12 months.

TABLE 21 Observational; stage 4 CRF: cranioplasty and shunt use

		Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	*p*-values (associated test in table footer)
Had DC before 12 months	Yes	11 (8%)	233 (100%)	
	No	120(92%)	0	
	Missing	10	12	
Had cranioplasty by 12 months		**(*n* = 11)**	**(*n* = 233)**	0.466
	Yes	7 (64%)	120 (52%)	
	No	4 (36%)	109 (48%)	
			4	
Had a cranioplasty		**(*n* = 7)**	**(*n* = 120)**	

continued

TABLE 21 Observational; stage 4 CRF: cranioplasty and shunt use (*continued*)

		Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	*p*-values (associated test in table footer)
Material	Autograft	2 (29%)	53 (46%)	
	Non-metallic	1 (14%)	22 (19%)	
	Metallic	4 (57%)	39 (34%)	
			6	
		(*n* = 141)	**(*n* = 245)**	
Did the patient develop hydrocephalus	Yes	3 (2%)	13 (6%)	0.145
	No	123 (98%)	213 (94%)	
	Missing	15	19	
Did the patient have a shunt	Yes	1	9	0.247
	No	2	4	

If a patients had a DC, then there was no difference between the allocated groups in whether they had a cranioplasty by 12 months (χ^2 p = 0.466) (*Table 21*).

There was no difference in the rate of hydrocephalus between the two patient treatment groups (χ^2 p = 0.145) or in the use of a shunt if they did develop hydrocephalus (Fisher's exact p = 0.247).

Adverse events: observational

One hundred and twenty-three AEs are reported by 76 (54%) of the 141 patients having craniotomy as initial treatment. The maximum number of events reported for a single patient was 7, and the average number of events reported by those randomised to craniotomy was 0.87. One hundred and sixty-seven AEs were reported by 105 (43%) of the 245 patients having DC as initial treatment. The maximum number of events reported for a single patient in this group was 4, and the average number of events reported by a patient randomised to DC was 0.68. There are no differences in the types of AEs experienced between the two treatment groups (*Table 22*).

TABLE 22 Observational: AEs

Event	Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	Total observed (*n* = 386)
Pneumonia	46 (33%)	61 (25%)	107 (28%)
Pneumothorax	1 (1%)	4 (2%)	5 (1%)
Atelectasis	4 (3%)	2 (1%)	6 (2%)
Aspiration	5 (4%)	5 (2%)	10 (3%)
Pleural effusion/empyema	4 (3%)	3 (1%)	7 (2%)
Ventilator-related complications	7 (5%)	9 (4%)	16 (4%)
Adult respiratory distress syndrome	1 (1%)	2 (1%)	3 (1%)

TABLE 22 Observational: AEs (*continued*)

Event	Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	Total observed (*n* = 386)
Respiratory failure	4 (3%)	3 (1%)	7 (2%)
Need for prolonged mechanical or positive pressure airway ventilation	9 (6%)	24 (10%)	33 (9%)
Other respiratory	4 (3%)	3 (1%)	7 (2%)
Myocardial infarction	2 (1%)	0	2 (1%)
Arrhythmia	9 (6%)	7 (3%)	16 (4%)
Heart failure	1 (1%)	1 (–%)	2 (1%)
Angina	0	0	0
Pericardial effusion	0	0	0
Other cardiac	1 (1%)	3 (1%)	4 (1%)
Urinary tract infection	8 (6%)	6 (2%)	14 (4%)
Renal failure may require full renal support	0	0	0
Renal dysfunction	3 (2%)	1 (–%)	4 (1%)
Urinary retention	1 (1%)	0	1 (–%)
Haematuria	3 (2%)	2 (1%)	5 (1%)
Other renal	1 (1%)	2 (1%)	3 (1%)
Deep-vein thrombosis	3 (2%)	3 (1%)	6 (2%)
Pulmonary embolism	0	1 (–%)	1 (–%)
Other thrombosis	0	1 (–%)	1 (–%)
Other	1 (1%)	1 (–%)	2 (1%)
Pancreatitis	0	1 (–%)	1 (–%)
Liver failure	0	3 (1%)	3 (1%)
Other	2 (1%)	3 (1%)	5 (1%)
Infective diarrhoea or colitis	1 (1%)	4 (2%)	5 (1%)
Diarrhoea of other causes	10 (7%)	8 (3%)	18 (5%)
Bowel ischaemia	0	1 (–%)	1 (–%)
Ileus	1 (1%)	3 (1%)	4 (1%)
Other	4 (3%)	2 (1%)	6 (2%)
Wound infection	0	9 (4%)	9 (2%)
Dehiscence	1 (1%)	0	1 (–%)
Other	1 (1%)	2 (1%)	2 (1%)
Decubitus ulcer	0	2 (1%)	2 (1%)
Other infections, for example, MRSA	3 (2%)	8 (3%)	11 (3%)
Anaesthetic-related complications	1 (1%)	1 (–%)	2 (1%)
Anaemia, coagulopathy	10 (7%)	15 (6%)	25 (7%)

continued

TABLE 22 Observational: AEs (*continued*)

Event	Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	Total observed (*n* = 386)
Pyrexia	27 (19%)	59 (24%)	86 (22%)
Septicaemia	9 (6%)	10 (4%)	19 (5%)
Hypertension	2 (1%)	0	2 (1%)
Hypotension	0	1 (–%)	1 (–%)
Electrolyte and endocrine disorders	0	3 (1%)	3 (1%)
Dizziness and physical impairment	6 (4%)	1 (–%)	7 (2%)
Agitation and confusion	0	2 (1%)	2 (1%)
Number of AEs	123	167	290
Number of patients experiencing an event	76	105	181
Total number of patients	141	245	386

MRSA, meticillin-resistant *Staphylococcus aureus*.

Procedure-related adverse events: observational

The maximum number of events reported for a single patient was five. Please see *Appendix 10* for full table.

Chapter 5 Within-trial economic evaluation

Introduction

Background

Prior to analysis, a Health Economic Analysis Plan (HEAP) was developed (see: www.rescueasdh.org/trial-documents), though here, for ease of reading, we present the Methods and Results in sufficient detail that readers should not need to refer to the HEAP. Since the development of the HEAP (in 2021), new methods guide for NICE health technology evaluations has been published;[6] we, however, refer to the previous methods guide, as that informed our HEAP, and the new methods guide was not available when we began our analysis.

Study rationale

There is potential for there to be differences in costs and benefits between craniotomy and DC. For example, DC involves an extra planned procedure (cranioplasty, with associated costs), but such costs could be partly/wholly offset if DC were found to have associated benefits, which in turn resulted in fewer AEs. Given this uncertainty, the high costs associated with such procedures, and the variation in practice as to whether craniotomy or DC is currently undertaken, a comparison as to the cost-effectiveness of craniotomy and DC was undertaken.

Objective

To estimate the cost-effectiveness of craniotomy, compared with DC, based on UK data from a multicentre, pragmatic, parallel-group randomised trial of DC versus craniotomy for patients undergoing evacuation of ASDH (RESCUE-ASDH).[8]

Methods

Trial design

As previously described, the RESCUE-ASDH trial was a multicentre, international, pragmatic, parallel-group randomised trial. For the purposes of this economic evaluation, the analysis was based on UK participants who were involved in the randomised controlled trial (i.e. excluding participants outside the UK and those who took part in the observation study). The trial compared DC, in which the bone flap is removed prior to closing the skin, with craniotomy, in which the bone flap is restored before skin closure. DC is undertaken on the basis that the missing part of the skull will be restored later (cranioplasty), in those patients who survive. Patients were eligible for enrolment if they were 16 years of age and older, had an ASDH on CT scan and the admitting surgeon felt that the haematoma needed evacuating either by craniotomy or DC.

Intervention

When an ASDH is evacuated, the bone flap can be left out (DC) or replaced (craniotomy) prior to closing the skin. Participants were randomly assigned in a 1 : 1 ratio to receive DC or craniotomy.

Additionally, there was an observation (non-randomised) cohort of patients who were also followed up and fulfilled the following criteria: (1) eligible patients who could not be randomised after evacuation of haematoma due to significant swelling of the brain, (2) patients who had a traumatic ASDH removed as part of their standard care and were enrolled postoperatively. These patients were not included in the economic evaluation.

Measuring costs

In line with the NICE methods guide,[9] in the base-case analysis, costs were estimated from the viewpoint of the UK NHS and Personal Social Services (PSS). Subsequently described resource use data were collected, to which unit costs [estimated in Great British pounds (£) for the 2018–9 financial year] were assigned (see *Table 35*). Where unit costs were taken from previous years, they were inflated using the NHS Cost Inflation Index (NHSCII).[10]

There were two main sources for the resource use data: hospital-recorded data and a patient self-report (1-year follow-up) questionnaire. Both were specifically developed for the study (in consultation with hospital staff/non-trial patients) and informed by the guidance that one should focus on the large cost drivers and those resource items that might differ between study arms.[11] Costs were not assigned to resource items that were undertaken for research purposes.

Hospital-recorded data

The hospital-recorded data included (if applicable) details of the operation to which participants were randomised (craniotomy or DC), including length of operation and graft details. Time spent in the ICU and NSU and any further neurosurgical procedures received during their initial (index) admission were also recorded, along with cranioplasties and shunt placements received after discharge from the NSU.

Unit costs were assigned to hospital-recorded data resource use items (see *Table 23* for further details). In terms of the intervention costs, several procedure details were recorded, but costs were not assigned to all items, if they were considered relatively small or unlikely to differ between arms. For all procedures, a common unit cost of £1422[12] per hour (mean theatre direct costs per hour for neurosurgery) was applied. For the index procedures (DC or craniotomy),

TABLE 23 Unit costs, for the 2018–9 financial year

Resource use	Unit cost (£)	Assumptions
Neurosurgical costs		
Index craniotomy or DC (hourly rate)	1422[12]	Hourly rate applied to the duration of the operation, whether craniotomy or DC. Includes the time from entering pre-med until leaving theatre
DC, not index procedure (hourly rate)	1422[12]	Hourly rate applied to two-thirds of the mean length recorded for index DC. This accounts for the presence of previous skin incision and bone cuts
Cranioplasty (index or revision)	2464[12,13]	Based on hourly rate above and 104-minute duration
HE (all types)	2132[12]	Based on hourly rate above and 90-minute duration (expert opinion)
Wound revision	2132[12]	Based on hourly rate above and 90-minute duration (expert opinion)
'Other' neurosurgical intervention	2132[12]	Based on hourly rate above and 90-minute duration (expert opinion)
Shunt placement (index or revision)	2132[12]	Based on hourly rate above and 90-minute duration (expert opinion)
Material costs (design and parts) for cranioplasty	2500	Estimated based on expert opinion
Material costs for shunt	500	Estimated based on expert opinion
Overnight stay costs		
Cost per bed-day in neurorehabilitation unit	504[14]	
Cost per bed-day in NSU	365[10,15]	
Cost per bed-day in ICU	1691[16]	Assumes neuroscience for adult patient in critical care, two or more organs supported (ICU)
Cost per bed-day (other ward type)	354[10,15]	Weighted average of elective and non-elective excess bed-days

TABLE 23 Unit costs, for the 2018–9 financial year (*continued*)

Resource use		Unit cost (£)		Assumptions
Health professional visit costs	***Community***	***Hospital***	***Home***	***Assumptions***
Hospital doctor	33.00[10]	186.74[15]	59.40[10,17]	Community: as hospital doctors do not work in the community, the unit cost for a community GP visit was applied Home: as hospital doctors do not usually visit homes, the unit cost for a home GP visit was applied
Nurse	12.31[10,14]	69.51[15]	19.64[10,14]	Home: costed as for community visit, plus 12-minute travel time
GP	33.00[10]	186.74[13]	59.40[10,14]	Hospital: as GPs do not work in hospitals, the unit cost for a hospital doctor visit was applied Home: costed as for community visit, plus 12-minute travel time
Physiotherapist	62.90[13]	54.96[13]	69.67[10,13,14]	Home: costed as for community visit, plus 12-minute travel time
Occupational therapist	83.17[13]	65.54[13]	89.94[10,13,14]	Home: costed as for community visit, plus 12 minutes travel time
Speech therapist	106.51[13]	100.06[13]	113.28[10,13,14]	Home: costed as for community visit, plus 12-minute travel time
Social worker	118.81[10,15]	118.81[10,15]	127.72[10,14,15]	Home: costed as for community visit, plus 12-minute travel time
Community care assistant	19.87[10,16]	19.87[10,16]	24.64[10,14,16]	Home: costed as for community visit, plus 12-minute travel time
Emergency department	166.05[13]	166.05[13]	166.05[13]	Single rate costed for an emergency visit
Psychologist/ neuropsychologist	141.17[10,17]	146.67[10,17]	156.57[10,14,17]	Home: costed as for community visit, plus 12-minute travel time
Other	33.00[10]	186.74[13]	69.67[10,13,14]	The cost of the most commonly reported visits from each location are assigned. Community: GP, hospital: hospital doctor, home: physiotherapist
Other costs				***Assumptions***
MRI scan		120.83[13]		
CT scan		77.95[13]		
Unknown scan		77.95[13]		Assumed the cost of a CT scan
Care home (cost per week in residence)		1854[11]		As no cost for adults with these specific needs has been estimated, we have used a cost for adults with autism and complex needs
Carer time		17.27[18]		Gross hourly rate. Used to value carer time whether paid or not
Work time		17.27[18]		Gross hourly rate. Used to value lost work time, assigned to estimated time worked since their brain injury

HE, haematoma evacuation; GP, general practitioner; MRI, magnetic resonance imaging.

Note

Inflated to 2018–9 financial year prices, where necessary, using the NHSCII pay and prices.[10]

the length of operation was recorded, and the hourly rate was therefore applied accordingly. Furthermore, for participants who received DC, the method of bone flap storage was recorded. It was, however, assumed that the cost of storage inside the participant's body was captured by the length of operation and that the marginal cost of storage outside the body was negligible, as tissue banks already exist in hospitals. In many cases, however, the bone flap was discarded, and synthetic materials used for replacement during a later cranioplasty procedure. Any cranioplasties were recorded (whether during index admission or post discharge from NSU), including the type of graft. If this indicated the use of a synthetic graft or, if this information was missing, the bone flap was recorded as 'disposed', 'sent for implant modelling' or 'other' postoperatively, an estimated synthetic material cost of £2500 (design and parts) was used. Additionally, as the length of time associated with cranioplasty was not recorded, it was assumed that this was 104 minutes.[13] In addition, if the cranioplasty took place after discharge from NSU, an associated LOS of 4 days was assumed and costed. These costs and timings were informed by expert opinion.

Shunt placements were also recorded during index admission and post discharge from NSU. In line with expert opinion, an assumed length of procedure of 90 minutes was applied and costed, along with an estimated materials cost of £500. In addition, if the shunt took place after discharge from NSU, an associated LOS of 2 days was assumed and costed.

Revisions to cranioplasties and shunts were also recorded, and these were assumed to have the same procedure duration and associated LOS (post discharge only) as that described for the relevant index procedure, but without the materials costs.

Where a date was missing for cranioplasties or shunts, whether primary or revision, the operation was assumed to have occurred post discharge from NSU, if recorded on the post-discharge form, but during index admission if recorded on the neurosurgical intervention form used at NSU discharge.

As cranioplasties and shunts were recorded on several different forms during the study, there was potential for duplication of recording. To avoid this, the total number of cranioplasties was summed, having discounted any with duplicate dates. It was then assumed that one of these cranioplasties represented the primary cranioplasty operation and a materials cost (assuming synthetic graft was used and/or bone flap was recorded as 'discarded', 'sent for implant modelling' or 'other') was applied to this operation (as this was the most common type of graft). Any further cranioplasties, whether recorded as revisions or not, were assumed to be revisions, with no materials cost applied. The same principle was applied to shunt operations. If a cranioplasty and shunt (primary or revision) were recorded as having occurred on the same day, it was assumed that this was the same operation, and a duration of 150 minutes (expert opinion) was applied, along with a LOS of 4 days and relevant materials costs. These costs for cranioplasties and shunts are summarised in *Table 35*.

Details of further neurosurgical interventions were also requested at NSU discharge (i.e. during index admission), along with a date of procedure. Further craniectomies (DC), haematoma evacuations (HEs) (of any description) and wound revisions that were confirmed, by the procedure date, to have occurred during index admission (i.e. before NSU discharge/death date), were costed. Any DCs that were recorded as having occurred on the same date as the index DC procedure were excluded from the analysis, on the assumption this represented duplicate recording. As the length of HEs and wound revisions were not recorded, following expert opinion, these were assumed to be 90 minutes. External ventricular drain (EVD) placement and ICP monitoring insertions were also recorded but not costed, as these were deemed to be relatively inexpensive and unlikely to differ between arms (expert opinion). Where 'other' procedure was recorded on the form, these were recoded, following expert opinion, using the free-text responses that accompanied this response. Those that did not fit one of the pre-specified descriptions (DC, HE and wound revision), but were deemed to have resource use implications, were coded as 'other' and assumed to have an associated length of procedure of 90 minutes also. The remainder were not costed. Only those procedures that were costed were analysed and reported.

Details of LOS in NSU and ICU were also recorded for the index admission; this was assigned an appropriate cost per bed-day, as described in *Table 35*. The length of NSU stay was calculated from baseline (date of index surgery) to NSU discharge/death and mutually exclusive of any ICU stay recorded:

If ICU stay ≥ 0 and ICU admission date ≥ baseline date:

ICU stay = [(date of discharge from ICU or death) − (date of admission to ICU) + 1]

If ICU stay ≥ 0 and ICU admission date ≤ baseline date:

ICU stay = [(date of discharge from ICU or death) − (baseline date) + 1]

NSU stay

NSU stay = {[(date of final discharge/death) − (baseline date) + 1] − (ICU stay)}

'Date of final discharge' refers to the final NSU discharge date, excluding any previous discharges from NSU to ICU. For participants who had multiple stays in ICU, their total ICU stay was calculated as above, and all ICU stays summed.

For each participant, the component costs associated with the index procedure (craniotomy or DC), cranioplasty and shunt procedures (for index admission and post discharge), any other neurosurgical interventions during index admission and LOS in ICU and/or NSU (for the index admission) could thereby be estimated and were summed to estimate the total hospital-recorded costs.

Patient self-reported resource use

At the 12-month follow-up point, UK participants were sent a questionnaire that requested the following resource use data (where a participant was unable to fill in the questionnaire, proxy responses by a relative/friend/carer were requested). The questionnaire only requested information in relation to the time since discharge from the NSU, as the resource use prior to NSU discharge was assumed to be captured by the aforementioned hospital-recorded data. Participants who died during their index admission, that is, were reported as having a discharge destination of 'died' at any point, were given a value of '0' in response to all questions in the patient-reported questionnaire. Those who died after discharge from NSU were reported as 'missing' in response to all questions (this allows these data to be imputed for the base-case analysis, while adjusting for time to death – see *Missing data*).

Participants were asked to report any overnight stays in a hospital or other healthcare facility (for any reason), where information was also requested (if applicable) in relation to the number of nights, type of unit, and whether there was an associated operation on the skull/brain. Participants were also asked to report any healthcare professional (HCP) visits (for any reason), where (if applicable) information was requested in relation to the type of HCP seen, frequency of visit and where (most) visits took place (home, community or hospital). Additionally, participants were asked to report any scans of the head/brain, where (if applicable) information as to the type [magnetic resonance imaging (MRI), CT or 'other'] and number of investigations was requested.

Participants were also asked to report if they had spent any time in a care home, where (if applicable) the associated time in weeks/months was requested. Participants were similarly asked to report if they had received any help from a family member/friend or other carer. If a respondent reported 'yes', then (for each carer) they were asked to report the average number of hours of care received (per week since discharge from NSU).

Finally, participants were asked several questions in relation to work, including: (1) whether they were currently working (paid/unpaid), and if yes: (a) the number of hours per week they work, and (b) their return-to-work date. Within the HEAP, it was specified that we would estimate the 'mean lost work time over the 12-month follow-up period'. However, implementation of this was difficult, as (in error) those who reported they were not currently working at the 12-month follow-up were not asked (1) whether they were working before their brain injury and, if they were, (2) the number of hours they worked. Consequently, we did not seek to estimate/value lost work time. We did, however, seek to estimate the number of hours participants had worked since their brain injury (in the 12-month follow-up period) in the following manner. Participants were asked how many hours they currently work and the date they returned to work (if applicable). Assuming the reported current working hours were applicable to the time between the date they returned to work and

the 12-month follow-up point, it was possible to estimate (for responding participants) the number of hours they have worked since their brain injury (in the 12-month follow-up period).

Unit costs were assigned to each item of resource use data reported by participants (see *Table 35*). This enabled the component costs associated with any overnight stays (post NSU discharge), HCP visits, scans, care home and carer costs to be estimated for participants from UK sites. However, to avoid the potential for cost duplication, pre-analysis we stated that patient self-reported overnight stays with an associated skull/brain operation would only be included in the base-case analysis if the total number reported was greater than the total reported number of post-discharge cranioplasties/revisions and shunt placements/revisions, as reported in the hospital-recorded data. This was seen as possible as hospital-recorded data would only record operations that took place at the same hospital as their index admission. If this was not the case, only costs associated with self-reported overnight stays, where an operation to the skull/brain was not noted, would be included in the base case, along with the costs associated with post-discharge cranioplasties and shunt placements (based on hospital-recorded data). Component costs were summed in order to estimate the total post-discharge costs, though in order to align with the NHS and PSS cost perspective recommended in the NICE methods guide,[4] care home and carer costs (the same hourly cost was assigned to all reported hours of care regardless of whether, for example, a payment was made/the carer lived with the participant) were not included in the base-case analysis.

Measuring outcomes

To estimate HRQoL, and in line with the NICE guidance,[18,20] the EQ-5D-5L was used, and respondents were asked to report the level of problems (none to extreme/unable) they had on five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).[7] Participants were asked to complete the EQ-5D-5L at discharge from NSU, and again at 6- and 12-month follow-up (though this was not applicable if they were yet to be discharged from NSU at these time points). Where a participant was unable to fill in the questionnaire, proxy responses by a relative/friend/carer were requested. As recommended in the NICE position statement,[21] the crosswalk mapping function[22] was then used to convert responses into utility scores, where a score of zero corresponds to death and one to full health.[22] NICE[18] has recently updated the preferred mapping function to be used in reference-case analyses for the EQ-5D-5L from that published by Van Hout *et al.*[22] to that of Hernández Alava *et al.*[23,24] We have adhered to the earlier guidelines[9] as the analysis started prior to the change in guidelines. Participants who died were assigned a utility score of zero on their date of death (assuming this occurred within the 12-month follow-up period). The quality-adjusted life-year (QALY) score that was accrued over the trial period was then estimated for each individual for whom the EQ-5D had been completed at the three aforementioned time points. This was based on the total area under the curve method and the assumption of linear interpolation.[25] In the base-case analysis, the score at the date of discharge was assumed to be the baseline score (12 months prior to the final follow-up point).

To undertake the cost-effectiveness analysis (CEA), the primary outcome measure, the GOSE[26–29] was used, with the GOSE collapsed onto a binary scale (i.e. favourable vs. unfavourable). Favourable outcomes were defined as upper severe disability or better, while unfavourable outcomes included death, vegetative state and lower severe disability. The favourable versus unfavourable scoring was based on the participants' 12-month responses.

A further binary (favourable vs. unfavourable) categorisation was also used: if GCS at randomisation was between 3 and 8 (patient comatosed),[4] a favourable outcome was defined as upper severe disability or better, but if GCS at randomisation was between 9 and 15 (responsive patient), a favourable outcome was defined as lower moderate disability or better.

Analyses

Missing data

Missing data is common in randomised trials and can lead to bias and lack of precision.[30] As recommended for within-trial analysis of cost-effectiveness, in line with previously described methods[30] in the base-case analysis multiple imputation (MI) was thereby undertaken.

Based on the pattern of missing data, costs were aggregated and imputed at the level of 'index admission costs' (from hospital-recorded data), 'cranioplasty and shunt costs', including both pre- and post-discharge procedures (also from hospital-recorded data) and 'post-discharge costs' (from patient self-report questionnaire). Costs were imputed at this level as the hospital-recorded and patient self-report data had different levels of missing data, whereas individual questions within each of these data types had similar levels of completion. Cranioplasty and shunt forms were completed separately to other hospital-recorded data and therefore had different levels of completion to those previously mentioned. Similarly, where missing, overall EQ-5D utility scores were imputed at NSU discharge and at 6- and 12-month follow-up, as response rates differed over time, though if EQ-5D data were missing, in over 50% of cases it was missing in all dimensions. Missing data for GCS score at baseline and GOSE at 12 months were also imputed, though both had a low level of missing data (< 5%).

Based on a descriptive analysis demonstrating the association between costs and outcomes and baseline variables and between missing costs and outcomes and baseline variables, the data were assumed missing at random (MAR). MI via chained equations under MAR was therefore used and the missing data imputed, by treatment group, using the 'mi impute chained' command [Stata 17.0 (StataCorp LP, College Station, TX)] to create 30 data sets (it is recommended the number of imputed data sets should be similar to the percentage of incomplete cases[30]), which were then pooled using Rubin's rules.[31]

In addition to the costs (index admission, cranioplasty and shunt, and post discharge), EQ-5D scores (baseline and 6 and 12 months), GCS (baseline) and GOSE scores (12 months), the MI model included baseline covariates associated ($p < 0.05$) with missing data, costs or outcomes: age (years) and sex. Finally, the MI model was validated by comparing the distributions of the observed and imputed data to check that the distributions were similar.[30]

Cost–utility

The NICE methods guide recommends that costs be estimated from the viewpoint of the NHS and PSS.[18] Therefore, in the base-case analysis, the previously defined total hospital-recorded costs and total patient-questionnaire reported costs (excluding care home and carer costs) were summed to estimate overall costs.

A 12-month within-trial analysis was undertaken, where (after excluding any participants randomised in error) an ITT approach was adopted, where participants were analysed within the group to which they were allocated, regardless of whether they received craniotomy or DC. A within-trial analysis was deemed appropriate, as we are not aware of any previous economic evaluations that have compared craniotomy with DC for patients with ASDH. No discounting was undertaken, as the analysis period matched that of the trial duration (1 year).

To estimate the mean incremental cost and mean incremental effect (QALY gain) associated with DC compared with craniotomy, seemingly unrelated regression analysis was undertaken, which is generally robust for skewed data and allows for any correlation between costs and effects.[32] All regressions included those baseline variables expected to be predictive of total costs and outcomes: age (years), sex and baseline utility score.

Where appropriate, the incremental cost-effectiveness ratio (ICER), defined as the mean incremental cost/mean incremental effect,[18] or DC compared with craniotomy, was estimated. If one intervention was both less costly and more effective, estimating the ICER was not necessary, and instead, that intervention could be categorised as 'dominant'.[33] The ICER can be used to assess whether the extra cost of an intervention (in this case, DC) constitutes value for money. In the UK, NICE refers to a cost-effectiveness threshold value of £20,000–30,000 per QALY.[18] As such, if DC had an ICER (incremental cost per QALY) lower than this level, it could be argued to be cost-effective.

Cost-effectiveness

With the following exceptions, the analysis replicated that of the previously described cost–utility analysis (CUA). For the first CEA, the aforementioned GOSE favourable versus unfavourable categorisation (see *Measuring*

outcomes) was used for the measure of effect, and in the absence of dominance, the ICER was the cost per additional favourable outcome. In a second CEA, this was repeated but with the favourable versus unfavourable categorisation based on GCS score at baseline, as described previously. As the outcome is binary (favourable/unfavourable), logistic (logit) regression was undertaken to estimate the OR (95% CI) of a favourable outcome for DC compared with craniotomy. Mean incremental costs associated with DC compared with craniotomy were estimated using linear regression. All regressions included variables age (years) and sex, which were expected to be predictive of total costs and GOSE outcomes. Given the measure of effect in the second CEA took account of the baseline GCS score, baseline GCS was only included as a covariate in the linear regression to estimate mean incremental costs.

Decision uncertainty

To estimate the level of uncertainty associated with the decision regarding cost-effectiveness, Fieller's theorem was used to calculate[30] the probability of being cost-effective at different thresholds of cost-effectiveness: the cost-effectiveness acceptability curve (CEAC).[34] Here we report the estimated probability that craniotomy is cost-effective compared with DC at the recommended[18] threshold of £20,000 per QALY.

Sensitivity analyses

The following sensitivity analyses (SAs)[34] were undertaken to assess the robustness of conclusions to changes in key assumptions. Unless otherwise stated, all other assumptions remain as in the aforementioned base-case analysis. To analyse the data from a wider societal perspective, the care home and carer costs (which were excluded from the base-case analysis) were included in the first SA (SA1) (it should be noted that this is in contrast to the HEAP, as lost productivity costs were not included for reasons given above). A second SA (SA2) excluded patient self-reported resource use data altogether (there was expected to be more missing data from this source) and used only total hospital-recorded costs. Additionally, as there may be differences in the reported levels of post-discharge operations from different sources, a third SA (SA3) was conducted, which included only patient-reported post-discharge skull/brain operations, along with their associated LOS data, instead of the hospital-reported data on post-discharge cranioplasties and shunts (where LOS data were not recorded and instead assumptions about LOS had to be made). The fourth SA (SA4) tested the use of the EQ-5D score at discharge from NSU as the baseline point for QALY. As any benefits associated with the interventions could already have been partially/wholly achieved by discharge, the QALY scores were therefore re-estimated in SA4 with the assumption that, given the grave nature of the condition and following expert advice, participants had the lowest possible EQ-5D score at baseline (date of index surgery), that is, −0.594 was assumed to be the baseline score. On this basis, the total QALY scores were re-estimated for each patient. A fifth SA (SA5) re-analysed the data on a per-protocol basis, as defined in the SAP, that is, all patients included in the ITT population, except patients where the primary treatment was not as allocated, for example, patients allocated to DC who had craniotomy and vice versa. A complete-case analysis based on the base case was also undertaken in a sixth SA (SA6), where participants were only included if they have complete hospital records, participant self-report and QALY data, with no imputation undertaken. Aside from SA4, the above SAs were also applied to the GOSE.

Results

Participants

Between September 2014 and April 2019, 452 patients were recruited and randomly assigned to a trial group, though two patients were withdrawn owing to ineligibility [see the Consolidated Standards of Reporting Trials (CONSORT) diagram, *Report Supplementary Material 3*]. Thus, 450 patients were enrolled in the trial, 228 in the craniotomy arm and 222 in the DC arm. These patients constitute the full analysis population and their baseline characteristics have been outlined previously (see *Table 18*) or the purposes of the economic evaluation, as the perspective is from the viewpoint of the UK NHS and PSS, only participants from UK sites were evaluated and their baseline characteristics are outlined in *Table 24*. The UK economic evaluation base-case population included

TABLE 24 Baseline characteristics of UK patients

Characteristics	Craniotomy (*N* = 126)	DC (*N* = 122)
Age (mean ± SD) year	52.3 ± 16.4	51.7 ± 15.9
Male sex – number/total number (%)	96/126 (76.2)	101/122 (82.8)
Any antithrombotic medication – number/total number (%)	21/115 (18.3)	22/110 (20.0)
Presence of major extracranial injury requiring admission – number/total number (%)	66/123 (53.7)	57/120 (47.5)
GCS 3–8[a]	85/120 (70.8)	72/119 (60.5)
Initial CT brain findings		
Presence of midline shift > 5 mm – number/total number (%)	106/124 (85.5)	105/121 (86.8)
Compression/absence of basal cisterns – number/total number (%)	101/124 (81.5)	102/121 (84.3)
Presence of parenchymal contusions < 25 cc – number/total number (%)	58/125 (46.4)	60/121 (49.6)

a A GCS score of 3–8 is defined as 'severe brain injury' (unfavourable).

TABLE 25 Proportion of missing values (%) for key variables

Variable	Craniotomy	DC	Total
Baseline variables			
Treatment allocation	0	0	0
Age	0	0	0
Sex	0	0	0
EQ-5D-5L at baseline	39/126 (31.0%)	31/122 (25.4%)	70/248 (28.2%)
GCS score	6/126 (4.8%)	3/122 (2.5%)	9/248 (3.6%)
Cost variables			
Index admission costs[a]	17/126 (13.5%)	20/122 (16.4%)	37/248 (14.9%)
Cranioplasty and shunt costs[b]	2/126 (1.6%)	4/122 (3.3%)	6/248 (2.4%)
Post-discharge costs (patient self-report)	27/126 (21.4%)	41/122 (33.6%)	68/248 (27.4%)
Outcome variables for HRQoL			
EQ-5D-5L at 6 months	24/126 (19.1%)	28/122 (23.0%)	52/248 (21.0%)
EQ-5D-5L at 12 months	15/126 (11.9%)	19/122 (15.6%)	34/248 (13.7%)
Outcome variables for GOSE			
GOSE at 6 months	13/126 (10.3%)	16/122 (13.1%)	29/248 (11.7%)
GOSE at 12 months	5/126 (4.0%)	7/122 (5.7%)	12/248 (4.8%)
Outcomes for cost–utility and cost-effectiveness analyses			
Total costs	40/126 (31.8%)	55/122 (45.1%)	95/248 (38.3%)
Total QALYs	58/126 (46.0%)	58/122 (47.5%)	116/248 (46.8%)

continued

TABLE 25 Proportion of missing values (%) for key variables (*continued*)

Variable	Craniotomy	DC	Total
Binary GOSE at 12 months	5/126 (4.0%)	7/122 (5.7%)	12/248 (4.8%)
Binary GOSE GCS-dependent at 12 months	11/126 (8.7%)	10/122 (8.2%)	21/248 (8.5%)

a Includes hospital-recorded index surgery, LOS, neurosurgical interventions (excluding cranioplasties and shunts) during index admission.
b Includes hospital-recorded cranioplasties and shunts (including revisions) during index admission and post discharge.

TABLE 26 Levels of resource use, from hospital-recorded data: index surgery, LOS, neurosurgical interventions[a] (index admission)

Resource use	Statistics	Craniotomy (*N* = 126)	DC (*N* = 122)	*p*-value
Duration of index surgery (hours)	*n*	122	110	0.603
	Mean (SD)	2.57 (0.89)	2.50 (0.93)	
ICU LOS (index admission) (days)	*n*	126	122	0.189
	Mean (SD)	11.85 (8.61)	13.52 (11.28)	
NSU LOS (index admission) (days)	*n*	122	120	0.210
	Mean (SD)	16.75 (24.92)	21.30 (31.10)	
Further (after initial surgery) neurosurgical interventions	Yes	27	24	–
	No	75	79	
	Dead	14	13	
	Missing	10	6	
	Total	**126**	**122**	
Further neurosurgical interventions, associated with resource use (index admission), *n* interventions	DC	15	4	–
	HE	9	2	
	Wound revision	1	6	
	Other	3	2	
	Total	**28**	**14**	
Further neurosurgical intervention: DC (index admission)	0	102	113	–
	1	13	2	
	2	1	1	
	Missing	10	6	

TABLE 26 Levels of resource use, from hospital-recorded data: index surgery, LOS, neurosurgical interventions[a] (index admission) (*continued*)

Resource use	Statistics	Craniotomy (*N* = 126)	DC (*N* = 122)	*p*-value
Further neurosurgical intervention: DC (index admission) (*n*)	*n*	116	116	0.017
	Mean (SD)	0.129 (0.362)	0.034 (0.227)	
Further neurosurgical intervention: HE (index admission), *n* interventions	0	108	114	–
	1	7	2	
	2	1	0	
	Missing	10	6	
Further neurosurgical intervention: HE (index admission) (*n*)	*n*	116	116	0.048
	Mean (SD)	0.078 (0.299)	0.017 (0.131)	
Further neurosurgical intervention: wound revision (index admission), *n* interventions	0	115	111	–
	1	1	4	
	2	0	1	
	Missing	10	6	
Further neurosurgical intervention: wound revision (index admission) (*n*)	*n*	116	116	0.092
	Mean (SD)	0.009 (0.093)	0.052 (0.259)	
Further neurosurgical intervention: other cranial operation (index admission), *n* interventions	0	113	114	–
	1	3	2	
	Missing	10	6	
Further neurosurgical intervention: other cranial operation (index admission) (*n*)	*n*	116	116	0.653
	Mean (SD)	0.026 (0.159)	0.017 (0.131)	

SD, standard deviation.
a Excluding cranioplasties and shunts.

248 patients, 126 in the craniotomy arm and 122 in the DC arm. Unless specified otherwise, this constitutes the population used in the base-case and other analyses in this economic evaluation. Compared with the full analysis population, these UK patients are slightly older (3.5 years on average) and more likely to be on antithrombotic medication. They are also more likely to have an extracranial injury requiring admission, combined with a lower GCS score.

Some patients did not receive their allocated treatment and were dropped from the per-protocol analysis (SA5), leaving 113 patients who were allocated to and received craniotomy and 114 patients who were allocated to and received DC.

Costs

At NSU discharge 211/248 (85%) of participants had complete hospital-recorded resource use data (index admission) (*Table 26*).

Table 28 presents the reported levels of resource use at discharge, based on available hospital-recorded data for both the craniotomy and DC groups. This includes reported levels of resource use associated with the mean duration of index surgery, mean LOS in NSU and ICU, and details of further neurosurgical interventions, including additional DCs, HEs, wound revisions and 'other' neurosurgical interventions. Duration of index surgery was comparable across groups, as was LOS in ICU. There was a slightly higher non-significant mean LOS in NSU reported for the craniotomy group compared with the DC group (16.75 vs. 21.30 days, $p = 0.210$). With regard to further neurosurgical interventions received during index admission, there were more HEs (9 vs. 2) and DCs (15 vs. 4) in the craniotomy group compared with the DC group (see *Table 28*). This is not unexpected as it represents the fact some patients who initially had a craniotomy, went on to have a DC. There were, however, less wound revisions (one vs. six) in the craniotomy group compared with the DC group (see *Table 28*). When combined with associated unit costs (see *Table 35*) this enabled costs to be estimated for the same resource components and, in turn, the total index admission costs (excluding cranioplasties and shunts) (see *Table 29*), which were slightly lower in the craniotomy group compared with the DC group, though not significantly (£30,790 vs. £34,759, $p = 0.195$).

With regard to cranioplasty and shunt procedures, 242/248 (98%) had complete resource use data (*Table 27*). *Table 27* presents the levels of resource use relating to these cranioplasties and shunts (index and revision procedures), as reported in the hospital-recorded data. These occurred during index admission to hospital and/or post discharge, up to 12 months. As cranioplasty is only conducted after a craniectomy has taken place, as would be expected the mean number of primary cranioplasties per patient was significantly lower in the craniotomy group than in the DC group (0.169 vs. 0.512, $p < 0.0001$). Of note, however, there were 30/126 patients who were randomised to craniotomy that went on to have a DC at some point; 13 received DC instead of their randomised treatment, while the remainder received the treatment to which they were randomised (craniotomy) but went on to have a DC at a later date. Twenty-two of these (1 missing) were recorded as having a cranioplasty in the 12-month follow-up period. The majority of patients that received a cranioplasty did so using a synthetic material plate (81% in the craniotomy group, 74% in the DC group), as opposed to replacement of their own stored skull. As expected, the mean costs for cranioplasties were significantly lower in the craniotomy group than in the DC group ($p < 0.0001$, for all related costs, see *Table 29*).

With regard to shunt procedures, *Table 27* shows that the numbers were broadly similar between the groups, and this was also true for shunt-related costs (see *Table 27*). When cranioplasty and shunt costs were combined, due to the high costs associated with cranioplasty procedures, they were significantly lower in the craniotomy group compared with the DC group (£1258 vs. £3,228, $p < 0.0001$) (see *Table 29*).

Eighty-two post-discharge cranioplasty and shunt (index or revision) procedures were reported in the hospital-recorded data. This exceeds the 45 overnight stays with associated skull/brain operations reported in the patient self-report questionnaire. Therefore, as described in the methods, we have not included patient-reported overnight stays with an associated skull/brain operation in the base-case analysis, to avoid the potential for double-counting and cost duplication.

In terms of patient self-reported resource use data, at 12 months, 180/248 (73%) had complete resource use data (see *Table 27*) based on available data, *Table 28* presents the associated levels of post-discharge resource use, including overnight stays not associated with a skull/brain operation, HCP visits and number of scans. Levels were broadly similar in both groups, with no significant differences between any of the resource use items or costs (see *Tables 28* and *29*).

TABLE 27 Levels of resource use, from hospital-recorded data: cranioplasties and shunts (index admission and post discharge)

Resource use	Statistics	Craniotomy (*N* = 126)	DC (*N* = 122)	*p*-value
DC reported	Yes	30	115	–
	No	96	7	
	Missing	0	0	
Cranioplasty	Yes	22	63	–
	No	7	52	
	Missing	1	0	
Primary cranioplasties (pre and post discharge)	No	103	59	–
	Yes	21	62	
	Missing	2	1	
Primary cranioplasties (pre and post discharge)	*n*	124	121	< 0.0001
	Mean (SD)	0.169 (0.377)	0.512 (0.502)	
Proportion of primary cranioplasties requiring synthetic material plate (pre and post discharge)	*n*	21	62	–
	No	4 (19.1%)	16 (25.8%)	
	Yes	17 (81.0%)	46 (74.2%)	
	Missing	0	0	
Primary cranioplasties requiring synthetic material plate (pre and post discharge)	*n*	124	121	< 0.0001
	Mean (SD)	0.137 (0.345)	0.380 (0.487)	
Cranioplasty revisions (pre and post discharge)[a]	0	120	115	–
	1	3	5	
	2	1	1	
	Missing	2	1	
Cranioplasty revisions (pre and post discharge)[a]	*n*	124	121	0.587
	Mean (SD)	0.040 (0.235)	0.058 (0.268)	
Cranioplasties (primary/revision) requiring re-admission (i.e. post discharge)	0	109	69	–
	1	13	47	
	2	2	4	
	3	0	1	
	Missing	2	1	
Cranioplasties (primary/revision) requiring re-admission (i.e. post discharge)	*n*	124	121	
	Mean (SD)	0.137 (0.390)	0.479 (0.607)	< 0.0001

continued

TABLE 27 Levels of resource use, from hospital-recorded data: cranioplasties and shunts (index admission and post discharge) (*continued*)

Resource use	Statistics	Craniotomy (*N* = 126)	DC (*N* = 122)	*p*-value
Hydrocephalus reported	Yes	9	8	–
	No	117	110	
	Missing	0	4	
Shunt placement	Yes	5	4	–
	No	4	4	
	Missing	0	4	
Primary shunt (pre and post discharge)	No	121	114	–
	Yes	5	4	
	Missing	0	4	
Primary shunt (pre and post discharge)	*n*	126	118	0.812
	Mean (SD)	0.397 (0.196)	0.034 (0.182)	
Shunt revisions (pre and post discharge)[a]	0	123	116	–
	1	1	2	
	2	2	0	
	Missing	0	4	
Shunt revisions (pre and post discharge)[a]	*n*	126	118	0.401
	Mean (SD)	0.040 (0.265)	0.017 (0.130)	
Shunts (primary/revisions) requiring re-admission (i.e. post discharge)	0	123	115	–
	1	2	2	
	2	1	1	
	Missing	0	4	
Shunts (primary/revisions) requiring re-admission (i.e. post discharge)	*n*	126	118	
	Mean (SD)	0.032 (0.217)	0.034 (0.224)	0.939
Cranioplasty/shunt procedures occurring on same date (pre and post discharge)[b]	0	122	118	–
	1	2	0	
Index and revisions	Missing	2	4	

N, number of patients in receipt; *n*, number of patient for whom data were available; SD, standard deviation; only the most frequently reported items are reported.

a Revision cranioplasties were calculated as total cranioplasties (revision or otherwise) − 1. It was assumed that, regardless of how they were recorded on the forms, patients could only receive one index cranioplasty and could not receive a revision cranioplasty without first receiving and index cranioplasty.

b Cranioplasties and shunts that occurred on the same date are recorded here. These are also included in the figures above for shunts and cranioplasties separately.

TABLE 28 Levels of resource use, from patient self-report data: overnight stays, HCP visits, brain scans (post discharge, UK only)

Resource use	Statistics	Craniotomy (*N* = 126)	DC (*N* = 122)	*p*-value
Overnight stays (excluding those that included an operation to skull/brain)	Yes	61	54	–
	No	25	18	
	Dead (by discharge)	25	23	
	Missing	15	27	
Overnight stays on rehabilitation unit (excluding those with associated skull/brain operation) (days)	*n*	111	90	0.782
	n reporting stay > 0	45	36	
	Mean (SD)	32.505 (63.091)	35.089 (68.799)	
Overnight stays on NSU (excluding those with associated skull/brain operation) (days)	*n*	111	95	0.252
	n reporting stay > 0	8	5	
	Mean (SD)	0.486 (1.999)	1.137 (5.565)	
Overnight stays on ICU (excluding those with associated skull/brain operation) (days)	*n*	111	95	0.731
	n reporting stay > 0	1	1	
	Mean (SD)	0.126 (1.329)	0.074 (0.718)	
Overnight stays on other ward (excluding those with associated skull/brain operation) (days)	*n*	109	93	0.447
	n reporting stay > 0	20	10	
	Mean (SD)	4.936 (18.081)	3.043 (17.004)	
HCP contact	Yes	64	47	–
	No	20	24	
	Dead (by discharge)	25	23	
	Missing	17	28	
HCP visits – hospital doctor (visits)	*n*	106	92	0.980
	n reporting > 0 visits	28	24	
	Mean (SD)	0.604 (1.329)	0.609 (1.460)	
HCP visits – nurse (visits)	*n*	107	92	0.426
	n reporting > 0 visits	8	7	
	Mean (SD)	2.196 (16.530)	0.761 (5.280)	
HCP visits – GP (visits)	*n*	106	93	0.656
	n reporting > 0 visits	36	30	
	Mean (SD)	1.226 (2.443)	1.086 (1.926)	
HCP visits – physiotherapist (visits)	*n*	105	91	0.213
	n reporting > 0 visits	29	19	
	Mean (SD)	2.381 (7.114)	4.033 (11.191)	
HCP visits – occupational therapist (visits)	*n*	105	92	0.407
	n reporting > 0 visits	32	19	

continued

TABLE 28 Levels of resource use, from patient self-report data: overnight stays, HCP visits, brain scans (post discharge, UK only) (*continued*)

Resource use	Statistics	Craniotomy (*N* = 126)	DC (*N* = 122)	*p*-value
	Mean (SD)	1.562 (3.414)	2.217 (7.221)	
HCP visits – speech therapist (visits)	*n*	107	90	0.386
	n reporting > 0 visits	10	9	
	Mean (SD)	0.551 (2.291)	0.311 (1.395)	
HCP visits – social worker (visits)	*n*	107	92	0.665
	n reporting > 0 visits	6	7	
	Mean (SD)	0.159 (0.767)	0.120 (0.441)	
HCP visits –CCA (visits)	*n*	106	92	0.958
	n reporting > 0 visits	3	3	
	Mean (SD)	2.679 (21.438)	2.837 (20.451)	
HCP visits – emergency department (visits)	*n*	107	93	0.321
	n reporting > 0 visits	5	10	
	Mean (SD)	0.103 (0.531)	0.183 (0.607)	
HCP visits – psychologist/neuropsychologist (visits)	*n*	107	93	0.514
	n reporting > 0 visits	7	7	
	Mean (SD)	0.271 (1.241)	0.462 (2.717)	
HCP visits – other (visits)	*n*	107	93	0.699
	n reporting > 0 visits	2	2	
	Mean (SD)	0.028 (0.215)	0.043 (0.327)	
Head/brain scan	Yes	47	44	–
	No	39	26	
	Dead (by discharge)	25	23	
	Missing	15	29	
Head/brain scans – MRI (number of scans)	*n*	111	93	0.745
	n reporting > 0 scans	27	28	
	Mean (SD)	0.306 (0.615)	0.333 (0.558)	
Head/brain scans – CT (number of scans)	*n*	111	93	0.228
	n reporting > 0 scans	27	33	
	Mean (SD)	0.333 (0.665)	0.452 (0.730)	
Head/brain scans – other (number of scans)	*n*	111	93	0.543
	n reporting > 0 scans	4	2	
	Mean (SD)	0.036 (0.187)	0.022 (0.146)	
Time in a care home	Yes	12	17	–
	No	74	56	
	Dead (by discharge)	25	23	

TABLE 28 Levels of resource use, from patient self-report data: overnight stays, HCP visits, brain scans (post discharge, UK only) (*continued*)

Resource use	Statistics	Craniotomy (*N* = 126)	DC (*N* = 122)	*p*-value
	Missing	15	26	
Time in a care home since NSU discharge (weeks)	*n*	109	91	0.164
	Mean (SD)	1.792 (7.137)	3.533 (10.395)	
Help from carer	Yes	53	39	–
	No	28	27	
	Dead (by discharge)	25	23	
	Missing	20	33	
Total carer time since NSU discharge (hours)	*n*	99	86	0.925
	Mean (SD)	971 (2017)	1000 (2225)	
Currently in paid/unpaid work	Yes	18	8	–
	No	68	65	
	Dead (by discharge)	25	23	
	Missing	15	26	
Hours working per week (paid or unpaid)	*n*	109	96	0.126
	Mean (SD)	4.615 (12.105)	2.333 (8.477)	
Reported return-to-work date	Yes	18	8	–
	Not applicable	68	65	
	Dead (by discharge)	25	23	
	Missing	15	26	
Time worked since brain injury (hours)[a]	*n*	107	96	0.063
	Mean (SD)	152.263 (473.814)	53.528 (217.943)	

CCA, community care assistant; GP, general practitioner; *N*, number of patients in receipt; *n*, number of patient for whom data were available; SD, standard deviation; only the most frequently reported items are reported.
a Combines 'Currently in paid/unpaid work' with 'hours working per week (paid or unpaid)' and 'reported return-to-work date' to estimate mean hours worked per participant in 12-month follow-up period.

Results between arms were also similar when the index admission, cranioplasty and shunt, and post-discharge costs (excluding care home and carer costs) were summed to estimate per patient overall NHS and PSS costs (mean per patient cost, craniotomy vs. DC group: £48,509 vs. £53,573, $p = 0.510$, see *Table 29*).

Outcomes

There was 132/248 (53%) complete EQ-5D data (see total QALYs in *Table 27*) at all time points (NSU discharge, 6 and 12 months post randomisation), 72% at baseline, 79% at 6 months and 86% at 12 months (those that died were given an EQ-5D score of '0' and would therefore not be recorded as 'missing').

Table 30 shows the mean EQ-5D utility scores at each time point on an available case basis, along with the change in score. The EQ-5D scores at follow-up were higher (non-significant at 6 months, $p = 0.016$ at 12 months) in the

TABLE 29 Summary of costs in Great British pounds (£)

Cost component	Statistics	Craniotomy (*N* = 126)	DC (*N* = 122)	*p*-value
Index admission costs – hospital-recorded data				
Index neurosurgical procedure	*n* Mean cost (SD)	122 £3648 (£1264)	110 £3560 (£1315)	0.603
LOS in NSU	*n* Mean cost (SD)	122 £6109 (£9085)	120 £7766 (£11,339)	0.210
LOS in ICU	*n* Mean cost (SD)	126 £20,039 (£14,566)	122 £22,873 (£19,077)	0.189
Further neurosurgical intervention: DC[a]	*n* Mean cost (SD)	116 £307 (£859)	116 £82 (£536)	0.017
Further neurosurgical intervention: HE	*n* Mean cost (SD)	116 £165 (£638)	116 £37 (£279)	0.048
Further neurosurgical intervention: wound revision	*n* Mean cost (SD)	116 £18 (£198)	116 £110 (£551)	0.092
Further neurosurgical intervention: other	*n* Mean cost (SD)	116 £55 (£340)	116 £37 (£279)	0.653
Total cost per patient (index admission)	*n* Missing Mean (SD)	109 17 £30,790 (£19,710)	102 21 £34,759 (£24,481)	0.195
Cranioplasty and shunt costs (index and post discharge) – hospital-recorded data				
Cranioplasty – operation costs	*n* Mean cost (SD)	124 £517 (£1268)	121 £1405 (£1520)	< 0.0001
Cranioplasty – materials costs	*n* Mean cost (SD)	124 £343 (£863)	121 £950 (£1219)	< 0.0001
Cranioplasty – associated NSU stay costs	*n* Mean cost (SD)	124 £200 (£568)	121 £699 (£885)	< 0.0001
Shunt – operation costs	*n* Mean cost (SD)	126 £169 (£919)	118 £108 (£614)	0.547
Shunt – materials costs	*n* Mean cost (SD)	126 £20 (£98)	118 £17 (£91)	0.812
Shunt – associated NSU stay costs	*n* Mean cost (SD)	126 £23 (£158)	118 £25 (£163)	0.939
Cranioplasty/shunt operation costs[b]	*n* Mean cost (SD)	124 −£17 (£132)	118 £0 (£0)	0.167
Cranioplasty/shunt NSU stay costs discount[b]	*n* Mean cost (SD)	124 £0 (£0)	118 £0 (£0)	–
Total cost per patient (cranioplasties and shunts)	*n* Missing Mean (SD)	124 2 £1258 (£2983)	118 4 £3228 (£3677)	< 0.0001
Post-discharge costs – recorded on patient self-report questionnaire				
Overnight stays on rehabilitation unit[c]	*n* Mean cost (SD)	111 £16,375 (£31,784)	90 £17,677 (£34,660)	0.782
Overnight stays on NSU[c]	*n* Mean cost (SD)	111 £177 (£729)	95 £415 (£2029)	0.252
Overnight stays on ICU/HDU[c]	*n* Mean cost (SD)	111 £213 (£2247)	95 £125 (£1215)	0.731
Overnight stays on 'other' ward[c]	*n* Mean cost (SD)	109 £1746 (£6396)	93 £1076 (£6015)	0.447

TABLE 29 Summary of costs in Great British pounds (£) (*continued*)

Cost component	Statistics	Craniotomy (*N* = 126)	DC (*N* = 122)	*p*-value
HCP visits – hospital doctor	*n* Mean cost (SD)	106 £113 (£248)	92 £103 (£260)	0.784
HCP visits – nurse	*n* Mean cost (SD)	107 £51 (£329)	92 £17 (£106)	0.346
HCP visits – GP	*n* Mean cost (SD)	106 £53 (£117)	93 £52 (£135)	0.932
HCP visits – physiotherapist	*n* Mean cost (SD)	105 £154 (£426)	91 £269 (£767)	0.188
HCP visits – occupational therapist	*n* Mean cost (SD)	105 £135 (£300)	92 £192 (£645)	0.421
HCP visits – speech therapist	*n* Mean cost (SD)	107 £59 (£245)	90 £34 (£156)	0.393
HCP visits – social worker	*n* Mean cost (SD)	107 £20 (£98)	92 £15 (£54)	0.629
HCP visits – CCA	*n* Mean cost (SD)	106 £66 (£528)	92 £70 (£504)	0.959
HCP visits – emergency department	*n* Mean cost (SD)	107 £17 (£88)	93 £30 (£101)	0.321
HCP visits – psychologist/ neuropsychologist	*n* Mean cost (SD)	107 £40 (£184)	93 £69 (£403)	0.504
HCP visits – other	*n* Mean cost (SD)	107 £5 (£40)	93 £3 (£23)	0.635
Head/brain scans – MRI	*n* Mean cost (SD)	111 £37 (£74)	93 £40 (£67)	0.745
Head/brain scans – CT	*n* Mean cost (SD)	111 £26 (£52)	93 £35 (£57)	0.228
Head/brain scans – Other	*n* Mean cost (SD)	111 £3 (£15)	93 £2 (£11)	0.543
Time in a care home (wider perspective only)	*n* Mean cost (SD)	109 £3321 (£13,230)	91 £6550 (£19,272)	0.164
Carer time (wider perspective only)	*n* Mean cost (SD)	99 £16,762 (£34,828)	86 £17,271 (£38,419)	0.925
Total cost per patient (post-discharge PSRQ)	*n* Missing Mean (SD)	99 27 £19,699 (£34,193)	81 41 £17,948 (£32,183)	0.726
Total cost per patient (post-discharge PSRQ wider perspective)	*n* Missing Mean (SD)	85 41 £36,122 (£45,201)	72 50 £41,713 (£56,131)	0.491
Overall NHS and PSS cost per patient	*n* Missing Mean (SD)	86 40 £48,509 (£46,934)	67 55 £53,573 (£47,092)	0.510

CCA, community care assistant; GP, general practitioner; HDU, high dependency unit; *n*, number of patients for whom data were available; PSRQ, patient self-report questionnaire; SD, standard deviation.

a Based on mean duration of DC (from all index procedures) of 2.5042 (*n* = 110) hours for all randomised patients.

b A discount was applied to account for those shunt and cranioplasty procedures that occurred in the same operation and were therefore associated with a slightly shorter operation duration and NSU stay.

c Overnight stays excluding those associated with a skull/brain operation.

TABLE 30 Outcomes: EQ-5D-5L

Item	Statistics	Craniotomy (*N* = 126)	DC (*N* = 122)	Difference (95% CI)	*p*-value
Baseline EQ-5D-5L score	*n* Mean (SD)	87 0.260 (0.353)	91 0.302 (0.366)	−0.042 (−0.148 to 0.065)	0.441
6-month EQ-5D-5L score	*n* Mean (SD)	102 0.427 (0.392)	94 0.370 (0.393)	0.057 (−0.054 to 0.168)	0.311
6-month change in EQ-5D-5L score	*n* Mean (SD)	74 0.184 (0.345)	71 0.073 (0.319)	0.111 (0.002 to 0.220)	0.046
12-month EQ-5D-5L score	*n* Mean (SD)	111 0.471 (0.402)	103 0.336 (0.414)	0.135 (0.025 to 0.245)	0.016
12-month change in EQ-5D-5L score	*n* Mean (SD)	79 0.218 (0.367)	78 0.073 (0.361)	0.146 (0.031 to 0.260)	0.013
Total QALY score	*n* Mean (SD)	68 0.351 (0.335)	64 0.338 (0.366)	0.013 (−0.108 to 0.134)	0.830

n, number for whom data were available; SD, standard deviation.

craniotomy group compared with the DC group. Furthermore, the change in EQ-5D score from baseline to 12 months was significantly higher in the craniotomy group compared with the DC group (difference: 0.146, $p = 0.013$). There was no significant difference between groups for the total QALY score, based on available data.

Table 31 shows the percentage of favourable and unfavourable outcomes, as defined previously in the methods, for the GCS score at baseline, the GOSE score at 12 months and the GOSE score at 12 months dependent on the GCS score at baseline (where a lower GCS score at baseline means a lower GOSE score at 12 months is required to be defined as 'favourable'). The percentage of favourable GCS scores at baseline were lower in the craniotomy arm compared with the DC arm, though not significantly (29% vs. 40%, $p = 0.093$). At 12 months, the percentage of favourable GOSE scores was higher, but not significantly so, in the craniotomy arm compared with the DC arm, both in the GCS-independent measure (48% vs. 37%, $p = 0.102$) and GCS-dependent measures (44% vs. 32%, $p = 0.7$).

TABLE 31 Outcomes: GCS and GOSE

Item	Statistics	Craniotomy (*N* = 126)	DC (*N* = 122)	*p*-value
GCS score at baseline (% favourable/unfavourable[a])	*n* % favourable % unfavourable	120 29.2 70.8	119 39.5 60.5	0.093
12-month GOSE score (% favourable/unfavourable)[b]	*n* % favourable % unfavourable	121 47.9 52.1	115 37.4 62.6	0.102
Favourable/unfavourable outcome based on 12-month GOSE scores compared with GCS score at baseline[c]	*n* % favourable % unfavourable	115 43.5 56.5	112 32.1 67.9	0.078

n, number for whom data were available.

a Favourable for the GCS score was defined as 9–15 points (moderate to minor brain injury) while unfavourable was defined as 3–8 points (severe brain injury).

b Favourable for the GOSE score was defined as upper severe disability or better.

c If GCS at baseline is between 3 and 8, a favourable outcome will be defined as upper severe disability or better on 12-month GOSE. If GCS at baseline is between 9 and 15, a favourable outcome will be defined as lower moderate disability or better on 12-month GOSE.

Analyses

Cost–utility analysis

Table 32 presents estimates of mean incremental costs and incremental QALYs, generated from the regression analysis (both costs and QALYs adjusted for baseline EQ-5D, age and sex), along with the ICER and probability of being cost-effective at a threshold (λ) of £20,000 per QALY.

For the base case (based on ITT/MI), the mean difference in cost for the craniotomy group compared with the DC group was −£5520 (95% CI −£18,060 to £7020), with a mean QALY difference of 0.093 (95% CI 0.029 to 0.156). That is to say that the mean total cost was lower (non-significantly) and the mean QALY scores were higher (significantly) in the craniotomy group compared with the DC group, which means that craniotomy is dominant over DC; it is estimated to be less costly and more effective.

Cost-effectiveness analysis

Table 33 presents estimates of the mean incremental costs and OR of a favourable outcome, generated from linear regression and logistic (logit) regression, respectively. For the craniotomy group compared with the DC group, the mean difference in cost was −£4536 (95% CI −£17,374 to £8301), with an OR of favourable outcome on the GOSE score of 1.682 (95% CI 0.995 to 2.842, $p = 0.052$). That is to say that the mean total cost was lower (non-significantly) and the odds of a favourable score was higher (non-significantly) in the craniotomy group compared with the DC group, which means that craniotomy again dominated DC. Similar results were found for the GCS-adjusted binary GOSE score (see *Table 33*).

TABLE 32 Cost–utility analysis: estimates of the mean incremental cost, incremental effect (QALY gain), ICER and CEAC at £20,000, for craniotomy compared with DC, in the base-case analysis and SA

Analysis (*N* craniotomy, *N* DC)	Incremental cost (95% CI)	QALY gain (95% CI)	ICER	CEAC at £20,000/ QALY threshold[a] (%)
Base case: (126,122) MI	−£5520 (−£18,060 to £7020)	0.093 (0.029 to 0.156)	Dominant	87
SA1: (126,122) MI	−£17,793 (−£34,658 to −£928)	0.094 (0.030 to 0.159)	Dominant	99
SA2: (126,122) MI	−£6252 (−£12,180 to −£325)	0.092 (0.031 to 0.153)	Dominant	99
SA3: (126,122) MI	−£6328 (−19,389 to £6733)	0.093 (0.032 to 0.154)	Dominant	89
SA4: (126,122) MI	−£5445 (-£17,547 to £6658)	0.089 (0.025 to 0.152)	Dominant	87
SA5: (113,114) MI	−£10,711 (−£23,361 to £1939)	0.121 (0.056 to 0.185)	Dominant	98
SA6: (60,44) CCA	−£1917 (−£15,564 to £11,729)	0.071 (−0.0106 to 0.153)	Dominant	68

CCA, community care assistant; Dominant, lower mean costs and higher mean effect; *N* craniotomy (*N* DC), number randomised to craniotomy/DC who were included in the analysis; SA1–SA6 refer to the different SAs described in the *Methods*.

a Probability of being cost-effective on the CEAC at the threshold (λ) of £20,000 per QALY. Incremental cost and incremental QALY were adjusted for baseline utility, age and sex (see *Methods*).

TABLE 33 Cost-effectiveness: incremental cost and OR (craniotomy/DC) of having a favourable GOSE outcome, craniotomy compared with DC

Analysis (*N* craniotomy, *N* DC)	Incremental cost (95% CI)	OR (craniotomy/DC) (95% CI)	*p*-value for OR	Cost per favourable outcome
Base case – 12-month GOSE (126, 122)	−£4536 (−£17,374 to £8301)	1.682 (0.995 to 2.842)	0.052	Dominant
Base case – 12-month GCS-adjusted GOSE (126, 122)	−£6091 (−£18,857 to £6675)	1.741 (1.019 to 2.977)	0.043	Dominant
SA1 – 12-month GOSE (126, 122)	−£16,900 (−£33,807 to £7)	1.693 (0.998 to 2.871)	0.051	Dominant
SA1 – 12-month GCS-adjusted GOSE (126, 122)	−£17,697 (−£34,634 to −£760)	1.742 (1.011 to 3.003)	0.046	Dominant
SA2 – 12-month GOSE (126, 122)	−£5709 (−£11,783 to £365)	1.704 (1.010 to 2.888)	0.048	Dominant
SA2 – 12-month GCS-adjusted GOSE (126, 122)	−£6321 (−£12,395 to −£247)	1.753 (1.023 to 3.004)	0.041	Dominant
SA3 – 12-month GOSE (126, 122)	−£5374 (−£18,782 to £8033)	1.687 (0.999 to 2.849)	0.050	Dominant
SA3 – 12-month GCS-adjusted GOSE (126, 122)	−£6936 (−£20,358 to £6486)	1.745 (1.021 to 2.985)	0.042	Dominant
SA5 – 12-month GOSE (113, 114)	−£10,567 (−£23,434 to £2299)	2.189 (1.252 to 3.827)	0.006	Dominant
SA5 – 12-month GCS-adjusted GOSE (113, 114)	−£11,380 (−£24,197 to £1438)	2.063 (1.172 to 3.631)	0.012	Dominant
SA6 – 12-month GOSE (83, 67)	−£4335 (−£18,545 to £9876)	1.360 (0.698 to 2.649)	0.366	Dominant
SA6 – 12-month GCS-adjusted GOSE (83, 67)	−£4406 (−£18,599 to £9786)	1.406 (0.713 to 2.774)	0.326	Dominant

Decision uncertainty

In terms of uncertainty, the base-case probability that craniotomy is cost-effective compared with DC at a threshold of £20,000 was 87% according to the CEAC (see *Table 32*). This indicates that there is a high degree of certainty associated with the decision that craniotomy compared with DC is cost-effective at a threshold of £20,000 per QALY.

Sensitivity analyses

The results of the SAs that were undertaken for the CUA are shown in *Table 32*, and for the CEA in *Table 33*. Of note, when, carer and care home costs were included in the wider perspective analysis (SA1) the cost difference increased between craniotomy and DC. In all these analyses craniotomy dominates DC, it is less costly and more effective. In every cost–utility SA, other than the complete-case analysis (SA6), the probability that craniotomy is cost-effective compared with DC at a threshold of £20,000 per QALY is ≥ 87%, which reinforces the high degree of certainty associated with the decision. For the complete-case analysis (SA6) the mean difference (craniotomy vs. DC) in cost was −£1917 (95% CI −£15,564 to £11,729) with a mean QALY difference of 0.071 (95% CI −0.011 to 0.153). Craniotomy

therefore still dominates DC, though there was a slightly lower probability of cost-effectiveness (68%) at a threshold of £20,000 per QALY. This may reflect the nature of the missing data.

Discussion

Main findings

Based on the results of the cost–utility and cost-effectiveness analyses craniotomy dominates DC, it is less costly and more effective (see *Tables 32* and *33*). There is a high degree of certainty associated with the conclusion of the CUA, as choosing DC would be estimated to be associated with an 87% probability (at a willingness-to-pay threshold of £20,000 per QALY) of making the wrong decision. Furthermore, this is supported by the results of the SAs, all of which also found craniotomy to be less costly and more effective, with a 68–99% probability (at a willingness-to-pay threshold of £20,000 per QALY) of making the wrong decision by using DC rather than craniotomy in these patients.

Comparisons with other studies

We are not aware of any previous economic evaluations that have compared craniotomy with DC for patients with ASDH, although the general literature on this topic shows that there is much clinical uncertainty as to which operation to undertake.[19,32,35]

Study limitations

In line with good practice recommendations for cost-effectiveness analyses,[5] we concentrated on the large cost drivers and excluded resources that were not expected to differ between the two treatment arms (e.g. routine monitoring scans or tests). That said, the mean costs could be heavily influenced by outliers, due to the high unit costs associated with resource use, such as LOS in ICU and operation costs.

An additional potential limitation is that we specified, within the HEAP, that lost productivity costs would be estimated, but this was not undertaken for the aforementioned reasons (details of working patterns before their brain injury were not requested). We did, however, estimate the number of hours participants had worked since their brain injury (in the 12-month follow-up period), where the results in *Table 28* (based on available data) show that the estimated mean number of hours worked was higher in the craniotomy arm compared to DC. Assuming that, due to randomisation, the number of hours worked was broadly similar between groups at baseline, then this would suggest that had lost productivity costs been estimated, this would not have changed the base-case or SA1 results that craniotomy had a lower mean cost compared to DC. Indeed, as the estimated mean number of hours worked was lower in the DC arm, this might suggest lost productivity costs were higher in the DC arm, which would only reinforce the base-case and SA1 results that craniotomy was associated with lower costs.

Regarding HRQoL, QALY scores (EQ-5D recorded at all time points) were available for 53% of participants only, and the amount of missing data were greater at discharge than at 6 (79%) and 12 months (86%) (see *Table 27*). Some of the missing EQ-5D baseline (NSU discharge) data may be due to participants being discharged at short notice or at the weekend when a research nurse was not available. As some patients had not yet been discharged from hospital by 6 months, this may also explain why there was a greater degree of missing EQ-5D data at this time point compared with 12 months. Such missing data is a limitation, but it should be noted that the same conclusion can be drawn from both the results of the complete-case and imputed (base-case) analyses.

A further potential limitation is that, for ethical reasons, baseline HRQoL (EQ-5D) scores were taken at discharge from NSU rather than at the point of randomisation. The date of discharge from NSU is post intervention, and there is, therefore, the potential for any benefits to be underestimated by assuming the score at the date of discharge to be the baseline score. To test the potential impact of this, a SA (SA4) was done, where the baseline EQ-5D score was assumed to be that of worst possible health (−0.594). The results of this SA differed little from the base case (see *Table 32*), with craniotomy still dominant over DC; less costly and more effective.

A further potential limitation is that the conclusions might differ if results were estimated over a longer follow-up period. However, if the treatment effect found in this study was maintained beyond 12 months, the conclusions would

be unchanged, because extrapolation would result in further QALY gain for the craniotomy group compared with the DC group, while the costs would remain similar between the two groups.

The main strength of this economic evaluation is that it is based on a large, multicentre, randomised study. Previous evidence was inconclusive and highlighted the uncertainty in how to treat patients with ASDH.[32,35,36] Furthermore, until now, there were no randomised studies investigating this topic.

Implications

It has been argued that decisions should be based on the mean estimates (of cost and effect), regardless of, for example, the associated level of the *p*-value.[37] This is advocated on the basis that decisions (about implementation or not) need to be made, regardless of the associated quality of the evidence, and that the mean value is the best estimate to use, for example, to predict total cost. As such, economists tend to focus on the mean estimates of cost and effect when making recommendations as to whether treatments should be provided by the NHS or not.

Conclusion

Our economic evaluation has shown that in a UK population of patients with traumatic ASDH, craniotomy had lower mean costs and a higher mean effect (dominating DC). There was an associated high degree of certainty that craniotomy compared with DC was cost-effective at a threshold of £20,000 per QALY. Additionally, when several SAs were conducted, the main conclusion remained unchanged. Consequently, the health economic analysis supports the aforementioned recommendation (based on the primary outcome) that a craniotomy should be undertaken, rather than a DC, if it is operatively feasible to replace the bone flap.

Chapter 6 Long-run health economic model

Background

The study described in this report included a 'within-trial' economic evaluation to estimate the costs and effects of craniotomy compared to DC for ASDH. This enabled data taken from UK randomised trial participants to be used to estimate whether one intervention could be considered cost-effective compared to the comparator intervention. The advantage of a within-trial evaluation is that it uses data collected from randomised individuals. It also enables appropriate data to be collected prospectively. However, one issue with a within-trial analysis is that it is limited to the follow-up period of the trial. Individuals may live for many years after the conclusion of a trial. If one intervention is associated with clinical improvements, then these improvements may persist for many years. In the case of TBI, if one treatment was more effective than another, it could lead to differences in mortality between groups. It could also mean there are differences in levels of disability and morbidity, which may mean that there are long-term implications in terms of healthcare resource use, costs borne by individuals and accrued HRQoL. And this could lead to differences in results between analyses that take a shorter time frame and ones which have looked at costs and benefits further into the future. One common tool for estimating long-term costs and consequences is the decision-analytic model.

'In the context of economic evaluation, a decision-analytic model uses mathematical relationships to define a series of possible consequences that would flow from a set of alternative options being evaluated'.[38]

A decision-analytic model allows for data from a variety of sources to be used in a single model to extrapolate beyond the limits of a clinical trial. Examples could include: extrapolation to a different healthcare setting; including additional relevant comparators; and increasing the time horizon of the analysis. An example of why a longer time horizon may be important was provided from an analysis of extracorporeal membrane oxygenation.[39] This included both a 6-month within-trial analysis and a long-term model. The intervention had extremely high costs which were incurred at the time treatment was given. It was also found to be effective, with potential long-term consequences. Estimates of cost per QALY were £1,631,124 for the within-trial analysis and £19,252 for a lifetime model.

For the comparison of craniotomy compared to DC, there was a concern that the conclusion of the within-trial analysis could differ from a longer time horizon. This was because DC would require additional surgery and higher costs. Any potential benefits would likely accrue over a long time horizon, so there was the potential for the within-trial analysis to not capture all relevant costs and benefits. For this reason, an additional analysis looking at a long-run time horizon was planned. The aim of this component was to construct a health economic decision-analytic model to evaluate the long-term costs and effects of the interventions from the perspective of the UK NHS.

Methods

Model development

The model comprised two parts. Firstly, a decision tree was used to allocate individuals to different model states based on the results of the within-trial analysis. The model states correspond to the outcomes in the trial, with individuals being classified as favourable or unfavourable based on the GOSE at 12 months. Unfavourable includes the dead state. The structure of the decision tree model is given in *Figure 5*. The square node represents the choice between the two interventions. In either case, individuals can have a favourable or unfavourable outcome at 12 months. For those who have an unfavourable outcome, individuals can either be alive or dead. All individuals who have a favourable outcome at 12 months are assumed to be alive at 12 months. The decision tree model covers the 12-month period from randomisation to the end of follow-up. And all costs and effects in this time are taken from the within-trial analysis, *Chapter 5*.

The model also comprised a long-run Markov model. This is shown in *Figure 6*. At the end of year 1, individuals are classified as in *Figure 5*. All those with a favourable outcome at 12 months are alive. For those with an unfavourable

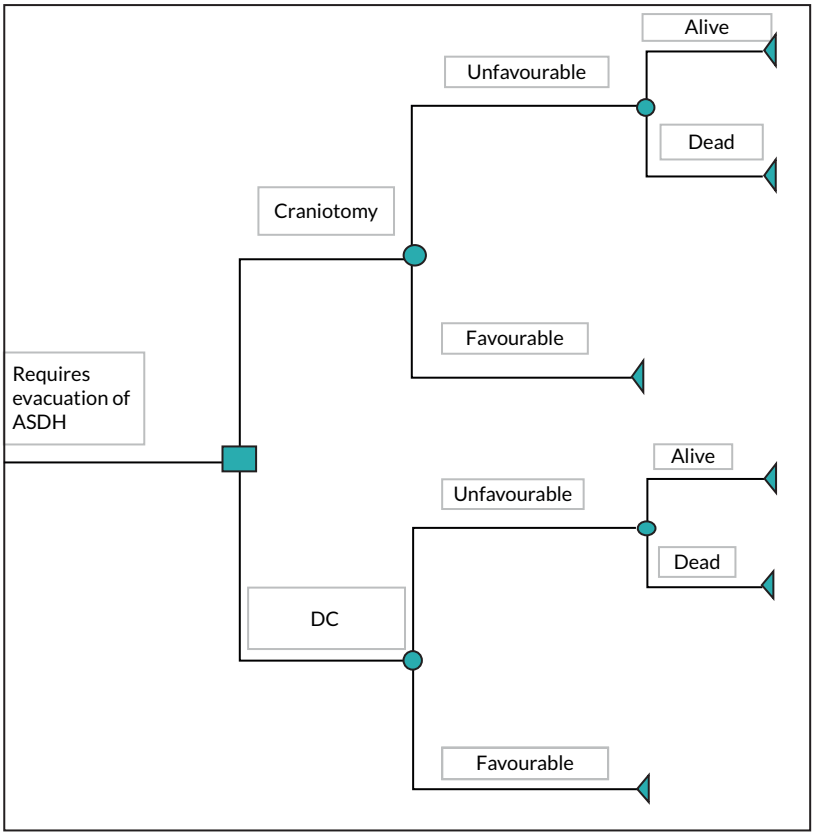

FIGURE 5 Decision tree structure used in the long-run health economic model.

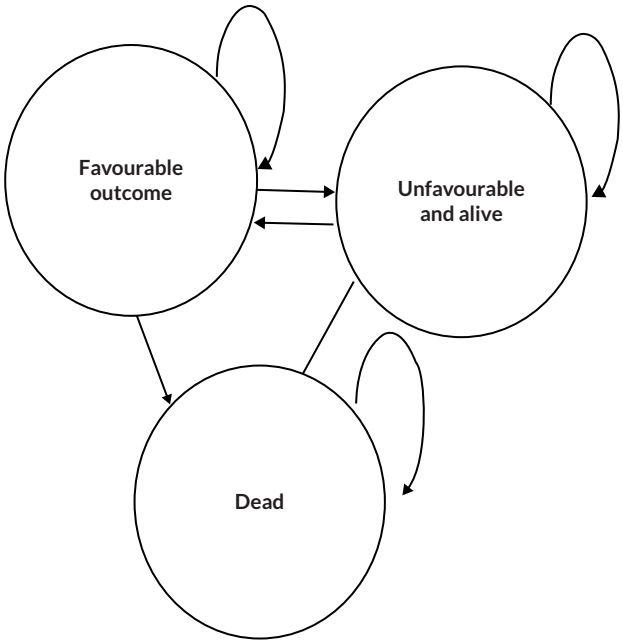

FIGURE 6 Structure of the long-run Markov model.

outcome, individuals can either be unfavourable and alive, or they can be in dead. Therefore, the Markov model has three states: favourable outcome; unfavourable and alive; and dead. At the start of the Markov process (end of year 1), the individuals in the dead state would be those who were classified as having an unfavourable outcome and who were dead at the end of follow-up. In the long-run model, individuals can transition to the dead state from both 'favourable outcome' and the 'unfavourable and alive' states. Additionally, individuals in the favourable outcome state can either

remain in that state or transition to the 'unfavourable but alive' state, that is, the model allows for health to deteriorate. Similarly, individuals in the 'unfavourable and alive' state can either remain in that state or transition to the 'favourable outcome' state, that is, individuals can improve. The dead state is what is termed an absorbing state – individuals in the model can enter the state, but they cannot leave it.

The model was developed in collaboration with a clinical expert (Harry Mee), who advised on the structure and data within the model. It was also informed with reference to a published model in a similar area by Behranwala *et al.*[40] These authors presented two decision tree model structures, a simple decision tree based on outcomes of unfavourable or favourable, and a more complex tree structure with outcomes based on the individual GOSE scores. However, these authors only presented analyses over a 1-year time frame. The decision tree model used in the current analysis follows a similar structure to the simpler decision tree presented in Behranwala *et al.*; however, the model presented here specifically splits the unfavourable state into alive and dead to correspond with health states in the Markov model.

Characteristics of the model

The decision tree model uses data wholly taken from the within-trial analysis presented in this report (*Chapter 5*). It is used to estimate the accrued costs and QALYs for the two interventions in year 1. It is also used to assign numbers of individuals to each of the Markov states at the start of the Markov model. The decision tree model covers a period of 1 year. The Markov model covers 39 years. This gives a total duration of the model of 40 years. The Markov model has a cycle length of 1 year. It is a cohort model with an assumed cohort size of 1000. All individuals are assumed to have a starting age equal to the mean age for the sample used in the economic evaluation; this was 52 years of age. A duration of 40 years was chosen as this was assumed to be sufficient time for the majority of the cohort to enter the dead state. As the model covers a time span of 40 years, it is important to allow for the differential timing of costs and benefits. Discounting is not used in the first year, which is the convention in economic analysis and was the approach taken in the within-trial analysis. In subsequent years, both costs and benefits (QALYs) are discounted at an annual rate of 3.5%, as recommended by NICE.[18] The proportion who are male was also based on the UK sample and was 79% (see *Table 24*). In a Markov model, all events, such as a transition to another state, are assumed to occur either at the beginning or the end of a cycle. Transitions in the real world would occur throughout the cycle. Assuming events happen either at the beginning or end of a cycle, it can generate results that may differ from those that would have been if events can happen at any point in the cycle. A half-cycle correction assumes that transitions occur, on average, half-way through the cycle and therefore approximates the situation where transitions happen continuously.[41] A half-cycle correction was used in the Markov model.

Both the decision tree model component and the Markov model component were modelled using a probabilistic sensitivity analysis (PSA) in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA). In this process, rather than using a fixed value for a parameter, such as the cost of spending a year in the favourable outcome state, a random draw from a distribution with specified characteristics is used. This allows sampling uncertainty to be allowed for in the model and will give more realistic results. The model is then rerun for a large number of simulations. Model results, such as means and 95% percentiles, are then taken from these simulations.

Model parameters

The parameters used to build the decision tree and Markov models are given in *Table 34*. Parameters can be divided into several categories. These are probabilities, QALYs or utilities, and costs. Where possible, parameters were assigned a distribution. The appropriate distribution used in each case varies with the characteristics of each parameter. Also provided is the distribution used, characteristics of this distribution and notes detailing the source of the data.

For the decision tree model, probabilities were used to determine the numbers of individuals allocated to each branch of the model after each chance node (chance nodes are represented as round nodes on the decision tree presented). For the Markov model, transition probabilities were required. These are the probabilities that an individual transitions from one state to another and are represented by the arrows in *Figure 6*. The probabilities used in the model are given in *Table 34*.

TABLE 34 Parameters used in the model

Parameter	Mean	Distribution	Characteristics	Source
Decision tree model				
Probability of favourable outcome with DC at 12 months	0.374	Beta	(alpha = 45, beta = 76)	Within-trial analysis
OR of favourable outcome with craniotomy compared to DC	1.68	Log-normal	(95% CI 1 to 2.84)	Within-trial analysis
Probability of death in first year – craniotomy	0.24	Beta	(alpha = 29, beta = 93)	Within-trial analysis
Probability of death in first year – DC	0.27	Beta	(alpha = 32, beta = 87)	Within-trial analysis
QALY generated in year 1 – DC	0.338	Gamma	(alpha = 209, beta = 0.0032)	Within-trial analysis
QALY difference, craniotomy compared to DC	0.093	Normal	(95% CI 0.029 to 0.16)	Within-trial analysis
Costs in year 1 – DC	£53,573	Gamma	(alpha = 87, beta = 618)	Within-trial analysis
Cost difference, craniotomy compared to DC	−£5520	Normal	(95% CI −£18,060 to £7020)	Within-trial analysis
Markov model				
Probability of going from favourable to unfavourable – craniotomy	0			Assumed
Probability of going from unfavourable to favourable – craniotomy	0			Assumed
Probability of going from favourable to unfavourable – DC	0			Assumed
Probability of going from unfavourable to favourable – DC	0			Assumed
Utility for favourable – craniotomy	0.746	Gamma	(alpha = 53.8, beta = 0.0047)	Within-trial analysis
Utility of unfavourable – craniotomy	0.22	Gamma	(alpha = 296.5, beta = 0.0026)	Within-trial analysis
Utility for favourable – DC	0.701	Gamma	(alpha = 26.4, beta = 0.0011)	Within-trial analysis
Utility of unfavourable – DC	0.14	Gamma	(alpha = 558, beta = 0.0015)	Within-trial analysis
Cost for favourable – craniotomy	3556	Gamma	(alpha = 9.3, beta = 381)	Within-trial analysis
Cost for unfavourable – craniotomy	5060	Gamma	(alpha = 5.2, beta = 968)	Within-trial analysis
Cost for favourable – DC	1645	Gamma	(alpha = 11.4, beta = 145)	Within-trial analysis
Cost for unfavourable – DC	3988	Gamma	(alpha = 4.0, beta = 992)	Within-trial analysis

The probability of a favourable outcome with DC was taken from the within-trial analysis (*Table 31*). All probabilities included in the model would be constrained to have values between zero and one; for this reason, directly estimated probabilities were modelled using beta distributions. To infer the probability of a favourable outcome with craniotomy, we used the probability for DC multiplied by the estimated relative risk for craniotomy as compared to DC. The relative risk was derived from the OR presented in *Table 33*. This relative risk was modelled using a log-normal distribution. The probability of death in the first year was taken from the within-trial analysis. The QALYs generated in the first year in the DC group were taken from *Table 30*. As the QALY is for 1 year, it would have a maximum value of 1 (utility score of 1 for 1 year). Negative values of the QALY would also have been possible. These properties do not match commonly used distributions. So, it is common with QALYs or utilities to model them using a transformed distribution D, where D = 1-QALY.[38] This then has a minimum value of zero, with scores above 1 possible, and this was modelled using a gamma distribution. The costs in the first year for DC were taken from the within-trial analysis (see *Table 29*). To estimate the costs in the craniotomy arm, we adjusted the DC costs by the estimated cost difference for craniotomy (see *Table 32*). The cost difference was modelled using a normal distribution. Uncertainty in cost estimates are derived from differences in resource use between participants; we did not assume uncertainty in unit cost estimates.

For the Markov model, we were unable to find long-run data on the transition of individuals between the favourable and unfavourable states. Therefore, these transitions were modelled with a value of zero, that is, assuming that individuals remained in the state they were in at the 1-year follow-up. However, these parameters were included in the model to allow for future updating should data become available. These assumptions were also varied in a SA to show the effects of allowing state transitions between favourable and unfavourable states. The utility value assigned to being in each state for the two interventions was estimated from the 12-month utility values from the within-trial analysis (see *Table 30*). As cycle lengths are 1 year in the Markov model, the utility values correspond to the QALYs generated per year. The distribution for utilities was modelled in the same way as QALYs, that is, with a transformed variable being created, and this transformed variable was modelled using a gamma distribution. Again, we did not find credible long-run data for the future costs of individuals with ASDH treated with surgery. The 1-year costs for those alive at 1 year, excluding inpatient costs, were used as a proxy for these. These values are not reported in *Chapter 5* and were obtained from the within-trial analysis (SP – personal communication). Again, these were modelled using gamma distributions, and uncertainty would have originated from differences in resource use.

For the first 2 years of the Markov model – that is, years 2 and 3 after suffering the ASDH – an annual probability of mortality was used based on data suggesting that for a population of blunt trauma survivors, the death rate was 0.089 in the 2-year period, covering the second and third years after injury.[42] This was transformed into an annual probability of 0.0455 for the unfavourable group only, using a formula to convert rates to probabilities from a published source.[38] For the favourable group and for all other cycles of the model for the unfavourable group, mortality was estimated based on age- and sex-adjusted population estimates for England and Wales for 2020.[43]

Analysis

The model was constructed in Microsoft Excel. The PSA was repeated for 5000 samples. Mean costs and QALYs were calculated for the simulated cohort. To evaluate the effects of uncertainty, a CEAC was created. This shows the probability that any intervention would be cost-effective at varying valuations of a unit of outcome – in this case, cost per QALY.

Sensitivity analysis

To show the effects of varying model parameters on results, we conducted a series of deterministic one-way SAs. In these analyses, parameters were varied in isolation between defined limits, and the effects on the model ICERs were noted. The following parameters were varied: OR of favourable outcomes with craniotomy compared to DC; QALY difference in year 1; cost difference in year 1; probability of transition from favourable to unfavourable (for both interventions); probability of transition from unfavourable to favourable (for both interventions); utility values for favourable and unfavourable for both interventions; yearly state costs for favourable and unfavourable for both

TABLE 35 Probabilistic SA results for craniotomy compared to DC

	Total QALYs	Total cost	Incremental QALY	Incremental cost (£)	ICER (£)
DC	7.2	£89,787			
	(5.5–9.0)	(64,891–124,255)			
Craniotomy	10.4	£100,501	3.2	10,715	3352
	(8.3–13.4)	(70,035–138,662)			

Note
Figures in brackets are 95% percentiles.

interventions. For transitions between favourable and unfavourable states, an arbitrary range of 0–0.05 was used. For all other variables, we either used 95% CIs or 95% percentiles from the distributions.

Results

The results of the probabilistic SA are given in *Table 35*. These are estimates of QALYs accrued over a 40-year period, so estimated QALYs are much higher than for the within-trial analysis. The craniotomy arm generates an estimate of 3.2 additional QALYs, with an additional cost of £10,715. This gives an ICER of £3352.

A scatter plot of the 5000 separate simulations is given in *Figure 7*. Each point represents the individual results of each of the 5000 simulations. From *Figure 7*, it can be seen that craniotomy generated additional QALYs in almost all cases. This was because more individuals were in the favourable health state for this intervention, and the favourable health state had a higher utility value and hence generated more QALY for each individual spending a year in that state. It can also be seen that there are more points above the *X*-axis than below it. Generally, simulations, therefore, suggested a higher cost for craniotomy as compared to DC. This was because there was a higher cost associated with each year in the favourable and unfavourable health states than for DC. This difference was sufficient to offset the higher year 1 costs for the DC intervention, as shown in the within-trial analysis.

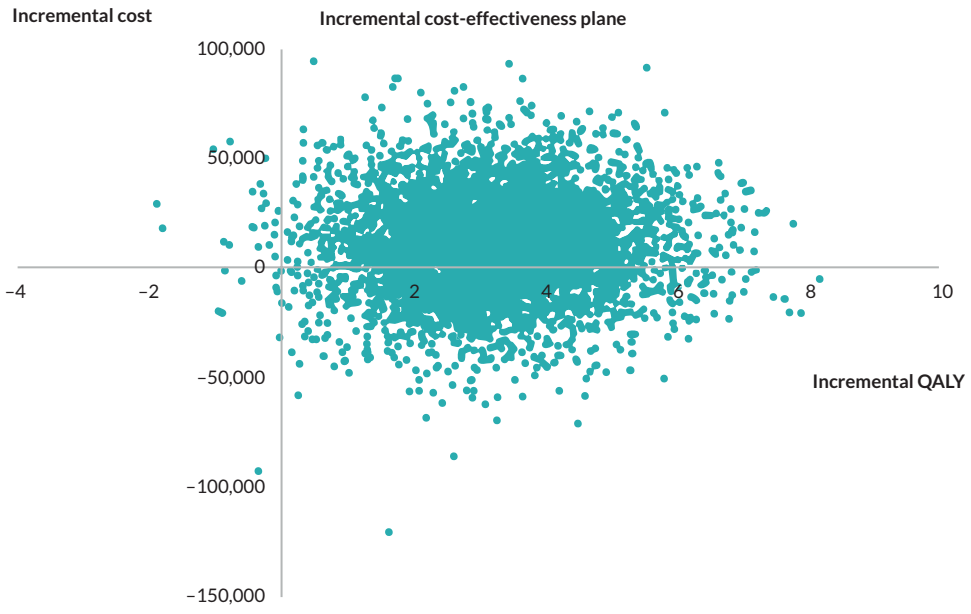

FIGURE 7 Incremental cost-effectiveness plane for craniotomy compared to DC.

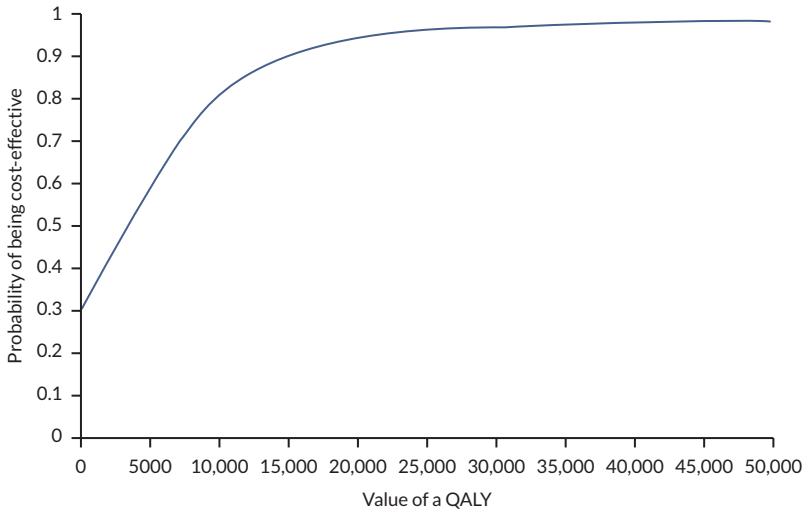

FIGURE 8 Cost-effectiveness acceptability curve for craniotomy compared to DC.

The CEAC for craniotomy compared to DC is shown in *Figure 8*. This shows the probability that craniotomy is cost-effective compared to DC at different values of a QALY. At a value of a QALY of £20,000, there is a 94% probability that craniotomy is cost-effective compared to DC. This is similar to the 'within-trial' results, where craniotomy is also given a high probability of being cost-effective at £20,000 per QALY (87%).

Sensitivity analyses

The results of the various deterministic one-way SAs performed are given in *Table 36*. The model results were particularly sensitive to values used for some of the state transitions between favourable and unfavourable. Also important to the model results were long-term costs associated with being in the favourable and unfavourable states.

TABLE 36 One-way deterministic SAs

One-way SA	Base-case value	Low	High	ICER with low value	ICER with high value
OR of favourable outcomes with craniotomy	1.68	1.00	2.84	£7736	£2043
QALY difference in year 1	0.09	0.03	0.16	£3645	£3500
Cost difference in year 1	−£5520	−£18,060	£7020	Craniotomy dominates DC	£7555
Craniotomy – probability of favourable to unfavourable	0.00	0.00	0.05	£3570	£35,339
Craniotomy – probability of unfavourable to favourable	0.00	0.00	0.05	£3570	£1342
DC – probability of favourable to unfavourable	0.00	0.00	0.05	£3570	£1303
DC – probability of unfavourable to favourable	0.00	0.00	0.05	£3570	DC dominates craniotomy
Craniotomy – utility value for favourable	0.75	0.68	0.81	£3570	£2963
Craniotomy – utility value for unfavourable	0.22	0.13	0.31	£4948	£2830

TABLE 36 One-way deterministic SAs (*continued*)

One-way SA	Base-case value	Low	High	ICER with low value	ICER with high value
DC – utility value for favourable	0.70	0.58	0.80	£2757	£4737
DC – utility value for unfavourable	0.14	0.07	0.21	£2831	£4802
Craniotomy – cost for favourable	£3556	£1630	£6225	Craniotomy dominates DC	£9000
Craniotomy – cost for unfavourable	£5060	£1639	£10,276	Craniotomy dominates DC	£13,331
DC – cost for favourable	£1645	£843	£2706	£4737	£2026
DC – cost for unfavourable	£3988	£1137	£8563	£9992	Craniotomy dominates DC

Discussion

Main findings

The results of the health economic model are similar to those of the 'within-trial' analysis and would lead to the same conclusions. Compared to DC, craniotomy generates increased numbers of QALY, with an additional 3.2 QALYs per person generated over the 40-year time horizon of the model. The ICER was £3352 per QALY; this is clearly below the NICE threshold of £20,000–30,000 per QALY as the point at which interventions can be considered cost-effective. Uncertainty analysis suggests a 94% probability of the intervention being cost-effective at £20,000 per QALY.

Comparison with the within-trial analysis

The original rational for including a modelling component in addition to the within-trial analysis (see *Chapter 5*) was to allow for longer-term considerations should these be relevant. As mentioned in the introduction to this chapter, there may be cases where an intervention has a much larger 'upfront' cost than a comparator but may generate advantages such as reduced mortality and/or increased quality of life that may persist over the long term. In these cases, a within-trial analysis may not give a true picture of the economic efficiency of that intervention. In this situation, a long-run decision-analytic model would be required.

However, the within-trial analysis shows that this was not the case in this trial. Craniotomy had a lower cost and generated more QALYs, and hence dominated DC. For this reason, the long-term model does not alter the conclusions drawn from the within-trial analysis. The main conclusion from the longer-term model is the same, being strongly suggestive of economic advantages for craniotomy. In terms of uncertainty, the CEACs suggest less uncertainty compared to the within-trial analysis, with a probability of being cost-effective of 94% at a value of £20,000. This suggests the long-run model is consistent with the conclusions of the within-trial analysis. However, unlike the within-trial analysis, it was not cost saving, with an expected additional discounted cost of £10,715 per person over the 40-year run of the model.

Study limitations

The long-run economic model draws heavily from the within-trial analysis, so the study limitations outlined in *Chapter 5* also apply to this work. The main additional limitation relating to the model concern the paucity of reliable long-term follow-up data from patients who have received either craniotomy or DC for ASDH. Firstly, we did not have credible data on long-term transition between the favourable and unfavourable but alive health states. If these are similar for the two interventions, then conclusions would not be altered. In the case where transitions between these states were very different in the long term for the two interventions, then it would be possible that conclusions would be altered. SA performed on these variables suggests that long-term transition probabilities are likely to be important to model results. In terms of utilities, we estimated these based on the values of the EQ-5D-5L at 12 months from this

trial. And these were assumed to remain constant over time. In reality, these would likely change, particularly if there were gradual health improvements over time. Similarly, mortality was assumed to be the same as the population of England and Wales, except for the first year, where mortality was high, and years 2 and 3, where a small increase in mortality was assumed. This may understate long-term mortality, particularly in the unfavourable but alive health state, and hence the estimates of total QALYs generated may be overstated. Finally, to estimate long-term costs, we used the within-trial estimate of non-inpatient stay costs in the 1-year follow-up as an estimate of long-run costs in the Markov model. These were higher in the craniotomy intervention than for DC, meaning that long-term costs were higher for craniotomy. However, these results were based on very small numbers, with 24 participants having data in each intervention group for the unfavourable but alive health state. For the favourable health state, there were 48 and 34 participants who had these data in the craniotomy and DC interventions, respectively. This means these estimates are likely to be subject to high levels of uncertainty. Again, one-way SA (see *Table 36*) suggests values for long-term costs are likely to be important for model conclusions. Also, there is no clear reason to conclude these costs would be constant over time. Additionally, there were numbers of individuals in the DC arm who had not had their reconstructive surgery by the 12-month follow-up. If these individuals went on to have this surgery in subsequent years, it would affect the cost results obtained in the model and may well lead to different estimates of cost.

Implications for future work

In this trial, the within-trial health economic analysis was sufficient for informing the efficient use of healthcare resources. However, in the treatment of ASDH, it is likely that evaluations of future interventions may cover situations where one intervention is associated with increased short-term costs and be more effective than a comparator. For good decision-making in these cases, it would be important to have reliable and credible long-term data to inform long-term modelling. This model may be able to be incorporated into the cranial reconstruction registry, a prospective registry following patients' trajectory of recovery after decompression and how the cranioplasty influences such recovery. Being able to closely monitor healthcare resources will be an invaluable addition to this resource.

Conclusion

The results from a long-run economic model are consistent with the results of the 'within-trial' economic evaluation. To develop a reliable model on the longer-term costs and benefits of treatments for ASDH, improved data on long-term costs and effectiveness are needed.

Chapter 7 Discussion

Within this trial involving adult patients with traumatic ASDHs requiring surgical evacuation, there were two cohorts of patients; the first were those randomised intraoperatively to either craniotomy or craniectomy, and secondly, the observational cohort, who did not meet the eligibility criteria for randomisation but who underwent surgery and followed up. In the randomised cohort, we found no significant difference across GOSE outcomes between the craniotomy (bone flap replaced) and DC (bone flap left out) at 12 months.

There were significant differences in the functional outcome of patients between the DC and craniotomy groups at both 6 and 12 months in the observed cohort, but these patients had significantly different baselines, with the DC group being younger, with more extracranial injuries, lower GCS and more likely to have had parenchymal lesions and traumatic subarachnoid haemorrhages. This would reflect what might be expected in current clinical practice in that those patients with more severe brain injuries requiring surgery often have the bone flap left out.

To our knowledge, there are no universally accepted criteria that predict the development of postoperative brain swelling and elevated ICP in this setting. Systematic reviews of the literature have identified no other randomised trials, and conclusions have been limited due to confounding by indication, with more severely injured patients undergoing craniectomy more frequently than craniotomy in non-randomised studies.[44,45] Therefore, the role of a pre-emptive DC in this setting is not known and has been identified as a research priority.[3]

The two previously published multicentre trials of DC examined its role as a secondary treatment for post-traumatic intracranial hypertension. The Decompressive Craniectomy in Diffuse Traumatic Brain Injury trial reported similar mortality between early craniectomy and medical management, with worse outcomes in survivors in the surgical group.[46] The Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intracranial Pressure trial found a substantial mortality reduction with last-tier DC and a wide range of outcomes in survivors.[47,48]

Although the present trial found no significant difference in mortality or GOSE outcomes between the DC and the craniotomy groups, additional cranial operations within 2 weeks after randomisation were performed more frequently in the craniotomy group (and most of them were DC for brain swelling). However, patients in the DC group experienced more wound-related complications and surgical site infections.

Although the null hypothesis of no difference between the two groups cannot be formally rejected, the trial may have practical implications. If the bone flap can be replaced without compressing the brain, surgeons should consider doing so, as opposed to performing a pre-emptive DC. These findings may not be relevant for resource-limited or military settings, where an upfront craniectomy is often used due to absence of sophisticated ICU facilities for postoperative care.[49,50]

Limitations

First, the clinicians caring for patients were not blinded to trial group assignments. However, outcome adjudication was performed by personnel who were unaware of the group assignments. Second, 8.8% of patients allocated to craniotomy had a craniectomy, and 5.4% of patients allocated to craniectomy had a craniotomy. This intraoperative non-adherence with allocation did not influence the primary analysis, which was based on the ITT principle. Third, 36 patients (8%) who were randomised were not included in the final analysis due to consent withdrawal and/or loss to follow-up. However, the sample size of the trial allowed for a loss to follow-up up to 10%. Finally, the trial did not formally examine other surgical techniques, such as a floating/hinge craniotomy, removal of contusions that may have a role to play in this setting.

Generalisability

In cases where replacing the bone flap is a feasible option, these results will help guide the surgeon's decisions. Not replacing the bone usually requires future skull reconstruction, requiring further operation and the risks of associated complications.

These patients often require extensive periods of rehabilitation, and now with clear evidence that the decision of replacing the bone flap in relevant cases does not result in worse outcomes is very useful in the overall management of these patients, both in the acute management and in the longer-term rehabilitation planning.

Patient and public involvement

There was a PPI lead who was also a co-applicant for this project, with a personal experience of critical illness, TBI and rehabilitation, and had a wide experience of research and clinical trials. There was engagement throughout, both during developing the application and protocol as well as through the study. They were involved in reviewing the patient-facing documentation as well as being involved in the running of the study.

Equality, diversity and inclusion

This was an international study with participating sites and patients from many different cultural and religious backgrounds. Patients who were enrolled in this study had suffered a TBI and sustained an ASDH requiring an operation to evacuate it. As our eligible study population was dependent on uncontrollable factors, there was no discrimination, and equal opportunities of neurosurgical care was available for all participants.

Recommendations for future research

- Evaluation of the timing and material of cranial reconstruction on functional recovery.
- Long-term outcome following DC.

Implications for future work

In those patients who have undergone a decompressive craniectomy, the optimal time for cranial reconstruction is not yet known, further research is required and a RCT is planned to help improve the evidence base. The current cranial reconstruction registry in the UK captures operative details of cranial reconstruction surgery with a short 30-day follow-up. Expansion of this registry to record details from the DC with longer-term functional and quality-of-life follow-up will allow for an increased understanding of the recovery and long-term outcomes for this cohort of patients. In this trial, the 'within-trial' health economic analysis was sufficient for informing the efficient use of healthcare resources. However, in the treatment of ASDH, it is likely that evaluations of future interventions may cover situations where one intervention is associated with increased short-term costs and be more effective than a comparator. For good decision-making in these cases, it would be important to have reliable and credible long-term data to inform long-term modelling. This model may be able to be incorporated into the cranial reconstruction registry, a prospective registry following patients' trajectory of recovery after decompression and how the cranioplasty influences such recovery. Being able to closely monitor healthcare resources will be an invaluable addition to this resource.

Chapter 8 Conclusions

In conclusion, among adult patients undergoing evacuation of acute traumatic subdural haematoma, DC and craniotomy gave similar results in overall outcomes at 12 months in the randomised cohort. There were significant differences seen in the observed cohort. Additional craniectomies were required more frequently in the craniotomy group, but wound complications and surgical site infections occurred more frequently in the craniectomy group.

Registration

The trial was registered as ISRCTN87370545.

Protocol

The published trial protocol is available online.

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Patient data statement

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation

Data-sharing statement

The data are managed and shared in a way that safeguards the confidentiality and anonymity of participants and is consistent with the terms of consent signed by participants. All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Ethics statement

This research has been conducted in accordance with the World Medical Association Declaration of Helsinki. Ethics approval was granted from NRES committee North West – Haydock for the trial on 17 July 2014, REC references were UK Ref 14 NW 1076, and Scotland REC Ref 15 SS 0193.

Information governance statement

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Disclosure of interests

Full disclosure of interests: Completed ICMJE forms for all authors, including all related interests, are available in the toolkit on the NIHR Journals Library report publication page at https://doi.org/10.3310/GJPH0512.

Primary conflicts of interest: Peter Hutchinson was a member of the HTA IP Panel (1 January 2016–31 May 2018) and HTA Prioritisation Committee B (in hospital) (1 January 2016–31 March 2022).

Garry Barton was a member of the HTA General Committee (1 March 2023–30 November 2026).

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Publications

Hutchinson PJ, Kolias AG, Timofeev IS, Corteen EA, Czosnyka M, Timothy J, *et al.* RESCUEicp Trial Collaborators. Trial of decompressive craniectomy for traumatic intracranial hypertension. *N Engl J Med* 2016;**375**:1119–30. https://doi.org/10.1056/NEJMoa1605215

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Appendix 2 Vital status at admission (randomised)

		Randomised craniotomy (*n* = 228)	Randomised DC (*n* = 222)
Admission systolic BP (mmHg)	Mean (SD)	134.3 (26.8)	135.2 (29.2)
	Median	130	130
	IQR	36	31
	Minimum, maximum	61, 230	70, 266
	Missing	8	2
Admission diastolic BP (mmHg)	Mean (SD)	78.1 (16.0)	78.3 (14.9)
	Median	78	79.5
	IQR	18	18
	Minimum, maximum	30, 137	40, 123
	Missing	8	2
Admission heart rate (beats per minute)	Mean (SD)	81.6 (18.8)	84.0 (17.5)
	Median	82	82
	IQR	20	21
	Minimum, maximum	14, 161	40, 141
	Missing	13	6
Admission core temperature (°C)	Mean (SD)	36.4 (1.0)	36.4 (1.3)
	Median	36.7	36.7
	IQR	1	1
	Minimum, maximum	31, 38.5	28.4, 39
	Missing	35	28
Admission respiratory rate (breaths per minute)	Mean (SD)	18.5 (4.9)	18.9 (4.9)
	Median	18	18
	IQR	6	4
	Minimum, maximum	3, 42	8, 40
	Missing	27	12

IQR, interquartile range.

Appendix 3 Pre-intubation Glasgow Coma Scale and pupil reactivity (randomised)

Randomised		Randomised craniotomy (*n* = 228)	Randomised DC (*n* = 222)	Total randomised (*n* = 450)
GCS – eye (pre-intubation)	E4	27 (12%)	27 (12%)	54 (12%)
	E3	34 (15%)	30 (14%)	64 (14%)
	E2	44 (19%)	44 (20%)	88 (20%)
	E1	116 (51%)	116 (52%)	232 (52%)
	Untestable	1 (–%)	0	1 (–%)
	Number unknown	6 (3%)	5 (2%)	11 (2%)
GCS – motor (pre-intubation)	M6	42 (18%)	39 (18%)	81 (18%)
	M5	76 (33%)	80 (36%)	156 (35%)
	M4	27 (12%)	43 (19%)	70 (16%)
	M3	10 (4%)	14 (6%)	24 (5%)
	M2	24 (11%)	18 (8%)	42 (9%)
	M1	41 (18%)	23 (10%)	64 (14%)
	Untestable	2 (1%)	0	2 (–%)
	Number unknown	6 (3%)	5 (2%)	11 (2%)
GCS – verbal (pre-intubation)	V5	14 (6%)	14 (6%)	28 (6%)
	V4	30 (13%)	27 (12%)	57 (13%)
	V3	25 (11%)	23 (10%)	48 (11%)
	V2	41 (18%)	37 (17%)	78 (17%)
	V1	105 (46%)	111 (50%)	216 (48%)
	% untestable	8 (4%)	5 (2%)	13 (3%)
	Number unknown	5 (2%)	5 (2%)	10 (2%)
GCS total score (pre-intubation)	Scoring 3	34 (16%)	22 (10%)	56 (13%)
	Scoring 4	25 (12%)	17 (8%)	42 (10%)
	Scoring 5	7 (3%)	11 (5%)	18 (4%)
	Scoring 6	15 (7%)	31 (14%)	46 (11%)
	Scoring 7	25 (12%)	25 (12%)	50 (12%)
	Scoring 8	22 (10%)	17 (8%)	39 (9%)
	Scoring 9	18 (8%)	20 (9%)	38 (9%)
	Scoring 10	14 (7%)	13 (6%)	27 (6%)
	Scoring 11	8 (4%)	15 (7%)	23 (5%)
	Scoring 12	11 (5%)	11 (5%)	22 (5%)

Randomised		Randomised craniotomy (*n* = 228)	Randomised DC (*n* = 222)	Total randomised (*n* = 450)
	Scoring 13	13 (6%)	11 (5%)	24 (6%)
	Scoring 14	16 (7%)	10 (5%)	26 (6%)
	Scoring 15	7 (3%)	9 (4%)	16 (4%)
	Number untestable	8	5	13
	Number unknown	5	5	10
Pupil reactivity – left eye	Negative	41 (18%)	52 (23%)	93 (21%)
	Positive	171 (75%)	160 (72%)	331 (74%)
	Untestable	3 (1%)	3 (1%)	6 (1%)
	Unknown	12 (5%)	7 (3%)	19 (4%)
	Not available	1	0	1
Pupil reactivity – right eye	Negative	55 (24%)	55 (25%)	110 (24%)
	Positive	155 (68%)	158 (71%)	313 (70%)
	Untestable	5 (2%)	2 (1%)	7 (2%)
	Unknown	13 (6%)	7 (3%)	20 (4%)
Pupil reactivity	Neither pupil reactive	31 (14%)	36 (16%)	67 (15%)
	At least one reactive	182 (80%)	176 (79%)	358 (80%)
	Both untestable	2 (1%)	3 (1%)	5 (1%)
	Unknown	13 (6%)	7 (3%)	20 (4%)

E, eye; M, motor; V, verbal.

Appendix 4 Treatment received (randomised)

		Randomised craniotomy	Randomised DC
Number of patients		228	222
Treatment	Allocated treatment (%)	208 (91%)	210 (95%)
Received	Alternative treatment (%)	20 (9%)	12 (5%)
Reason did not receive allocated treatment	Intraoperative brain swelling	15 (94%)	1 (14%)
	Brain relaxed	0 (%)	5 (71%)
	Other	1 (6%)	1 (14%)
	Not recorded	4	5

Appendix 5 Stage 2 case report form: discharge from the intensive care unit (randomised)

		Randomised craniotomy (*n* = 171)	Randomised DC (*n* = 166)
Discharge destination from ICU	Died	26 (15%)	27 (16%)
	NSU	126 (74%)	128 (77%)
	Different hospital	14 (8%)	7 (4%)
	Nursing home	0	1 (1%)
	Other	5 (3%)	3 (2%)
Number discharged alive from ICU		**(*n* = 145)**	**(*n* = 139)**
GCS total score of patients discharged alive from ICU	Score 3	4 (4%)	3 (3%)
	Score 4	1 (1%)	6 (6%)
	Score 5	1 (1%)	0
	Score 6	2 (2%)	3 (3%)
	Score 7	3 (3%)	2 (2%)
	Score 8	3 (3%)	1 (1%)
	Score 9	3 (3%)	1 (1%)
	Score 10	5 (5%)	11 (11%)
	Score 11	10 (10%)	6 (6%)
	Score 12	3 (3%)	6 (6%)
	Score 13	18 (18%)	9 (9%)
	Score 14	21 (21%)	31 (30%)
	Score 15	28 (27%)	25 (24%)
	Untestable	42	34
	Missing	1	1

Appendix 6 Stage 3 case report form: neurosurgical interventions within 14 days (randomised)

		Randomised craniotomy (*n* = 228)	Randomised DC (*n* = 222)
Neurosurgical interventions within 14 days	Yes	28 (15%)	13 (7%)
	No	164	175
	Missing	36	34
Number of interventions	1	23	11
	2	4	2
	3	1	0
	4	0	0
Total number of interventions		*N* = 34	*N* = 15
Intervention	Craniectomy	18 (53%)	1 (7%)
	Cranioplasty	0	2 (13%)
	SDH evacuation	4 (12%)	2 (13%)
	EDH evacuation	2 (6%)	0
	ICH evacuation	1 (3%)	1 (7%)
	EVD inserted	3 (9%)	3 (20%)
	Shunt placement	0	0
	ICP monitor	5 (15%)	3 (20%)
	Wound revision	0	0
	Other	1 (3%)	3 (20%)

Appendix 7 Therapy intensity level (randomised)

		Randomised craniotomy (*n* = 169)	Randomised DC (*n* = 164)
Peak TIL level by treatment arm	Peak TIL 0	8 (4.7%)	7 (4.3%)
	Peak TIL 1	26 (15.4%)	34 (20.7%)
	Peak TIL 2	75 (44.4%)	57 (34.8%)
	Peak TIL 3	32 (18.9%)	32 (19.5%)
	Peak TIL 4	28 (16.6%)	34 (20.7%)

Appendix 8 Adverse events and procedure-related complications

Randomised: AEs

Event	Randomised craniotomy (*n* = 228)	Randomised DC (*n* = 222)
Pneumonia	38(17%)	48 (22%)
Pneumothorax	5 (2%)	2 (1%)
Atelectasis	6 (3%)	6 (3%)
Aspiration	14 (6%)	8 (4%)
Pleural effusion/empyema	3 (1%)	1 (–%)
Ventilator-related complications	9 (4%)	11 (5%)
Adult respiratory distress syndrome	5 (2%)	2 (1%)
Respiratory failure	6 (3%)	3 (1%)
Need for prolonged mechanical or positive pressure airway ventilation	16 (7%)	22 (10%)
Other respiratory	7 (3%)	2 (1%)
Myocardial infarction	1 (–%)	2 (1%)
Arrhythmia	12 (5%)	7 (3%)
Heart failure	3 (1%)	1 (–%)
Angina	0	0
Pericardial effusion	1 (–%)	1 (–%)
Other cardiac	2 (1%)	1 (–%)
Urinary tract infection	13 (6%)	11 (5%)
Renal failure may require full renal support	3 (1%)	3 (1%)
Renal dysfunction	1 (–%)	3 (1%)
Urinary retention	1 (–%)	2 (1%)
Haematuria	0 (0%)	3 (1%)
Other renal	1 (–%)	1 (–%)
Deep-vein thrombosis	1 (–%)	3 (1%)
Pulmonary embolism	2 (1%)	1 (–%)
Other thrombosis	3 (1%)	2 (1%)
Other thrombotic	0	3 (1%)
Pancreatitis	0	1 (–%)
Liver failure	3 (1%)	3 (1%)
Other hepatobiliary	3 (1%)	1 (–%)
Infective diarrhoea or colitis	6 (3%)	3 (1%)
Diarrhoea of other causes	6 (3%)	12 (5%)

Event	Randomised craniotomy (*n* = 228)	Randomised DC (*n* = 222)
Bowel ischaemia	0	0
Ileus	2 (1%)	4 (2%)
Other bowel-related	1 (–%)	4 (2%)
Wound infection (not craniotomy or craniectomy)	8 (3%)	6 (3%)
Dehiscence (not craniotomy or craniectomy)	2 (1%)	1 (–%)
Other wound-related (not craniotomy or craniectomy)	2 (1%)	2 (1%)
Decubitus ulcer	5 (2%)	0
Other infections, for example, MRSA	4 (2%)	6 (3%)
Anaesthetic-related complications	0	0
Anaemia, coagulopathy	7 (3%)	15 (7%)
Pyrexia	52 (23%)	59 (27%)
Septicaemia	7 (3%)	11 (5%)
Other	8 (3.5%)	12 (5%)
Number of AEs	270	289
Number of patients experiencing an event	**113**	**104**

MRSA, meticillin-resistant *Staphylococcus aureus*.

Procedure-related complications: randomised

	Randomised craniotomy (*n* = 228)	Randomised DC (*n* = 222)
Number of patients with procedure-related complication	60 (26.3%)	57 (25.7%)
Number of procedure-related complication	93	97
Average procedure-related complication per patient	0.40	0.44
Average procedure-related complication per patient with complication	1.55	1.70
Procedure-related complications		
External herniation of the brain	6	3
Expansion of mass lesion	5	6
Development of mass lesions	7	7
Intraoperative vascular injury	2	1
Stroke	11	9
Surgical site infections	5	10
Wound complications other than infections	4	17
Subdural hygromas	3	4
Subdural empyema	1	0
Intracerebral abscess	0	1
Meningitis	2	2
Seizures	11	9
Hydrocephalus	4	4
Other	32	24

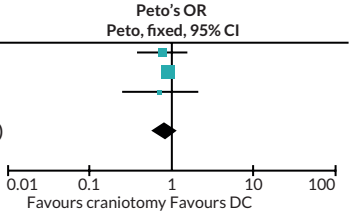
Appendix 9 Randomised arm: subgroup analysis at 12 months

The pre-specified subgroup analyses are based on dichotomous outcome (events are death, vegetative state and lower severe disability).

Age

Study or subgroup	Craniotomy Events	Craniotomy Total	DC Events	DC Total	Peto's OR Peto, Fixed, 95% CI
Age less than 40	24	68	27	65	0.77 (0.38 to 1.54)
Age 40–65	58	111	59	109	0.93 (0.55 to 1.57)
Age greater than 65	26	36	29	37	0.72 (0.25 to 2.08)
Total (95% CI)		**215**		**211**	**0.84 (0.57 to 1.25)**
Total events	108		115		

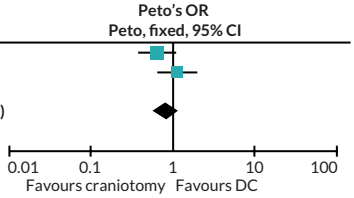
Heterogeneity: $\chi^2 = 0.28$, df = 2 ($p = 0.87$); $I^2 = 0\%$
Test for overall effect: z = 0.84 ($p = 0.40$)



UK vs. non-UK

Study or subgroup	Craniotomy Events	Craniotomy Total	DC Events	DC Total	Peto's OR Peto, Fixed, 95% CI
UK	63	121	72	115	0.65 (0.39 to 1.09)
Non UK	45	94	43	96	1.13 (0.64 to 2.00)
Total (95% CI)		**215**		**211**	**0.84 (0.57 to 1.22)**
Total events	108		115		

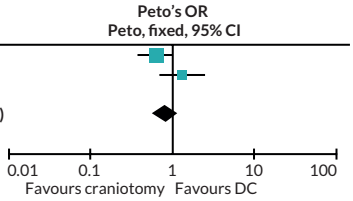
Heterogeneity: $\chi^2 = 1.99$, df = 1 ($p = 0.16$); $I^2 = 50\%$
Test for overall effect: z = 0.93 ($p = 0.35$)



LMIC vs. HIC

Study or subgroup	Craniotomy Events	Craniotomy Total	DC Events	DC Total	Peto's OR Peto, Fixed, 95% CI
HIC	71	134	84	131	0.63 (0.39 to 1.03)
LMIC	37	81	31	80	1.33 (0.71 to 2.47)
Total (95% CI)		**215**		**211**	**0.84 (0.57 to 1.23)**
Total events	108		115		

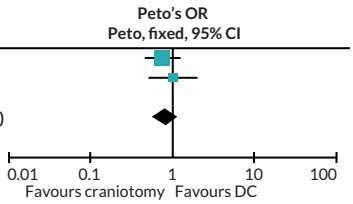
Heterogeneity: $\chi^2 = 3.35$, df = 1 ($p = 0.07$); $I^2 = 70\%$
Test for overall effect: z = 0.90 ($p = 0.37$)



Severity of injury

Study or subgroup	Craniotomy Events	Craniotomy Total	DC Events	DC Total	Peto's OR Peto, Fixed, 95% CI
GCS 3–8	82	139	91	139	0.76 (0.47 to 1.23)
GCS 9–15	26	76	24	72	1.04 (0.53 to 2.05)
Total (95% CI)		**215**		**211**	**0.84 (0.57 to 1.25)**
Total events	108		115		

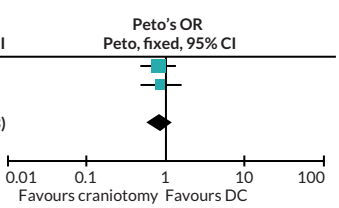
Heterogeneity: $\chi^2 = 0.54$, df = 1 ($p = 0.46$); $I^2 = 0\%$
Test for overall effect: z = 0.84 ($p = 0.40$)



Parenchymal lesions

Study or subgroup	Craniotomy Events	Craniotomy Total	DC Events	DC Total	Peto's OR Peto, Fixed, 95% CI
Parenchymal lesions	62	125	69	126	0.81 (0.50 to 1.33)
No parenchymal lesions	46	90	46	85	0.89 (0.49 to 1.60)
Total (95% CI)		**215**		**211**	**0.84 (0.58 to 1.23)**
Total events	108		115		

Heterogeneity: $\chi^2 = 0.05$, df = 1 ($p = 0.83$); $I^2 = 0\%$
Test for overall effect: z = 0.88 ($p = 0.38$)



Appendix 10 Observational data

Vital signs at admission

		Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	Total observed (*n* = 386)	Mann–Whitney U-test *p*-values
Vital status at admission-Systolic BP	Mean (SD)	142.0 (31.7)	131.8 (28.6)	135.5 (30.1)	0.002
	Median	139.5	128	130	
	IQR	42.5	34	38	
	Minimum, maximum	73, 240	55, 221	55, 240	
	Missing	9	16	25	
Vital status at admission-Diastolic BP	Mean (SD)	79.3 (20.2)	79.4 (18.9)	79.4 (19.4)	0.744
	Median	77.5	76	77	
	IQR	24.7	20	21.5	
	Minimum, maximum	48, 160	29, 180	29, 180	
	Missing	9	16	25	
Vital status at admission-Heart rate	Mean (SD)	77.3 (19.4)	85.7 (21.1)	82.6 (20.9)	< 0.0001
	Median	74	85	82	
	IQR	28	28	29.5	
	Minimum, maximum	38, 132	24, 160	24, 160	
	Missing	10	19	29	
Vital status at admission-Core temperature (°C)	Mean (SD)	36.0 (1.3)	36.5 (2.0)	36.3 (1.8)	< 0.0001
	Median	36.2	36.8	36.5	
	IQR	1.4	1	1.1	
	Minimum, maximum	30.2, 38	28, 57	28.0, 57	
	Missing	37	52	89	
Vital status at admission-Respiratory rate	Mean (SD)	17.3 (5.1)	19.0 (7.4)	18.4 (6.7)	0.003
	Median	16	18	18	
	IQR	6	6	5	
	Minimum, maximum	10, 42	6, 95	6, 95	
	Missing	22	31	53	

IQR, interquartile range; SD, standard deviation.

Computed tomography scan results

		Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	Total observed (*n* = 386)	χ^2 – *p*-values
Midline shift	None	2 (1.4%)	4 (1.6%)	6 (2%)	0.069
	≤ 5 mm	17 (12.2%)	34 (13.9%)	51 (13%)	
	5.1–10 mm	45 (32.4%)	108 (44.3%)	153 (40%)	
	> 10 mm	75 (54.0%)	98 (40.2%)	173 (45%)	
	Not available	2	1	3	
Obliteration of basal cisterns	Normal	32 (23.0%)	31 (12.8%)	63 (16.5%)	0.033
	Compressed	77 (55.4%)	155 (63.8%)	232 (61.7%)	
	Absent	30 (21.6%)	57 (23.5%)	87 (22.8%)	
	Not available	2	2	4	
Parenchymal lesions	No	89 (64%)	76 (31.4%)	165 (43.3%)	< 0.0001
	Yes	50 (36%)	166 (68.6%)	216 (56.7%)	
	Not available	2	3	5	
Intraventricular blood	No	130 (93.5%)	215 (88.1%)	345 (90.1%)	0.089
	Yes	9 (6.5%)	29 (11.9%)	38 (9.9%)	
	Missing	2	1	3	
Traumatic SAH	No	78 (56.1%)	80 (32.8%)	158 (41.3%)	< 0.0001
	Yes	61 (43.9%)	164 (67.2%)	225 (58.7%)	
	Missing	2	1	3	
Extradural haematoma	Absent	134 (96.4%)	220 (90.5%)	354 (92.7%)	0.056
	≤ 25 cc	5 (3.6%)	16 (6.6%)	21 (5.1.8%)	
	> 25 cc	0	7 (2.9%)	7 (2%)	
	Missing	2	2	4	
Subdural haematoma	Absent	97 (69.8%)	179 (73.4%)	276 (72.1%)	0.236
	≤ 25 cc	21 (15.1%)	42 (17.2%)	63 (16.4%)	
	> 25 cc	21 (15.1%)	23 (9.4%)	44 (11.5%)	
	Missing	2	1	3	
Intracerebral haematoma	Absent	113 (81.32%)	171 (71.0%)	284 (74.7%)	0.074
	≤ 25 cc	22 (15.8%)	56 (23.2%)	78 (20.5%)	
	> 25 cc	4 (2.9%)	14 (5.8%)	18 (4.7%)	
	Missing	2	4	6	
Posterior fossa haematoma	No	138 (99.3%)	235 (96.3%)	373 (97.4%)	0.080
	Yes	1 (0.7%)	9 (3.7%)	10 (2.6%)	
	Missing	2	1	3	

		Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	Total observed (*n* = 386)	χ^2 – *p*-values
Depressed skull fracture	No	129 (92.8%)	217 (88.7%)	346 (90.3%)	0.218
	Yes	10 (7.2%)	26 (11.1%)	37 (9.7%)	
	Missing	2	1	3	

Pre-intubation Glasgow Coma Scale and pupil reactivity

		Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	Total observed (*n* = 386)
GCS – eye (pre-intubation)	E4	31 (22%)	25 (10%)	56 (15%)
	E3	27 (19%)	33 (14%)	60 (16%)
	E2	15 (11%)	28 (12%)	43 (11%)
	E1	57 (40%)	154 (63%)	211 (55%)
	Untestable	2 (1%)	0	2 (1%)
	Number unknown	9 (6%)	3 (1%) 2	12 (3%) 2
GCS – motor (pre-intubation)	M6	43 (30%)	31 (13%)	74 (19%)
	M5	34 (24%)	69 (28%)	103 (27%)
	M4	11 (8%)	32 (13%)	43 (11%)
	M3	8 (6%)	25 (10%)	33 (9%)
	M2	10 (7%)	31 (13%)	41 (11%)
	M1	22 (16%)	51 (21%)	73 (19%)
	Untestable	3 (2%)	1 (–%)	4 (1%)
	Number unknown	10 (7%)	3 (1%) 2	13 (3%) 2
GCS – verbal (pre-intubation)	V5	16 (11%)	8 (3%)	24 (6%)
	V4	27 (19%)	26 (11%)	53 (14%)
	V3	8 (6%)	18 (7%)	26 (7%)
	V2	22 (16%)	40 (16%)	62 (16%)
	V1	56 (40%)	139 (57%)	195 (51%)
	Untestable	3 (2%)	9 (4%)	12 (3%)
	Number unknown	9 (6%)	3 (1%) 2	12 (3%) 2

		Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	Total observed (*n* = 386)
GCS total score (pre-intubation)	Scoring 3	21 (16%)	46 (20%)	67 (19%)
	Scoring 4	8 (6%)	26 (11%)	34 (9%)
	Scoring 5	8 (6%)	21 (9%)	29 (8%)
	Scoring 6	5 (4%)	20 (9%)	25 (7%)
	Scoring 7	8 (6%)	27 (12%)	35 (10%)
	Scoring 8	7 (5%)	16 (7%)	23 (6%)
	Scoring 9	13 (10%)	12 (5%)	25 (7%)
	Scoring 10	9 (7%)	17 (7%)	26 (7%)
	Scoring 11	6 (5%)	12 (5%)	18 (5%)
	Scoring 12	9 (7%)	12 (5%)	21 (6%)
	Scoring 13	8 (6%)	11 (5%)	19 (5%)
	Scoring 14	16 (13%)	9 (4%)	25 (7%)
	Scoring 15	10 (8%)	2 (1%)	12 (3%)
	Number untestable/NR	13	14	27
	Mean (SD)	8.9 (4.1)	7.1 (3.5)	7.7 (3.8)
	Median (IQR)	9 (5, 13)	7 (4, 10)	7 (4, 11)
Pupil reactivity – left eye	Negative	24 (17%)	65 (27%)	89 (23%)
	Positive	104 (74%)	155 (64%)	259 (68%)
	Untestable	1 (1%)	7 (3%)	8 (2%)
	Unknown	11 (8%)	15 (6%)	26 (7%)
	Not available	1	3	4
Pupil reactivity – right eye	Negative	26 (19%)	62 (26%)	88 (23%)
	Positive	102 (73%)	160 (66%)	262 (69%)
	Untestable	1 (1%)	6 (2%)	7 (2%)
	Unknown	11 (8%) 1	14 (6%) 3	25 (7%) 4
Pupil reactivity	Neither pupil reactive	15 (11%)	51 (21%)	66 (17%)
	At least one reactive	115 (82%)	173 (71%)	288 (75%)
	Both untestable	0 ()	6 (2%)	6 (2%)
	Unknown	11 (8%)	15 (6%)	26 (7%)

IQR, interquartile range; SD, standard deviation.

Status and destination at discharge from any part of the neurosurgical unit

		Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	Total observed (*n* = 386)
Discharge destination from NSU	Died	21 (15%)	61 (25%)	82 (21%)
	Home	35 (25%)	51 (21%)	86 (22%)
	Rehabilitation	27 (19%)	58 (24%)	85 (22%)
	Different hospital	54 (39%)	64 (26%)	118 (31%)
	Nursing home	1 (1%)	6 (2%)	7 (2%)
	Other	1 (1%)	4 (2%)	5 (1%)
	Unknown	0	1 (–%)	1 (–%)
	Missing (still on ward at 12 months)	2		2
Patients discharged alive from NSU		**Observed craniotomy (*n* = 118)**	**Observed DC (*n* = 184)**	**Total observed (*n* = 302)**
GCS – motor (discharge from hospital)	M6	104 (89%)	117 (64%)	221 (74%)
	M5	4 (3%)	40 (22%)	44 (15%)
	M4	2 (2%)	7 (4%)	9 (3%)
	M3	0	9 (5%)	9 (3%)
	M2	1 (1%)	3 (2%)	4 (1%)
	M1	5 (4%)	4 (2%)	9 (3%)
	Unknown	1 (1%)	3 (2%)	4 (1%)
	Number missing	1	1	2
GCS – total score (discharge from hospital)	Scoring 3–8	2 (2%)	9 (6%)	11 (4%)
	Scoring 9–12	12 (11%)	27 (18%)	39 (15%)
	Scoring 13–15	93 (87%)	110 (75%)	203 (80%)
	Number untestable	9	35	44
	Number unknown	1	1	2
	Number missing	1	2	3

Procedure-related complications

Event	Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	Total observed (*n* = 386)
Number of patients with event	50 (35%)	64 (26%)	114 (30%)
Number of events	70	115	186
Average events per patient	0.50	0.47	0.48
Average events per patient with event	1.40	1.80	1.63

Event	Observed craniotomy (*n* = 141)	Observed DC (*n* = 245)	Total observed (*n* = 386)
Events as recorded in CRF			
External herniation of the brain	0	6	6
Expansion of mass lesion	2	8	10
Development of mass lesions	5	7	12
Intraoperative vascular injury	0	1	1
Stroke	6	6	12
Surgical site infections	3	15	18
Wound complications other than infections	8	10	18
Subdural hygromas	2	8	10
Subdural empyema	1	0	1
Intracerebral abscess	1	1	2
Meningitis	0	2	2
Seizures in epilepsy	17	10	27
Hydrocephalus	3	7	10
Other	22	34	56

EME
HSDR
HTA
PGfAR
PHR

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