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A randomised, double blind, placebo-controlled trial of a two-week course of dexamethasone for adult patients with a symptomatic Chronic Subdural Haematoma (Dex-CSDH trial)

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Primary conflicts of interest: Peter J Hutchinson was a member of the Health Technology Assessment (HTA) Programme Intellectual Property Panel (January 2016 to May 2018), and is currently a member of the HTA Prioritisation Committee B (in hospital). Antonio Belli reports being employed by and owning shares in Marker Diagnostics (Birmingham, UK). Elizabeth A Warburton is currently a member of the HTA Clinical Evaluation and Trials Committee (2019–present). Garry Barton was a member of the Norwich Clinical Trials Unit funded by the National Institute for Health and Care Research (NIHR) (until August 2021). Ian Wilkinson was a member of the Cambridge Clinical Trials Unit funded by NIHR (until August 2021). Simon Bond was a member of the Efficacy and Mechanism Evaluation Funding Committee (May 2015 to May 2019). Ellie Edlmann reports grants from Royal College of Surgeons and Rosetrees Trust Research Fellowship, during the conduct of the study. Carol Davis-Wilkie was funded as an employee of the Cambridge Clinical Trials Unit.

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Abstract

A randomised, double blind, placebo-controlled trial of a two-week course of dexamethasone for adult patients with a symptomatic Chronic Subdural Haematoma (Dex-CSDH trial)

Peter J Hutchinson,[1*] Ellie Edlmann,[1,2,3] John G Hanrahan,[1] Diederik Bulters,[4] Ardalan Zolnourian,[4] Patrick Holton,[4] Nigel Suttner,[5] Kevin Agyemang,[5] Simon Thomson,[6] Ian A Anderson,[6] Yahia Al-Tamimi,[7] Duncan Henderson,[7] Peter Whitfield,[3] Monica Gherle,[3] Paul M Brennan,[8] Annabel Allison,[9] Eric P Thelin,[1,10] Silvia Tarantino,[1] Beatrice Pantaleo,[9] Karen Caldwell,[1] Carol Davis-Wilkie,[9] Harry Mee,[1] Elizabeth A Warburton,[1] Garry Barton,[11] Aswin Chari,[12] Hani J Marcus,[13] Sarah Pyne,[11] Andrew T King,[14] Antonio Belli,[15] Phyo K Myint,[16] Ian Wilkinson,[9,17] Thomas Santarius,[1] Carole Turner,[1] Simon Bond[9] and Angelos G Kolias[1] on behalf of the British Neurosurgical Trainee Research Collaborative and Dex-CSDH Trial Collaborators[†]

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Background: Chronic subdural haematoma is a collection of 'old blood' and its breakdown products in the subdural space and predominantly affects older people. Surgical evacuation remains the mainstay in the management of symptomatic cases.

Objective: The Dex-CSDH (DEXamethasone in Chronic SubDural Haematoma) randomised trial investigated the clinical effectiveness and cost-effectiveness of dexamethasone in patients with a symptomatic chronic subdural haematoma.

Design: This was a parallel, superiority, multicentre, pragmatic, randomised controlled trial. Assigned treatment was administered in a double-blind fashion. Outcome assessors were also blinded to treatment allocation.

Setting: Neurosurgical units in the UK.

Participants: Eligible participants included adults (aged ≥ 18 years) admitted to a neurosurgical unit with a symptomatic chronic subdural haematoma confirmed on cranial imaging.

Interventions: Participants were randomly assigned in a 1 : 1 allocation to a 2-week tapering course of dexamethasone or placebo alongside standard care.

Main outcome measures: The primary outcome was the Modified Rankin Scale score at 6 months dichotomised to a favourable (score of 0–3) or an unfavourable (score of 4–6) outcome. Secondary outcomes included the Modified Rankin Scale score at discharge and 3 months; number of chronic subdural haematoma-related surgical interventions undertaken during the index and subsequent admissions; Barthel Index and EuroQol 5-Dimension 5-Level utility index score reported at discharge, 3 months and 6 months; Glasgow Coma Scale score reported at discharge and 6 months; mortality at 30 days and 6 months; length of stay; discharge destination; and adverse events. An economic evaluation was also undertaken, during which the net monetary benefit was estimated at a willingness-to-pay threshold of £20,000 per quality-adjusted life-year.

Results: A total of 748 patients were included after randomisation: 375 were assigned to dexamethasone and 373 were assigned to placebo. The mean age of the patients was 74 years and 94% underwent evacuation of their chronic subdural haematoma during the trial period. A total of 680 patients (91%) had 6-month primary outcome data available for analysis: 339 in the placebo arm and 341 in the dexamethasone arm. On a modified intention-to-treat analysis of the full study population, there was an absolute reduction in the proportion of favourable outcomes of 6.4% (95% confidence interval 11.4% to 1.4%; $p = 0.01$) in the dexamethasone arm compared with the control arm at 6 months. At 3 months, the between-group difference was also in favour of placebo (−8.2%, 95% confidence interval −13.3% to −3.1%). Serious adverse events occurred in 60 out of 375 (16.0%) in the dexamethasone arm and 24 out of 373 (6.4%) in the placebo arm. The net monetary benefit of dexamethasone compared with placebo was estimated to be −£97.19.

Conclusions: This trial reports a higher rate of unfavourable outcomes at 6 months, and a higher rate of serious adverse events, in the dexamethasone arm than in the placebo arm. Dexamethasone was also not estimated to be cost-effective. Therefore, dexamethasone cannot be recommended for the treatment of chronic subdural haematoma in this population group.

Future work and limitations: A total of 94% of individuals underwent surgery, meaning that this trial does not fully define the role of dexamethasone in conservatively managed haematomas, which is a potential area for future study.

Trial registration: This trial is registered as ISRCTN80782810.

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List of abbreviations

AE	adverse event
AESI	adverse event of special interest
BI	Barthel Index
CACE	complier-average causal effect
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
CONSORT	Consolidated Standard of Reporting Trials
CRF	case report form
CSDH	chronic subdural haematoma
CT	computerised tomography
DMEC	Data Monitoring and Ethics Committee
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
GCS	Glasgow Coma Scale
HCP	healthcare professional
HDU	high-dependency unit
HEAP	health economic analysis plan
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IMP	investigational medicinal product
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MRI	magnetic resonance imaging
mRS	Modified Rankin Scale
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMB	net monetary benefit
NSU	neurosurgical unit
OR	odds ratio
PPI	patient and public involvement
PSRQ	patient self-report questionnaire
PSS	Personal Social Services
PT	preferred term
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SA	sensitivity analysis
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOC	system organ class
TSC	Trial Steering Committee

Plain language summary

Chronic subdural haematoma is one of the most common conditions managed in adult neurosurgery and mainly affects older people. It is an 'old' collection of blood and blood breakdown products found on the surface of the brain. Surgery to drain the liquid collection is effective, with most patients improving. Given that inflammation is involved in the disease process, a commonly used steroid, dexamethasone, has been used alongside surgery or instead of surgery since the 1970s. However, there is no consensus or high-quality studies confirming the effectiveness of dexamethasone for the treatment of chronic subdural haematoma.

This study was designed to determine the effectiveness of adding dexamethasone to the normal treatment for patients with a symptomatic chronic subdural haematoma. The benefit of adding dexamethasone was measured using a disability score called the Modified Rankin Scale, which can be divided into favourable and unfavourable outcomes. This was assessed at 6 months after entry into the study.

In total, 748 adults with a symptomatic chronic subdural haematoma treated in neurosurgical units in the UK participated. Each participant had an equal chance of receiving either dexamethasone or a placebo because they were assigned randomly. Neither the patients nor the investigators knew who received dexamethasone and who received placebo.

Most patients in both groups had an operation to drain the haematoma and experienced significant functional improvement at 6 months compared with their initial admission to hospital. However, patients who received dexamethasone had a lower chance than patients who received placebo of favourable recovery at 6 months. Specifically, 84% of patients who received dexamethasone had recovered well at 6 months, compared with 90% of patients who received placebo. There were more complications in the group that received dexamethasone.

This trial demonstrates that adding dexamethasone to standard treatment reduced the chance of a favourable outcome compared with standard treatment alone. Therefore, this study does not support the use of dexamethasone in treating patients with a symptomatic chronic subdural haematoma.

Scientific summary

Background

Chronic subdural haematoma (CSDH) is a common neurological disorder predominantly affecting older people, affecting approximately 5000 people aged over 65 years in the UK each year. Its incidence is increasing owing to an ageing population, alongside the growing use of antithrombotic agents.

The majority of CSDHs do not cause symptoms and are managed conservatively. In those that do cause symptoms, surgical evacuation remains the mainstay of management, which achieves a good recovery in approximately 80% of patients. The remaining 10–20% of patients may suffer a recurrence, requiring further surgery.

Additional and alternative measures to surgery are sought to improve outcomes in this patient group. Inflammation has been implicated in the pathogenesis of CSDHs, which suggests a role for anti-inflammatory medications, such as steroids. Therefore, steroids may serve as a useful adjunct or even alternative to surgery. However, to date, there is a lack of high-quality evidence in the form of a randomised clinical trial or meta-analysis. This trial investigates the clinical effectiveness of a steroid, dexamethasone, in patients with symptomatic CSDH.

Objectives

Primary objective

The primary objective of the trial was to determine the clinical effectiveness of a 2-week course of dexamethasone for adult patients with a symptomatic CSDH, assessed by comparing the rate of favourable outcomes [defined as a Modified Rankin Scale (mRS) score of 0–3] at 6 months after randomisation between the treatment and the control arm. This outcome was reviewed centrally by a clinically trained investigator blinded to treatment allocation.

Secondary objectives

The secondary objectives were to compare the following outcomes between the treatment and the control arm of the trial:

- number of CSDH-related surgical interventions undertaken during the index admission
- number of CSDH-related surgical interventions undertaken during subsequent admissions in the follow-up period
- Glasgow Coma Scale (GCS) score at discharge from the neurosurgical unit (NSU) and at 6 months
- Modified Rankin Scale score at discharge from the NSU and at 3 months
- Barthel Index score at discharge from the NSU and at 3 and 6 months
- mortality (30 days and 6 months)
- EuroQol-5 Dimensions, five-level version (EQ-5D-5L), utility index at discharge from the NSU and at 3 and 6 months
- length of stay in the NSU
- discharge destination from the NSU
- length of stay in secondary care
- rates of adverse events (AEs).

An economic evaluation was also undertaken to estimate the cost-effectiveness of dexamethasone compared with placebo.

Tertiary objectives

Postoperative recurrence is a tertiary outcome measure and is defined as a symptomatic recurrence requiring reoperation of a previously evacuated ipsilateral CSDH.

Methods

Trial design

The Dex-CSDH (DEXamethasone in Chronic SubDural Haematoma) trial is a multicentre, pragmatic, clinical phase III, randomised, double-blind, placebo-controlled trial of a tapering 2-week course of dexamethasone in patients with a symptomatic CSDH. The pragmatic design meant that the trial ran in parallel with standard clinical care, with the only difference being the addition of the trial drug (dexamethasone) or placebo.

Intervention

Two-week tapering course of dexamethasone (with matching placebo as the control).

Participants

Participants were screened for eligibility from 23 NSUs across the UK, with the admitting neurosurgical team determining eligibility for participation. Participants were adult patients aged ≥ 18 years with a symptomatic CSDH confirmed on cranial imaging (computerised tomography or magnetic resonance imaging of the brain). The patient or their legal representative had to provide informed consent. In the absence of a legal representative, an independent healthcare professional provided authorisation for enrolment.

Patients were excluded in the presence of any of the following criteria:

- presence of a condition for which steroids are clearly contraindicated
- patients who are (or within 1 month of) receiving regular oral or intravenous glucocorticoid steroids (this did not include inhaled or topical steroids, nor did it include those receiving a single intraoperative dose of dexamethasone for anti-emesis)
- previous enrolment in this trial for a prior episode
- time interval from time of admission to the NSU to first dose of trial medication exceeded 72 hours
- chronic subdural haematoma in the presence of a cerebrospinal fluid shunt
- severe lactose intolerance or a known hypersensitivity to dexamethasone or other excipients
- a history of psychotic disorders
- unwillingness to take products containing gelatine.

Patients who were screened but not included in the study were recorded on a screening log and reported centrally, with both the number of failures and the reasons for failure to recruit to the trial documented.

Trial procedures

Patients were managed in NSUs in accordance with standard practice. In the UK, this typically includes burr hole evacuation with the use of a subdural drain for most symptomatic patients. The decision for surgery or active monitoring was made on an individual patient basis by the blinded admitting clinical team in conjunction with the patient, in keeping with the pragmatic nature of the trial. Enrolment in the trial took place irrespective of the decision to operate and the timing of surgical intervention.

Patients were randomised in 1 : 1 allocation using a computer-generated randomisation schedule, stratified by site using permuted blocks of random sizes (two or four). An interactive web-based response system was used to allocate treatment packs of 62 overencapsulated 2-mg dexamethasone tablets or 62 identical placebo capsules.

The enrolled participants, clinical and research team and outcome assessors were blinded to the treatment allocation. The assigned treatment was administered as part of the routine drug round by the ward nurses. Oral administration was the preferred option, but administration via a nasogastric tube was offered to those unable to swallow. The latter method required opening of the capsules for crushing of the contents, allowing potential unblinding of the ward nurse. Therefore, the content of any opened capsules was not documented in the patient notes to maintain the blinding of the neurosurgeons and research staff. Trial drug compliance was recorded through inpatient drug charts during admission or by completion of a medication diary.

Data were collected at baseline (on admission to the neurosurgical department) as part of routine standard of care, on discharge from the acute NSU, at 30 days, at 3 months and at 6 months. Patients were monitored in line with routine clinical practice until discharge, and at 3 and 6 months, to score clinical outcomes.

Sample size

This sample size was calculated with the following assumptions: a favourable outcome rate of 80–85% in the control arm and allowing for up to 15% loss to follow-up. A target sample size of 750 patients was needed to detect an increase in favourable outcome rate from 80–85% to 88–93%, with a power of 81–92% at the 5% significance level (two sided). An 8% increase in the rate of favourable outcome (mRS score of 0–3) at 6 months represents a clinically important treatment effect.

Statistical analysis

Data were analysed in accordance with the prespecified statistical analysis plan that was agreed prior to unblinding of data. Outcome data were analysed using a modified intention-to-treat analysis (all patients were included as randomised, except for those who withdrew consent for participation in the trial and those lost to follow-up).

The primary outcome (mRS score at 6 months) was dichotomised into favourable (0–3) or unfavourable (4–6) outcomes. Primary analysis estimated the absolute difference between the intervention arm and the control arm in the proportions achieving a favourable outcome. A normal approximation was used to produce 95% confidence intervals (CIs) and a two-sided *p*-value testing the null hypothesis of no difference.

Secondary analysis included a logistic regression and proportional odds logistic regression of the original mRS score adjusting for baseline covariates of age and Glasgow Coma Scale (GCS) score.

Economic evaluation

In the base-case analysis, costs were estimated over the 6-month trial period from an NHS and a Personal Social Services perspective. Outcomes were quality-adjusted life-years (QALYs) derived from the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), at NSU discharge and at the 3- and 6-month follow-ups. Analyses were undertaken to estimate the mean incremental cost and effect, and enable the net monetary benefit (NMB) (a negative score indicates that the intervention is not estimated to be cost-effective) to be calculated, along with the cost-effectiveness acceptability curve (CEAC) (probability that dexamethasone was cost-effective). NMB and CEAC values at a willingness-to-pay threshold of £20,000 per QALY are reported.

Results

Primary outcome

An outcome of mRS score of 0–3 occurred in 286 out of 341 patients (83.9%) in the dexamethasone arm and 306 out of 339 patients (90.3%) in the placebo arm at 6 months (difference −6.4%, 95% CI −11.4% to −1.4%; $p = 0.01$).

After adjustment for prespecified covariates (age > 70 years and GCS score on admission), the odds ratio (OR) of a favourable outcome with dexamethasone was 0.55 (95% CI 0.33 to 0.91; $p = 0.022$), favouring placebo.

Secondary outcomes

Modified Rankin Scale at discharge and 3 months

At 3 months, 268 out of 322 patients (83.2%) in the dexamethasone arm and 298 out of 326 patients (91.4%) in the placebo arm had a favourable outcome, for a between-group difference of −8.2% (95% CI −13.3% to −3.1%) in favour of the placebo arm.

There was no significant difference in mRS score between the two arms at discharge [255/318 (80.2%) in the dexamethasone arm and 263/316 (83.2%) in the placebo arm for a difference of −3.0% (95% CI −9.1% to 3.0%)].

Mortality

At discharge, 8 out of 375 patients (2.1%) in the dexamethasone arm and 2 out of 373 patients (0.5%) in the placebo arm had died (OR 4.08, 95% CI 1.01 to 27.2). At 6 months, 30 out of 341 patients (8.8%) in the dexamethasone arm and 17 out of 339 patients (5.0%) in the placebo arm had died (OR 1.83, 95% CI 0.99 to 3.45).

Number of chronic subdural haematoma-related surgical interventions undertaken

The number of surgical interventions undertaken during the index admission or during subsequent admissions during the follow-up period was similar in both arms. However, in the subset of patients who received surgery, repeat surgery for recurrence of the CSDH was performed in 6 out of 349 patients (1.7%) in the dexamethasone arm and in 25 out of 350 patients (7.1%) in the placebo arm.

EuroQol-5 Dimensions, five-level version, utility index (at discharge and at 3 and 6 months)

The mean EQ-5D-5L, utility index scores were compared. At discharge, the difference was −0.03 (95% CI −0.07 to 0.01), favouring placebo. At 3 months, the difference was −0.07 (95% CI −0.12 to −0.02), favouring placebo. At 6 months, the difference was −0.03 (95% CI −0.09 to 0.02), favouring placebo.

Glasgow Coma Scale (at discharge and at 6 months)

Glasgow Coma Scale was grouped into scores of 9–12 and 13–15. The percentage of patients with a score of 13–15 was similar at discharge (99.7% in the placebo arm vs. 99.2% in the dexamethasone arm). Insufficient data at 6 months prevented analysis.

Barthel Index (at discharge and at 3 and 6 months)

No significant difference was seen between the placebo arm and the dexamethasone arm at discharge, 3 months or 6 months.

Length of stay in the neurosurgical unit

The mean length of stay was 9.03 days in the placebo arm and 9.32 days in the dexamethasone arm.

Length of stay in secondary care

The mean length of stay was 13.0 days in the dexamethasone arm and 13.7 days in the placebo arm, with no significant difference between the two arms (0.95, 95% CI 0.835 to 1.09; $p = 0.467$).

Discharge destination from the neurosurgical unit

No significant difference was observed between the placebo arm and the dexamethasone arm when comparing discharge destinations.

Rates of adverse events

The odds of an adverse event of special interest were greater in the dexamethasone arm than in the placebo arm (OR 3.40, 95% CI 1.81 to 6.85). Similarly, the odds of a serious adverse event occurring were greater in the dexamethasone arm than in the placebo arm (OR 2.49, 95% CI 1.54 to 4.15).

Economic evaluation

The mean incremental cost for dexamethasone was estimated to be −£143.73 (95% CI −£1793 to £1505), with a QALY of −0.012 (95% CI −0.027 to 0.003), compared with placebo. The associated NMB of dexamethasone compared with placebo was −£97.19, with an estimated 46% probability of being cost-effective.

Conclusions

Implications for healthcare

Dexamethasone for the treatment of symptomatic CSDH resulted in a lower proportion of favourable outcomes, as measured with the mRS, and a larger number of AEs than placebo. This treatment regime was also not estimated to be cost-effective (based on the NMB). Therefore, dexamethasone is not recommended in the treatment of CSDH.

Implications for research

The results of our literature review indicate that this study is the first multicentre randomised controlled trial to investigate the clinical effectiveness and cost-effectiveness of dexamethasone in the management of symptomatic CSDH. It provides evidence to inform the role of dexamethasone in this condition.

Trial registration

This trial is registered as ISRCTN80782810.

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Chapter 1 Introduction

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Parts of this chapter have been reproduced from Hutchinson *et al.*[3]

Background

Chronic subdural haematoma (CSDH) is an 'old' collection of blood and blood breakdown products in the subdural space. It is radiologically defined as a predominantly hypodense or isodense collection in the subdural space along the cerebral convexity on computerised tomography (CT).[1] It is especially common in older patients and in the UK: 5000 people aged > 65 years are diagnosed with a CSDH each year. It can happen following even a minor injury to the head or in the absence of a known trauma.

The incidence of CSDH is increasing[4] and is projected to rise further, matching the ageing global population.[5] Therefore, surgical evacuation of CSDH is projected to become the most common cranial neurosurgical operation in the USA by 2030.[6] Although many patients remain asymptomatic, some patients experience symptoms such as headache, gait disturbance, falls, cognitive decline, focal neurological deficit, speech disturbance, decreased consciousness and seizures.

Current practice

Surgery remains the mainstay of managing symptomatic CSDH, typically through evacuation by burr holes or mini-craniotomy.[1] Additional measures, such as correction of coagulopathy or thrombopathy and subdural drains postoperatively, are established in treating CSDH.[1,7]

However, other aspects of CSDH management remain controversial owing to the lack of level 1 evidence to inform their role,[8] such as adjuvant medications (antiepileptic drugs or steroids) and postoperative care protocols.[1] Determining the clinical effectiveness of adjuncts to surgical evacuation is essential, particularly in the light of the considerable morbidity and mortality associated with cranial surgery in an ageing population.

Rationale

It is postulated that following a traumatic injury to the head an inflammatory reaction drives the growth of abnormal blood vessels and fluid accumulation over the surface of the brain. Several studies have demonstrated locally elevated cytokine levels in the subdural fluid of patients with CSDH,[9–13] suggesting a role of inflammation in CSDH pathophysiology.

Therefore, anti-inflammatory agents, such as steroids, may counter this inflammatory response, with evidence suggesting potential to reduce CSDH recurrence and even the rate of primary surgical intervention.[10–12] This, in turn, might be expected to reduce mortality and morbidity, and improve long-term functional outcomes in patients with CSDH. Non-randomised studies have pursued this hypothesis, with promising observational data supporting the use of dexamethasone in treating symptomatic CSDH.[14–16] A single Phase II randomised controlled trial (RCT), published in 2015, 9 years

after it was completed, suggested a benefit of combining steroids with surgical evacuation, with a trend towards a lower recurrence rate.[17] However, there was a high risk of bias in the pilot study. Higher-quality evidence through a larger, definitive RCT was, therefore, necessary to determine the clinical effectiveness of dexamethasone in CSDH.[18]

Dexamethasone is one of the most potent synthetic analogues of the naturally occurring glucocorticoid hydrocortisone and has practically no water- and salt-retaining properties, so it is suitable for use in patients with cardiac failure or hypertension.[19] The earliest application of steroids in neurosurgery was for patients with brain tumours and surrounding oedema, for whom 4 mg four times per day was established as the dose with maximum effect.[20] This dosing, with subsequent gradual weaning, continues to be used in neuro-oncology, and a 2-week course of dexamethasone was considered likely to provide the best balance in terms of clinical efficacy and risks in this study.[21] Median time to recurrence after surgical evacuation of CSDH has been shown to be 12–15 days,[7,8] and longer courses of corticosteroids have greater risks of side effects.[22] The dose and duration are also reflective of other studies in the field.[23]

Risks and benefits

The potential impact of this trial is significant because the results will determine whether or not steroids should be prescribed routinely for patients with symptomatic CSDH. If steroids are found to be effective, an impact on the speed of recovery and functional outcome of patients is expected. In addition, this could reduce the rate of surgical interventions required, reduce length of hospital stay, influence discharge destination and reduce adverse events (AEs). In addition to the impact on clinical outcome, there are health economic considerations that will be addressed by the trial.

Steroids are commonly used to treat neurosurgical conditions and are generally well tolerated. However, side effects have been observed in patients with CSDH, including hyperglycaemia, infections, mental disturbance and mortality.[18] Therefore, the clinical effectiveness of steroids must be elucidated to determine their role in CSDH management.

The Dex-CSDH (DEXamethasone in Chronic SubDural Haematoma) trial is a multicentre, pragmatic, clinical phase III, randomised, double-blind, placebo-controlled trial of dexamethasone for up to 2 weeks in patients diagnosed with CSDH.

Objectives

Primary objective

The primary objective was to determine the clinical effectiveness of a 2-week tapering course of dexamethasone for adult patients with a symptomatic CSDH by detecting an 8% absolute difference in the rate of favourable outcome at 6 months between the two arms.

Secondary objectives

The secondary objectives were to compare the following outcomes between the treatment arm and the control arm of the trial:

- number of CSDH-related surgical interventions undertaken during the index admission
- number of CSDH-related surgical interventions undertaken during subsequent admissions in the follow-up period
- Glasgow Coma Scale (GCS)[24] at discharge from the neurosurgical unit (NSU) and at 6 months
- Modified Rankin Scale (mRS)[25] score at discharge from the NSU and at 3 months
- Barthel Index (BI)[26] score at discharge from the NSU and at 3 and 6 months
- mortality (30 days and 6 months)
- EuroQol-5 Dimensions, five-level version (EQ-5D-5L),[27] utility index at discharge from the NSU and at 3 and 6 months

- length of stay in the NSU
- discharge destination from the NSU
- length of stay in secondary care
- rates of AEs.

Postoperative recurrence is a tertiary outcome measure and is defined as a symptomatic recurrence requiring reoperation of a previously evacuated ipsilateral CSDH.

To estimate the cost-effectiveness of dexamethasone, compared with placebo, an economic evaluation was also undertaken (see *Chapter 4*).

Chapter 2 Trial design and methods

Parts of this chapter have been reproduced from Kolias *et al.*[1]

Parts of this chapter have been reproduced from Hutchinson *et al.*[3]

Trial design

This was a pragmatic, multicentre, parallel-group, double-blind, Phase III, randomised (1 : 1 randomisation stratified by site), superiority, placebo-controlled trial.

Ethics approval and research governance

Ethics approval in the UK was obtained from the North-West Haydock Research and Ethics Committee (reference 15/NW/0171) in 2015.

The trial protocol was designed collaboratively with input from neurosurgeons, neurologists, stroke physicians and care of the elderly physicians from multiple hospitals and universities in the UK. The Cambridge Clinical Trials Unit led the methodological design.

The protocol has been published previously.[2] *Appendix 2* outlines the protocol amendments.

Participants

Patients were eligible if they were aged ≥ 18 years, had a symptomatic CSDH confirmed on cranial imaging [e.g. CT/magnetic resonance imaging (MRI) – predominantly hypodense or isodense crescentic collection along the cerebral convexity on CT] and were willing (or had a willing legal representative) and able to provide informed consent. In the absence of a legal representative, an independent healthcare professional (HCP) provided authorisation for patient enrolment.

Exclusion criteria were:

- patients with conditions for which steroids were clearly contraindicated
- patients who were on (or within 1 month of) regular oral or intravenous glucocorticosteroids (patients on topical or inhaled steroids were allowed to be recruited into the trial, as were patients who had one intraoperative dose of dexamethasone for anti-emesis)
- previous enrolment in the trial for a prior episode
- the time interval from the time of admission to NSU to first dose of trial medication exceeded 72 hours
- CSDH in the presence of a cerebrospinal fluid shunt

- severe lactose intolerance or any known hypersensitivity to dexamethasone or any of the investigational medicinal product (IMP) excipients
- patients with a previous history of psychotic disorders
- unwillingness to take products containing gelatine
- concurrent enrolment in any other trial of an IMP.

Patients were reviewed for eligibility on admission to the NSU by the admitting team. The trial was run in parallel with standard clinical care and, therefore, the need for surgical intervention for the CSDH was determined by the clinical team and did not affect eligibility for trial involvement.

A Consolidated Standards of Reporting Trials (CONSORT) diagram was produced to show patient disposition (*Figure 1*).

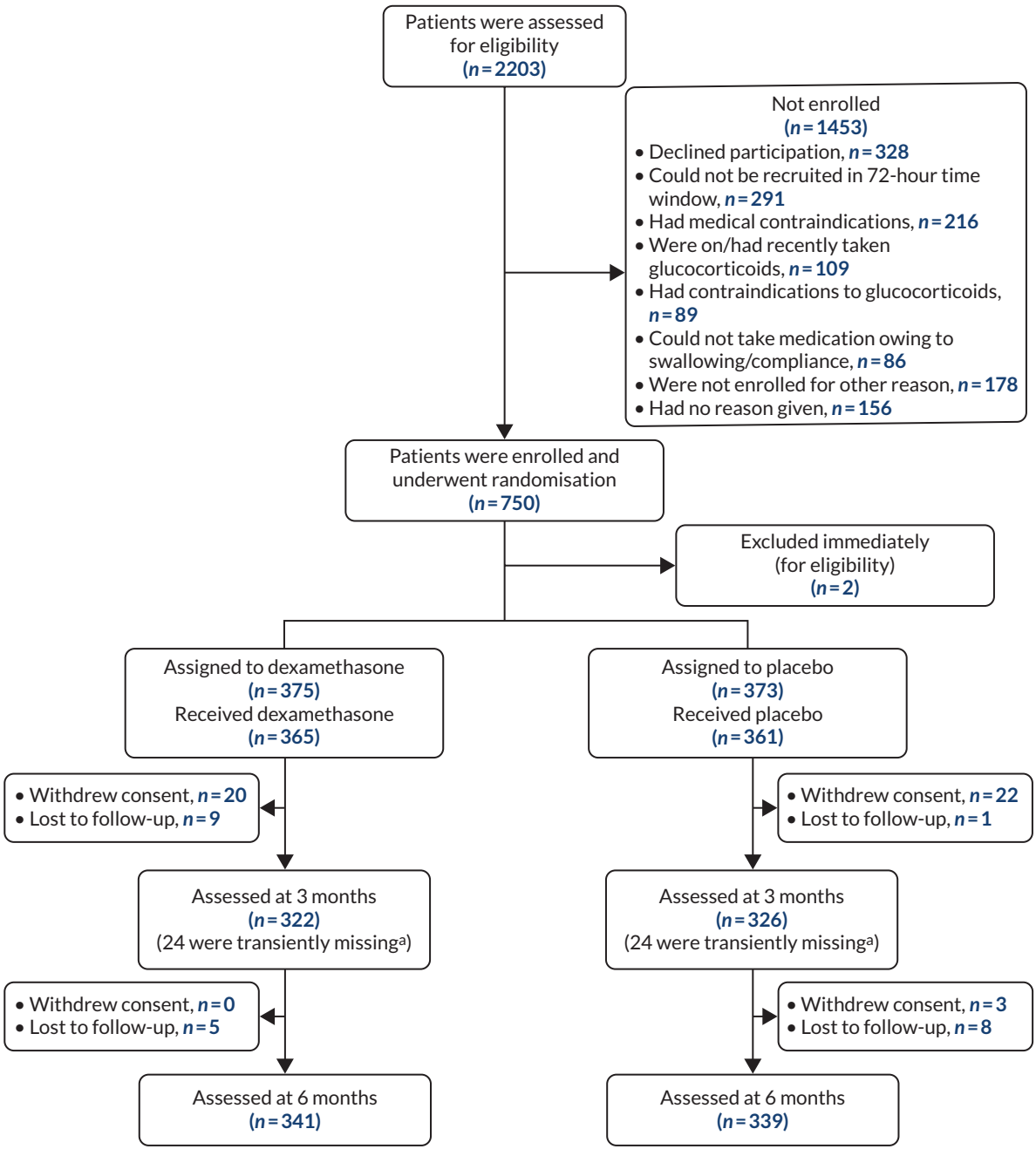

FIGURE 1 The CONSORT flow diagram. a, Transiently missing refers to patients whose follow-up data were missing at 3 months but available at 6 months.

Study setting

This multicentre study took place from August 2015 to November 2018 in 23 NSUs providing 24-hour acute care in the UK NHS from.

Interventions

Participants received the allocated treatment after randomisation as part of the routine drug rounds by ward nurses once admitted to the NSU. The allocated treatment was a 2-week tapering course of either dexamethasone (overencapsulated 2-mg tablets) or matched placebo (visually indistinguishable from the active treatment and containing inactive excipients only). The excipients used for backfilling the dexamethasone capsules were the same as those used to fill the placebo capsules and were standard tableting excipients.

Dosing schedule

The dosing schedule was as follows:

- four capsules in the morning and four at lunchtime for days 1, 2 and 3
- three capsules in the morning and three at lunchtime for days 4, 5 and 6
- two capsules in the morning and two at lunchtime for days 7, 8 and 9
- one capsule in the morning and one at lunchtime for days 10, 11 and 12
- one capsule once daily for days 13 and 14
- end of allocated treatment.

The maximum duration of treatment was 14 days. This regime was felt to provide the best balance in terms of clinical effectiveness and risks.[21]

A missed medication could be taken later, provided that it was taken on the same day and the patient was not nil by mouth for surgery. In the event of missing a dose of medication, doses could be taken when remembered, but only up to the time of the next planned dose on the same day.

Administration and maximum dosage allowed

The drug was administered orally or via nasogastric tube, as required. The maximum dose allowed in a single day was 16 mg (8 mg twice daily for days 1, 2 and 3). The preferred time of administration of once-daily doses (days 13 and 14) was in the morning.

For nasogastric administration, blinded capsules were opened at the point of administration by ward nursing staff. The contents were then dispersed in water to allow administration. This method was also used orally in patients with swallowing difficulties.

All patients completed the 14-day course of trial medication. If discharged or transferred to another hospital, letters were provided to the pharmacy and medical teams at the local hospital alongside any remaining medications. However, if a patient receiving the trial medication via the nasogastric route was transferred or discharged, the medication was stopped at transfer/discharge. Further details on the interventions can be found in the published protocol.[2]

Outcomes

Primary outcome measure

The prespecified primary outcome measure was the mRS score at 6 months after randomisation, which was dichotomised into favourable (score of 0–3) versus unfavourable (score of 4–6).[25] This has

previously been employed as an outcome measure in CSDH studies.[28] Questionnaires were distributed to patients via post and were collected by the central trial co-ordination team. If after 2 weeks the questionnaire was not returned, patients were followed up by telephone, an equally reliable method of data collection.[25] The mRS scores were calculated by a blinded, clinically trained investigator using a standard algorithm.

Secondary outcome measures

Secondary outcomes were (as detailed in protocol[2]):

- number of CSDH-related surgical interventions undertaken during the index admission
- number of CSDH-related surgical interventions undertaken during subsequent admissions in the follow-up period
- GCS score at discharge from NSU and at 6 months
- mRS score at discharge from NSU and at 3 months
- BI score at discharge from a NSU and at 3 and 6 months
- mortality at 30 days and at 6 months
- EQ-5D-5L[29] at discharge from NSU and at 3 and 6 months
- length of stay in NSU
- discharge destination from NSU
- length of stay in secondary care
- AEs.

Recurrence, defined as a symptomatic recurrence requiring reoperation of a previously evacuated ipsilateral CSDH during the study period, was a tertiary outcome measure applying to surgically treated patients only.

Data collection

Patient questionnaires (mRS, BI and EQ-5D-5L) were collected by the local site research team at discharge and the central trial co-ordination team at 3 and 6 months. GCS score was collected by the local site research team. The length of stay in a NSU was a derived variable calculated as:

$$\sum \left[(\text{date of discharge of death}) - (\text{date of admission to NSU}) + 1\right], \tag{1}$$

where the summation was taken over all admissions. Length of stay in secondary care was also a derived variable calculated as the length of stay in NSU plus the self-reported length of stay in hospital or healthcare facility based on the 6-month health service questionnaire.

The EQ-5D-5L questionnaire is a self-report measure consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).[27] The responses were converted into a utility score (where 0 is death and 1 is full health) using the cross-walk algorithm,[30] in accordance with the National Institute for Health and Care Excellence (NICE) position statement.[31] Participants who died during the study were given a score of zero.

Recurrence was defined as a symptomatic recurrence requiring reoperation of a previously evacuated ipsilateral CSDH during the study period.[32]

Trial assessments

Table 1 presents a full list and timeline of trial assessments. Participants were followed up for 6 months after randomisation.

TABLE 1 Summary of trial assessments

Trial assessment	Prior to randomisation (< 72 hours from admission)	Randomisation (preferable, but not essential for this to occur before surgery)	Day 1 of trial drug (< 72 hours from admission)	Days 2–14 of trial drug	Day 15 (± 1 week)	Day 30 (± 1 week)	Discharge from NSU or at death (± 1 week)	3-month follow-up (± 4–8 weeks)	6-month follow-up (± 4–8 weeks)
Eligibility assessment	✗								
Informed consent	✗						✗		If attends OPA
Randomisation		✗							
Part 1 of CRF sent to co-ordinating centre		✗							
IMP administration			✗	✗					
Review of AEs		✗	✗	✗	✗	✗	✗		
Review of concomitant medication			✗	✗					
Telephone call to assess medication diary					✗				
Completed CRF faxed to trial co-ordinating centre							✗		
Review of routine lab results	✗		✗	✗			✗		
GCS							✗		If attends OPA
mRS							✗	✗	✗
Mortality						✗			✗
EQ-5D-5L							✗	✗	✗
BI							✗	✗	✗
Health service questionnaire									✗

CRF, case report form; OPA, outpatient appointment.

Sample size

Using a two-sided test at the 5% significance level and assuming a favourable outcome rate of 80–85% in the control arm,[14] a sample size of 750 patients (allowing for a 15% loss to follow-up) would have a power of 80–92% to detect an 8% absolute difference in the rate of favourable outcome. An 8% increase in the rate of favourable outcome at 6 months (mRS score of 0–3) was determined to be a plausible and clinically important treatment effect based on the opinion and experiences of the clinicians from multiple specialties involved in the design of the study.

Interim analysis

A pre-planned blinded interim analysis of pooled outcome data was performed after 450 patients had completed 6 months of follow-up to decide if the sample size needed to be adjusted. The possible alternatives after the interim analysis were to increase the sample size (with a maximum of 1000 patients) or to stop the trial for futility if the revised sample size was more than 1000 patients. Because the trial could be stopped only for futility, we did not adjust the confidence interval (CI) and *p*-value at the end of the trial to account for the interim analysis. The independent Data Monitoring and Ethics Committee (DMEC) recommended that recruitment should continue to the original target sample size of 750 patients.

Trial stopping criteria and end point

No specific criteria were defined for premature discontinuation of the trial. However, both patient safety and efficacy data were under review by the independent DMEC and Trial Steering Committee (TSC) to make recommendations on discontinuation at regular intervals throughout the study. The trial end date was defined as the date of the last expected 6-month follow-up questionnaire completed for the final patient recruited into the trial.

Randomisation

All patients admitted to the NSU with a confirmed CSDH were screened for eligibility, which was assessed by a member of the admitting neurosurgical team. Randomisation took place either before or after initial index surgery.

Patients were randomly assigned to either the dexamethasone or the placebo arm in a 1 : 1 allocation, as per a computer-generated randomisation schedule stratified by NSU using permuted blocks of random sizes (two or four). An interactive web-based response system was used to allocate treatment packs to individual patients once the inclusion criteria being met had been confirmed.

Blinding

Capsules and packaging for the dexamethasone arm and the placebo arm were identical in appearance at the point of issue to patients.

It was estimated that < 10% of eligible patients would have (or develop during the trial) swallowing difficulties making oral IMP administration difficult or impossible/unsafe. To ensure that the trial could proceed in as representative a population as possible, a pragmatic and cost-effective approach to dosing IMP was proposed. The strategy for managing IMP administration in patients with swallowing difficulties was developed after discussion with and advice from the Medicines and Healthcare products

Regulatory Agency. The blinded capsules were, with investigator and local pharmacy approval, opened at the point of administration via either the oral route or the nasogastric tube if one had been inserted during the routine course of care. If this scenario occurred, the administering nurse, NHS site pharmacy and, potentially, the trial patient would no longer be blinded because the active dexamethasone was in overencapsulated tablet form, and may have required crushing before dispersal in 15–20 ml of water for nasogastric administration, while the placebo was in powder form. To maintain blinding of the neurosurgeons, the presence of tablets inside the opened capsule was not documented in the medical notes but referred to in generic terms. Although every effort was made to maintain blinding when nasogastric administration was used, if the patient discovered their treatment they were asked not to disclose the information to any of the other medical personnel they interacted with. The research staff and outcome assessors remained blinded.

There were also clinical aspects that could potentially have unblinded trial team members to the treatments allocated. Patients receiving dexamethasone were more likely to have higher blood glucose levels than those receiving placebo. This may have provided an indication, although not proof, that a patient was in the dexamethasone arm. The concealment of glucose measurements was difficult because it may have required clinical action. However, any decision about surgery was made based on the severity of symptoms and/or progression of symptoms, so this was highly unlikely to influence treatment decisions.

The trial statistician performing the analysis was blinded to treatment allocation until version 2.0 of the statistical analysis plan (SAP) had been approved and the database hard locked. Unblinding of the interim DMEC reports, including the interim analysis, was performed by a statistician independent of the trial.

Statistical analysis

Full details of the statistical analyses can be found in the published SAP.[32]

Analysis populations

The assignment of participants to analysis populations was undertaken prior to breaking the blinding. The following analysis populations were defined.

Full analysis population

The full analysis population included all participants apart from those who withdrew consent for participation in the trial and those lost to follow-up. Participants were analysed as randomised using a modified intention-to-treat analysis.

Per-protocol population

Separate per-protocol populations were defined for each assessment time point (discharge, 3 months and 6 months). Participants were included if they satisfied the following conditions:

- were eligible to take part in the study
- took at least 80% of their medication (50 tablets) based on the daily medication compliance table – if missing, percentage of medication taken was based on remaining pill count
- completed their assessments within the prespecified time windows (± 1 week for discharge, −4/+ 8 weeks for 3 and 6 months).

Participants in the placebo arm were excluded if they received > 8 mg of dexamethasone during the IMP course. This was based on information on the concomitant medications form and the non-compliance log, and was determined on a per-patient basis by members of the Trial Management Group.

The third criterion (completing assessments within a given time window) applied only to questionnaire outcomes (mRS, GCS, BI and EQ-5D-5L); therefore, a fourth per-protocol population excluding this criterion from the definition was used to analyse non-questionnaire outcomes (surgery outcomes, mortality and discharge information).

Safety population

All randomised participants.

Missing data

The sample sizes of non-missing values were reported for summary tables, with the percentage of missing outcome data shown for the primary and secondary outcomes. The prespecified SAP assumed that any missing data were missing at random and, therefore, missing data were not imputed. Sensitivity analysis (SA) was planned in the event that > 15% of data were missing for the primary outcome. Given that < 15% of data were missing, the primary analysis was based on complete cases.

Patients who died during the study were given a score of '6 – Dead' for all mRS assessments occurring after the date of death (based on the upper time window limit for the assessment) and a score of zero for the EQ-5D-5L utility index. This is in accordance with established practices and user guides for both scores. Management of missing data is explained in *Appendix 4*.

Summary of study data

Summary statistics were produced for demographics and baseline variables; concurrent illnesses and medical conditions; prior and concurrent medications; treatment compliance; and the primary and secondary outcomes. Continuous variables were summarised using the following descriptive statistics: *n* (non-missing sample size), mean, standard deviation (SD), median, maximum and minimum. For categorical measures, frequency and percentages (based on the non-missing sample size) of observed levels were reported.

Primary analysis

The primary end point was the proportion of favourable outcomes (mRS score of 0–3 at 6 months) in the two treatment arms. The primary analysis estimated the absolute difference in the proportions achieving a favourable outcome between the two treatment arms. A simple normal approximation (*z*-test) was used to produce a 95% CI and two-sided *p*-value testing the null hypothesis that there was no difference in the primary outcome between the two treatment arms. As there was only one primary outcome, no adjustment for multiple testing was required. The analysis was repeated for both the full analysis and the per-protocol populations.

Secondary analyses

All secondary analyses (with the exception of the listing and bar chart of deaths) were performed on both the full analysis and the per-protocol populations.

Surgery

Poisson regression was used to model the effect of treatment (dexamethasone vs. placebo) on the following surgery outcomes:

- number of CSDH-related surgical interventions undertaken during the index admission
- number of CSDH-related surgical interventions undertaken during subsequent admissions in the follow-up period.

The former was defined in two ways:

- including pre-randomisation surgical procedures (which occurred within 72 hours prior to randomisation)
- excluding pre-randomisation surgical procedures.

The latter was also modelled in two ways:

- including only patients who had a subsequent admission
- including all patients – those without a subsequent admission were given a value of zero for number of surgeries.

The treatment effect, 95% CI and *p*-value were produced for each fitted model.

Questionnaires

The mRS outcomes (original score at discharge from NSU and 3 months) were analysed using proportional odds logistic regression. The following statistics were reported: cumulative probabilities for the placebo arm at each cut-off point of the mRS; global odds ratio (OR) together with the 95% CI and *p*-value; frequency and percentage of patients with a mRS score less than or equal to each cut-off point for both the dexamethasone arm and the placebo arm; and the marginal OR (95% CI) at each cut-off point.

A stacked bar chart showing the mRS outcomes by treatment arm and assessment time points (pre morbid, admission to NSU, discharge from NSU, 3 months and 6 months) was produced both including and excluding missing data.

Although a proportional odds logistic regression was originally planned, no model fitting was performed on the GCS outcomes (measured at discharge and 6 months). At discharge, this was because the majority of participants received a score of 15, and at 6 months this was due to the lack of data.

Linear regression was used to model the effect of treatment (dexamethasone vs. placebo) on the BI total score and the EQ-5D-5L utility index (both measured at discharge from NSU and at 3 and 6 months). The treatment effect, standard error, 95% CI and *p*-value were produced for each fitted model. As a secondary analysis, non-parametric Mann–Whitney *U*-tests (*p*-value reported) were also performed on the BI outcomes owing to the skewed nature of the data.

No adjustments for baseline covariates were made.

Mortality

The effect of treatment (dexamethasone vs. placebo) on the binary outcome death (yes/no) at 30 days and at 6 months was modelled using logistic regression, and the OR, 95% CI and *p*-value were produced.

A listing of deaths, including information on site, treatment arm, gender, age and time in the trial, and a bar chart showing the number of deaths by key time points (≤ 14 days, 15–30 days, 31–90 days and ≥ 90 days) were also produced using the full analysis population.

Discharge information

Negative binomial regression was used to model the effect of treatment (dexamethasone vs. placebo) on the length of stay in NSU and length of stay in secondary care. The rate ratio, 95% CI and *p*-value were reported.

Logistic regression was used to model the effect of treatment on discharge destination from NSU, with the OR, 95% CI and *p*-value reported. Two separate regression models were fitted for the following outcome categories: home versus other and local hospital versus other (excluding home). This was due to the spread of data in the different discharge destination categories.

Ancillary analyses

A number of additional analyses were performed on the primary outcome.

Model fitting

A logistic regression model adjusted for the baseline covariates, age and GCS on admission, was fitted to the primary outcome, and the OR for the treatment effect (dexamethasone vs. placebo), 95% CI and *p*-value were reported.

A proportional odds logistic regression model adjusted for age and GCS on admission was fitted to the ordinal mRS at 6 months and the following output: cumulative probabilities for the placebo arm at each cut-off point of the mRS; global OR together with the 95% CI and *p*-value; frequency and percentage of patients with a mRS score less than or equal to each cut-off point for both the dexamethasone arm and the placebo arm; and the marginal OR (95% CI) at each cut-off point.

Both models were fitted using the full analysis and per-protocol populations.

Mediation

A mediation analysis to investigate the direct effect of treatment on the primary outcome and the indirect effect of treatment via the mediator variable recurrent CSDH was performed by estimating the causal parameters using parametric regression models for the mediator and outcome. The assumption of no unmeasured confounders was made. A plot showing the direct, indirect and total effects (given as an increase in the probability of having a favourable outcome) was produced. The analysis was performed using both the full analysis and the per-protocol populations.

Compliance

The effect of treatment compliance on the primary outcome was explored in three ways. First, a logistic regression model was fitted to test for the interaction between treatment and the percentage of medication taken. The ORs, 95% CIs and *p*-values were produced for both the main and the interaction effects.

Second, a complier-average causal effect (CACE) analysis was performed.[33] The CACE was calculated for different cut-off points of compliance (> 50%, > 60%, > 70%, > 80%, > 90% and 100% of medication taken). A plot showing the CACE and 95% CI at each cut-off point was produced.

Finally, an instrumental variable analysis was performed to estimate the effect of compliance measured on a continuous percentage scale using randomisation as the instrumental variable and a two-stage residual inclusion method.[34] The OR for the percentage of medication taken and bootstrapped 95% CI were produced.

The above analyses were performed using only the full analysis population, as treatment compliance is a condition of the per-protocol population.

Subgroups

Exploratory subgroup analyses looked for a treatment interaction effect (using logistic regression) with the following subgroups measured at baseline:

- Cambridge versus other sites
- age (< 70 years vs. ≥ 70 years)
- head trauma (no head trauma, occurred ≤ 4 weeks ago, occurred > 4 weeks ago and unknown timing)
- use of anticoagulants or platelets versus none
- GCS score on admission to NSU
- unilateral versus bilateral CSDH – as defined in imaging findings.

The ORs, 95% CIs and *p*-values were reported for both the main and the interaction effects. The subgroup-specific treatment effect estimates were calculated only if the interaction effect was judged to be statistically and clinically significant.

Summary statistics (frequency and percentage of patients achieving a favourable mRS outcome at 6 months) were produced by treatment arm for the following post-baseline subgroups:

- recurrent CSDH (one or more reoperation vs. no reoperations)
- surgical intervention during primary surgery (burr hole, mini-craniotomy)
- drain during primary surgery versus no drain during primary surgery
- conservative management versus non-conservative management (no surgery on any admission vs. one or more operation)
- trial conservative management (surgery within 7 days of randomisation vs. surgery > 7 days after randomisation vs. no surgery at any time point).

All subgroup analyses were performed using both the full analysis and the per-protocol populations.

Adverse event analyses

These analyses were performed on the safety population. Listings of safety events were produced and included:

- participant ID
- site
- treatment arm
- onset and resolution dates
- Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT) and system organ class (SOC)
- causality
- outcome.

For serious adverse events (SAEs), the severity, seriousness and SAE reference number were also reported.

The frequency and percentage of MedDRA SOC codes were calculated, with each participant counted only once and the total population size used as the denominator. Figures showing the incidence of safety events and the relative risk (with 95% CI) by treatment arm based on the MedDRA SOC codes were produced.

Safety events were categorised as adverse events of special interest (AESIs), SAEs or AEs. A listing was produced only for AEs.

Adverse events of special interest

Adverse events of special interest were defined as:

- hyperglycaemia necessitating stopping of trial medication
- new-onset diabetes necessitating ongoing medical treatment at day 30 follow-up
- hyperosmolar hyperglycaemic state
- new-onset psychosis
- upper gastrointestinal side effects (e.g. heartburn and vomiting)
- peptic ulceration and gastrointestinal bleeding.

Separate listings and summary statistics were produced for non-serious AESIs and serious AESIs. The incidence and relative risk plot were produced only for non-serious AESIs owing to the small number of serious AESIs.

The following AESI was also summarised by past medical history of diabetes (yes/no) and treatment group: hyperglycaemia necessitating stopping of trial medication.

Serious adverse events

Serious adverse events were defined as any untoward medical occurrence or effect that:

- resulted in death
- was life-threatening
- required hospitalisation or prolongation of existing inpatients' hospitalisation
- resulted in persistent or significant disability or incapacity
- was a congenital anomaly or birth defect
- was another important medical event.

Initial index surgery was not reported as a SAE unless any of the above criteria were met.

Serious adverse events were categorised into non-reportable SAEs, reportable SAEs occurring within 30 days of starting the IMP and reportable SAEs post day 30. Listings and summary statistics were produced as previously described for each category. Summary statistics were also produced for the outcome of reportable SAEs (split by timing). A post hoc analysis for the difference in proportion of reportable SAEs occurring within 30 days of starting treatment was also performed.

Patient and public involvement

Our trial team sought key stakeholder perspectives in the design of the trial. These included a charity (Age UK, London, UK) and a patient representative from the Public Involvement in Research Group for Cambridgeshire & Bedfordshire. Their views guided the development of the proposed protocol and selection of appropriate outcome measures to ensure acceptability among patients and their families. In addition, we undertook two community consultations to shape participant consenting and enrolment.

Four questions were asked with regard to dissemination of the Dex-CSDH trial to the Cambridge University Hospital patient and public involvement (PPI) panel in July 2019:

1. As trial participants were recruited from all over the UK and many are elderly, and may be in care homes, a post-trial meeting to share findings directly with participants will not be feasible. Would putting a summary of the trial results, in a patient-friendly style of reporting, on the trial website (www.dexcsdh.org/) and the Headway website (URL: www.headway.org.uk) be helpful?
2. From your experience, can you suggest other ways of sharing the results/findings with the general and target population?
3. Will the panel be willing to help design/review dissemination materials from a patient viewpoint?
4. We are aware of the potential difficulties with dissemination of results through social media platforms. Please may we ask your opinions regarding the use of social media for this purpose?

Summary of responses:

1. Responses should primarily be by post owing to the likely demographic of the participants, but an online version would be welcome as well. A separate leaflet for relatives and friends would be welcome.
2. Posters in general practices and care home visits may support the dissemination of results.
3. Widespread interest in helping with this.
4. Very cautious of social media dissemination for the public – often not trusted.

The questionnaire completed by the Cambridge University Hospital PPI panel guided the dissemination plan. It was clear that social media were not the most appropriate platform for this, although it was felt that they should still be utilised cautiously. Owing to unforeseen circumstances, there was a change of PPI lead during the study, which inevitably resulted in a loss of focus for a period of time. However, good engagement with local advisory groups and the Cambridge University Hospital panel helped us to develop a robust dissemination plan. Engagement with a PPI group, rather than an individual lead, from the start would have helped with integration of PPI throughout; however, the advisory groups that we did approach were very helpful with the areas that were discussed.

Chapter 3 Trial results

Recruitment

Patients were recruited between August 2015 and November 2018. The trial was stopped when the required sample size of 750 patients had been reached.

Patient disposition

A CONSORT flow diagram is shown in *Figure 1*.

A total of 2203 patients were screened, with 750 randomised. Two patients were excluded immediately after randomisation owing to ineligibility; neither patient had received their assigned intervention and no data were collected from these patients. Of the 748 eligible patients, 375 were randomised to receive dexamethasone (with 365 receiving at least one dose of the intervention) and 373 were randomised to receive placebo (with 361 receiving at least one dose of the intervention). Therefore, the full analysis and safety population comprised 748 participants.

In total, 45 patients withdrew consent to participate in the trial (25 in the placebo arm, 20 in the dexamethasone arm) and 23 patients were lost to follow-up (9 in the placebo arm and 14 in the dexamethasone arm). Therefore, 680 patients were followed up to the primary outcome measure at 6 months (339 in the placebo arm and 341 in the dexamethasone arm) and analysed using the modified intention-to-treat analysis.

The main per-protocol population (not taking into account time windows) comprised 597 patients (307 in the placebo arm and 290 in the dexamethasone arm). The number of patients in the per-protocol population at discharge was 491 (252 in the placebo arm and 239 in the dexamethasone arm), at 3 months was 539 (280 in the placebo arm and 259 in the dexamethasone arm) and at 6 months was 553 (283 in the placebo arm and 270 in the dexamethasone arm).

Baseline information

Demographic details and health status prior to CSDH are provided in *Table 2* and show no apparent differences between the treatment arms. Injury background and imaging details are provided in *Table 3*. For details of medical conditions and prior and concurrent medications based on the full analysis population, see *Appendix 3*, *Tables 26–28*. *Appendix 3* also shows summary statistics for the blood and clotting products given on admission, which were similar between treatment arms.

Treatment compliance

Treatment compliance was similar between treatment arms, with the mean percentage of tablets taken being 89% in the placebo arm and 87% in the dexamethasone arm based on the daily medication records, and 94% compared with 94% for the placebo arm and the dexamethasone arm, respectively, based on remaining pill count for those who completed treatment in the hospital.

TABLE 2 Baseline demographics and health status (full analysis population)

Demographic	Treatment arm		Total
	Placebo	Dexamethasone	
Age (years)			
n	373	375	748
Mean (SD)	74.3 (11.0)	74.5 (11.8)	74.4 (11.4)
Median	76	76	76
Minimum, maximum	21, 95	23, 97	21, 97
Gender, *n/N* (%)			
Male	286/373 (76.7)	268/375 (71.5)	554/748 (74.1)
Female	87/373 (23.3)	107/375 (28.5)	194/748 (25.9)
Ethnicity, *n/N* (%)			
Caucasian/white	353/372 (94.9)	360/373 (96.5)	713/745 (95.7)
Black	7/372 (1.9)	4/373 (1.1)	11/745 (1.5)
Asian	11/372 (3)	7/373 (1.9)	18/745 (2.4)
Hispanic	1/372 (0.3)	0/373 (0)	1/745 (0.1)
Other	0/372 (0)	2/373 (0.5)	2/745 (0.3)
Residence prior to CSDH, *n/N* (%)			
Independent	328/372 (88.2)	327/374 (87.4)	655/746 (87.8)
Carers at home	30/372 (8.1)	24/374 (6.4)	54/746 (7.2)
Residential home	1/372 (0.3)	3/374 (0.8)	4/746 (0.5)
Nursing home	4/372 (1.1)	6/374 (1.6)	10/746 (1.3)
Other	9/372 (2.4)	14/374 (3.7)	23/746 (3.1)
Mobility prior to CSDH, *n/N* (%)			
Independent	307/372 (82.5)	294/375 (78.4)	601/747 (80.5)
Stick	40/372 (10.8)	43/375 (11.5)	83/747 (11.1)
Walking frame	20/372 (5.4)	17/375 (4.5)	37/747 (5)
Wheelchair	1/372 (0.3)	3/375 (0.8)	4/747 (0.5)
Bedbound	0/372 (0)	5/375 (1.3)	5/747 (0.7)
Other	4/372 (1.1)	13/375 (3.5)	17/747 (2.3)
Premorbid mRS score, *n/N* (%)			
0: No symptoms	182/373 (48.8)	178/373 (47.7)	360/746 (48.3)
1: No significant disability	53/373 (14.2)	55/373 (14.7)	108/746 (14.5)
2: Slight disability	40/373 (10.7)	36/373 (9.7)	76/746 (10.2)
3: Moderate disability	29/373 (7.8)	30/373 (8)	59/746 (7.9)
4: Moderately severe disability	14/373 (3.8)	20/373 (5.4)	34/746 (4.6)
5: Severe disability	0/373 (0)	3/373 (0.8)	3/746 (0.4)
Not available	55/373 (14.7)	51/373 (13.7)	106/746 (14.2)

TABLE 3 Injury background and imaging details (full analysis population)

Baseline data	Treatment arm, *n/N* (%)		Total, *n/N* (%)
	Placebo	Dexamethasone	
Timing of onset of symptoms related to CSDH			
< 7 days	133/373 (35.7)	140/373 (37.5)	273/746 (36.6)
7–14 days	116/373 (31.1)	100/373 (26.8)	216/746 (29)
15–28 days	75/373 (20.1)	64/373 (17.2)	139/746 (18.6)
29–42 days	22/373 (5.9)	26/373 (7)	48/746 (6.4)
> 42 days	19/373 (5.1)	35/373 (9.4)	54/746 (7.2)
Not known	8/373 (2.1)	8/373 (2.1)	16/746 (2.1)
Known head trauma			
Yes	267/373 (71.6)	253/373 (67.8)	520/746 (69.7)
If known head trauma, how long ago did it occur?			
< 2 weeks ago	56/267 (20.9)	59/253 (23.4)	115/518 (22.2)
2–4 weeks ago	77/267 (28.9)	72/253 (28.5)	149/518 (28.8)
1–3 months ago	110/267 (41.2)	94/253 (37.1)	204/518 (39.4)
4–6 months ago	10/267 (3.7)	17/253 (6.7)	27/518 (5.2)
> 6 months ago	6/267 (2.2)	1/253 (0.4)	7/518 (1.4)
Not known	7/267 (2.6)	9/253 (3.6)	16/518 (3.1)
Density of CSDH			
Hypodense	89/355 (25.1)	111/361 (30.7)	200/716 (27.9)
Isodense	96/355 (27.0)	73/361 (20.2)	169/716 (23.6)
Mixed density	170/355 (47.9)	177/361 (49.0)	347/716 (48.5)
Midline shift			
0–5 mm	74/318 (23.3)	68/314 (21.7)	142/632 (22.5)
6–10 mm	115/318 (36.2)	126/314 (40.1)	241/632 (38.1)
> 10 mm	129/318 (40.6)	120/314 (38.2)	249/632 (39.4)

Outcomes

Primary analysis

Summary statistics for the primary outcome are presented in *Table 4* for the full analysis population, with dichotomous scores at discharge, 3 months and 6 months presented in *Figure 2*. The per-protocol results can be found in *Appendix 3*, *Table 29*. The absolute difference in the proportion achieving a favourable outcome (mRS score of 0–3) at 6 months was −6.4% in the dexamethasone arm compared with the placebo arm (95% CI −11.4% to −1.4%; $p = 0.01$), based on the full analysis population. The per-protocol analysis gave similar results, with an absolute difference in proportions of −6.4% (95% CI −12% to −1%; $p = 0.02$).

TABLE 4 Modified Rankin Scale at 6 months (full analysis population)

mRS	Treatment arm, *n/N* (%)		Total, *n/N* (%)
	Placebo	Dexamethasone	
Score			
0: No symptoms	164/339 (48.4)	163/341 (47.8)	327/680 (48.1)
1: No significant disability	55/339 (16.2)	49/341 (14.4)	104/680 (15.3)
2: Slight disability	21/339 (6.2)	14/341 (4.1)	35/680 (5.1)
3: Moderate disability	66/339 (19.5)	60/341 (17.6)	126/680 (18.5)
4: Moderately severe disability	9/339 (2.7)	10/341 (2.9)	19/680 (2.8)
5: Severe disability	7/339 (2.1)	15/341 (4.4)	22/680 (3.2)
6: Dead	17/339 (5.0)	30/341 (8.8)	47/680 (6.9)
Dichotomised			
Favourable	306/339 (90.3)	286/341 (83.9)	592/680 (87.1)
Unfavourable	33/339 (9.7)	55/341 (16.1)	88/680 (12.9)

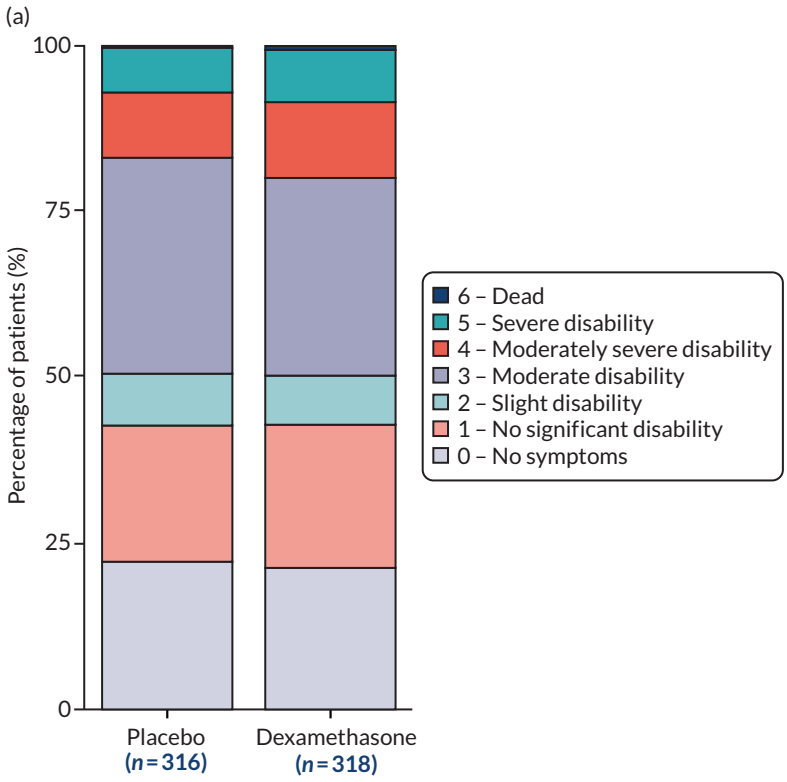

FIGURE 2 Modified Rankin Scale by treatment arm and time point. (a) Discharge mRS score; (b) 3-month mRS score; and (c) 6-month mRS score. *(continued)*

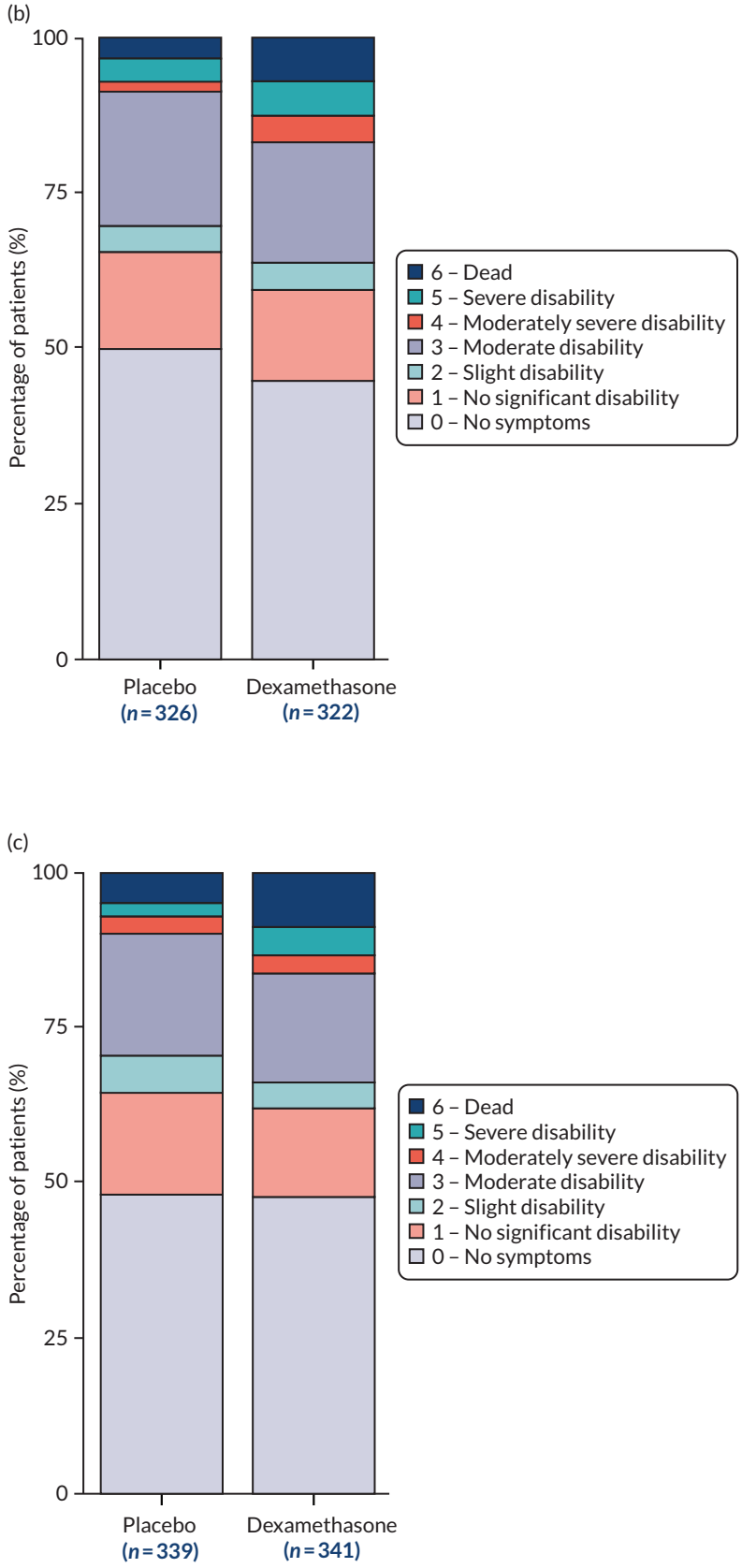

FIGURE 2 Modified Rankin Scale by treatment arm and time point. (a) Discharge mRS score; (b) 3-month mRS score; and (c) 6-month mRS score.

Secondary analyses

Surgery

Summary statistics for the number of surgical interventions undertaken during index and subsequent admissions based on the full analysis population are presented in *Table 5*, along with the recurrence rate in each treatment arm. For summary statistics based on the per-protocol population, see *Appendix 3*, *Table 30*.

The effect of dexamethasone compared with placebo on the number of surgeries undertaken during the index and during subsequent admissions was not significant for both the full analysis (*Table 6*) and the per-protocol populations (see *Appendix 3*, *Table 31*).

For full details of the type of surgical procedures undertaken during primary surgery, see *Appendix 3*, *Table 32*. The number and type of surgical procedures performed during primary surgery were similar between treatment arms. Similar details for recurrent surgery are also found in *Appendix 3*, *Table 33*.

TABLE 5 Number of surgical interventions (full analysis population)

Number of surgeries	Treatment arm, *n/N* (%)		Total, *n/N* (%)
	Placebo	Dexamethasone	
Index admission			
0	29/370 (7.8)	30/372 (8.1)	59/742 (8.0)
1	330/370 (89.2)	341/372 (91.7)	671/742 (90.4)
2	10/370 (3.0)	1/372 (0.2)	11/742 (1.5)
3	1/370 (0.23)	0/372 (0)	1/742 (0.1)
Subsequent admissions			
1	25/370 (6.7)	16/372 (4.3)	41/742 (5.5)
2	2/370 (0.5)	3/372 (0.8)	5/742 (0.7)
3	1/370 (0.3)	0/375 (0)	1/742 (0.1)
Repeat surgery for recurrence of CSDH[a]	25/350 (7.1)	6/349 (1.7)	31/699 (4.4)

a Denominator is the subset of patients who received surgery.

TABLE 6 Model-fitting results for the number of surgical interventions (full analysis population)

Outcome	Covariate	Estimate	95% CI	*p*-value
Number of surgeries: index admission (including pre randomisation)	(Intercept)	0.954	0.858 to 1.06	
	Dexamethasone vs. placebo	0.966	0.833 to 1.12	0.653
Number of surgeries: index admission (excluding pre randomisation)	(Intercept)	0.489	0.421 to 0.564	
	Dexamethasone vs. placebo	0.896	0.724 to 1.11	0.308
Number of surgeries: subsequent admissions (re-admissions only)	(Intercept)	0.489	0.421 to 0.564	
	Dexamethasone vs. placebo	0.896	0.724 to 1.11	0.308
Number of surgeries: subsequent admissions (all patients)	(Intercept)	0.0858	0.0594 to 0.119	
	Dexamethasone vs. placebo	0.684	0.392 to 1.17	0.17

Modified Rankin Scale

There was no significant difference in mRS scores between the dexamethasone arm and the placebo arm at discharge. At 3 months, the effect of dexamethasone compared with placebo was to significantly decrease the odds of achieving a favourable outcome. This can be clearly seen from both the global ORs and the marginal ORs in *Table 7*. Results were similar for both the full analysis and the per-protocol populations.

Figure 1 shows the percentage of patients in each mRS category at each assessment time point by treatment arm, including missing data. This shows that pre-morbid mRS score was similar between arms, on admission to NSU and at discharge, whereas, at 3 and 6 months, the outcomes in the placebo

TABLE 7 Model-fitting results for mRS at discharge and 3 months (full analysis population)

	Ordinal logistic regression			Sequential ORs		
Cut-off point	Probability mRS ≤ cut-off point (placebo arm)	Global OR (95% CI)[a]	*p*-value	Placebo (*n* = 316, discharge) (*n* = 326, 3 months), *n* (%)	Dexamethasone (*n* = 318, discharge) (*n* = 322, 3 months), *n* (%)	Marginal OR (95% CI)
mRS at discharge						
0	0.226	0.937 (0.71 to 1.24)	0.644	71 (22)	69 (22)	0.956 (0.657 to 1.392)
1	0.439			136 (43)	137 (43)	1.002 (0.732 to 1.372)
2	0.514			161 (51)	160 (50)	0.975 (0.714 to 1.331)
3	0.822			263 (83)	255 (80)	0.816 (0.545 to 1.222)
4	0.924			293 (93)	291 (92)	0.846 (0.474 to 1.51)
5	0.995			315 (100)	316 (99)	0.502 (0.045 to 5.56)
6	N/A			N/A	N/A	N/A
mRS at 3 months						
0	0.509	0.747 (0.561 to 0.993)	0.044	163 (50)	144 (45)	0.809 (0.594 to 1.102)
1	0.658			213 (65)	192 (60)	0.784 (0.57 to 1.078)
2	0.698			227 (70)	205 (64)	0.764 (0.551 to 1.06)
3	0.889			298 (91)	268 (83)	0.466 (0.287 to 0.758)
4	0.915			303 (93)	282 (88)	0.535 (0.313 to 0.916)
5	0.956			315 (97)	300 (93)	0.476 (0.227 to 0.999)
6	N/A			N/A	N/A	N/A

N/A, not applicable.
a Odds in direction of a favourable outcome (dexamethasone vs. placebo).

Note
Data show frequency (%) of patients with a mRS score more than or equal to the cut-off point.

arm were more favourable than those in the dexamethasone arm. The number of missing data was similar between arms. Summary statistics for the mRS score on admission to the NSU, at discharge and at 3 months are presented in *Appendix 3*, *Tables 34* and *35*, for the full analysis population and *Tables 36* and *37* for the per-protocol population. *Table 7* contains the model-fitting results at discharge and 3 months using the full analysis population. Model-fitting results for the per-protocol population can be found in *Appendix 3*, *Table 38*.

Glasgow Coma Scale

On admission to the NSU, 350 out of 371 (94%) patients in both the dexamethasone arm and the placebo arm had a GCS total score of 13–15, based on the full analysis population. These figures were similar for the per-protocol population, with 272 out of 289 (94%) in the dexamethasone arm and 286 out of 306 (94%) in the placebo arm receiving a total score of 13–15. Almost 100% of patients in both arms had a GCS total score of 13–15 on discharge from the NSU, using both the full analysis (dexamethasone: 351/354, 99.2%; placebo: 355/356, 99.7%) and the per-protocol populations (dexamethasone: 236/237, 99.6%; placebo: 250/251, 99.6%). Only 27 patients had 6-month GCS data, with 24 out of 27 (89%) patients having a total score of 13–15.

Barthel Index

The summary statistics for BI score at discharge, 3 months and 6 months using the full analysis and per-protocol populations can be found in *Appendix 3*, *Tables 39–44*. There was no significant effect of dexamethasone compared with placebo on BI total score at any time point for either the full analysis (*Table 8*) or the per-protocol populations (see *Appendix 3*, *Table 45*).

EuroQol-5 Dimensions, five-level version

The summary statistics for EQ-5D-5L at discharge, 3 months and 6 months using the full analysis and per-protocol populations can be found in *Appendix 3*, *Tables 46–51*. The effect of dexamethasone compared with placebo on the EQ-5D-5L utility index at discharge and 6 months using the full analysis population was not significant (*Table 9*); however, the results were significant at 3 months, with dexamethasone being associated with a worse outcome than placebo (a decrease in utility index of −0.07). Similar results were found using the per-protocol population (see *Appendix 3*, *Table 52*).

TABLE 8 Model-fitting results for BI at discharge, 3 months and 6 months (full analysis population)

	Linear regression				
Outcome	Covariate	Estimate (SE)	95% CI	*p*-value	Mann–Whitney *U*-test: *p*-value
BI at discharge	(Intercept)	80.5 (1.54)	77.4 to 83.5		0.414
	Dexamethasone vs. placebo	0.505 (2.18)	−3.78 to 4.79	0.817	
BI at 3 months	(Intercept)	89.4 (1.24)	87 to 91.8		0.305
	Dexamethasone vs. placebo	−2.68 (1.77)	−6.16 to 0.8	0.131	
BI at 6 months	(Intercept)	90.3 (1.17)	88 to 92.7		0.32
	Dexamethasone vs. placebo	−2.29 (1.67)	−5.57 to 0.995	0.172	

SE, standard error.

TABLE 9 Model-fitting results for EQ-5D-5L at discharge, 3 months and 6 months (full analysis population)

Outcome	Covariate	Estimate (SE)	95% CI	*p*-value
EQ-5D-5L utility index at discharge	(Intercept)	0.727 (0.016)	0.695 to 0.758	
	Dexamethasone vs. placebo	−0.03 (0.0226)	−0.0743 to 0.0142	0.183
EQ-5D-5L utility index at 3 months	(Intercept)	0.773 (0.0177)	0.739 to 0.808	
	Dexamethasone vs. placebo	−0.0666 (0.0251)	−0.116 to −0.0174	0.008
EQ-5D-5L utility index at 6 months	(Intercept)	0.766 (0.0188)	0.73 to 0.803	
	Dexamethasone vs. placebo	−0.0334 (0.0267)	−0.0858 to 0.019	0.211

SE, standard error.

Mortality

There were 17 deaths (5%) in the placebo arm, compared with 31 (8%) deaths in the dexamethasone arm. *Figure 3* shows a bar chart of the number of deaths by key time points. Although there were more deaths in the dexamethasone arm than in the placebo arm, the difference was not significant at either day 30 or 6 months (*Table 10*).

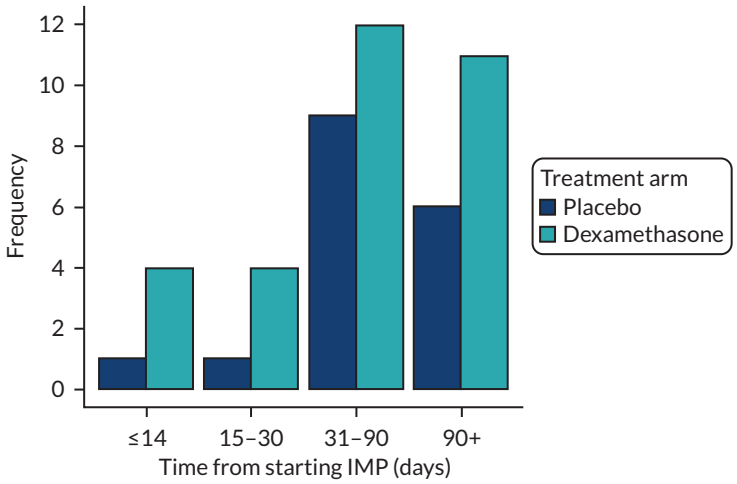

FIGURE 3 Number of deaths by time point and treatment arm.

TABLE 10 Model-fitting results for mortality at 30 days and 6 months

Outcome	OR[a]	95% CI	*p*-value
Full analysis population			
Mortality at 30 days	4.08	1.01 to 27.2	0.077
Mortality at 6 months	1.83	0.99 to 3.45	0.062
Per-protocol population			
Mortality at 30 days	2.13	0.413 to 15.5	0.384
Mortality at 6 months	1.97	0.908 to 4.5	0.094

a Odds of dexamethasone vs. placebo.

Discharge information

The summary statistics on the discharge destination after index admission and the length of stay in NSU, secondary care and intensive care unit (ICU)/high-dependency unit (HDU) are provided in *Table 11* for the full analysis population (see *Appendix 3*, *Table 53*). Discharge destination was similar for both treatment arms, with the majority of patients being discharged to either their home or a local hospital. Length of stay in NSU, secondary care and ICU/HDU, as well as the number of patients who stayed in ICU, were also similar between treatment arms. Model-fitting results showed that there were no statistically significant differences between treatment arms for either the full analysis population (*Table 12*) or the per-protocol population (see *Appendix 3*, *Table 54*).

TABLE 11 Discharge data (full analysis population)

Outcome	Treatment arm		Total
	Placebo	Dexamethasone	
Discharge destination after index admission, *n/N* (%)			
Home	253/362 (69.9)	239/361 (66.2)	492/723 (68)
Carers at home	13/362 (3.6)	6/361 (1.7)	19/723 (2.6)
Local hospital	66/362 (18.2)	84/361 (23.3)	150/723 (20.7)
Rehabilitation centre	8/362 (2.2)	8/361 (2.2)	16/723 (2.2)
Residential home	1/362 (0.3)	1/361 (0.3)	2/723 (0.3)
Nursing home	2/362 (0.6)	5/361 (1.4)	7/723 (1)
Other	19/362 (5.2)	18/361 (5)	37/723 (5.1)
Length of stay in NSU (days)			
n	359	362	721
Mean (SD)	9.03 (8)	9.3 (8.4)	9.18 (8.18)
Median	6	7	7
Minimum, maximum	1, 63	2, 70	1, 70
Length of stay in secondary care (days)[a]			
n	359	362	721
Mean (SD)	13.7 (23)	13.0 (17)	13.4 (20.0)
Median	7	8	7
Minimum, maximum	1, 219	2, 198	1, 219
Stayed in ICU/HDU, *n/N* (%)			
Yes	39/373 (10.5)	36/375 (9.6)	75/748 (10)
Length of stay in ICU/HDU (days)			
n	39	36	75
Mean (SD)	3.05 (3.19)	3.08 (2.41)	3.07 (2.82)
Median	2	2	2
Minimum, maximum	1, 17	1, 10	1, 17

a Length of stay in secondary care, calculated as length of stay in NSU plus the self-reported length of stay in hospital or healthcare facility based on the 6-month questionnaires.

TABLE 12 Model-fitting results for discharge data (full analysis population)

Outcome	Estimate[a]	95% CI	*p*-value
Negative binomial regression model			
Length of stay in NSU (days)	1.03	0.934 to 1.14	0.535
Length of stay in secondary care (days)	0.952	0.835 to 1.09	0.467
Logistic regression model			
Discharge destination after index admission[b]	1.18	0.867 to 1.62	0.288
Discharge destination after index admission[c]	0.694	0.402 to 1.19	0.188

a Dexamethasone vs. placebo: rate ratio (95% CI) and OR (95% CI).
b Discharge destination: home vs. other.
c Discharge destination: local hospital vs. other (excluding home).

Ancillary analyses

Model fitting

Model-fitting results for the primary outcome, adjusting for age and GCS on admission, are presented in *Table 13* for the full analysis population. The results show that, even after adjusting for baseline variables (both significant), the odds of achieving a favourable outcome are still significantly lower for dexamethasone than placebo. Per-protocol analyses gave similar results (see *Appendix 3*, *Table 55*).

Model-fitting results for the ordinal mRS score at 6 months, adjusted for age and GCS on admission, are presented in *Table 14* for the full analysis population. Although the global OR for dexamethasone compared with placebo was not statistically significant, it can be seen from the marginal ORs that at a cut-off point of 3, that is, the odds of achieving a favourable outcome, are significantly worse in the dexamethasone arm than the placebo arm. The per-protocol analysis gave similar results (see *Appendix 3*, *Table 56*).

Mediation

Figure 4 shows the results of the mediation analysis. The indirect effect of treatment via the mediator recurrent CSDH was not significant.

Compliance

Table 15 shows the results of the logistic regression to investigate the effect of compliance with medication on the primary outcome. The interaction between the treatment arm and the percentage of medication taken was not significant. *Figure 5* shows the results of the CACE analysis. This suggests that the more compliant that the patient was with medication in the dexamethasone arm, the worse their mRS outcome was at 6 months. The instrumental variables analysis gave an OR (95% CI) of 0.942 (0.891 to 0.994) of achieving a favourable outcome at 6 months for every 10% increase in medication taken.

TABLE 13 Model-fitting results for the primary outcome (full analysis population): mRS at 6 months (dichotomised)

Covariate	Odds ratio (95% CI)	*p*-value
Dexamethasone vs. placebo	0.553 (0.33 to 0.914)	0.022
Age (years)	0.902 (0.873 to 0.93)	< 0.001
GCS at baseline	1.46 (1.27 to 1.69)	< 0.001

TABLE 14 Model-fitting results for ordinal mRS at 6 months (full analysis population)

Ordinal logistic regression					Sequential ORs		
Covariate	Global OR (95% CI)[a]	*p*-value	Cut-off point	Probability mRS ≤ cut-off point (placebo arm)	Placebo (*n* = 339), *n* (%)	Dexamethasone (*n* = 341), *n* (%)	Marginal OR (95% CI)
Dexamethasone vs. placebo	0.866 (0.651 to 1.15)	0.324	0	0.483	164 (48)	163 (48)	0.977 (0.723 to 1.32)
Age (years)	0.945 (0.931 to 0.958)	< 0.001	1	0.656	219 (65)	212 (62)	0.9 (0.659 to 1.23)
GCS at baseline	1.41 (1.26 to 1.57)	< 0.001	2	0.715	240 (71)	226 (66)	0.811 (0.586 to 1.121)
			3	0.904	306 (90)	286 (84)	0.561 (0.354 to 0.889)
			4	0.929	315 (93)	296 (87)	0.501 (0.298 to 0.843)
			5	0.952	322 (95)	311 (91)	0.547 (0.296 to 1.012)
			6	.	.	.	.

a Odds in direction of a favourable outcome.

Note
Data show frequency (%) of patients with a mRS score less than or equal to the cut-off point.

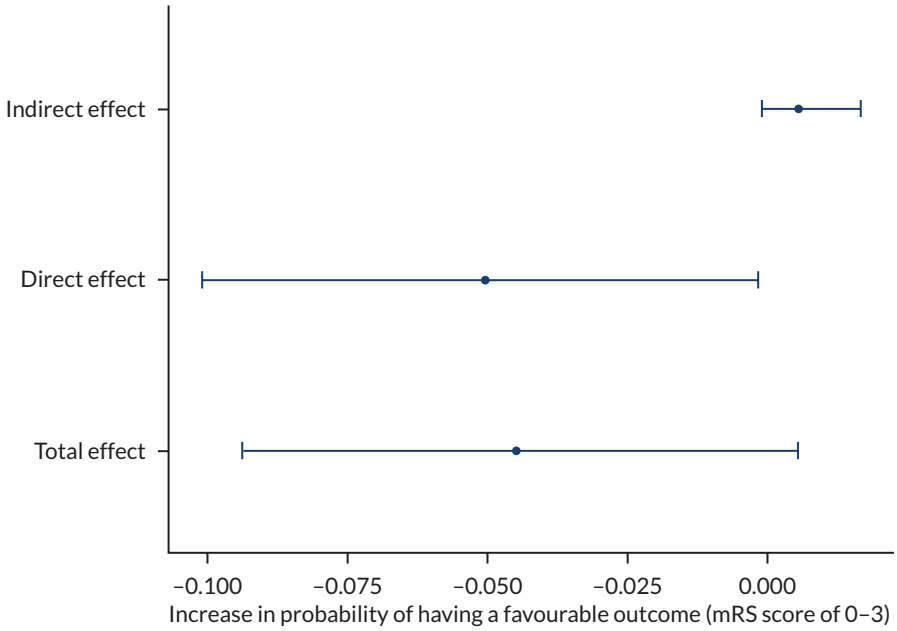

FIGURE 4 Mediation analysis (full analysis population).

TABLE 15 Model-fitting results for the interaction between treatment and percentage of medication taken: mRS at 6 months (dichotomised)

Covariate	OR	95% CI	*p*-value
Dexamethasone vs. placebo	1.06	0.195 to 5.43	0.941
Percentage of medication taken	1.02	1 to 1.03	0.034
Treatment: dexamethasone – percentage of medication taken	0.993	0.975 to 1.01	0.447

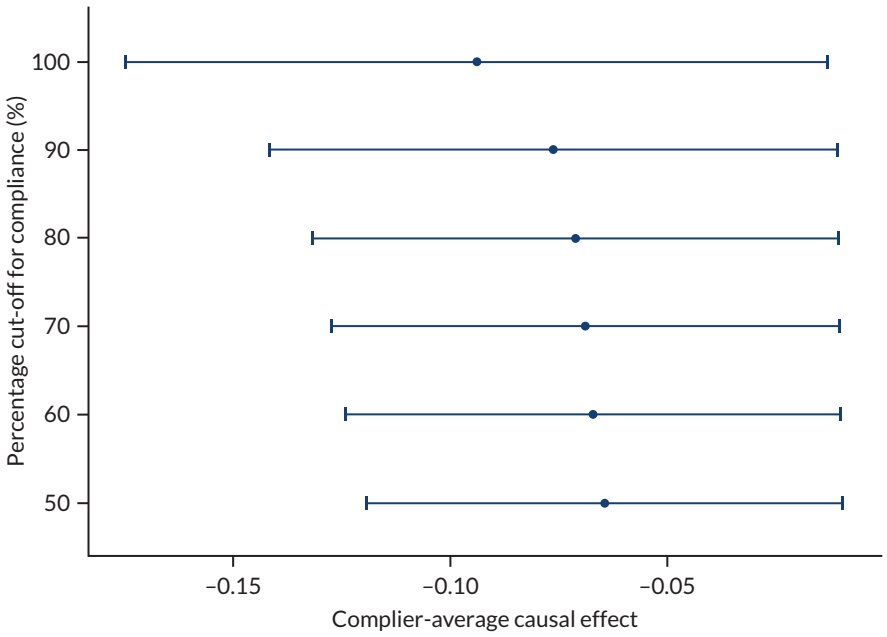

FIGURE 5 The CACE analysis results.

Subgroups

Table 16 shows the model-fitting results for the baseline subgroup analyses based on the full analysis population. The only subgroup to have a significant interaction effect with treatment was the side of the CSDH (bilateral vs. unilateral), suggesting that the association between the treatment arm and the probability of achieving a favourable mRS outcome at 6 months depends on the side of the CSDH. Further investigation of the subgroup-specific treatment effects showed that the odds of having a favourable outcome in the dexamethasone arm compared with the placebo arm were 0.422 (95% CI 0.244 to 0.711; $p = 0.001$; $n = 530$) in patients with a unilateral CSDH, whereas there was no significant difference for patients with a bilateral CSDH (OR 1.55, 95% CI 0.574 to 4.29; $p = 0.388$; $n = 150$). No subgroups were significant when analysed using the per-protocol population. *Appendix 3*, *Tables 57* and *58*, shows the post-baseline subgroup analyses using the full analysis population. This shows that, although there was a higher proportion of recurrences in the placebo arm (symptomatic recurrence requiring re-operation of a previously evacuated ipsilateral chronic subdural haematoma), 89% of these patients had a favourable mRS outcome at 6 months, compared with 64% of patients with a recurrence in the dexamethasone arm. Results were similar for the per-protocol population (see *Appendix 3*, *Table 59*). These comparisons must be interpreted with caution because there may be confounding biases as a result of the subgroups being defined post randomisation.

TABLE 16 Post-baseline subgroup analyses (full analysis population)

Subgroup	Favourable outcome (mRS score 0–3), *n/N* (%)	
	Placebo	Dexamethasone
Recurrence (one or more reoperation): yes	25/28 (89.3)	9/15 (60)
Surgical intervention during primary surgery		
Burr hole(s)	249/278 (89.6)	229/274 (83.6)
Craniotomy	33/37 (89.2)	30/35 (85.7)
Drain during primary surgery		
Yes	247/276 (89)	222/262 (85)
No	43/47 (91)	46/56 (82)
Conservative management (no surgery on any admission)	16/16 (100)	18/22 (82)
Surgery within 7 days of randomisation	280/313 (89)	264/313 (84)
Surgery > 7 days after randomisation	10/10 (100)	4/6 (67)

Adverse event analyses

Adverse events of special interest were reported in 41 out of 375 patients (10.9%) in the dexamethasone arm and in 12 out of 373 patients (3.2%) in the placebo arm (OR 3.4, 95% CI 1.81 to 6.85). SAEs occurred in 60 out of 375 (16.0%) and 24 out of 373 (6.4%) patients, respectively (OR 2.49, 95% CI 1.54 to 4.15). The risk of any infection was 6.4% in the dexamethasone arm and 1.1% in the placebo arm.

Adverse events of special interest

A listing of non-serious AESIs is available in *Appendix 3*, *Table 60*. *Figure 6* shows the incidence and relative risk plot for non-serious AESIs. Patients in the dexamethasone arm had more AESIs, with a significant increase in the relative risk of endocrine and psychiatric disorders. *Table 17* provides summary statistics for hyperglycaemia AESIs by past history of diabetes. The majority of patients in the dexamethasone arm with an AESI of hyperglycaemia necessitating treatment had a previous history of diabetes. A listing of serious AESIs is provided in *Appendix 3*, *Table 61*.

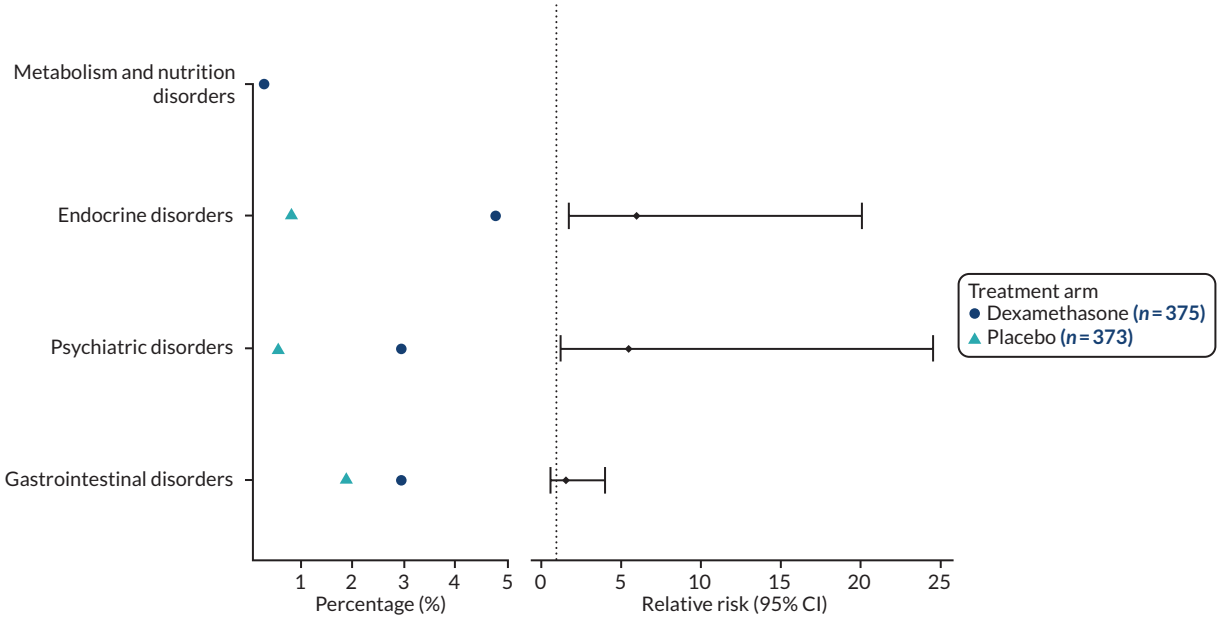

FIGURE 6 Incidence and relative risk plot for non-serious AESIs.

TABLE 17 Summary of hyperglycaemia AESIs by past history of diabetes

Variable	History of diabetes	Treatment arm, *n/N* (%)		Total, *n/N* (%)
		Placebo	Dexamethasone	
Hyperglycaemia necessitating treatment	Yes	1/373 (0.3)	13/375 (3.5)	14/748 (1.9)
	No	0/373 (0)	3/375 (0.8)	3/748 (0.4)
Hyperglycaemia necessitating stopping of trial medication	Yes	0/373 (0)	1/375 (0.3)	1/748 (0.1)

Serious adverse events

Non-reportable SAEs are listed in *Appendix 3*, *Table 62*. *Figure 7* shows the incidence and relative risk plot for non-reportable SAEs. The relative risk of a nervous system disorder was significantly lower in the dexamethasone arm than in the placebo arm.

Reportable SAEs (pre-study day 30) are reported in *Appendix 3*, *Table 63*. *Figure 8* shows the incidence and relative risk plot for reportable SAEs (pre-study day 30). In general, there were more reportable SAEs in the dexamethasone arm than the placebo arm, with the relative risk of infections and infestations significantly higher. *Table 18* provides a summary of the pre-study day 30 SAE outcomes by treatment arm. A post hoc analysis showed a significant difference in the number of pre-study day 30 SAEs between treatment arms (19% dexamethasone vs. 8% placebo).

Reportable SAEs (post-study day 30) are listed in *Appendix 3*, *Table 64*. *Figure 9* shows the incidence and relative risk plot for post-study day 30 reportable SAEs. *Table 19* provides a summary of the post-study day 30 SAE outcomes by treatment arm.

A list of AEs is provided in *Appendix 3*, *Table 65*.

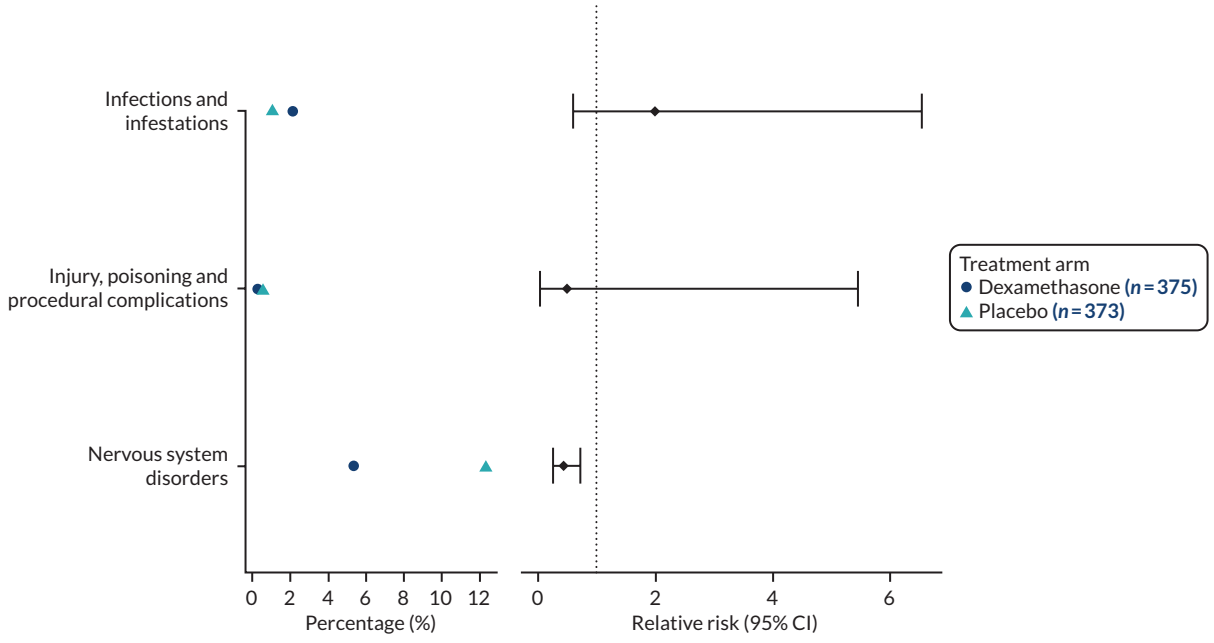

FIGURE 7 Incidence and relative risk plot for non-reportable SAEs.

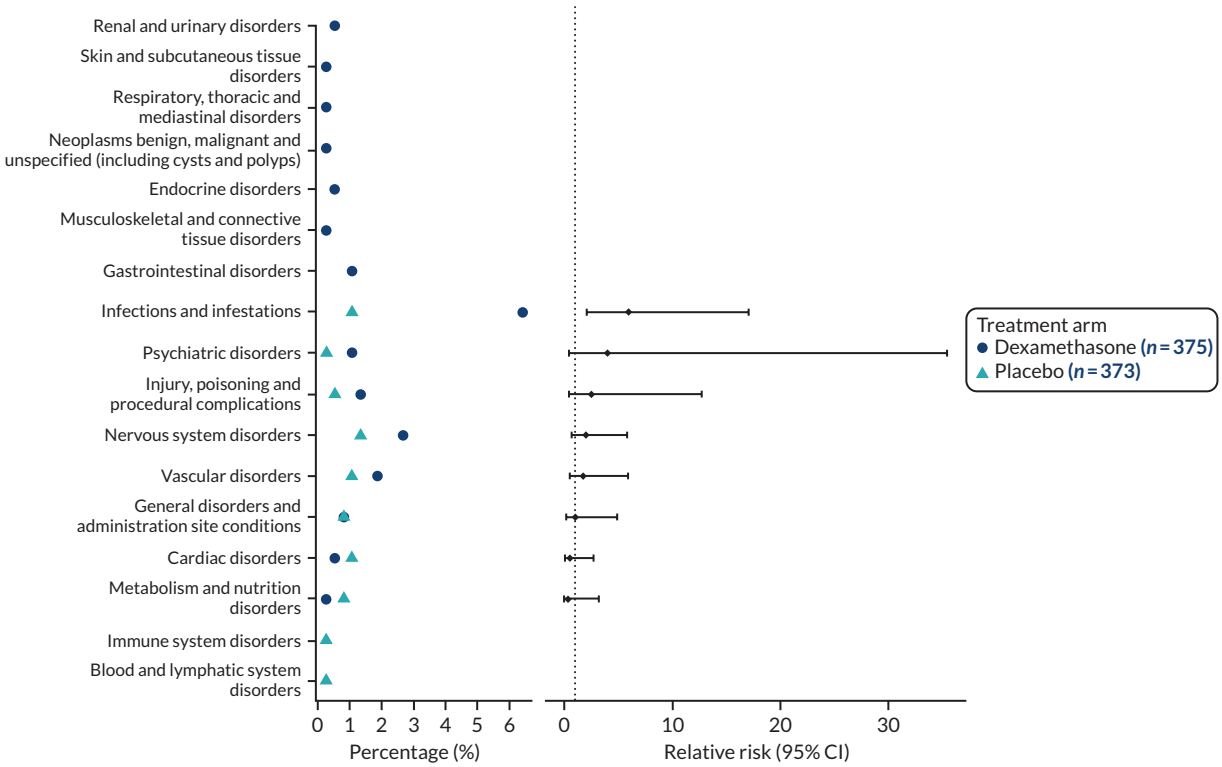

FIGURE 8 Incidence and relative risk plot for reportable SAEs (pre-study day 30).

TABLE 18 Summary of reportable SAE outcomes (pre-study day 30)

	Treatment arm, *n/N* (%)		
SAE outcome	**Placebo**	**Dexamethasone**	**Total, *n/N* (%)**
Death	3/373 (0.8)	13/375 (3.5)	16/748 (2.1)
Ongoing	5/373 (1.3)	7/375 (1.9)	12/748 (1.6)
Resolved no residual effects	14/373 (3.8)	37/375 (9.9)	51/748 (6.8)
Resolved with residual effects	2/373 (0.5)	8/375 (2.1)	10/748 (1.3)

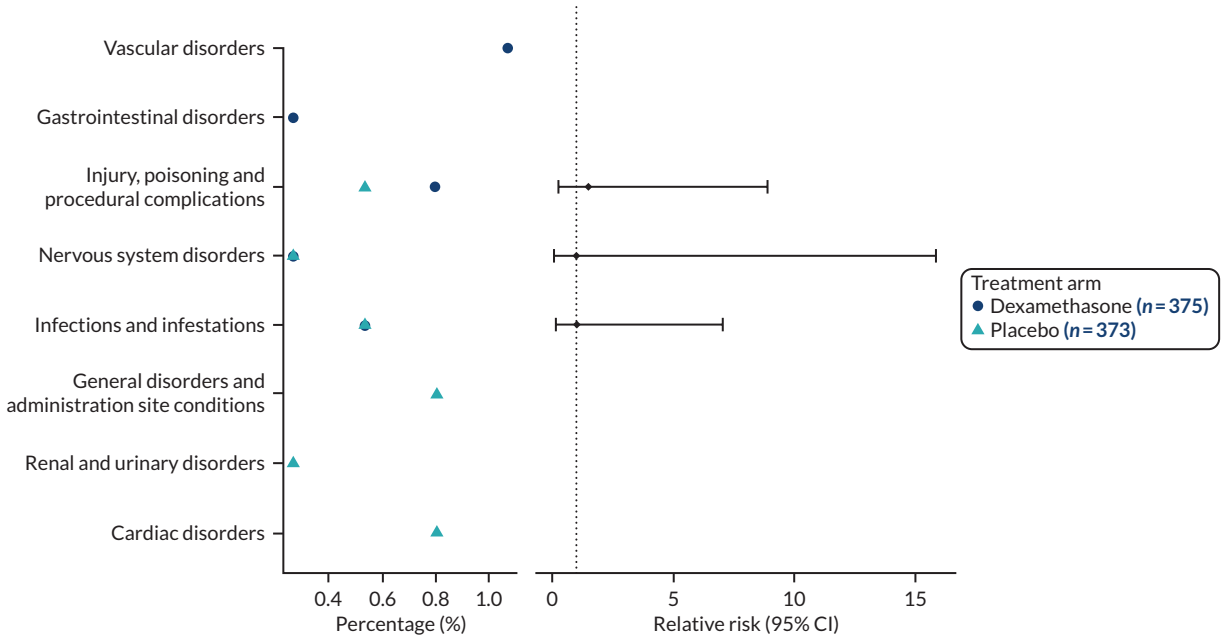

FIGURE 9 Incidence and relative risk plot for reportable SAEs (post-study day 30).

TABLE 19 Summary of reportable SAE outcomes (post-study day 30)

SAE outcome	Treatment arm, *n/N* (%)		Total, *n/N* (%)
	Placebo	Dexamethasone	
Death	7/373 (1.9)	2/375 (0.5)	9/748 (1.2)
Ongoing	1/373 (0.3)	0/375 (0)	1/748 (0.1)
Resolved no residual effects	3/373 (0.8)	8/375 (2.1)	11/748 (1.5)
Resolved with residual effects	1/373 (0.3)	1/375 (0.3)	2/748 (0.3)

Chapter 4 Economic evaluation

Objective

To estimate the cost-effectiveness of dexamethasone, compared with placebo, in patients with CSDH.

Background

Prior to analysis, a health economic analysis plan (HEAP) was developed, demonstrating that all analyses were prespecified (details of the HEAP are provided in this chapter). Here, for ease of reading, we present the methods and results (written in accordance with the Consolidated Health Economic Evaluation Reporting Standards checklist[35]) in sufficient detail that readers do not need to continually refer to the HEAP.

Methods

Trial design

As described above, the Dex-CSDH trial was a multicentre randomised trial conducted in the UK. The trial compared a tapering 2-week course of dexamethasone with matching placebo in patients with symptomatic CSDH. Patients were eligible for enrolment if they were aged ≥ 18 years and were admitted to a participating NSU with symptomatic CSDH that had been confirmed on cranial imaging.

Intervention

Eligible patients were randomly assigned in a 1: 1 ratio to receive a tapering 2-week course of oral dexamethasone (starting at 8 mg twice daily on day 1 and reducing to 2 mg once per day by day 14) or matching placebo.

Measuring costs

In line with the NICE methods guide,[36] in the base-case analysis, costs were estimated from the viewpoint of the NHS and Personal and Social Services (PSS). The subsequently described resource use data were collected, to which unit costs (estimated in Great British pounds for the 2017–18 financial year) were assigned. Where unit costs were taken from previous years, they were inflated using the NHS Cost Inflation Index.[37]

There were two main sources for the resource use data: a case report form (CRF) and a patient self-report (6-month follow-up) questionnaire (PSRQ). Both were specifically developed for the study and were informed by the guidance that one should focus on the large cost drivers and those resource items that might differ between study arms.[38] Costs were not assigned to resource items that were undertaken for research purposes.

Data from the case report form

Up to the point of discharge from the NSU, CRF data that were requested (to be completed by site staff) included details of any operation(s) undertaken during the index admission (there could be more than one operation), postoperative imaging, length of stay (in the NSU and any stay in an ICU/a HDU) and dexamethasone medication taken. In addition, sites were asked to record any re-admissions that included a CSDH-related surgical intervention (at any time in the 6-month follow-up period).

Unit costs were assigned to CRF data resource use items (*Table 20*). In terms of the intervention costs, it was assumed that each participant in the intervention arm was prescribed the aforementioned 14-day course of dexamethasone (62 2-mg tablets) and that tablets could not be reused if they were not taken (i.e. the same cost was incurred regardless of whether or not the regimen was completed). Each 2-mg tablet was costed at £0.24 (net ingredient cost per tablet),[39] giving a total dexamethasone regimen estimated cost of £15.01. No extra staff costs were included because the additional time was

TABLE 20 Unit costs

Resource use	Unit cost (£)	Assumptions
Primary admission costs		
14-day course of dexamethasone (124 mg in total)	15.01[40]	62 2-mg tablets (£0.24 per tablet), full regimen provided, not reuseable if not taken
Surgical procedure (one side)	1362.80[41]	Duration of 1 hour
Surgical procedure (on both sides)	2044.20[41]	Duration of 1.5 hours, e.g. left and right burr hole
Postoperative imaging	79.32[42]	CT scan
Cost per bed-day in critical care ward (ICU/HDU)	1441.42[42]	Neuroscience adult patients, critical care (mean)
Cost per bed-day in NSU	356.37[42]	
Post discharge from NSU		
Cost per bed-day in neurorehabilitation unit	492.41[43]	
Cost per bed-day in NSU	356.37[42]	
Cost per bed-day in critical care ward (ICU/HDU)	1441.42[42]	Neuroscience adult patients, critical care (mean)
Cost per bed-day (other ward type)	345.76[42]	Weighted average of elective and non-elective excess bed-days
Surgical procedure (post discharge)	1477.32[41]	Weighted average of one side two-sides operations, derived from primary admission CRF data
Health professional visits		
Hospital doctor		
Community	31.00[44]	As hospital doctors do not work in the community, the unit cost for a community GP visit was applied
Hospital	208.28[42]	
Home	55.91[44,45]	As hospital doctors do not usually visit homes, the unit cost for a home GP visit was applied
Nurse		
Community	12.10[44]	
Hospital	79.10[42]	
Home	19.30[44,45]	Costed as for community visit, plus 12 minutes of travel time
General practitioner		
Community	31.00[44]	
Hospital	208.28[42]	As GPs do not work in hospitals, the unit cost for a hospital doctor visit was applied
Home	55.91[44,45]	Costed as for community visit, plus 12 minutes of travel time

TABLE 20 Unit costs (*continued*)

Resource use	Unit cost (£)	Assumptions
Physiotherapist		
Community	57.26[42]	
Hospital	52.07[42]	
Home	64.02[42,45]	Costed as for community visit, plus 12 minutes of travel time
Occupational therapist		
Community	81.31[42]	
Hospital	65.58[42]	
Home	88.07[42,45]	Costed as for community visit, plus 12 minutes of travel time
Speech therapist		
Community	28.23[44]	
Hospital	97.62[42]	
Home	35.00[44,45]	Costed as for community visit, plus 12 minutes of travel time
Social worker		
Community	100.39[44,46]	
Hospital	100.39[44]	
Home	109.12[44,45]	Costed as for community visit, plus 12 minutes of travel time
Community care assistant		
Community	19.44[47]	
Hospital	19.44[47]	
Home	24.10[45,47]	Costed as for community visit, plus 12 minutes of travel time
Emergency department		
Community	160.32[42]	
Hospital	160.32[42]	
Home	160.32[42]	
Other		
Community	31.00[42]	The unit costs for the most commonly reported visit types from each location were used to cost 'other' visits. Community: GP; hospital: hospital doctor; home: occupational therapist
Hospital	208.28[42]	
Home	88.07[42,45]	
Other costs		
MRI scan	131.15[42]	
CT scan	79.32[42]	
'Other' scan	133.03[42]	Weighted average of CT and MRI scans derived from PSRQ data
Care home (cost per week in residence)	1812.00[44]	
Carer time	16.71[48]	Gross hourly wage used to value carer time, whether paid or not (opportunity cost method[49]). Average reported hours assumed to apply to all weeks post discharge

GP, general practitioner.

considered negligible and, therefore, captured by the associated admission costs. No medication costs were applied to those in the control arm (the placebo drug is a research-related cost and would not be provided as part of routine care outside the study).

For each participant, the component costs associated with any operation, imaging, length of stay in ICU/HDU and/or NSU (for the index admission), and dexamethasone could thereby be estimated and were summed to estimate the total index admission costs. Re-admissions that included a CSDH-related surgical intervention were also costed (based on surgery and length of stay details); however, to avoid potential duplication (with the overnight stays detailed in *Patient self-reported resource use*), these costs were not included in the base-case analysis.

Patient self-reported resource use

At the 6-month follow-up point, participants were sent a questionnaire that requested the following resource use data (if a participant was unable to fill in the questionnaire, proxy responses by a relative/friend/carer were requested). The questionnaire requested information only in relation to the time since discharge from the NSU, as the resource use associated with the time in the NSU was assumed to be captured by the aforementioned CRF data.

Participants were asked to report any overnight stays in a hospital or other healthcare facility (for any reason), and (if applicable) the number of nights, type of unit and whether or not there was an associated operation on the skull/brain. Participants were also asked to report any HCP visits (for any aspect of their health) and (if applicable) the type of HCP seen and where (most) visits took place. In addition, participants were asked to report any scans of the head/brain and (if applicable) the type and number of investigations. Participants were also asked to report if they had spent any time in a care home and (if applicable) the time in weeks/months. Finally, participants were asked to report if they had received any help from a family member/friend or other carer. If a respondent reported 'yes', for each carer they were asked to report the average number of hours of care received (per week in the past 6 months).

Unit costs were assigned to each aforementioned item of resource use data reported by participants (see *Table 20*). This enabled the component costs associated with any overnight stays (post NSU discharge), HCP visits, scans, stay in a care home and carer costs to be estimated. These were summed to estimate the total post-discharge costs; however, to align with the NHS and PSS cost perspective recommended in the NICE methods guide,[36] 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 the impact that the intervention had on health-related quality of life, and in line with the NICE methods guide,[36] the EQ-5D-5L was used, and respondents were asked to report the level of problems (none to extreme/unable) that they had on five dimensions (mobility, self-care, usual activities, pain/discomfort and anxiety/depression).[29] Participants were asked to complete the EQ-5D-5L at discharge from the NSU, and again at 3 and 6 months post randomisation (when 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,[31] the crosswalk mapping function[30] was then used to convert responses into utility scores, where a score of 0 corresponds to death and 1 to full health.[50] Participants who died were assigned a utility score of 0 on their date of death (assuming that this occurred within the 6-month follow-up period). The quality-adjusted life-year (QALY) score that was accrued over the trial period was then estimated for each individual based on the total area-under-the-curve method and the assumption of linear interpolation.[51] In the base-case analysis, the score at the date of discharge was assumed to be the baseline score.

Analyses

Missing data

Missing data are common in randomised trials and can lead to bias and lack of precision.[52] As recommended for within-trial analysis of cost-effectiveness, and in line with previously described methods,[52] multiple imputation (MI) was thereby undertaken in the base-case analysis.

Based on the pattern of missing data, costs were aggregated and imputed at the level of 'total index admission costs' and 'total post-discharge costs'. Costs were imputed at this level because the CRF and patient self-report data had different response rates, despite the fact that individual questions within each of these data types had similar levels of completion. Similarly, where missing, overall EQ-5D-5L utility scores were imputed at NSU discharge and at the 3- and 6-month follow-ups, as response rates differed over time, although if EQ-5D-5L data were missing it was generally across all dimensions.

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 to be missing at random. MI with chained equations under missing at random was, therefore, used and the missing data imputed, by treatment arm, using the 'mi impute chained' command (Stata version 16.0; StataCorp LP, College Station, TX) to create 40 data sets (it is recommended that the number of imputed data sets should be similar to the percentage of incomplete cases[52]), which were then pooled using Rubin's rules.[53]

In addition to the costs (index admission and post discharge) and outcomes (baseline, 3-month and 6-month EQ-5D-5L scores), the MI model included baseline covariates associated ($p < 0.05$) with missing data, costs, outcomes, age and gender.

The MI model was validated by comparing the distributions of the observed and imputed data to check that the distributions were similar.[52]

Cost-effectiveness

The NICE methods guide[36] recommends that costs are estimated from the viewpoint of the NHS and PSS. As a consequence, in the base-case analysis, the previously defined total index admission costs and total post-discharge costs (excluding care home and carer costs) were summed to estimate the overall costs.

A 6-month within-trial analysis was undertaken, for which (after excluding any patients randomised in error) an intention-to-treat approach was adopted, in which participants were analysed within the arm to which they were allocated, regardless of whether or not they adhered to the regimen in question. A within-trial analysis was deemed appropriate because we are not aware of any previous economic evaluations that have compared dexamethasone with placebo for patients with symptomatic CSDH. A previous systematic review[14–16] also failed to identify any RCTs in this population group. No discounting was undertaken because the analysis period matched that of the trial duration (6 months), which is less than 1 year.

To estimate the mean incremental cost and incremental effect (QALY gain) associated with dexamethasone compared with placebo, regression analysis was undertaken, which is generally robust for skewed data and allows for any correlation between costs and effects.[54] All regressions included those baseline variables found to be predictive of total costs and/or outcomes: age (years) and baseline utility score.

We sought to identify whether or not the use of dexamethasone was cost-effective by calculating the net monetary benefit (NMB).[55] The NMB was estimated at the cost-effectiveness thresholds of £20,000 and £30,000 per QALY; if the NMB is estimated to be > 0, the intervention is estimated

to be cost-effective, and if the NMB is estimated to be < 0, the intervention is estimated to be not cost-effective. The NMB was used rather than, for example, the incremental cost-effectiveness ratio (ICER) because a negative ICER is open to misinterpretation: both a negative cost/positive effect and negative effect/positive cost can give the same ICER value, but have different implications for cost-effectiveness.[55]

Decision uncertainty

Based on previous work,[52] the probability of being cost-effective at different thresholds of cost-effectiveness was estimated to enable the cost-effectiveness acceptability curve (CEAC)[56] to be calculated. Here, we report the estimated probability that dexamethasone is cost-effective at the recommended thresholds of £20,000 and £30,000 per QALY.[36]

Sensitivity analyses

The following sensitivity analyses 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[50]). 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 sensitivity analysis (SA1). A complete-case analysis was also undertaken, in which participants were included only if they had complete CRF, PSRQ and QALY data (SA6). No imputation was undertaken within this SA. Finally, to test for the influence of extreme values, a further SA (SA7, based on winsorising) was undertaken. Here, data values below the 5th percentile were replaced with the 5th percentile value and data values above the 95th percentile were replaced with the 95th percentile value. This was applied to the overall cost and total QALY score data for the base-case analysis. Four further sensitivity analyses (SA2, SA3, SA4 and SA5) were planned but not undertaken for reasons explained in the results.

Results

Participants

Between August 2015 and November 2018, 750 patients were randomly assigned to a treatment arm; however, two patients were excluded shortly after randomisation owing to ineligibility (see *Figure 1*). Therefore, 748 patients were enrolled in the trial: 375 in the dexamethasone arm and 373 in the placebo arm. These 748 patients, for whom the baseline characteristics have been outlined (see *Table 2*), constitute the full analysis population used in the base-case and other analyses (unless specified otherwise) in this economic evaluation.

Costs

At NSU discharge, 718 out of 745 (96%) (excluding those that died) participants had complete CRF resource use data.

Table 21 presents the reported levels of resource use for the associated index admission to hospital for both the dexamethasone arm and the placebo arm, based on the available CRF data. This includes the mean number of unilateral/bilateral procedures and postoperative imaging procedures and the mean length of stay in the NSU and ICU/HDU; it can be seen that resource levels are broadly comparable across groups. When combined with the associated unit costs (see *Table 20*), this enabled costs to be estimated for the same resource components and, in turn, the total index admission costs (*Table 22*), which were, again, similar between the two arms.

In terms of patient self-reported resource use data, 513 out of 700 (73%) (excluding those who died) participants had complete data at 6 months, all of whom also had complete CRF data. Based on available data, *Table 23* presents the associated levels of resource use, including overnight stays, further operations, HCP visits and number of scans. It can be seen that levels were again broadly similar in both arms, although the mean duration of stay on a rehabilitation unit was greater in the placebo arm than in the dexamethasone arm (2.023 vs. 1.274 days). This was in large part due to one participant

TABLE 21 Levels of resource use from CRF data (index admission)

Resource use	Treatment arm		Total
	Placebo	Dexamethasone	
Number of surgeries: unilateral or bilateral, *n/N* (%)			
0	29/373 (8)	30/375 (8)	59/748 (8)
1	330/373 (88)	341/375 (91)	671/748 (90)
2	10/373 (3)	1/375 (0.3)	11/748 (1)
3	1/373 (0.2)	0/375 (0)	1/748 (0.1)
Missing	3/373 (0.8)	3/375 (0.8)	6/748 (0.8)
Surgical procedure: unilateral (mean number of operations)			
n	370	372	742
Mean (SD)	0.805 (0.471)	0.755 (0.437)	0.780 (0.455)
Missing	3	3	6
Surgical procedure: bilateral (mean number of operations)			
n	370	372	742
Mean (SD)	0.149 (0.356)	0.167 (0.373)	0.158 (0.365)
Missing	3	3	6
Postoperative imaging, *n/N* (%)			
0	200/373 (54)	210/375 (56)	410/748 (55)
1	161/373 (43)	155/375 (41)	316/748 (42)
2	7/373 (2)	1/375 (0.3)	8/748 (1)
Missing	5/373 (1)	9/375 (2)	14/748 (2)
Postoperative imaging (mean number of procedures)			
n	368	366	734
Mean (SD)	0.476 (0.537)	0.429 (0.501)	0.452 (0.520)
Missing	5	9	14
Stayed in ICU/HDU, *n/N* (%)			
Yes	39/373 (10)	31/375 (8)	70/748 (9)
No	320/373 (86)	330/375 (88)	650/748 (87)
Missing	14/373 (4)	14/375 (4)	28/748 (4)
Length of stay in ICU/HDU (mean number of days)			
n	359	361	720
Mean (SD)	0.320 (1.320)	0.241 (0.997)	0.281 (1.169)
Missing	14	14	28
Length of stay in NSU (mean number of days)			
n	359	361	720
Mean (SD)	8.203 (6.958)	8.321 (6.591)	8.263 (6.772)
Missing	14	14	28

N = number of patients for whom data were available.

TABLE 22 Summary of costs

Cost component	Treatment arm, *n*; mean (SD) cost (£)		*p*-value
	Placebo	Dexamethasone	
Index admission costs			
14-day course of dexamethasone (124 mg in total)	373; 0 (0)	375; 15.01 (0)	–
Surgical procedures: unilateral	370; 1097.60 (642.39)	372; 1029.43 (595.08)	0.134
Surgical procedures: bilateral	370; 303.87 (728.19)	372; 340.70 (762.85)	0.501
Postoperative imaging	368; 37.72 (42.58)	366; 34.02 (39.75)	0.225
Length of stay in NSU	359; 2923.45 (2479.66)	361; 2965.51 (2348.85)	0.815
Length of stay in ICU/HDU	359; 461.74 (1903.25)	361; 347.38 (1437.41)	0.363
Total index admission cost per patient	359;[a] 4820.38 (3496.69)	361;[a] 4726.64 (2873.89)	0.694
Post-index admission costs			
Overnight stays on rehabilitation unit	309; 995.98 (6404.51)	303; 627.30 (3636.01)	0.383
Overnight stays on NSU	309; 146.47 (1080.79)	303; 108.21 (762.37)	0.614
Overnight stays on ICU/HDU	309; 65.31 (1147.99)	303; 66.60 (1159.30)	0.989
Overnight stays on 'other' ward	309; 1018.24 (5099.23)	303; 977.93 (3428.18)	0.909
Number of operations on skull/brain	313; 80.24[b] (355.60)	308; 76.75[b] (349.37)	0.902
HCP visits	272; 237.05 (740.79)	271; 289.67 (55.47)	0.461
Head/brain scans	310; 55.49 (91.66)	292; 54.08 (109.44)	0.863
Total post-discharge cost per patient	258;[c] 2313.38 (8831.96)	255;[d] 1997.36 (6345.51)	0.642
Overall NHS and PSS cost per patient	258;[c] 6869.56 10 to 347.44	255;[d] 6540.55 (7299.00)	0.641

a Data missing for 14 patients.
b Cost per operation based on the proportion of bilateral and unilateral operations reported in the CRF in each treatment arm.
c Data missing for 115 patients.
d Data missing for 120 patients.

Note
n = number of patients for whom data were available.

TABLE 23 Levels of resource use from patient self-report data (post discharge from index admission)

Resource use	Treatment arm		Total
	Placebo	Dexamethasone	
Overnight stays, *n*/*N* (%)			
Yes	78/373 (21)	86/375 (23)	164/748 (22)
No	235/373 (63)	222/375 (59)	457/748 (61)
Missing	60/373 (16)	67/375 (18)	127/748 (17)
Length of stay in rehabilitation unit			
n	309	303	612
Mean (SD)	2.023 (13.006)	1.274 (7.384)	1.652 (10.600)
Missing	64	72	136

TABLE 23 Levels of resource use from patient self-report data (post discharge from index admission) (*continued*)

Resource use	Treatment arm		Total
	Placebo	Dexamethasone	
Length of stay in NSU			
n	309	303	612
Mean (SD)	0.411 (3.033)	0.304 (2.139)	0.358 (2.627)
Missing	64	72	136
Length of stay in ICU/HDU			
n	309	303	612
Mean (SD)	0.045 (0.796)	0.046 (0.804)	0.046 (0.800)
Missing	64	72	136
Length of stay on other ward			
n	309	303	612
Mean (SD)	2.945 (14.75)	2.828 (9.915)	2.887 (12.58)
Missing	64	72	136
Operations to skull/brain			
n	313	308	748
Mean (SD)	0.054 (0.241)	0.052 (0.236)	0.053 (0.238)
Missing	60	67	127
HCP contact			
Yes	159/373 (43)	162/375 (43)	321/748 (43)
No	155/373 (42)	144/375 (38)	299/748 (40)
Missing	59/373 (16)	69/375 (18)	128/748 (17)
HCP visits[a]			
n	302	297	599
Mean (SD)	7.463 (34.922)	8.199 (42.437)	7.828 (38.800)
Missing	71	78	149
Head/brain scans, *n*/*N* (%)			
Yes	126/373 (38)	110/375 (29)	236/748 (32)
No	187/373 (50)	188/375 (50)	375/748 (50)
Missing	60/373 (16)	77/375 (21)	137/748 (18)
Head/brain scans[b]			
n	310	292	602
Mean (SD)	0.597 (0.996)	0.589 (1.202)	0.593 (1.100)
Missing	63	83	146

a Summary of variables, which were broken down and reported as described in *Table 20*.
b Summary of variables, which were broken down into MRI scans, CT scans, other scans and unknown scans.

Note
n = number of patients for whom data were available.

in the placebo arm, who had an exceptionally long single stay of 200 days on a rehabilitation unit. By combining these resource levels with associated unit costs (see *Table 20*) post-discharge costs were estimated (see *Table 22*). Again, costs were broadly similar between arms, and if the aforementioned participant (in the placebo arm) who had an extended stay in a rehabilitation unit is removed from the analysis, then the mean difference is reduced [£1997 (n = 255) dexamethasone arm vs. £1932 (n = 257) placebo arm; p = 0.907]. Results between arms were also similar when the index admission and post-discharge costs (excluding care home and carer costs) were summed to estimate per-patient overall NHS and PSS costs (see *Table 22*). Again, if the participant who had an extended stay in a rehabilitation unit is removed from the analysis, the mean difference is reduced [£6541 (n = 255) dexamethasone arm vs. £6458 (n = 257) placebo arm; p = 0.903].

Outcomes

There were ≥ 82% complete EQ-5D-5L data at all time points (NSU discharge and 3 and 6 months post randomisation), and 504 out of 748 (67%) participants had complete EQ-5D-5L data at all time points (those who died were given an EQ-5D-5L score of '0' and would, therefore, not be recorded as 'missing') (*Table 24*).

Table 24 shows the mean EQ-5D-5L utility scores at each time point on an available case basis, along with the change in score at each time point. The EQ-5D-5L scores at each time point were higher (non-significant at baseline and 6 months; p = 0.008 at 3 months) in the placebo arm than the dexamethasone arm. This is in keeping with the primary end point of the study, which reported a favourable outcome in the placebo arm compared with the dexamethasone arm.

Analyses

Cost-effectiveness

Table 25 presents estimates of mean incremental costs and incremental QALYs, which were generated from multiple regression (both costs and QALYs adjusted for EQ-5D-5L at NSU discharge and age), along with NMB and probability of being cost-effective at thresholds (λ) of £20,000 and £30,000 per QALY.

For the base-case analysis (based on intention to treat/MI), the mean difference in cost for the dexamethasone arm compared with the placebo arm was −£143.73 (95% CI −£1793 to £1505), with a mean QALY difference of −0.012 (95% CI −0.027 to 0.003). That is, the mean total cost and QALY scores were both slightly lower in the dexamethasone arm than in the placebo arm, although neither of these differences was significantly different. The resulting NMB for the base-case analysis at a £20,000 threshold was −£97.19, which means that dexamethasone was not estimated to be cost-effective compared with placebo.

TABLE 24 Secondary outcomes used in economic analysis

Item	Treatment arm, *n*; mean (SD)		*p*-value
	Placebo	Dexamethasone	
Baseline EQ-5D-5L score	306; 0.727 (0.265)	307; 0.697 (0.293)	0.183
3-month EQ-5D-5L score	316; 0.773 (0.291)	316; 0.707 (0.337)	0.008
3-month change in EQ-5D-5L score	275; 0.065 (0.273)	273; 0.282 (0.287)	0.126
6-month EQ-5D-5L score	315; 0.766 (0.320)	311; 0.733 (0.348)	0.211
6-month change in EQ-5D-5L score	276; 0.054 (0.294)	271; 0.036 (0.300)	0.456
QALY score	256; 0.395 (0.117)	248; 0.367 (0.146)	0.020

n = number of patients for whom data were available.

TABLE 25 Estimates of the mean incremental cost, incremental effect and cost-effectiveness of dexamethasone, compared with placebo, in the base-case and sensitivity analyses

Analysis (*Nd*, *Np*)	Incremental cost (£) (95% CI)	QALY gain (95% CI)	NMB at £20,000 threshold (£)	CEAC at £20,000 threshold (%)	NMB at £30,000 threshold (£)	CEAC at £30,000 threshold (%)
Base case: MI 375, 373	−143.73 (−1793 to 1505)	−0.012 (−0.027 to 0.003)	−97.19	46	−217.65	41
SA0 [analysis without patient N36112 (outlier)]: MI 375, 372	381.98 (−1265 to 2029)	−0.013 (−0.028 to 0.002)	−632.39	24	−757.59	21
SA1: MI 375, 373	2446.70 (−1339 to 6233)	−0.011 (−0.026 to 0.004)	−2664.08	9	−2773.00	8
SA6: MI 189, 196	−64.46 (−1099 to 970)	−0.008 (−0.022 to 0.006)	−93.27	44	−172.14	39
SA7: MI 375, 373	292.66 (−615 to 1201)	−0.011 (−0.025 to 0.004)	−508.66	17	−616.67	14

Nd/*Np*, number of patients randomised to dexamethasone/placebo who were included in the analysis.
Estimated probability of being cost-effective on the CEAC at the threshold (λ) of £20,000/£30,000 per QALY.

Note
SA0, SA1, SA6 and SA7 refer to the different sensitivity analyses described in the Methods.

Decision uncertainty

In terms of uncertainty, the base-case probability that dexamethasone is cost-effective at a threshold of £20,000 was 46% (see *Table 25*). This indicates that there was a high degree of uncertainty associated with the decision that dexamethasone was not cost-effective (*Figure 10*). However, given that it is argued that decisions about provision should be based on the mean estimates of costs and benefits (regardless of the quality of data available[57]), this does not alter the assertion that dexamethasone was not estimated to be cost-effective compared with placebo.

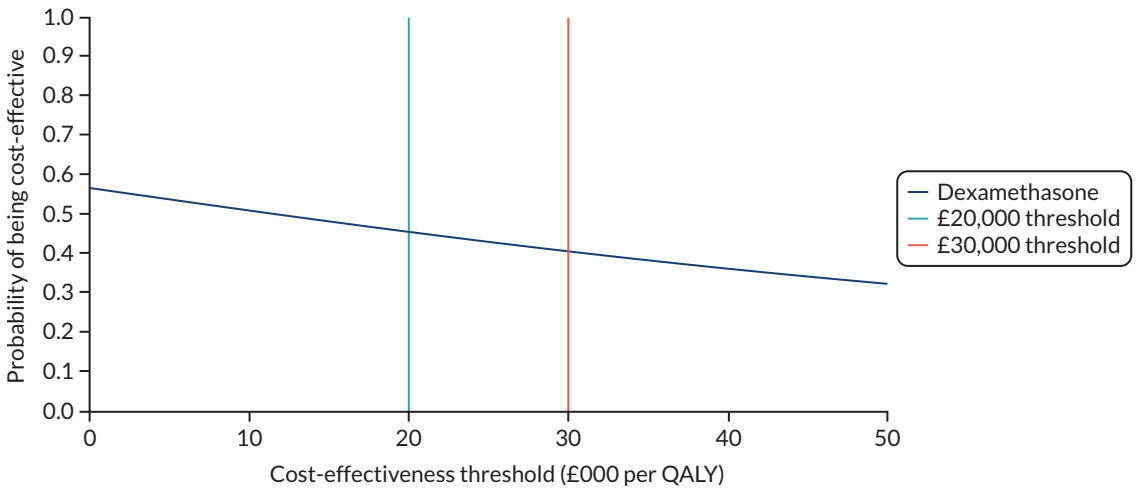

FIGURE 10 Cost-effectiveness acceptability curve for dexamethasone compared with placebo.

Sensitivity analyses

The results of the sensitivity analyses that were undertaken are shown in *Table 25*. In all of these analyses (at a willingness-to-pay threshold of both £20,000 and £30,000 per QALY), dexamethasone is not estimated to be cost-effective compared with placebo. SA2 was deemed unnecessary because the mean length of stay in the NSU was estimated to be only 8 days and virtually the same in both arms (see *Table 2*). Consequently, using linear interpolation to estimate what the EQ-5D-5L scores would have been at the date of admission to the NSU (an average of 8 days prior to their discharge date) was deemed superfluous because it would have had a negligible impact on estimated QALY scores. SA3 was not undertaken for similar reasons: for the primary outcome the results for the full analysis population (see *Table 4*) were virtually the same as that for the per-protocol analyses (see *Table 29*). This was also true for the EQ-5D-5L (see *Tables 9* and *52*). In addition, there would be no impact on intervention costs because it was assumed that each participant in the intervention arm was prescribed the same course of dexamethasone and that the medication could not be reused if it was not taken (see Methods). Similarly, SA4 and SA5 were deemed unnecessary because there was no significant difference between arms in terms of the number of subsequent admissions based on CRF data.

Discussion

Main findings

On the basis of the estimated negative NMB (at willingness-to-pay thresholds of £20,000 and £30,000 per QALY), dexamethasone is not estimated to be cost-effective compared with placebo for the treatment of patients with symptomatic CSDH (see *Table 25*). This is in keeping with the results for the primary outcome, which also favoured the placebo arm (see *Table 25*), and the same result was found in each of the sensitivity analyses that were conducted (see *Table 25*). That said, there is a degree of uncertainty associated with the decision regarding cost-effectiveness, with an estimated 46% probability (at a willingness-to-pay threshold of £20,000 per QALY) of making the wrong decision by not using dexamethasone in these patients. However, given that economists tend to focus on mean values[57] (here that is the negative NMB estimates) the implication is not to use dexamethasone in this population of patients.

Comparisons with other studies

We are not aware of any previous economic evaluations that have compared dexamethasone with placebo for patients with symptomatic CSDH. Most patients in this study were treated surgically during their index admission, which limits the ability of the study to draw conclusions regarding the use of dexamethasone as a non-surgical alternative. The DECSA trial,[58] which includes an economic evaluation but was yet to report at the time of writing, seeks to compare the effect of primary dexamethasone therapy with primary burr hole craniotomy on functional outcome and cost-effectiveness in a similar population group (symptomatic CSDH).

Study limitations

In line with good practice recommendations for cost-effectiveness analyses,[38] 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 resource use levels could be heavily influenced by outliers owing to the high unit costs associated with resource use, such as length of stay in critical care and rehabilitation units. One such example was the aforementioned participant (in the placebo arm) who had an extended stay in a rehabilitation unit, who, when removed from the analysis, resulted in an increase in the incremental cost for dexamethasone compared with placebo. The conclusions were, however, unchanged when winsorising was undertaken, and the influence of outliers was reduced (see *Table 25*).

Regarding health-related quality of life, QALY scores (EQ-5D-5L recorded at all time points) were available for approximately 67% of participants only (see *Table 24*). Some of the missing EQ-5D-5L

baseline (NSU discharge) data may be because of patients being discharged at short notice or at the weekend when a research nurse was not available. Such missing data are a limitation, but it should be noted that the same conclusion can be drawn from the results of both the complete-case and the imputed analyses.

A further potential limitation is that, for ethics reasons, baseline quality-of-life (EQ-5D-5L) scores were taken at discharge from the NSU rather than at the point of randomisation. The date of discharge from the NSU is post intervention and there is, therefore, the potential for any benefits associated with the intervention to be underestimated by assuming the score at the date of discharge to be the baseline score. In this study, the mean length of stay was approximately 8–9 days and was similar between arms. For this reason, if there had been an additional quality-of-life measurement point at randomisation, we consider that any change in QALY scores would have been negligible and not have changed the study conclusion. Similarly, given that a per-protocol analysis favoured the placebo arm, there is no evidence that any lack of compliance had an impact on study results.

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 placebo arm compared with the dexamethasone arm, while the costs would remain similar between the two arms.

The main strength of this economic evaluation is that it is based on a large, multicentre, randomised study. Previous evidence, in the form of a systematic review,[14–16] was based on five small observational studies and stated that there is a lack of well-designed trials to support or refute the use of corticosteroids for CSDH.

Conclusion

Our economic evaluation has shown that in a UK population of patients with symptomatic CSDH, most of whom underwent surgery during their index admission, dexamethasone was not estimated to be cost-effective compared with placebo. Some uncertainty was estimated to be associated with that decision. In addition, when a number of sensitivity analyses were conducted, the main conclusion, that dexamethasone was not estimated to be cost-effective compared with placebo, was unchanged. Consequently, given that economists tend to focus on the mean estimated values of cost and effect, the health economic analysis supports the aforementioned recommendation (based on the primary outcome) not to use dexamethasone in this population of patients.

Chapter 5 Discussion

Key findings

The results of our literature review indicate that this is the first multicentre RCT of dexamethasone in addition to standard care (including surgery) in patients with CSDH. There was a higher rate of unfavourable outcome (mRS score of 4–6) at 6 months among patients who received a 14-day course of dexamethasone (16.1%), than among those who received placebo (9.70%). Therefore, dexamethasone resulted in an absolute risk increase of 6.4%. This finding does not support routine use of dexamethasone as part of standard care in this patient population because it is associated with harm. In addition, given that there is a cost associated with the medication, which would be saved if it was no longer provided, it is estimated that dexamethasone is not cost-effective and that scarce NHS resources would be better spent on other healthcare interventions.

Consistent with previous studies, dexamethasone did reduce the recurrence rate compared with that in the placebo arm. Previous studies have shown that reductions in recurrence also appear to be related to a reduction in mortality.[7] In this study, patients with recurrent CSDH in the dexamethasone arm also did worse than those with recurrent CSDH in the placebo arm. Overall, despite fewer CSDH recurrences, patients had a worse outcome with dexamethasone and a higher mortality at 6 months (8% vs. 5% for the dexamethasone and placebo arm, respectively).

There is widespread reporting of the potential adverse effects of dexamethasone, which are dose related. A short course of only 14 days was applied in this study; however, the number of SAEs reported was larger in the dexamethasone arm than in the placebo arm. In particular, there were more infections (6.4% vs. 1.1%) in the dexamethasone arm than the placebo arm.

Limitations of this study include the fact that 94% of patients received surgery in addition to the trial treatment; therefore, these results cannot necessarily be generalised to patients who are managed conservatively with medication alone. Exploratory subgroup analysis of patients non-operatively managed were in the same direction of effect as the primary analysis, which could be examined further in appropriately powered research.

The co-ordinating centre recruited approximately one-third of patients, meaning that a large proportion of patients originated from one region of the UK. There was no significant difference in outcome between this site and others, which suggests that this has little impact on the generalisability of the data. The pragmatic study design allowed the recruitment target to be met, and the baseline characteristics of patients reflect those reported in previous CSDH studies; therefore, we think that these results are generalisable to the surgical CSDH population.

In total, 9% of patients were lost to follow-up at 6 months, which reduced the sample size informing the primary outcome measure of the trial. This was, however, within the limits of our sample size calculation, which had allowed for up to 15% loss to follow-up. The percentage was similar in both arms, which suggests that this limitation did not influence the study's findings.

The characteristic adverse effects, such as steroid-induced hyperglycaemia, may have alerted clinical teams to the trial-arm assignment.

Follow-up imaging to assess the size of CSDHs were not mandated, meaning that the impact of dexamethasone of haematoma size was not assessed. This was unlikely to impact the results of this pragmatic trial given that such follow-up imaging after evacuation is not beneficial in terms of patient outcomes at 6 months.[59]

Chapter 6 Conclusions

In conclusion, dexamethasone increases the rate of unfavourable outcome at 6 months in surgically treated CSDH patients compared with placebo. Therefore, this study does not recommend its use in routine clinical practice for this patient group.

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Protocol

The published trial protocol is available online.[2]

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All authors drafted and/or critically revised the report for important intellectual content. Please note that job titles may reflect those at the time of the trial rather than current position.

Publications

Kolias A, Edlmann E, Hutchinson PJ. The role of pharmacotherapy in the management of chronic subdural haematoma. *Swiss Med Wkly* 2017;**147**:w14479.

Kolias AG, Edlmann E, Thelin EP, Bulters D, Holton P, Suttner N, *et al*. Dexamethasone for adult patients with a symptomatic chronic subdural haematoma (Dex-CSDH) trial: study protocol for a randomised controlled trial. *Trials* 2018;**19**:670.

Allison A, Edlmann E, Kolias AG, Davis-Wilkie C, Mee H, Thelin EP, *et al*. Statistical analysis plan for the Dex-CSDH trial: a randomised, double-blind, placebo-controlled trial of a 2-week course of dexamethasone for adult patients with a symptomatic chronic subdural haematoma. *Trials* 2019;**20**:698.

Edlmann E, Thelin EP, Caldwell K, Turner C, Whitfield P, Bulters D, *et al*. Dex-CSDH randomised, placebo-controlled trial of dexamethasone for chronic subdural haematoma: report of the internal pilot phase. *Sci Rep* 2019;**9**:5885.

Edlmann E, Whitfield PC, Kolias A, Hutchinson PJ. Pathogenesis of chronic subdural hematoma: a cohort evidencing de novo and transformational origins. *J Neurotrauma* 2021;**38**:2580–9.

Hutchinson PJ, Edlmann E, Bulters D, Zolnourian A, Holton P, Suttner N, *et al*. Trial of dexamethasone for chronic subdural hematoma. *N Engl J Med* 2020;**383**:2616–27.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data are 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 is important that there are safeguards to make sure that they are 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.

References

1. Kolias AG, Chari A, Santarius T, Hutchinson PJ. Chronic subdural haematoma: modern management and emerging therapies. *Nat Rev Neurol* 2014;**10**:570–8. https://doi.org/10.1038/nrneurol.2014.163
2. Kolias AG, Edlmann E, Thelin EP, Bulters D, Holton P, Suttner N, *et al.* Correction to: dexamethasone for adult patients with a symptomatic chronic subdural haematoma (Dex-CSDH) trial: study protocol for a randomised controlled trial. *Trials* 2019;**20**:1–14. https://doi.org/10.1186/s13063-019-3283-x
3. Hutchinson PJ, Edlmann E, Bulters D, Zolnourian A, Holton P, Suttner N, *et al.* Trial of dexamethasone for chronic subdural hematoma. *N Engl J Med* 2020;**383**:2616–27. https://doi.org/10.1056/NEJMoa2020473
4. Ducruet AF, Grobelny BT, Zacharia BE, Hickman ZL, DeRosa PL, Andersen KN, *et al.* The surgical management of chronic subdural hematoma. *Neurosurg Rev* 2012;**35**:155–69. https://doi.org/10.1007/s10143-011-0349-y
5. Beard JR, Officer A, de Carvalho IA, Sadana R, Pot AM, Michel JP, *et al.* The World report on ageing and health: a policy framework for healthy ageing. *Lancet* 2016;**387**:2145–54. https://doi.org/10.1016/S0140-6736(15)00516-4
6. Balser D, Farooq S, Mehmood T, Reyes M, Samadani U. Actual and projected incidence rates for chronic subdural hematomas in United States Veterans Administration and civilian populations. *J Neurosurg* 2015;**123**:1209–15. https://doi.org/10.3171/2014.9.JNS141550
7. Santarius T, Kirkpatrick PJ, Ganesan D, Chia HL, Jalloh I, Smielewski P, *et al.* Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: a randomised controlled trial. *Lancet* 2009;**374**:1067–73. https://doi.org/10.1016/S0140-6736(09)61115-6
8. Brennan PM, Kolias AG, Joannides AJ, Shapey J, Marcus HJ, Gregson BA, *et al.* The management and outcome for patients with chronic subdural hematoma: a prospective, multicenter, observational cohort study in the United Kingdom. *J Neurosurg* 2017;**127**:732–9. https://doi.org/10.3171/2016.8.JNS16134
9. Wada T, Kuroda K, Yoshida Y, Ogasawara K, Ogawa A, Endo S. Local elevation of the anti-inflammatory interleukin-10 in the pathogenesis of chronic subdural hematoma. *Neurosurg Rev* 2006;**29**:242–5. https://doi.org/10.1007/s10143-006-0019-7
10. Hong HJ, Kim YJ, Yi HJ, Ko Y, Oh SJ, Kim JM. Role of angiogenic growth factors and inflammatory cytokine on recurrence of chronic subdural hematoma. *Surg Neurol* 2009;**71**:161–5. https://doi.org/10.1016/j.surneu.2008.01.023
11. Stanisic M, Aasen AO, Pripp AH, Lindegaard KF, Ramm-Pettersen J, Lyngstadaas SP, *et al.* Local and systemic pro-inflammatory and anti-inflammatory cytokine patterns in patients with chronic subdural hematoma: a prospective study. *Inflamm Res* 2012;**61**:845–52. https://doi.org/10.1007/s00011-012-0476-0
12. Frati A, Salvati M, Mainiero F, Ippoliti F, Rocchi G, Raco A, *et al.* Inflammation markers and risk factors for recurrence in 35 patients with a posttraumatic chronic subdural hematoma: a prospective study. *J Neurosurg* 2004;**100**:24–32. https://doi.org/10.3171/jns.2004.100.1.0024
13. Suzuki M, Endo S, Inada K, Kudo A, Kitakami A, Kuroda K, Ogawa A. Inflammatory cytokines locally elevated in chronic subdural haematoma. *Acta Neurochir* 1998;**140**:51–5. https://doi.org/10.1007/s007010050057

14. Sun TF, Boet R, Poon WS. Non-surgical primary treatment of chronic subdural haematoma: preliminary results of using dexamethasone. *Br J Neurosurg* 2005;**19**:327–33. https://doi.org/10.1080/02688690500305332

15. Delgado-López PD, Martín-Velasco V, Castilla-Díez JM, Rodríguez-Salazar A, Galacho-Harriero AM, Fernández-Arconada O. Dexamethasone treatment in chronic subdural haematoma. *Neurocirugia* 2009;**20**:346–59. https://doi.org/10.1016/S1130-1473(09)70154-X

16. Berghauser Pont LM, Dirven CM, Dippel DW, Verweij BH, Dammers R. The role of corticosteroids in the management of chronic subdural hematoma: a systematic review. *Eur J Neurol* 2012;**19**:1397–403. https://doi.org/10.1111/j.1468-1331.2012.03768.x

17. Chan DYC, Sun TFD, Poon WS. Steroid for chronic subdural hematoma? A prospective phase IIB pilot randomized controlled trial on the use of dexamethasone with surgical drainage for the reduction of recurrence with reoperation. *Chinese Neurosurg J* 2015;**1**:30–2. https://doi.org/10.1186/s41016-015-0005-4

18. Holl DC, Volovici V, Dirven CMF, van Kooten F, Miah IP, Jellema K, *et al.* Corticosteroid treatment compared with surgery in chronic subdural hematoma: a systematic review and meta-analysis. *Acta Neurochir* 2019;**161**:1231–42. https://doi.org/10.1007/s00701-019-03881-w

19. Kawai S, Ichikawa Y, Homma M. Differences in metabolic properties among cortisol, prednisolone, and dexamethasone in liver and renal diseases: accelerated metabolism of dexamethasone in renal failure. *J Clin Endocrinol Metab* 1985;**60**:848–54. https://doi.org/10.1210/jcem-60-5-848

20. Reulen HJ, Hadjidimos A, Hase U. Steroids in the treatment of brain edema. In Schürmann K, Brock M, Reulen HJ, Voth D, editors. *Brain Edema/Cerebello Pontine Angle Tumors. Advances in Neurosurgery, vol 1*. Berlin: Springer; 1973. pp. 92–105.

21. Lipman AG. MARTINDALE: 'Martindale – the Extra Pharmacopoeia' (30th ed), edited by J. E. F. Reynolds. *Int J Pharm Pract* 1993;**2**:124. https://doi.org/10.1111/j.2042-7174.1993.tb00740.x

22. Manson SC, Brown RE, Cerulli A, Vidaurre CF. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. *Respir Med* 2009;**103**:975–94. https://doi.org/10.1016/j.rmed.2009.01.003

23. Emich S, Richling B, McCoy MR, Al-Schameri RA, Ling F, Sun L, *et al.* The efficacy of dexamethasone on reduction in the reoperation rate of chronic subdural hematoma – the DRESH study: straightforward study protocol for a randomized controlled trial. *Trials* 2014;**15**:6. https://doi.org/10.1186/1745-6215-15-6

24. Teasdale G, Allan D, Brennan P, McElhinney E, Mckinnon L. Forty years on: updating the Glasgow Coma Scale. *Nurs Times* 2014;**110**:12–6.

25. Bruno A, Akinwuntan AE, Lin C, Close B, Davis K, Baute V, *et al.* Simplified modified rankin scale questionnaire: reproducibility over the telephone and validation with quality of life. *Stroke* 2011;**42**:2276–9. https://doi.org/10.1161/STROKEAHA.111.613273

26. Sulter G, Steen C, De Keyser J. Acute stroke trials. *Stroke* 1999:1538–1541. https://doi.org/10.1161/01.STR.30.8.1538

27. Janssen MF, Pickard AS, Golicki D, Gudex C, Niewada M, Scalone L, *et al.* Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study. *Qual Life Res* 2013;**22**:1717–27. https://doi.org/10.1007/s11136-012-0322-4

28. Chari A, Hocking KC, Broughton E, Turner C, Santarius T, Hutchinson PJ, Kolias AG. Core outcomes and common data elements in chronic subdural hematoma: a systematic review of the literature focusing on reported outcomes. *J Neurotrauma* 2016;**33**:1212–9. https://doi.org/10.1089/neu.2015.3983

29. Herdman M, Gudex C, Lloyd A, Janssen M, Kind P, Parkin D, *et al.* Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res* 2011;**20**:1727–36. https://doi.org/10.1007/s11136-011-9903-x

30. van Hout B, Janssen MF, Feng YS, Kohlmann T, Busschbach J, Golicki D, *et al.* Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health* 2012;**15**:708–15. https://doi.org/10.1016/j.jval.2012.02.008

31. National Institute for Health and Care Excellence (NICE). *Position Statement on Use of the EQ-5D-5L Value Set for England (Updated October 2019)*. London: NICE; 2019. URL: www.nice.org.uk/ about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l (accessed 5 October 2020).

32. Allison A, Edlmann E, Kolias AG, Davis-Wilkie C, Mee H, Thelin EP, *et al.* Statistical analysis plan for the Dex-CSDH trial: a randomised, double-blind, placebo-controlled trial of a 2-week course of dexamethasone for adult patients with a symptomatic chronic subdural haematoma. *Trials* 2019;**20**:698. https://doi.org/10.1186/s13063-019-3866-6

33. Peugh JL, Strotman D, Mcgrady M, Rausch J, Kashikar-Zuck S. Beyond intent to treat (ITT): a complier average causal effect (CACE) estimation primer. *J Sch Psychol* 2017;**60**:7–24. https://doi.org/10.1016/j.jsp.2015.12.006

34. Koladjo BF, Escolano S, Tubert-Bitter P. Instrumental variable analysis in the context of dichotomous outcome and exposure with a numerical experiment in pharmacoepidemiology. *BMC Med Res Methodol* 2018;**18**:61. https://doi.org/10.1186/s12874-018-0513-y

35. Husereau D, Drummond M, Petrou S, Carswell C, Moher D, Greenberg D, *et al.* Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Cost Eff Resour Alloc* 2013;**11**:6. https://doi.org/10.1186/1478-7547-11-6

36. National Institute for Health and Care Excellence (NICE). *Guide to the Methods of Technology Appraisal 2013. Process and Methods [PMG9]*. London: NICE; 2013. URL: www.nice.org.uk/guidance/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781 (accessed 15 September 2021).

37. Curtis L, Burns A. *Unit Costs of Health and Social Care 2019*. Canterbury: PSSRU, University of Kent; 2019.

38. Ramsey SD, Willke RJ, Glick H, Reed SD, Augustovski F, Jonsson B, *et al.* Cost-effectiveness analysis alongside clinical trials II-An ISPOR Good Research Practices Task Force report. *Value Health* 2015;**18**:161–72. https://doi.org/10.1016/j.jval.2015.02.001

39. NHS Digital. *Prescription Cost Analysis – England, 2018 [PAS]*. 2018. URL: https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/2018. *Published* 2017 (accessed 5 September 2021).

40. NHS Digital. *Prescription Cost Analysis – England, 2017*. 2017. URL: https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/prescription-cost-analysis-england-2017 (accessed January 2020).

41. Public Health Scotland. *R142X: Theatre – Direct Cost per Hour, by Specialty*. Edinburgh: Public Health Scotland; 2018.

42. NHS Improvement. *NHS Reference Costs*. London: NHS Improvement; 2018.

43. Turner-Stokes L, Williams H, Bill A, Bassett P, Sephton K. Cost-efficiency of specialist inpatient rehabilitation for working-aged adults with complex neurological disabilities: a multicentre cohort analysis of a national clinical data set. *BMJ Open* 2016;**6**:e010238. https://doi.org/10.1136/bmjopen-2015-010238

44. Curtis L, Burns A. *Unit Costs of Health and Social Care 2018*. Canterbury: PSSRU, University of Kent; 2018.
45. Curtis L. *Unit Costs of Health and Social Care 2015*. Canterbury: PSSRU, University of Kent; 2015.
46. Curtis L. *Unit Costs of Health and Social Care 2010*. Canterbury: PSSRU, University of Kent; 2010.
47. Curtis L, Burns A. *Unit Costs of Health and Social Care 2017*. Canterbury: PSSRU, University of Kent; 2017.
48. Office for National Statistics. *Earnings and Hours Worked, All Employees: ASHE Table 1*. London: Office for National Statistics; 2018.
49. Hoefman RJ, van Exel J, Brouwer W. How to include informal care in economic evaluations. *PharmacoEconomics* 2013;**31**:1105–19. https://doi.org/10.1007/s40273-013-0104-z
50. Drummond M, Sculpher M, Claxton K, Stoddart G, Torrance G. *Methods for the Economic Evaluation of Health Care Programmes*. 4th edn. Oxford: Oxford University Press; 2015.
51. Manca A, Palmer S. Handling missing data in patient-level cost-effectiveness analysis alongside randomised clinical trials. *Appl Health Econ Health Policy* 2005;**4**:65–75. https://doi.org/10.2165/00148365-200504020-00001
52. Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *PharmacoEconomics* 2014;**32**:1157–70. https://doi.org/10.1007/s40273-014-0193-3
53. Little R, Rubin D. *Statistical Analysis with Missing Data*. 2nd edn. Hoboken, NJ: Wiley; 2014.
54. Willan AR, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Econ* 2004;**13**:461–75. https://doi.org/10.1002/hec.843
55. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making* 1998;**18**(Suppl. 2):68–80. https://doi.org/10.1177/0272989X98018002S09
56. Fenwick E, O'Brien BJ, Briggs A. Cost-effectiveness acceptability curves – facts, fallacies and frequently asked questions. *Health Econ* 2004;**13**:405–15. https://doi.org/10.1002/hec.903
57. Claxton K. The irrelevance of inference: a decision-making approach to the stochastic evaluation of health care technologies. *J Health Econ* 1999;**18**:341–64. https://doi.org/10.1016/S0167-6296(98)00039-3
58. Miah IP, Holl DC, Peul WC, Walchenbach R, Kruyt N, de Laat K, *et al.* Dexamethasone therapy versus surgery for chronic subdural haematoma (DECSA trial): study protocol for a randomised controlled trial. *Trials* 2018;**19**:575. https://doi.org/10.1186/s13063-018-2945-4
59. Schucht P, Fischer U, Fung C, Bernasconi C, Fichtner J, Vulcu S, *et al.* Follow-up computed tomography after evacuation of chronic subdural hematoma. *N Engl J Med* 2019;**380**:1186–7. https://doi.org/10.1056/NEJMc1812507

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Appendix 2 List of protocol amendments

The following changes were introduced in version 2 of the protocol (1 March 2016):

- Removal of Montreal Cognitive Assessment (MOCA) from secondary outcomes.
- Eligibility criteria refined with respect to previous history of steroids.
- Exclusion criterion changed from 'patients who are on steroids' to 'patients who are on (or within 1 month of) regular oral or intravenous steroids'.
- It was also clarified that 'patients on topical or inhaled steroids are allowed to be recruited into the trial, as are patients who have had 1 intraoperative dose of dexamethasone for anti-emesis'.
- Addition of objectives/end points for a mechanistic substudy (blood and CSDH fluid biomarkers and imaging – this study recruited only at Addenbrooke's and is not part of the accompanying publication 'Trial of dexamethasone for chronic subdural hematoma').

The following changes were introduced in version 3 of the protocol (27 April 2017):

- The interim analysis wording was amended from 'after 100 patients in the stage 1 phase have observed 6-month follow-up in order to confirm the sample size' to 'after an appropriate number of patients have observed 6-month follow-up, in order to confirm the sample size, the TSC, independent DMEC and statistical team will agree jointly on the most appropriate timing of this interim analysis, taking into account the case mix and parameters the independent DMEC wishes to estimate'.
- 'CT/MRI' was added in the second inclusion criterion to further clarify what 'cranial imaging' stands for.
- 'Glucocorticoids' was added in the second exclusion criterion to clarify the type of steroids.
- The eligibility criteria for the mechanistic substudy were refined (please note that these did not affect the eligibility criteria for the main study reported in the accompanying publication).
- The windows for the 3-month and 6-month follow-up periods changed from ± 3 weeks to −4 weeks/+ 8 weeks.
- 'Hyperglycaemia necessitating stopping of trial medication' was added as an AESI.

Appendix 3 Trial results

TABLE 26 Concurrent illnesses and medical conditions

Comorbidity	Treatment arm, *n/N* (%)		Total, *n/N* (%)
	Placebo	Dexamethasone	
Diabetes	54/373 (14.5)	55/375 (14.7)	109/748 (14.6)
Ischaemic heart disease	50/373 (13.4)	58/375 (15.5)	108/748 (14.4)
Atrial fibrillation	68/373 (18.2)	88/375 (23.5)	156/748 (20.9)
Metallic heart valve	7/373 (1.9)	9/375 (2.4)	16/748 (2.1)
DVT/PE	19/373 (5.1)	24/375 (6.4)	43/748 (5.7)
Stroke	39/373 (10.5)	34/375 (9.1)	73/748 (9.8)
Previous CSDH	5/373 (1.3)	9/375 (2.4)	14/748 (1.9)
Epilepsy	11/373 (2.9)	15/375 (4)	26/748 (3.5)
Dementia	21/373 (5.6)	19/375 (5.1)	40/748 (5.3)
COPD	25/373 (6.7)	33/375 (8.8)	58/748 (7.8)
Liver disease	9/373 (2.4)	9/375 (2.4)	18/748 (2.4)
Current malignancy	16/373 (4.3)	13/375 (3.5)	29/748 (3.9)
Other	284/373 (76.1)	273/375 (72.8)	557/748 (74.5)

COPD, chronic obstructive pulmonary disease; DVT, deep-vein thrombosis; PE, pulmonary embolism.

TABLE 27 Prior and current conditions (full analysis population)

Treatment	Treatment arm, *n/N* (%)		Total, *n/N* (%)
	Placebo	Dexamethasone	
Anticoagulants			
Aspirin only	57/368 (15.5)	63/370 (17)	120/738 (16.3)
Clopidogrel only	18/368 (4.9)	16/370 (4.3)	34/738 (4.6)
Warfarin only	52/368 (14.1)	77/370 (20.8)	129/738 (17.5)
Other anticoagulant only	21/368 (5.7)	17/370 (4.6)	38/738 (5.1)
Combination of anticoagulants	18/368 (4.9)	5/370 (1.4)	23/738 (3.1)
Other anticoagulant categories			
Apixaban	8/373 (2.1)	7/375 (1.9)	15/748 (2)
Dabigatran	1/373 (0.3)	1/375 (0.3)	2/748 (0.3)
Dipyridamole	3/373 (0.8)	1/375 (0.3)	4/748 (0.5)
Edoxaban	1/373 (0.3)	1/375 (0.3)	2/748 (0.3)
LMWH	6/373 (1.6)	2/375 (0.5)	8/748 (1.1)
Rivaroxaban	8/373 (2.1)	7/375 (1.9)	15/748 (2)
Ticagrelor	2/373 (0.5)	1/375 (0.3)	3/748 (0.4)

continued

TABLE 27 Prior and current conditions (full analysis population) (*continued*)

Treatment	Treatment arm, *n/N* (%)		Total, *n/N* (%)
	Placebo	Dexamethasone	
Other treatments			
Non-steroidal anti-inflammatory drugs	22/368 (6)	30/371 (8.1)	52/739 (7)
Diuretics	52/368 (14.1)	53/371 (14.3)	105/739 (14.2)
Immunosuppressants	7/368 (1.9)	3/371 (0.8)	10/739 (1.4)
ACE inhibitors	91/368 (24.7)	75/371 (20.2)	166/739 (22.5)
Antacids/proton pump inhibitors	102/368 (27.7)	115/371 (31)	217/739 (29.4)

ACE, angiotensin-converting enzyme; LMWH, low-molecular-weight heparin.

TABLE 28 Summary of blood or clotting products given (full analysis population)

	Treatment arm, *n/N* (%)		Total, *n/N* (%)
	Placebo	Dexamethasone	
Blood or clotting products given			
Yes	80/373 (21.4)	96/374 (25.7)	176/747 (23.6)
Product type			
Vitamin K only	6/373 (1.6)	13/374 (3.5)	19/747 (2.5)
PCC only	5/373 (1.3)	7/374 (1.9)	12/747 (1.6)
Platelets only	36/373 (9.7)	28/374 (7.5)	64/747 (8.6)
FFP only	0/373 (0)	1/374 (0.3)	1/747 (0.1)
PRBCs only	0/373 (0)	1/374 (0.3)	1/747 (0.1)
Other only	1/373 (0.3)	3/374 (0.8)	4/747 (0.5)
Combination of treatments	32/373 (8.6)	43/374 (11.5)	75/747 (10)

FFP, fresh-frozen plasma; PCC, prothrombin complex concentrate; PRBCs, packed red blood cells.

TABLE 29 Modified Rankin Scale at 6 months (per-protocol population)

mRS	Treatment arm, *n/N* (%)		Total, *n/N* (%)
	Placebo	Dexamethasone	
Score			
0: No symptoms	142/283 (50.2)	129/270 (47.8)	271/553 (49)
1: No significant disability	45/283 (15.9)	40/270 (14.8)	85/553 (15.4)
2: Slight disability	18/283 (6.4)	12/270 (4.4)	30/553 (5.4)
3: Moderate disability	53/283 (18.7)	48/270 (17.8)	101/553 (18.3)
4: Moderately severe disability	8/283 (2.8)	9/270 (3.3)	17/553 (3.1)
5: Severe disability	6/283 (2.1)	12/270 (4.4)	18/553 (3.3)
6: Dead	11/283 (3.9)	20/270 (7.4)	31/553 (5.6)
Dichotomised			
Favourable	258/283 (91.2)	229/270 (84.8)	487/553 (88.1)
Unfavourable	25/283 (8.8)	41/270 (15.2)	66/553 (11.9)

TABLE 30 Number of surgical interventions (per-protocol population)

	Treatment arm, *n/N* (%)		
	Placebo	Dexamethasone	Total, *n/N* (%)
Number of surgeries: all admissions			
0	15/307 (4.9)	19/290 (6.6)	34/597 (5.7)
1	268/307 (87.3)	260/290 (89.7)	528/597 (88.4)
2	21/307 (6.8)	10/290 (3.4)	31/597 (5.2)
3	1/307 (0.3)	1/290 (0.3)	2/597 (0.3)
5	2/307 (0.7)	0/290 (0)	2/597 (0.3)
Number of surgeries: all admissions (excluding pre randomisation)			
0	146/307 (47.6)	151/290 (52.1)	297/597 (49.7)
1	146/307 (47.6)	132/290 (45.5)	278/597 (46.6)
2	13/307 (4.2)	7/290 (2.4)	20/597 (3.4)
4	2/307 (0.7)	0/290 (0)	2/597 (0.3)
Number of surgeries: index admission			
0	23/307 (7.5)	24/290 (8.3)	47/597 (7.9)
1	275/307 (89.6)	266/290 (91.7)	541/597 (90.6)
2	8/307 (2.6)	0/290 (0)	8/597 (1.3)
3	1/307 (0.3)	0/290 (0)	1/597 (0.2)
Number of surgeries: index admission (excluding pre randomisation)			
0	161/307 (52.4)	161/290 (55.5)	322/597 (53.9)
1	141/307 (45.9)	129/290 (44.5)	270/597 (45.2)
2	5/307 (1.6)	0/290 (0)	5/597 (0.8)
Number of surgeries: subsequent admissions			
0	1/307 (0.3)	5/290 (1.7)	6/597 (1)
1	22/307 (7.2)	13/290 (4.5)	35/597 (5.9)
2	2/307 (0.7)	2/290 (0.7)	4/597 (0.7)
3	1/307 (0.3)	0/290 (0)	1/597 (0.2)
Recurrence (one or more reoperation)[a]			
Yes	24/292 (8.2)	11/271 (4.1)	35/563 (6.2)

a Denominator is the subset of patients who receive surgery.

TABLE 31 Model-fitting results for the number of surgical interventions (per-protocol population)

Outcome	Covariate	Estimate	95% CI	*p*-value
Number of surgeries: index admission (including pre randomisation)	(Intercept)	0.958	0.852 to 1.07	
	Dexamethasone vs. placebo	0.958	0.811 to 1.13	0.61
Number of surgeries: index admission (excluding pre randomisation)	(Intercept)	0.492	0.418 to 0.575	
	Dexamethasone vs. placebo	0.904	0.714 to 1.14	0.402
Number of surgeries: subsequent admissions (re-admissions only)	(Intercept)	0.492	0.418 to 0.575	
	Dexamethasone vs. placebo	0.904	0.714 to 1.14	0.402
Number of surgeries: subsequent admissions (all patients)	(Intercept)	0.0945	0.0641 to 0.133	
	Dexamethasone vs. placebo	0.621	0.334 to 1.12	0.118

TABLE 32 Surgical procedures during primary surgery (full analysis population)

Variable	Treatment arm, *n/N* (%)	
	Placebo	Dexamethasone
Primary surgery[a]		
Burr hole(s) evacuation	304/350 (86.8)	302/349 (86.5)
Mini-craniotomy	44/350 (12.6)	40/349 (11.5)
Other	2/350 (0.6)	7/349 (2)
Postoperative drain[b]		
Subdural	287/350 (82)	277/349 (79.4)
Subgaleal	11/350 (3)	11/349 (3.2)
No drain/not recorded	53/350 (15)	61/349 (17.4)
Anaesthesia used		
General	293/340 (86.2)	297/342 (86.8)
Local	23/340 (6.8)	18/342 (5.3)
Sedation	24/340 (7)	27/342 (7.9)
Primary surgery		
Burr hole(s) (total)	304/350 (86.8)	302/349 (86.5)
One burr hole	78/304	63/302
Two burr holes	217/304	232/302
Three burr holes	1/304	0/302
Unknown number of burr holes	1/304	0/302
Combination of one/two (in bilateral cases)	7/304	6/302
Mini-craniotomy	44/305 (12.6)	40/349 (11.5)
Other	2/350 (0.6)	7/349 (2)
Bilateral surgery with combination of burr hole(s) and mini-craniotomy	1/2	4/7
Reopening of old burr hole(s) or mini-craniotomy from previous surgery	1/2	2/7
Craniectomy	0/2	1/7

a Primary surgery refers to the first surgery for CSDH, performed on index or subsequent admissions. Primary surgery was performed in 699/742 patients (94%) (no data available for six patients owing to early withdrawal). Six per cent of all patients (43/742) were managed without any surgery during the trial period (*n* = 20, 5.4% in placebo arm; *n* = 23, 6.1% in dexamethasone arm).
b One patient in the placebo arm had both a subgaleal and a subdural drain inserted.

TABLE 33 Surgical procedures during recurrent surgery (full analysis population)

Recurrent surgery	Treatment arm, *n/N* (%)	
	Placebo	Dexamethasone
New burr hole(s)	3/28 (10.7)	1/14 (7.1)
Mini-craniotomy	5/28 (17.8)	2/14 (14.3)
Previous burr hole(s) reopened	21/28 (75)	9/14 (64.3)
Previous burr hole(s) extended to mini-craniotomy	6/28 (21.4)	3/14 (21.4)
Subdural/subgaleal drain	27/28 (96.4)	14/14 (100)

Numbers equal more than total as several patients had a combination of procedures.

TABLE 34 Modified Rankin Scale at discharge (full analysis population)

mRS	Treatment arm, *n/N* (%)		Total, *n/N* (%)
	Placebo	Dexamethasone	
Score			
0: No symptoms	71/316 (22.5)	69/318 (21.7)	140/634 (22.1)
1: No significant disability	65/316 (20.6)	68/318 (21.4)	133/634 (21)
2: Slight disability	25/316 (7.9)	23/318 (7.2)	48/634 (7.6)
3: Moderate disability	102/316 (32.3)	95/318 (29.9)	197/634 (31.1)
4: Moderately severe disability	30/316 (9.5)	36/318 (11.3)	66/634 (10.4)
5: Severe disability	22/316 (7)	25/318 (7.9)	47/634 (7.4)
6: Dead	1/316 (0.3)	2/318 (0.6)	3/634 (0.5)
Dichotomised			
Favourable	263/316 (83.2)	255/318 (80.2)	518/634 (81.7)
Unfavourable	53/316 (16.8)	63/318 (19.8)	116/634 (18.3)

TABLE 35 Modified Rankin Scale at 3 months (full analysis population)

mRS	Treatment arm, *n/N* (%)		Total, *n/N* (%)
	Placebo	Dexamethasone	
Score			
0: No symptoms	163/326 (50)	144/322 (44.7)	307/648 (47.4)
1: No significant disability	50/326 (15.3)	48/322 (14.9)	98/648 (15.1)
2: Slight disability	14/326 (4.3)	13/322 (4)	27/648 (4.2)
3: Moderate disability	71/326 (21.8)	63/322 (19.6)	134/648 (20.7)
4: Moderately severe disability	5/326 (1.5)	14/322 (4.3)	19/648 (2.9)
5: Severe disability	12/326 (3.7)	18/322 (5.6)	30/648 (4.6)
6: Dead	11/326 (3.4)	22/322 (6.8)	33/648 (5.1)
Dichotomised			
Favourable	298/326 (91.4)	268/322 (83.2)	566/648 (87.3)
Unfavourable	28/326 (8.6)	54/322 (16.8)	82/648 (12.7)

TABLE 36 Modified Rankin Scale at discharge (per-protocol population)

mRS	Treatment arm, *n/N* (%)		Total, *n/N* (%)
	Placebo	Dexamethasone	
Score			
0: No symptoms	60/251 (23.9)	55/239 (23)	115/490 (23.5)
1: No significant disability	53/251 (21.1)	48/239 (20.1)	101/490 (20.6)
2: Slight disability	21/251 (8.4)	20/239 (8.4)	41/490 (8.4)
3: Moderate disability	82/251 (32.7)	76/239 (31.8)	158/490 (32.2)
4: Moderately severe disability	19/251 (7.6)	25/239 (10.5)	44/490 (9)
5: Severe disability	16/251 (6.4)	15/239 (6.3)	31/490 (6.3)
Dichotomised			
Favourable	216/251 (86.1)	199/239 (83.3)	415/490 (84.7)
Unfavourable	35/251 (13.9)	40/239 (16.7)	75/490 (15.3)

TABLE 37 Modified Rankin Scale at 3 months (per-protocol population)

mRS	Treatment arm, *n/N* (%)		Total, *n/N* (%)
	Placebo	Dexamethasone	
Score			
0: No symptoms	148/280 (52.9)	118/259 (45.6)	266/539 (49.4)
1: No significant disability	38/280 (13.6)	41/259 (15.8)	79/539 (14.7)
2: Slight disability	12/280 (4.3)	9/259 (3.5)	21/539 (3.9)
3: Moderate disability	59/280 (21.1)	51/259 (19.7)	110/539 (20.4)
4: Moderately severe disability	4/280 (1.4)	10/259 (3.9)	14/539 (2.6)
5: Severe disability	11/280 (3.9)	15/259 (5.8)	26/539 (4.8)
6: Dead	8/280 (2.9)	15/259 (5.8)	23/539 (4.3)
Dichotomised			
Favourable	257/280 (91.8)	219/259 (84.6)	476/539 (88.3)
Unfavourable	23/280 (8.2)	40/259 (15.4)	63/539 (11.7)

TABLE 38 Model-fitting results for mRS at discharge and 3 months (per-protocol population)

	Ordinal logistic regression			Sequential ORs		
Cut-off point	Probability mRS ≤ cut-off (placebo arm)	Global OR (95% CI)[a]	*p*-value	Placebo (*n* = 251, discharge) (*n* = 280, 3 months), *n* (%)	Dexamethasone (*n* = 239, discharge) (*n* = 259, 3 months), *n* (%)	Marginal OR (95% CI)
mRS score at discharge						
0	0.243	0.913 (0.665 to 1.25)	0.572	60 (24)	55 (23)	0.952 (0.626 to 1.446)
1	0.452			113 (45)	103 (43)	0.925 (0.647 to 1.322)
2	0.535			134 (53)	123 (51)	0.926 (0.649 to 1.32)
3	0.853			216 (86)	199 (83)	0.806 (0.492 to 1.32)
4	0.939			235 (94)	224 (94)	1.017 (0.491 to 2.105)
5	.			.	.	.
6	.			.	.	.
mRS score at 3 months						
0	0.532	0.724 (0.528 to 0.992)	0.045	148 (53)	118 (46)	0.746 (0.532 to 1.048)
1	0.675			186 (66)	159 (61)	0.804 (0.565 to 1.143)
2	0.712			198 (71)	168 (65)	0.765 (0.532 to 1.099)
3	0.899			257 (92)	219 (85)	0.49 (0.284 to 0.844)
4	0.922			261 (93)	229 (88)	0.556 (0.305 to 1.014)
5	0.964			272 (97)	244 (94)	0.478 (0.199 to 1.148)
6	.			.	.	.

a Odds in direction of a favourable outcome.

Note
Data show frequency (%) of patients with a mRS score less than or equal to the cut-off point.

TABLE 39 Barthel Index at discharge (full analysis population)

	Treatment arm		
	Placebo	Dexamethasone	Total
Eating my meals, n/N (%)			
I need help for all aspects of eating meals	18/316 (5.7)	17/317 (5.4)	35/633 (5.5)
I need some help eating my meal (e.g. cutting/spreading butter)	38/316 (12)	33/317 (10.4)	71/633 (11.2)
I can eat without help	260/316 (82.3)	267/317 (84.2)	527/633 (83.3)
Bathing/showering, n/N (%)			
I need help with bathing/showering	108/316 (34.2)	97/317 (30.6)	205/633 (32.4)
I can bath/shower without help	208/316 (65.8)	220/317 (69.4)	428/633 (67.6)
Personal care, n/N (%)			
I need help with personal care	79/316 (25)	79/317 (24.9)	158/633 (25)
I can do all my personal care without help	237/316 (75)	238/317 (75.1)	475/633 (75)
Getting dressed, n/N (%)			
I need help with all aspects of dressing	43/315 (13.7)	43/317 (13.6)	86/632 (13.6)
I need some help with dressing but can do about half without help	61/315 (19.4)	48/317 (15.1)	109/632 (17.2)
I can get dressed without help	211/315 (67)	226/317 (71.3)	437/632 (69.1)
Controlling bowels, n/N (%)			
I cannot control my bowel function	11/316 (3.5)	13/317 (4.1)	24/633 (3.8)
I sometimes have an accident with my bowels	33/316 (10.4)	26/317 (8.2)	59/633 (9.3)
I have no problems controlling my bowels	272/316 (86.1)	278/317 (87.7)	550/633 (86.9)
Controlling bladder, n/N (%)			
I cannot control my bladder function or I have a catheter	27/316 (8.5)	31/317 (9.8)	58/633 (9.2)
I sometimes have an accident with my bladder	35/316 (11.1)	37/317 (11.7)	72/633 (11.4)
I have no problems controlling my bladder	254/316 (80.4)	249/317 (78.5)	503/633 (79.5)
Toilet use: getting on/off the toilet, wiping and dressing, n/N (%)			
I need help to do all of these things when going to the toilet	38/316 (12)	38/317 (12)	76/633 (12)
I need help to do some of these things, but can do some things alone	38/316 (12)	35/317 (11)	73/633 (11.5)
I can do all of these things without help	240/316 (75.9)	244/317 (77)	484/633 (76.5)
Getting from the bed to the chair and back, n/N (%)			
I am unable to sit in a chair	7/316 (2.2)	13/317 (4.1)	20/633 (3.2)
I need one or two people to help me get into the chair and back	39/316 (12.3)	36/317 (11.4)	75/633 (11.8)
I need a little bit of help getting into the chair and back	33/316 (10.4)	23/317 (7.3)	56/633 (8.8)
I can get into the chair and back without help	237/316 (75)	245/317 (77.3)	482/633 (76.1)

TABLE 39 Barthel Index at discharge (full analysis population) (*continued*)

	Treatment arm		
	Placebo	Dexamethasone	Total
Walking on a flat surface, n/N (%)			
I cannot walk more than 50 yards	54/316 (17.1)	60/317 (18.9)	114/633 (18)
I use a wheelchair on my own to go more than 50 yards	4/316 (1.3)	4/317 (1.3)	8/633 (1.3)
I can walk more than 50 yards with another person helping me	54/316 (17.1)	39/317 (12.3)	93/633 (14.7)
I can walk more than 50 yards without help from another person	204/316 (64.6)	214/317 (67.5)	418/633 (66)
Walking up the stairs, n/N (%)			
I cannot walk up the stairs on my own	74/315 (23.5)	75/316 (23.7)	149/631 (23.6)
I can walk up the stairs with some help	65/315 (20.6)	53/316 (16.8)	118/631 (18.7)
I can walk up the stairs without help	176/315 (55.9)	188/316 (59.5)	364/631 (57.7)
Total score			
n	315	316	631
Mean (SD)	80.5 (26.7)	81.0 (28.0)	80.7 (27.4)
Median	95	95	95
Minimum, maximum	0, 100	0, 100	0, 100

TABLE 40 Barthel Index at 3 months (full analysis population)

	Treatment arm		
	Placebo	Dexamethasone	Total
Eating my meals, n/N (%)			
I need help for all aspects of eating meals	3/314 (1)	13/299 (4.3)	16/613 (2.6)
I need some help eating my meal (e.g. cutting/spreading butter)	20/314 (6.4)	16/299 (5.4)	36/613 (5.9)
I can eat without help	291/314 (92.7)	270/299 (90.3)	561/613 (91.5)
Bathing/showering, n/N (%)			
I need help with bathing/showering	61/313 (19.5)	59/299 (19.7)	120/612 (19.6)
I can bath/shower without help	252/313 (80.5)	240/299 (80.3)	492/612 (80.4)
Personal care, n/N (%)			
I need help with personal care	36/314 (11.5)	37/299 (12.4)	73/613 (11.9)
I can do all my personal care without help	278/314 (88.5)	262/299 (87.6)	540/613 (88.1)
Getting dressed, n/N (%)			
I need help with all aspects of dressing	14/313 (4.5)	25/299 (8.4)	39/612 (6.4)
I need some help with dressing but can do about half without help	46/313 (14.7)	37/299 (12.4)	83/612 (13.6)
I can get dressed without help	253/313 (80.8)	237/299 (79.3)	490/612 (80.1)

continued

TABLE 40 Barthel Index at 3 months (full analysis population) (*continued*)

	Treatment arm		
	Placebo	Dexamethasone	Total
Controlling bowels, n/N (%)			
I cannot control my bowel function	9/313 (2.9)	13/300 (4.3)	22/613 (3.6)
I sometimes have an accident with my bowels	33/313 (10.5)	33/300 (11)	66/613 (10.8)
I have no problems controlling my bowels	271/313 (86.6)	254/300 (84.7)	525/613 (85.6)
Controlling bladder, n/N (%)			
I cannot control my bladder function or I have a catheter	18/314 (5.7)	24/300 (8)	42/614 (6.8)
I sometimes have an accident with my bladder	51/314 (16.2)	42/300 (14)	93/614 (15.1)
I have no problems controlling my bladder	245/314 (78)	234/300 (78)	479/614 (78)
Toilet use: getting on/off the toilet, wiping and dressing, n/N (%)			
I need help to do all of these things when going to the toilet	15/314 (4.8)	20/299 (6.7)	35/613 (5.7)
I need help to do some of these things, but can do some things alone	24/314 (7.6)	23/299 (7.7)	47/613 (7.7)
I can do all of these things without help	275/314 (87.6)	256/299 (85.6)	531/613 (86.6)
Getting from the bed to the chair and back, n/N (%)			
I am unable to sit in a chair	6/314 (1.9)	7/299 (2.3)	13/613 (2.1)
I need one or two people to help me get into the chair and back	7/314 (2.2)	18/299 (6)	25/613 (4.1)
I need a little bit of help getting into the chair and back	13/314 (4.1)	15/299 (5)	28/613 (4.6)
I can get into the chair and back without help	288/314 (91.7)	259/299 (86.6)	547/613 (89.2)
Walking on a flat surface, n/N (%)			
I cannot walk more than 50 yards	31/314 (9.9)	39/299 (13)	70/613 (11.4)
I use a wheelchair on my own to go more than 50 yards	5/314 (1.6)	5/299 (1.7)	10/613 (1.6)
I can walk more than 50 yards with another person helping me	19/314 (6.1)	21/299 (7)	40/613 (6.5)
I can walk more than 50 yards without help from another person	259/314 (82.5)	234/299 (78.3)	493/613 (80.4)
Walking up the stairs, n/N (%)			
I cannot walk up the stairs on my own	37/313 (11.8)	54/299 (18.1)	91/612 (14.9)
I can walk up the stairs with some help	32/313 (10.2)	27/299 (9)	59/612 (9.6)
I can walk up the stairs without help	244/313 (78)	218/299 (72.9)	462/612 (75.5)
Total score			
n	312	298	610
Mean (SD)	89.4 (19.7)	86.7 (23.9)	88.1 (21.9)
Median	100	100	100
Minimum, maximum	0, 100	0, 100	0, 100

TABLE 41 Barthel Index at 6 months (full analysis population)

	Treatment arm		
	Placebo	Dexamethasone	Total
***Eating my meals*, n/N (%)**			
I need help for all aspects of eating meals	3/322 (0.9)	12/309 (3.9)	15/631 (2.4)
I need some help eating my meal (e.g. cutting/spreading butter)	23/322 (7.1)	11/309 (3.6)	34/631 (5.4)
I can eat without help	296/322 (91.9)	286/309 (92.6)	582/631 (92.2)
***Bathing/showering*, n/N (%)**			
I need help with bathing/showering	52/322 (16.1)	62/310 (20)	114/632 (18)
I can bath/shower without help	270/322 (83.9)	248/310 (80)	518/632 (82)
***Personal care*, n/N (%)**			
I need help with personal care	32/322 (9.9)	41/310 (13.2)	73/632 (11.6)
I can do all my personal care without help	290/322 (90.1)	269/310 (86.8)	559/632 (88.4)
***Getting dressed*, n/N (%)**			
I need help with all aspects of dressing	16/322 (5)	21/309 (6.8)	37/631 (5.9)
I need some help with dressing but can do about half without help	38/322 (11.8)	35/309 (11.3)	73/631 (11.6)
I can get dressed without help	268/322 (83.2)	253/309 (81.9)	521/631 (82.6)
***Controlling bowels*, n/N (%)**			
I cannot control my bowel function	8/321 (2.5)	13/309 (4.2)	21/630 (3.3)
I sometimes have an accident with my bowels	38/321 (11.8)	37/309 (12)	75/630 (11.9)
I have no problems controlling my bowels	275/321 (85.7)	259/309 (83.8)	534/630 (84.8)
***Controlling bladder*, n/N (%)**			
I cannot control my bladder function or I have a catheter	9/321 (2.8)	20/309 (6.5)	29/630 (4.6)
I sometimes have an accident with my bladder	56/321 (17.4)	50/309 (16.2)	106/630 (16.8)
I have no problems controlling my bladder	256/321 (79.8)	239/309 (77.3)	495/630 (78.6)
***Toilet use: getting on/off the toilet, wiping and dressing*, n/N (%)**			
I need help to do all of these things when going to the toilet	14/321 (4.4)	21/309 (6.8)	35/630 (5.6)
I need help to do some of these things, but can do some things alone	19/321 (5.9)	18/309 (5.8)	37/630 (5.9)
I can do all of these things without help	288/321 (89.7)	270/309 (87.4)	558/630 (88.6)
***Getting from the bed to the chair and back*, n/N (%)**			
I am unable to sit in a chair	4/321 (1.2)	5/310 (1.6)	9/631 (1.4)
I need one or two people to help me get into the chair and back	10/321 (3.1)	15/310 (4.8)	25/631 (4)
I need a little bit of help getting into the chair and back	10/321 (3.1)	10/310 (3.2)	20/631 (3.2)
I can get into the chair and back without help	297/321 (92.5)	280/310 (90.3)	577/631 (91.4)

continued

TABLE 41 Barthel Index at 6 months (full analysis population) (*continued*)

	Treatment arm		
	Placebo	Dexamethasone	Total
Walking on a flat surface, n/N (%)			
I cannot walk more than 50 yards	28/322 (8.7)	31/310 (10)	59/632 (9.3)
I use a wheelchair on my own to go more than 50 yards	9/322 (2.8)	9/310 (2.9)	18/632 (2.8)
I can walk more than 50 yards with another person helping me	26/322 (8.1)	18/310 (5.8)	44/632 (7)
I can walk more than 50 yards without help from another person	259/322 (80.4)	252/310 (81.3)	511/632 (80.9)
Walking up the stairs, n/N (%)			
I cannot walk up the stairs on my own	35/319 (11)	51/310 (16.5)	86/629 (13.7)
I can walk up the stairs with some help	28/319 (8.8)	26/310 (8.4)	54/629 (8.6)
I can walk up the stairs without help	256/319 (80.3)	233/310 (75.2)	489/629 (77.7)
Total score			
n	318	309	627
Mean (SD)	90.3 (19.0)	88.1 (22.8)	89.2 (20.9)
Median	100	100	100
Minimum, maximum	0, 100	0, 100	0, 100

TABLE 42 Barthel Index at discharge (per-protocol population)

	Treatment arm		
	Placebo	Dexamethasone	Total
Eating my meals, n/N (%)			
I need help for all aspects of eating meals	17/252 (6.7)	11/239 (4.6)	28/491 (5.7)
I need some help eating my meal (e.g. cutting/spreading butter)	29/252 (11.5)	22/239 (9.2)	51/491 (10.4)
I can eat without help	206/252 (81.7)	206/239 (86.2)	412/491 (83.9)
Bathing/showering, n/N (%)			
I need help with bathing/showering	84/252 (33.3)	71/239 (29.7)	155/491 (31.6)
I can bath/shower without help	168/252 (66.7)	168/239 (70.3)	336/491 (68.4)
Personal care, n/N (%)			
I need help with personal care	60/252 (23.8)	53/239 (22.2)	113/491 (23)
I can do all my personal care without help	192/252 (76.2)	186/239 (77.8)	378/491 (77)
Getting dressed, n/N (%)			
I need help with all aspects of dressing	31/251 (12.4)	29/239 (12.1)	60/490 (12.2)
I need some help with dressing but can do about half without help	47/251 (18.7)	31/239 (13)	78/490 (15.9)
I can get dressed without help	173/251 (68.9)	179/239 (74.9)	352/490 (71.8)

TABLE 42 Barthel Index at discharge (per-protocol population) (*continued*)

	Treatment arm		
	Placebo	Dexamethasone	Total
Controlling bowels, n/N (%)			
I cannot control my bowel function	8/252 (3.2)	8/239 (3.3)	16/491 (3.3)
I sometimes have an accident with my bowels	28/252 (11.1)	18/239 (7.5)	46/491 (9.4)
I have no problems controlling my bowels	216/252 (85.7)	213/239 (89.1)	429/491 (87.4)
Controlling bladder, n/N (%)			
I cannot control my bladder function or I have a catheter	17/252 (6.7)	17/239 (7.1)	34/491 (6.9)
I sometimes have an accident with my bladder	30/252 (11.9)	32/239 (13.4)	62/491 (12.6)
I have no problems controlling my bladder	205/252 (81.3)	190/239 (79.5)	395/491 (80.4)
Toilet use: getting on/off the toilet, wiping and dressing, n/N (%)			
I need help to do all of these things when going to the toilet	28/252 (11.1)	22/239 (9.2)	50/491 (10.2)
I need help to do some of these things, but can do some things alone	31/252 (12.3)	26/239 (10.9)	57/491 (11.6)
I can do all of these things without help	193/252 (76.6)	191/239 (79.9)	384/491 (78.2)
Getting from the bed to the chair and back, n/N (%)			
I am unable to sit in a chair	6/252 (2.4)	7/239 (2.9)	13/491 (2.6)
I need one or two people to help me get into the chair and back	27/252 (10.7)	24/239 (10)	51/491 (10.4)
I need a little bit of help getting into the chair and back	26/252 (10.3)	14/239 (5.9)	40/491 (8.1)
I can get into the chair and back without help	193/252 (76.6)	194/239 (81.2)	387/491 (78.8)
Walking on a flat surface, n/N (%)			
I cannot walk more than 50 yards	43/252 (17.1)	39/239 (16.3)	82/491 (16.7)
I use a wheelchair on my own to go more than 50 yards	2/252 (0.8)	3/239 (1.3)	5/491 (1)
I can walk more than 50 yards with another person helping me	37/252 (14.7)	28/239 (11.7)	65/491 (13.2)
I can walk more than 50 yards without help from another person	170/252 (67.5)	169/239 (70.7)	339/491 (69)
Walking up the stairs, n/N (%)			
I cannot walk up the stairs on my own	52/251 (20.7)	52/239 (21.8)	104/490 (21.2)
I can walk up the stairs with some help	52/251 (20.7)	39/239 (16.3)	91/490 (18.6)
I can walk up the stairs without help	147/251 (58.6)	148/239 (61.9)	295/490 (60.2)
Total score			
n	251	239	490
Mean (SD)	81.5 (26.4)	83.2 (26.2)	82.3 (26.3)
Median	95	100	95
Minimum, maximum	0, 100	0, 100	0, 100

TABLE 43 Barthel Index at 3 months (per-protocol population)

	Treatment arm		
	Placebo	Dexamethasone	Total
Eating my meals, n/N (%)			
I need help for all aspects of eating meals	3/272 (1.1)	10/243 (4.1)	13/515 (2.5)
I need some help eating my meal (e.g. cutting/spreading butter)	18/272 (6.6)	15/243 (6.2)	33/515 (6.4)
I can eat without help	251/272 (92.3)	218/243 (89.7)	469/515 (91.1)
Bathing/showering, n/N (%)			
I need help with bathing/showering	50/271 (18.5)	46/243 (18.9)	96/514 (18.7)
I can bath/shower without help	221/271 (81.5)	197/243 (81.1)	418/514 (81.3)
Personal care, n/N (%)			
I need help with personal care	28/272 (10.3)	28/243 (11.5)	56/515 (10.9)
I can do all my personal care without help	244/272 (89.7)	215/243 (88.5)	459/515 (89.1)
Getting dressed, n/N (%)			
I need help with all aspects of dressing	11/271 (4.1)	20/243 (8.2)	31/514 (6)
I need some help with dressing but can do about half without help	42/271 (15.5)	28/243 (11.5)	70/514 (13.6)
I can get dressed without help	218/271 (80.4)	195/243 (80.2)	413/514 (80.4)
Controlling bowels, n/N (%)			
I cannot control my bowel function	7/271 (2.6)	11/244 (4.5)	18/515 (3.5)
I sometimes have an accident with my bowels	28/271 (10.3)	29/244 (11.9)	57/515 (11.1)
I have no problems controlling my bowels	236/271 (87.1)	204/244 (83.6)	440/515 (85.4)
Controlling bladder, n/N (%)			
I cannot control my bladder function or I have a catheter	14/272 (5.1)	18/244 (7.4)	32/516 (6.2)
I sometimes have an accident with my bladder	45/272 (16.5)	36/244 (14.8)	81/516 (15.7)
I have no problems controlling my bladder	213/272 (78.3)	190/244 (77.9)	403/516 (78.1)
Toilet use: getting on/off the toilet, wiping and dressing, n/N (%)			
I need help to do all of these things when going to the toilet	12/272 (4.4)	16/244 (6.6)	28/516 (5.4)
I need help to do some of these things, but can do some things alone	22/272 (8.1)	17/244 (7)	39/516 (7.6)
I can do all of these things without help	238/272 (87.5)	211/244 (86.5)	449/516 (87)
Getting from the bed to the chair and back, n/N (%)			
I am unable to sit in a chair	5/272 (1.8)	5/243 (2.1)	10/515 (1.9)
I need one or two people to help me get into the chair and back	7/272 (2.6)	13/243 (5.3)	20/515 (3.9)
I need a little bit of help getting into the chair and back	12/272 (4.4)	13/243 (5.3)	25/515 (4.9)
I can get into the chair and back without help	248/272 (91.2)	212/243 (87.2)	460/515 (89.3)

TABLE 43 Barthel Index at 3 months (per-protocol population) (*continued*)

	Treatment arm		
	Placebo	Dexamethasone	Total
Walking on a flat surface, n/N (%)			
I cannot walk more than 50 yards	30/272 (11)	29/243 (11.9)	59/515 (11.5)
I use a wheelchair on my own to go more than 50 yards	4/272 (1.5)	2/243 (0.8)	6/515 (1.2)
I can walk more than 50 yards with another person helping me	13/272 (4.8)	19/243 (7.8)	32/515 (6.2)
I can walk more than 50 yards without help from another person	225/272 (82.7)	193/243 (79.4)	418/515 (81.2)
Walking up the stairs, n/N (%)			
I cannot walk up the stairs on my own	33/271 (12.2)	40/243 (16.5)	73/514 (14.2)
I can walk up the stairs with some help	26/271 (9.6)	22/243 (9.1)	48/514 (9.3)
I can walk up the stairs without help	212/271 (78.2)	181/243 (74.5)	393/514 (76.5)
Total score			
n	270	243	513
Mean (SD)	89.4 (19.9)	87.3 (23.4)	88.4 (21.6)
Median	100	100	100
Minimum, maximum	0, 100	0, 100	0, 100

TABLE 44 Barthel Index at 6 months (per-protocol population)

	Treatment arm		
	Placebo	Dexamethasone	Total
Eating my meals, n/N (%)			
I need help for all aspects of eating meals	3/272 (1.1)	10/248 (4)	13/520 (2.5)
I need some help eating my meal (e.g. cutting/spreading butter)	18/272 (6.6)	11/248 (4.4)	29/520 (5.6)
I can eat without help	251/272 (92.3)	227/248 (91.5)	478/520 (91.9)
Bathing/showering, n/N (%)			
I need help with bathing/showering	44/272 (16.2)	49/249 (19.7)	93/521 (17.9)
I can bath/shower without help	228/272 (83.8)	200/249 (80.3)	428/521 (82.1)
Personal care, n/N (%)			
I need help with personal care	26/272 (9.6)	36/249 (14.5)	62/521 (11.9)
I can do all my personal care without help	246/272 (90.4)	213/249 (85.5)	459/521 (88.1)
Getting dressed, n/N (%)			
I need help with all aspects of dressing	13/272 (4.8)	18/248 (7.3)	31/520 (6)
I need some help with dressing but can do about half without help	34/272 (12.5)	26/248 (10.5)	60/520 (11.5)
I can get dressed without help	225/272 (82.7)	204/248 (82.3)	429/520 (82.5)

continued

TABLE 44 Barthel Index at 6 months (per-protocol population) (*continued*)

	Treatment arm		
	Placebo	Dexamethasone	Total
Controlling bowels, n/N (%)			
I cannot control my bowel function	6/271 (2.2)	11/248 (4.4)	17/519 (3.3)
I sometimes have an accident with my bowels	32/271 (11.8)	30/248 (12.1%)	62/519 (11.9)
I have no problems controlling my bowels	233/271 (86)	207/248 (83.5)	440/519 (84.8)
Controlling bladder, n/N (%)			
I cannot control my bladder function or I have a catheter	8/271 (3)	17/248 (6.9)	25/519 (4.8)
I sometimes have an accident with my bladder	48/271 (17.7)	43/248 (17.3)	91/519 (17.5)
I have no problems controlling my bladder	215/271 (79.3)	188/248 (75.8)	403/519 (77.6)
Toilet use: getting on/off the toilet, wiping and dressing, n/N (%)			
I need help to do all of these things when going to the toilet	12/271 (4.4)	17/248 (6.9)	29/519 (5.6)
I need help to do some of these things, but can do some things alone	15/271 (5.5)	16/248 (6.5)	31/519 (6)
I can do all of these things without help	244/271 (90)	215/248 (86.7)	459/519 (88.4)
Getting from the bed to the chair and back, n/N (%)			
I am unable to sit in a chair	4/271 (1.5)	5/249 (2)	9/520 (1.7)
I need one or two people to help me get into the chair and back	9/271 (3.3)	12/249 (4.8)	21/520 (4)
I need a little bit of help getting into the chair and back	8/271 (3)	10/249 (4)	18/520 (3.5)
I can get into the chair and back without help	250/271 (92.3)	222/249 (89.2)	472/520 (90.8)
Walking on a flat surface, n/N (%)			
I cannot walk more than 50 yards	22/272 (8.1)	24/249 (9.6)	46/521 (8.8)
I use a wheelchair on my own to go more than 50 yards	9/272 (3.3)	6/249 (2.4)	15/521 (2.9)
I can walk more than 50 yards with another person helping me	23/272 (8.5)	15/249 (6)	38/521 (7.3)
I can walk more than 50 yards without help from another person	218/272 (80.1)	204/249 (81.9)	422/521 (81)
Walking up the stairs, n/N (%)			
I cannot walk up the stairs on my own	27/269 (10)	42/249 (16.9)	69/518 (13.3)
I can walk up the stairs with some help	24/269 (8.9)	21/249 (8.4)	45/518 (8.7)
I can walk up the stairs without help	218/269 (81)	186/249 (74.7)	404/518 (78)
Total score			
n	268	248	516
Mean (SD)	90.4 (18.9)	87.7 (23.4)	89.1 (21.2)
Median	100	100	100
Minimum, maximum	0, 100	0, 100	0, 100

TABLE 45 Model-fitting results for BI at discharge, 3 months and 6 months (per-protocol population)

Outcome	Linear regression				Mann–Whitney *U*-test: *p*-value
	Covariate	Estimate (SE)	95% CI	*p*-value	
BI at discharge	(Intercept)	81.5 (1.66)	78.2 to 84.7		0.319
	Dexamethasone vs. placebo	1.73 (2.38)	−2.94 to 6.39	0.468	
BI at 3 months	(Intercept)	89.4 (1.32)	86.8 to 92		0.432
	Dexamethasone vs. placebo	−2.08 (1.91)	−5.84 to 1.68	0.278	
BI at 6 months	(Intercept)	90.4 (1.29)	87.9 to 93		0.324
	Dexamethasone vs. placebo	−2.71 (1.86)	−6.36 to 0.953	0.147	

SE, standard error.

TABLE 46 The EQ-5D-5L at discharge (full analysis population)

Variable	Treatment arm		Total
	Placebo	Dexamethasone	
Mobility, n/N (%)			
I have no problems in walking about	159/308 (51.6)	149/306 (48.7)	308/614 (50.2)
I have slight problems in walking about	82/308 (26.6)	74/306 (24.2)	156/614 (25.4)
I have moderate problems in walking about	32/308 (10.4)	44/306 (14.4)	76/614 (12.4)
I have severe problems in walking about	23/308 (7.5)	21/306 (6.9)	44/614 (7.2)
I am unable to walk about	12/308 (3.9)	18/306 (5.9)	30/614 (4.9)
Self-care, n/N (%)			
I have no problems washing or dressing myself	196/308 (63.6)	197/306 (64.4)	393/614 (64)
I have slight problems washing or dressing myself	53/308 (17.2)	46/306 (15)	99/614 (16.1)
I have moderate problems washing or dressing myself	32/308 (10.4)	30/306 (9.8)	62/614 (10.1)
I have severe problems washing or dressing myself	16/308 (5.2)	16/306 (5.2)	32/614 (5.2)
I am unable to wash or dress myself	11/308 (3.6)	17/306 (5.6)	28/614 (4.6)
Usual activities, n/N (%)			
I have no problems doing usual activities	128/306 (41.8)	122/306 (39.9)	250/612 (40.8)
I have slight problems doing usual activities	89/306 (29.1)	74/306 (24.2)	163/612 (26.6)
I have moderate problems doing usual activities	45/306 (14.7)	44/306 (14.4)	89/612 (14.5)
I have severe problems doing usual activities	25/306 (8.2)	35/306 (11.4)	60/612 (9.8)
I am unable to do usual activities	19/306 (6.2)	31/306 (10.1)	50/612 (8.2)

continued

TABLE 46 The EQ-5D-5L at discharge (full analysis population) (*continued*)

Variable	Treatment arm		Total
	Placebo	Dexamethasone	
Pain/discomfort, n/N (%)			
I have no pain or discomfort	153/307 (49.8)	171/306 (55.9)	324/613 (52.9)
I have slight pain or discomfort	122/307 (39.7)	101/306 (33)	223/613 (36.4)
I have moderate pain or discomfort	26/307 (8.5)	30/306 (9.8)	56/613 (9.1)
I have severe pain or discomfort	6/307 (2)	3/306 (1)	9/613 (1.5)
I have extreme pain or discomfort	0/307 (0)	1/306 (0.3)	1/613 (0.2)
Anxiety/depression, n/N (%)			
I am not anxious or depressed	217/307 (70.7)	196/305 (64.3)	413/612 (67.5)
I am slightly anxious or depressed	53/307 (17.3)	71/305 (23.3)	124/612 (20.3)
I am moderately anxious or depressed	27/307 (8.8)	27/305 (8.9)	54/612 (8.8)
I am severely anxious or depressed	9/307 (2.9)	7/305 (2.3)	16/612 (2.6)
I am extremely anxious or depressed	1/307 (0.3)	4/305 (1.3)	5/612 (0.8)
Visual analogue scale			
n	285	293	578
Mean (SD)	72.3 (18.5)	74.3 (17.3)	73.3 (17.9)
Median	75	75	75
Minimum, maximum	5, 100	0, 100	0, 100
Utility index			
n	306	307	613
Mean (SD)	0.727 (0.265)	0.697 (0.293)	0.712 (0.279)
Median	0.795	0.767	0.778
Minimum, maximum	−0.166, 1	−0.358, 1	−0.358, 1

TABLE 47 The EQ-5D-5L at 3 months (full analysis population)

Variable	Treatment arm		Total
	Placebo	Dexamethasone	
Mobility, n/N (%)			
I have no problems in walking about	192/310 (61.9)	172/296 (58.1)	364/606 (60.1)
I have slight problems in walking about	61/310 (19.7)	42/296 (14.2)	103/606 (17)
I have moderate problems in walking about	37/310 (11.9)	51/296 (17.2)	88/606 (14.5)
I have severe problems in walking about	12/310 (3.9)	19/296 (6.4)	31/606 (5.1)
I am unable to walk about	8/310 (2.6)	12/296 (4.1)	20/606 (3.3)

TABLE 47 The EQ-5D-5L at 3 months (full analysis population) (*continued*)

Variable	Treatment arm		Total
	Placebo	Dexamethasone	
Self-care, n/N (%)			
I have no problems washing or dressing myself	237/309 (76.7)	223/296 (75.3)	460/605 (76)
I have slight problems washing or dressing myself	38/309 (12.3)	33/296 (11.1)	71/605 (11.7)
I have moderate problems washing or dressing myself	16/309 (5.2)	19/296 (6.4)	35/605 (5.8)
I have severe problems washing or dressing myself	11/309 (3.6)	8/296 (2.7)	19/605 (3.1)
I am unable to wash or dress myself	7/309 (2.3)	13/296 (4.4)	20/605 (3.3)
Usual activities, n/N (%)			
I have no problems doing usual activities	178/307 (58)	154/294 (52.4)	332/601 (55.2)
I have slight problems doing usual activities	63/307 (20.5)	59/294 (20.1)	122/601 (20.3)
I have moderate problems doing usual activities	41/307 (13.4)	41/294 (13.9)	82/601 (13.6)
I have severe problems doing usual activities	8/307 (2.6)	17/294 (5.8)	25/601 (4.2)
I am unable to do usual activities	17/307 (5.5)	23/294 (7.8)	40/601 (6.7)
Pain/discomfort, n/N (%)			
I have no pain or discomfort	195/308 (63.3)	185/296 (62.5)	380/604 (62.9)
I have slight pain or discomfort	71/308 (23.1)	64/296 (21.6)	135/604 (22.4)
I have moderate pain or discomfort	33/308 (10.7)	36/296 (12.2)	69/604 (11.4)
I have severe pain or discomfort	8/308 (2.6)	10/296 (3.4)	18/604 (3)
I have extreme pain or discomfort	1/308 (0.3)	1/296 (0.3)	2/604 (0.3)
Anxiety/depression, n/N (%)			
I am not anxious or depressed	222/307 (72.3)	202/296 (68.2)	424/603 (70.3)
I am slightly anxious or depressed	53/307 (17.3)	53/296 (17.9)	106/603 (17.6)
I am moderately anxious or depressed	24/307 (7.8)	32/296 (10.8)	56/603 (9.3)
I am severely anxious or depressed	6/307 (2)	8/296 (2.7)	14/603 (2.3)
I am extremely anxious or depressed	2/307 (0.7)	1/296 (0.3)	3/603 (0.5)
Visual analogue scale			
n	306	291	597
Mean (SD)	78.7 (20.4)	76.4 (22.2)	77.6 (21.3)
Median	85	80	85
Minimum, maximum	10, 100	0, 100	0, 100
Utility index			
n	316	316	632
Mean (SD)	0.773 (0.291)	0.707 (0.337)	0.740 (0.317)
Median	0.877	0.836	0.837
Minimum, maximum	−0.51, 1	−0.208, 1	−0.51, 1

TABLE 48 The EQ-5D-5L at 6 months (full analysis population)

Variable	Treatment arm		Total
	Placebo	Dexamethasone	
Mobility, n/N (%)			
I have no problems in walking about	190/300 (63.3)	186/287 (64.8)	376/587 (64.1)
I have slight problems in walking about	51/300 (17)	43/287 (15)	94/587 (16)
I have moderate problems in walking about	37/300 (12.3)	31/287 (10.8)	68/587 (11.6)
I have severe problems in walking about	15/300 (5)	18/287 (6.3)	33/587 (5.6)
I am unable to walk about	7/300 (2.3)	9/287 (3.1)	16/587 (2.7)
Self-care, n/N (%)			
I have no problems washing or dressing myself	240/299 (80.3)	225/284 (79.2)	465/583 (79.8)
I have slight problems washing or dressing myself	29/299 (9.7)	24/284 (8.5)	53/583 (9.1)
I have moderate problems washing or dressing myself	15/299 (5)	20/284 (7)	35/583 (6)
I have severe problems washing or dressing myself	9/299 (3)	5/284 (1.8)	14/583 (2.4)
I am unable to wash or dress myself	6/299 (2)	10/284 (3.5)	16/583 (2.7)
Usual activities, n/N (%)			
I have no problems doing usual activities	191/299 (63.9)	186/285 (65.3)	377/584 (64.6)
I have slight problems doing usual activities	47/299 (15.7)	37/285 (13)	84/584 (14.4)
I have moderate problems doing usual activities	33/299 (11)	34/285 (11.9)	67/584 (11.5)
I have severe problems doing usual activities	19/299 (6.4)	10/285 (3.5)	29/584 (5)
I am unable to do usual activities	9/299 (3)	18/285 (6.3)	27/584 (4.6)
Pain/discomfort, n/N (%)			
I have no pain or discomfort	203/300 (67.7)	199/285 (69.8)	402/585 (68.7)
I have slight pain or discomfort	56/300 (18.7)	48/285 (16.8)	104/585 (17.8)
I have moderate pain or discomfort	32/300 (10.7)	32/285 (11.2)	64/585 (10.9)
I have severe pain or discomfort	4/300 (1.3)	4/285 (1.4)	8/585 (1.4)
I have extreme pain or discomfort	5/300 (1.7)	2/285 (0.7)	7/585 (1.2)
Anxiety/depression, n/N (%)			
I am not anxious or depressed	222/300 (74)	210/283 (74.2)	432/583 (74.1)
I am slightly anxious or depressed	47/300 (15.7)	40/283 (14.1)	87/583 (14.9)
I am moderately anxious or depressed	23/300 (7.7)	27/283 (9.5)	50/583 (8.6)
I am severely anxious or depressed	3/300 (1)	5/283 (1.8)	8/583 (1.4)
I am extremely anxious or depressed	5/300 (1.7)	1/283 (0.4)	6/583 (1)
Visual analogue scale			
n	293	281	574
Mean (SD)	81.3 (19.7)	81.5 (18.2)	81.4 (19.0)
Median	90	85	85
Minimum, maximum	5, 100	10, 100	5, 100
Utility index			
n	315	311	626
Mean (SD)	0.766 (0.320)	0.733 (0.348)	0.750 (0.334)
Median	0.877	0.877	0.877
Minimum, maximum	−0.594, 1	−0.594, 1	−0.594, 1

TABLE 49 The EQ-5D-5L at discharge (per-protocol population)

Variable	Treatment arm		Total
	Placebo	Dexamethasone	
Mobility, n/N (%)			
I have no problems in walking about	134/248 (54)	122/232 (52.6)	256/480 (53.3)
I have slight problems in walking about	62/248 (25)	59/232 (25.4)	121/480 (25.2)
I have moderate problems in walking about	27/248 (10.9)	29/232 (12.5)	56/480 (11.7)
I have severe problems in walking about	17/248 (6.9)	13/232 (5.6)	30/480 (6.2)
I am unable to walk about	8/248 (3.2)	9/232 (3.9)	17/480 (3.5)
Self-care, n/N (%)			
I have no problems washing or dressing myself	162/248 (65.3)	155/232 (66.8)	317/480 (66)
I have slight problems washing or dressing myself	41/248 (16.5)	36/232 (15.5)	77/480 (16)
I have moderate problems washing or dressing myself	27/248 (10.9)	19/232 (8.2)	46/480 (9.6)
I have severe problems washing or dressing myself	9/248 (3.6)	10/232 (4.3)	19/480 (4)
I am unable to wash or dress myself	9/248 (3.6)	12/232 (5.2)	21/480 (4.4)
Usual activities, n/N (%)			
I have no problems doing usual activities	106/246 (43.1)	100/232 (43.1)	206/478 (43.1)
I have slight problems doing usual activities	70/246 (28.5)	59/232 (25.4)	129/478 (27)
I have moderate problems doing usual activities	36/246 (14.6)	30/232 (12.9)	66/478 (13.8)
I have severe problems doing usual activities	20/246 (8.1)	22/232 (9.5)	42/478 (8.8)
I am unable to do usual activities	14/246 (5.7)	21/232 (9.1)	35/478 (7.3)
Pain/discomfort, n/N (%)			
I have no pain or discomfort	123/247 (49.8)	136/232 (58.6)	259/479 (54.1)
I have slight pain or discomfort	98/247 (39.7)	75/232 (32.3)	173/479 (36.1)
I have moderate pain or discomfort	23/247 (9.3)	19/232 (8.2)	42/479 (8.8)
I have severe pain or discomfort	3/247 (1.2)	2/232 (0.9)	5/479 (1)
I have extreme pain or discomfort	0/247 (0)	0/232 (0)	0/479 (0)
Anxiety/depression, n/N (%)			
I am not anxious or depressed	182/247 (73.7)	155/231 (67.1)	337/478 (70.5)
I am slightly anxious or depressed	40/247 (16.2)	54/231 (23.4)	94/478 (19.7)
I am moderately anxious or depressed	17/247 (6.9)	14/231 (6.1)	31/478 (6.5)
I am severely anxious or depressed	7/247 (2.8)	6/231 (2.6)	13/478 (2.7)
I am extremely anxious or depressed	1/247 (0.4)	2/231 (0.9)	3/478 (0.6)
Visual analogue scale			
n	231	223	454
Mean (SD)	73.3 (17.6)	75.6 (16.4)	74.4 (17.0)
Median	77	80	80
Minimum, maximum	20, 100	10, 100	10, 100

continued

TABLE 49 The EQ-5D-5L at discharge (per-protocol population) (*continued*)

Variable	Treatment arm		Total
	Placebo	Dexamethasone	
Utility index			
n	245	231	476
Mean (SD)	0.743 (0.251)	0.730 (0.270)	0.737 (0.260)
Median	0.796	0.778	0.795
Minimum, maximum	−0.166, 1	−0.247, 1	−0.247, 1

TABLE 50 The EQ-5D-5L at 3 months (per-protocol population)

Variable	Treatment arm		Total
	Placebo	Dexamethasone	
Mobility, n/N (%)			
I have no problems in walking about	167/269 (62.1)	135/240 (56.2)	302/509 (59.3)
I have slight problems in walking about	51/269 (19)	37/240 (15.4)	88/509 (17.3)
I have moderate problems in walking about	32/269 (11.9)	46/240 (19.2)	78/509 (15.3)
I have severe problems in walking about	12/269 (4.5)	14/240 (5.8)	26/509 (5.1)
I am unable to walk about	7/269 (2.6)	8/240 (3.3)	15/509 (2.9)
Self-care, n/N (%)			
I have no problems washing or dressing myself	208/268 (77.6)	184/240 (76.7)	392/508 (77.2)
I have slight problems washing or dressing myself	32/268 (11.9)	26/240 (10.8)	58/508 (11.4)
I have moderate problems washing or dressing myself	13/268 (4.9)	15/240 (6.2)	28/508 (5.5)
I have severe problems washing or dressing myself	10/268 (3.7)	5/240 (2.1)	15/508 (3)
I am unable to wash or dress myself	5/268 (1.9)	10/240 (4.2)	15/508 (3)
Usual activities, n/N (%)			
I have no problems doing usual activities	164/266 (61.7)	127/238 (53.4)	291/504 (57.7)
I have slight problems doing usual activities	44/266 (16.5)	46/238 (19.3)	90/504 (17.9)
I have moderate problems doing usual activities	36/266 (13.5)	35/238 (14.7)	71/504 (14.1)
I have severe problems doing usual activities	8/266 (3)	12/238 (5)	20/504 (4)
I am unable to do usual activities	14/266 (5.3)	18/238 (7.6)	32/504 (6.3)
Pain/discomfort, n/N (%)			
I have no pain or discomfort	171/267 (64)	150/240 (62.5)	321/507 (63.3)
I have slight pain or discomfort	59/267 (22.1)	53/240 (22.1)	112/507 (22.1)
I have moderate pain or discomfort	31/267 (11.6)	28/240 (11.7)	59/507 (11.6)
I have severe pain or discomfort	6/267 (2.2)	8/240 (3.3)	14/507 (2.8)
I have extreme pain or discomfort	0/267 (0)	1/240 (0.4)	1/507 (0.2)

TABLE 50 The EQ-5D-5L at 3 months (per-protocol population) (*continued*)

Variable	Treatment arm		Total
	Placebo	Dexamethasone	
Anxiety/depression, n/N (%)			
I am not anxious or depressed	193/266 (72.6)	162/240 (67.5)	355/506 (70.2)
I am slightly anxious or depressed	45/266 (16.9)	44/240 (18.3)	89/506 (17.6)
I am moderately anxious or depressed	23/266 (8.6)	27/240 (11.2)	50/506 (9.9)
I am severely anxious or depressed	4/266 (1.5)	6/240 (2.5)	10/506 (2)
I am extremely anxious or depressed	1/266 (0.4)	1/240 (0.4)	2/506 (0.4)
Visual analogue scale			
n	265	236	501
Mean (SD)	78.6 (20.5)	77.1 (21.1)	77.9 (20.8)
Median	85	80	85
Minimum, maximum	10, 100	0, 100	0, 100
Utility index			
n	272	253	525
Mean (SD)	0.785 (0.278)	0.720 (0.327)	0.754 (0.304)
Median	0.877	0.836	0.837
Minimum, maximum	−0.071, 1	−0.208, 1	−0.208, 1

TABLE 51 The EQ-5D-5L at 6 months (per-protocol population)

Variable	Treatment arm		Total
	Placebo	Dexamethasone	
Mobility, n/N (%)			
I have no problems in walking about	160/254 (63)	147/230 (63.9)	307/484 (63.4)
I have slight problems in walking about	44/254 (17.3)	39/230 (17)	83/484 (17.1)
I have moderate problems in walking about	30/254 (11.8)	25/230 (10.9)	55/484 (11.4)
I have severe problems in walking about	14/254 (5.5)	12/230 (5.2)	26/484 (5.4)
I am unable to walk about	6/254 (2.4)	7/230 (3)	13/484 (2.7)
Self-care, n/N (%)			
I have no problems washing or dressing myself	203/253 (80.2)	180/227 (79.3)	383/480 (79.8)
I have slight problems washing or dressing myself	25/253 (9.9)	21/227 (9.3)	46/480 (9.6)
I have moderate problems washing or dressing myself	14/253 (5.5)	14/227 (6.2)	28/480 (5.8)
I have severe problems washing or dressing myself	8/253 (3.2)	5/227 (2.2)	13/480 (2.7)
I am unable to wash or dress myself	3/253 (1.2)	7/227 (3.1)	10/480 (2.1)

continued

TABLE 51 The EQ-5D-5L at 6 months (per-protocol population) (*continued*)

Variable	Treatment arm		Total
	Placebo	Dexamethasone	
Usual activities, n/N (%)			
I have no problems doing usual activities	161/253 (63.6)	148/228 (64.9)	309/481 (64.2)
I have slight problems doing usual activities	39/253 (15.4)	31/228 (13.6)	70/481 (14.6)
I have moderate problems doing usual activities	30/253 (11.9)	27/228 (11.8)	57/481 (11.9)
I have severe problems doing usual activities	17/253 (6.7)	8/228 (3.5)	25/481 (5.2)
I am unable to do usual activities	6/253 (2.4)	14/228 (6.1)	20/481 (4.2)
Pain/discomfort, n/N (%)			
I have no pain or discomfort	168/254 (66.1)	161/228 (70.6)	329/482 (68.3)
I have slight pain or discomfort	51/254 (20.1)	39/228 (17.1)	90/482 (18.7)
I have moderate pain or discomfort	27/254 (10.6)	23/228 (10.1)	50/482 (10.4)
I have severe pain or discomfort	3/254 (1.2)	3/228 (1.3)	6/482 (1.2)
I have extreme pain or discomfort	5/254 (2)	2/228 (0.9)	7/482 (1.5)
Anxiety/depression, n/N (%)			
I am not anxious or depressed	189/254 (74.4)	165/226 (73)	354/480 (73.8)
I am slightly anxious or depressed	41/254 (16.1)	36/226 (15.9)	77/480 (16)
I am moderately anxious or depressed	19/254 (7.5)	19/226 (8.4)	38/480 (7.9)
I am severely anxious or depressed	2/254 (0.8)	5/226 (2.2)	7/480 (1.5)
I am extremely anxious or depressed	3/254 (1.2)	1/226 (0.4)	4/480 (0.8)
Visual analogue scale			
n	250	225	475
Mean (SD)	81.3 (19.4)	81.4 (17.2)	81.4 (18.4)
Median	90	85	85
Minimum, maximum	5, 100	10, 100	5, 100
Utility index			
n	263	244	507
Mean (SD)	0.777 (0.304)	0.745 (0.336)	0.762 (0.320)
Median	0.877	0.877	0.877
Minimum, maximum	−0.594, 1	−0.594, 1	−0.594, 1

TABLE 52 Model-fitting results for EQ-5D-5L at discharge, 3 months and 6 months (per-protocol population)

Outcome	Covariate	Estimate (SE)	95% CI	*p*-value
EQ-5D-5L utility index at discharge	(Intercept)	0.743 (0.0166)	0.71 to 0.776	
	Dexamethasone vs. placebo	−0.0129 (0.0239)	−0.0598 to 0.034	0.588
EQ-5D-5L utility index at 3 months	(Intercept)	0.785 (0.0184)	0.749 to 0.821	
	Dexamethasone vs. placebo	−0.0652 (0.0265)	−0.117 to −0.0132	0.014
EQ-5D-5L utility index at 6 months	(Intercept)	0.777 (0.0197)	0.738 to 0.816	
	Dexamethasone vs. placebo	−0.0322 (0.0284)	−0.0881 to 0.0237	0.258

SE, standard error.

TABLE 53 Discharge data (per-protocol population)

Variable	Treatment arm		Total
	Placebo	Dexamethasone	
Discharge destination after index admission, *n*/*N* (%)			
Home	217/307 (70.7)	197/290 (67.9)	414/597 (69.3)
Carers at home	11/307 (3.6)	6/290 (2.1)	17/597 (2.8)
Local hospital	53/307 (17.3)	61/290 (21)	114/597 (19.1)
Rehabilitation centre	8/307 (2.6)	8/290 (2.8)	16/597 (2.7)
Residential home	1/307 (0.3)	1/290 (0.3)	2/597 (0.3)
Nursing home	1/307 (0.3)	4/290 (1.4)	5/597 (0.8)
Other	16/307 (5.2)	13/290 (4.5)	29/597 (4.9)
Length of stay in NSU (days)			
n	307	290	597
Mean (SD)	8.72 (7.25)	9.08 (8.52)	8.90 (7.89)
Median	6	6.5	6
Minimum, maximum	2, 57	2, 70	2, 70
Length of stay in secondary care (days)[a]			
n	307	290	597
Mean (SD)	13.7 (23.0)	13.1 (18.2)	13.4 (20.8)
Median	7	7	7
Minimum, maximum	2, 219	2, 198	2, 219
Stayed in ICU/HDU: yes, *n*/*N* (%)	32/307 (10.4)	29/290 (10)	61/597 (10.2)
Length of stay in ICU/HDU (days)			
n	32	29	61
Mean (SD)	3.03 (2.95)	3.07 (2.63)	3.05 (2.78)
Median	2	2	2
Minimum, maximum	1, 17	1, 10	1, 17

a Length of stay in secondary care calculated as length of stay in NSU plus the self-reported length of stay in hospital or healthcare facility based on the 6-month questionnaires.

TABLE 54 Model-fitting results for discharge data (per-protocol population)

Outcome	Estimate[a]	95% CI	*p*-value
Negative binomial regression model			
Length of stay in NSU (days)	1.04	0.934 to 1.16	0.468
Length of stay in secondary care (days)	0.962	0.831 to 1.12	0.611
Logistic regression model			
Discharge destination after index admission[b]	1.14	0.804 to 1.61	0.466
Discharge destination after index admission[c]	0.751	0.411 to 1.37	0.35

a Dexamethasone vs. placebo: rate ratio (95% CI) and OR (95% CI).
b Discharge destination: home vs. other.
c Discharge destination: local hospital vs. other (excluding home).

TABLE 55 Model-fitting results for the primary outcome (per-protocol population): mRS at 6 months (dichotomised)

Covariate	Odds ratio (95% CI)	*p*-value
Dexamethasone vs. placebo	0.506 (0.278 to 0.904)	0.023
Age (years)	0.893 (0.858 to 0.925)	< 0.001
GCS score at baseline	1.5 (1.29 to 1.76)	< 0.001

TABLE 56 Model-fitting results for ordinal mRS at 6 months (per-protocol population): mRS at discharge

Ordinal logistic regression			Sequential OR				
Covariate	Global OR (95% CI)[a]	*p*-value	Cut-off point	Probability mRS ≤ cut-off point (placebo arm)	Placebo (*N* = 283), *n* (%)	Dexamethasone (*N* = 270), *n* (%)	Marginal OR (95% CI)
Dexamethasone vs. placebo	0.818 (0.595 to 1.12)	0.215	0	0.498	142 (50)	129 (48)	0.908 (0.651 to 1.268)
Age (years)	0.944 (0.929 to 0.959)	< 0.001	1	0.671	187 (66)	169 (63)	0.859 (0.606 to 1.217)
GCS at baseline	1.4 (1.24 to 1.58)	< 0.001	2	0.732	205 (72)	181 (67)	0.774 (0.538 to 1.113)
			3	0.914	258 (91)	229 (85)	0.541 (0.319 to 0.918)
			4	0.94	266 (94)	238 (88)	0.475 (0.257 to 0.878)
			5	0.963	272 (96)	250 (93)	0.506 (0.237 to 1.076)

a Odds in direction of a favourable outcome.

Notes
Data show frequency (%) of patients with a mRS score less than or equal to the cut-off point.
Cut-off point 6 not included as all patients had an mRS score ≤6.

TABLE 57 Baseline subgroup analyses (full analysis population)

Subgroup	Odds ratio	95% CI	*p*-value
Site			
Dexamethasone vs. placebo	0.59	0.337 to 1.02	0.06
Cambridge vs. other sites	1.48	0.684 to 3.46	0.341
Treatment: dexamethasone: site – Cambridge	0.84	0.297 to 2.29	0.736
Age			
Dexamethasone vs. placebo	0.554	0.338 to 0.895	0.017
< 70 years vs. ≥ 70 years	6.77	1.99 to 42.3	0.01
Treatment: dexamethasone: age – < 70 years	1.14	0.14 to 7.46	0.892

TABLE 57 Baseline subgroup analyses (full analysis population) (*continued*)

Subgroup	Odds ratio	95% CI	*p*-value
Timing of head trauma			
Dexamethasone vs. placebo	0.445	0.153 to 1.15	0.109
≤ 4 weeks ago (reference: no head trauma)	0.404	0.141 to 1.02	0.068
> 4 weeks ago	0.816	0.265 to 2.35	0.71
Not known	0.404	0.0549 to 8.27	0.435
Treatment: dexamethasone: trauma – ≤ 4 weeks ago	1.07	0.335 to 3.71	0.907
Treatment: dexamethasone: trauma – > 4 weeks ago	1.94	0.496 to 8.06	0.348
Treatment: dexamethasone: trauma – not known	2.62	0.0804 to 86.2	0.547
Anticoagulants/platelets			
Dexamethasone vs. placebo	0.58	0.293 to 1.12	0.108
Anticoagulants/platelets vs. none	0.731	0.353 to 1.51	0.393
Treatment: dexamethasone: anticoagulants/platelets – yes	0.948	0.375 to 2.4	0.909
GCS at baseline			
Dexamethasone vs. placebo	0.019	0.00028 to 0.941	0.054
GCS at baseline	1.35	1.12 to 1.63	< 0.001
Treatment: dexamethasone: GCS score at baseline	1.27	0.96 to 1.71	0.105
Side of CSDH			
Dexamethasone vs. placebo	0.422	0.244 to 0.711	0.001
Bilateral vs. unilateral	0.549	0.254 to 1.26	0.14
Treatment: dexamethasone: side – bilateral	3.66	1.2 to 11.6	0.024

TABLE 58 Baseline subgroup analyses (per-protocol population)

Subgroup	Odds ratio	95% CI	*p*-value
Site			
Dexamethasone vs. placebo	0.568	0.293 to 1.08	0.086
Cambridge vs. other sites	1.22	0.521 to 3.08	0.66
Treatment: dexamethasone: site – Cambridge	0.867	0.275 to 2.64	0.803
Age			
Dexamethasone vs. placebo	0.527	0.298 to 0.914	0.024
< 70 years vs. ≥ 70 years	5.08	1.45 to 32.1	0.03
Treatment: dexamethasone: age – < 70 years	1.66	0.183 to 15	0.631
Timing of head trauma			

continued

TABLE 58 Baseline subgroup analyses (per-protocol population) (*continued*)

Subgroup	Odds ratio	95% CI	*p*-value
Dexamethasone vs. placebo	0.455	0.138 to 1.31	0.161
≤ 4 weeks ago (reference: no head trauma)	0.422	0.129 to 1.2	0.121
> 4 weeks ago	0.787	0.23 to 2.46	0.685
Not known	374,000	[3.81e-05 to 1.83e+ 96]	0.983
Treatment: dexamethasone: trauma – ≤ 4 weeks ago	1.04	0.278 to 4.24	0.949
Treatment: dexamethasone: trauma – > 4 weeks ago	2.3	0.498 to 11.6	0.295
Treatment: dexamethasone: trauma – not known	1.91e-06	[3.89e-97 to 18700]	0.982
Anticoagulants/platelets			
Dexamethasone vs. placebo	0.551	0.242 to 1.21	0.142
Anticoagulants/platelets vs. none	0.635	0.272 to 1.45	0.282
Treatment: dexamethasone: anticoagulants/platelets – yes	0.994	0.341 to 2.92	0.992
GCS at baseline			
Dexamethasone vs. placebo	0.046	0.000587 to 2.76	0.149
GCS at baseline	1.41	1.15 to 1.72	< 0.001
Treatment: dexamethasone: GCS at baseline	1.18	0.883 to 1.62	0.269
Side of CSDH			
Dexamethasone vs. placebo	0.46	0.247 to 0.833	0.012
Bilateral vs. unilateral	0.634	0.261 to 1.7	0.334
Treatment: dexamethasone: side – bilateral	2.09	0.579 to 7.58	0.257

TABLE 59 Post-baseline subgroup analyses (per-protocol population)

	Favourable outcome (mRS score 0–3), *n*/*N* (%)	
Subgroup	Placebo	Dexamethasone
Recurrence (one or more reoperation)		
Yes	20/21 (95)	6/10 (60)
No	224/248 (90)	208/242 (86)
Surgical intervention during primary surgery		
Burr hole(s)	211/232 (91)	185/218 (85)
Craniotomy	26/30 (87)	22/26 (85)
Drain during primary surgery		
Yes	212/234 (91)	181/212 (85)
No	32/35 (91)	33/40 (82)
Conservative management (no surgery on any admission)		
Yes	14/14 (100)	15/18 (83)
No	244/269 (91)	214/252 (85)
Trial conservative management		
No surgery	14/14 (100)	15/18 (83)
Surgery within 7 days of randomisation	235/260 (90)	211/249 (85)
Surgery > 7 days after randomisation	9/9 (100)	3/3 (100)

TABLE 60 Listing of non-serious AESIs

Participant ID	Site	Treatment arm	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Outcome
N17–104	Plymouth	Placebo	Upper gastrointestinal side effects	10 December 2015	10 December 2015	Dyspepsia	Gastrointestinal disorders	Unlikely	Resolved: no residual effects
N25–108	Glasgow	Placebo	New-onset psychosis	29 August 2016	29 August 2016	Acute psychosis	Psychiatric disorders	Possibly	Resolved: no residual effects
N01–218	Cambridge	Placebo	New-onset diabetes necessitating ongoing medical treatment at day 30 follow-up	16 November 2016	6 February 2017	Hyperglycaemia	Endocrine disorders	Possibly	Resolved: no residual effects
N35–129	Southampton	Placebo	New-onset psychosis	24 November 2016		Hallucination	Psychiatric disorders	Unlikely	Ongoing
N01–231	Cambridge	Placebo	Upper gastrointestinal side effects	12 January 2017	13 January 2017	Dyspepsia	Gastrointestinal disorders	Possibly	Resolved: no residual effects
N01–246	Cambridge	Placebo	Hyperglycaemia necessitating treatment	17 March 2017	19 March 2017	Hyperglycaemia	Endocrine disorders	Possibly	Resolved: no residual effects
N34–123	Sheffield	Placebo	Upper gastrointestinal side effects	28 July 2017	11 August 2017	Vomiting	Gastrointestinal disorders	Unlikely	Resolved: no residual effects
N23–104	Dundee	Placebo	Hyperglycaemia necessitating stopping of trial medication	21 October 2017	22 October 2017	Hyperglycaemia	Endocrine disorders	Definitely	Resolved: no residual effects
N24–105	Edinburgh	Placebo	Upper gastrointestinal side effects	16 December 2017	19 December 2017	Nausea	Gastrointestinal disorders	Possibly	Resolved: no residual effects
N24–105	Edinburgh	Placebo	Upper gastrointestinal side effects	16 December 2017	19 December 2017	Vomiting	Gastrointestinal disorders	Possibly	Resolved: no residual effects
N35–159	Southampton	Placebo	Upper gastrointestinal side effects	6 March 2018	4 October 2018	Vomiting	Gastrointestinal disorders	Possibly	Resolved: no residual effects
N26–111	Hull	Placebo	Upper gastrointestinal side effects	23 April 2018	24 April 2018	Vomiting	Gastrointestinal disorders	Unlikely	Resolved: no residual effects
N35–183	Southampton	Placebo	Upper gastrointestinal side effects	1 September 2018	2 September 2018	Vomiting	Gastrointestinal disorders	Unrelated	Resolved: no residual effects

continued

TABLE 60 Listing of non-serious AESIs (*continued*)

Participant ID	Site	Treatment arm	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Outcome
N01–105	Cambridge	Dexamethasone	Upper gastrointestinal side effects	26 August 2015	28 August 2015	Dyspepsia	Gastrointestinal disorders	Possibly	Resolved: no residual effects
N01–126	Cambridge	Dexamethasone	Hyperglycaemia necessitating treatment	27 October 2015	23 December 2015	Hyperglycaemia	Endocrine disorders	Probably	Resolved: no residual effects
N17–103	Plymouth	Dexamethasone	New-onset psychosis	5 November 2015	6 November 2015	Hallucination	Psychiatric disorders	Unlikely	Resolved: no residual effects
N01–130	Cambridge	Dexamethasone	Hyperglycaemia necessitating treatment	1 December 2015	4 December 2015	Hyperglycaemia	Endocrine disorders	Possibly	Resolved: no residual effects
N01–151	Cambridge	Dexamethasone	Upper gastrointestinal side effects	4 March 2016	4 April 2016	Dyspepsia	Gastrointestinal disorders	Possibly	Resolved: no residual effects
N01–159	Cambridge	Dexamethasone	Hyperglycaemia necessitating treatment	9 March 2016	11 March 2016	Hyperglycaemia	Endocrine disorders	Probably	Resolved: no residual effects
N01–158	Cambridge	Dexamethasone	Hyperglycaemia necessitating treatment	12 March 2016	21 March 2016	Hyperglycaemia	Endocrine disorders	Probably	Resolved: no residual effects
N35–105	Southampton	Dexamethasone	Hyperglycaemia necessitating stopping of trial medication	12 March 2016	17 March 2016	Hyperglycaemia	Endocrine disorders	Definitely	Resolved: no residual effects
N35–105	Southampton	Dexamethasone	Hyperglycaemia necessitating treatment	29 March 2016		Hyperglycaemia	Endocrine disorders	Probably	Ongoing
N12–101	Imperial	Dexamethasone	Hyperglycaemia necessitating treatment	4 April 2016		Hyperglycaemia	Endocrine disorders	Unrelated	Ongoing
N01–160	Cambridge	Dexamethasone	New-onset diabetes necessitating treatment	20 April 2016		Type 2 diabetes	Endocrine disorders	Possibly	Ongoing

Participant ID	Site	Treatment arm	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Outcome
N25–101	Glasgow	Dexamethasone	Hyperglycaemia necessitating treatment	25 May 2016	31 May 2016	Hyperglycaemia	Endocrine disorders	Definitely	Resolved: no residual effects
N07–104	Birmingham	Dexamethasone	New-onset diabetes necessitating treatment	25 June 2016		Type 2 diabetes mellitus	Metabolism and nutrition disorders	Unlikely	Ongoing
N01–195	Cambridge	Dexamethasone	Hyperglycaemia necessitating treatment	1 August 2016	15 August 2016	Hyperglycaemia	Endocrine disorders	Possibly	Resolved: no residual effects
N35–120	Southampton	Dexamethasone	New-onset psychosis	19 August 2016	21 August 2016	Hallucination	Psychiatric disorders	Probably	Resolved: no residual effects
N01–212	Cambridge	Dexamethasone	Upper gastrointestinal side effects	18 October 2016	18 October 2016	Gastrointestinal tract irritation	Gastrointestinal disorders	Possibly	Resolved: no residual effects
N35–127	Southampton	Dexamethasone	Upper gastrointestinal side effects	18 November 2016	3 December 2016	Dyspepsia	Gastrointestinal disorders	Possibly	Resolved: no residual effects
N25–117	Glasgow	Dexamethasone	Hyperglycaemia necessitating treatment	22 November 2016	24 November 2016	Hyperglycaemia	Endocrine disorders	Probably	Resolved: no residual effects
N01–221	Cambridge	Dexamethasone	New-onset psychosis	26 November 2016	29 November 2016	Acute psychosis	Psychiatric disorders	Possibly	Resolved: no residual effects
N12–103	Imperial	Dexamethasone	Upper gastrointestinal side effects	8 December 2016	8 December 2016	Dyspepsia	Gastrointestinal disorders	Possibly	Resolved: no residual effects
N01–230	Cambridge	Dexamethasone	Hyperglycaemia necessitating treatment	7 January 2017	19 January 2017	Hyperglycaemia	Endocrine disorders	Probably	Resolved: no residual effects
N34–113	Sheffield	Dexamethasone	New-onset psychosis	3 March 2017		Psychotic disorder	Psychiatric disorders	Definitely	Ongoing
N01–244	Cambridge	Dexamethasone	Upper gastrointestinal side effects	7 March 2017	10 March 2017	Vomiting	Gastrointestinal disorders	Possibly	Resolved: no residual effects
N25–119	Glasgow	Dexamethasone	New-onset psychosis	26 May 2017	27 May 2017	Euphoric mood	Psychiatric disorders	Unlikely	Resolved: no residual effects

continued

TABLE 60 Listing of non-serious AESIs (*continued*)

Participant ID	Site	Treatment arm	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Outcome
N01–262	Cambridge	Dexamethasone	Hyperglycaemia necessitating treatment	9 June 2017	14 June 2017	Hyperglycaemia	Endocrine disorders	Possibly	Resolved: no residual effects
N25–125	Glasgow	Dexamethasone	Hyperglycaemia necessitating treatment	5 July 2017		Hyperglycaemia	Endocrine disorders	Possibly	Ongoing
N25–126	Glasgow	Dexamethasone	Upper gastrointestinal side effects	9 July 2017	9 July 2017	Abdominal pain	Gastrointestinal disorders	Possibly	Resolved: no residual effects
N35–150	Southampton	Dexamethasone	New-onset psychosis	3 November 2017	29 November 2017	Delirium	Psychiatric disorders	Probably	Resolved with residual effects
N24–104	Edinburgh	Dexamethasone	New-onset psychosis	23 November 2017	29 November 2017	Delirium	Psychiatric disorders	Probably	Resolved: no residual effects
N34–127	Sheffield	Dexamethasone	Upper gastrointestinal side effects	6 December 2017	7 December 2017	Vomiting	Gastrointestinal disorders	Possibly	Resolved: no residual effects
N35–156	Southampton	Dexamethasone	New-onset psychosis	3 January 2018	6 January 2018	Hallucination	Psychiatric disorders	Possibly	Resolved: no residual effects
N34–130	Sheffield	Dexamethasone	Hyperglycaemia necessitating treatment	16 January 2018	8 February 2018	Hyperglycaemia	Endocrine disorders	Definitely	Resolved: no residual effects
N34–131	Sheffield	Dexamethasone	Hyperglycaemia necessitating treatment	24 January 2018	5 February 2018	Hyperglycaemia	Endocrine disorders	Definitely	Resolved: no residual effects
N25–138	Glasgow	Dexamethasone	New-onset psychosis	7 February 2018	13 February 2018	Agitation	Psychiatric disorders	Probably	Resolved: no residual effects
N25–141	Glasgow	Dexamethasone	New-onset psychosis	11 March 2018	12 March 2018	Delirium	Psychiatric disorders	Probably	Resolved: no residual effects
N34–133	Sheffield	Dexamethasone	Hyperglycaemia necessitating treatment	17 March 2018		Hyperglycaemia	Endocrine disorders	Possibly	Ongoing

Participant ID	Site	Treatment arm	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Outcome
N24–113	Edinburgh	Dexamethasone	Hyperglycaemia necessitating treatment	8 August 2018		Hyperglycaemia	Endocrine disorders	Unlikely	Unknown
N24–113	Edinburgh	Dexamethasone	Hyperglycaemia necessitating stopping of trial medication	16 August 2018		Hyperglycaemia	Endocrine disorders	Probably	Unknown
N48–149	Leeds	Dexamethasone	New-onset psychosis	25 September 2018		Delirium	Psychiatric disorders	Probably	Ongoing
N48–146	Leeds	Dexamethasone	Upper gastrointestinal side effects	2 October 2018	2 October 2018	Dyspepsia	Gastrointestinal disorders	Probably	Resolved: no residual effects
N36–113	St George's	Dexamethasone	Hyperglycaemia necessitating treatment	9 October 2018	11 October 2018	Hyperglycaemia	Endocrine disorders	Probably	Resolved with residual effects
N31–108	Newcastle	Dexamethasone	Upper gastrointestinal side effects	13 October 2018	13 October 2018	Dyspepsia	Gastrointestinal disorders	Probably	Resolved: no residual effects
N36–115	St George's	Dexamethasone	Gastrointestinal bleeding	9 November 2018	9 November 2018	Melaena	Gastrointestinal disorders	Unlikely	Resolved: no residual effects

TABLE 61 Listing of serious AESIs

Participant ID	Site	Treatment arm	SAE reference number	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N34–123	Sheffield	Placebo	N34–123–02	Upper gastrointestinal side effects	28 July 2017	11 August 2017	Intestinal obstruction	Gastrointestinal disorders	Unlikely	Moderate	Hospitalisation	Resolved: no residual effects
N48–104	Leeds	Dexamethasone	N48–104–01	New-onset psychosis	9 June 2016	10 June 2016	Acute psychosis	Psychiatric disorders	Possibly	Mild	Hospitalisation	Resolved: no residual effects
N01–193	Cambridge	Dexamethasone	N01–193–01	Hyperglycaemia necessitating treatment	4 August 2016	6 August 2016	Hyperglycaemia	Endocrine disorders	Probably	Moderate	Hospitalisation	Resolved: no residual effects
N01–345	Cambridge	Dexamethasone	N01–345–01	Upper gastrointestinal side effects	20 August 2018	27 August 2018	Dyspepsia	Gastrointestinal disorders	Probably	Moderate	Hospitalisation	Resolved: no residual effects

TABLE 62 Listing of non-reportable SAEs

Participant ID	Site	Treatment arm	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N01–117	Cambridge	Placebo	Seizure	1 October 2015	2 October 2015	Seizure	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N01–124	Cambridge	Placebo	Subdural empyema	15 November 2015	20 November 2015	Brain empyema	Infections and infestations	Unlikely	Severe	Hospitalisation	Resolved: no residual effects
N01–128	Cambridge	Placebo	Recurrent CSDH	17 November 2015	20 November 2015	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N35–103	Southampton	Placebo	Recollection of CSDH	18 February 2016	18 February 2016	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N35–106	Southampton	Placebo	Partial seizures	13 March 2016	13 March 2016	Seizure	Nervous system disorders	Unlikely	Mild	Hospitalisation	Resolved: no residual effects
N35–106	Southampton	Placebo	Seizures	13 March 2016	14 March 2016	Seizure	Nervous system disorders	Unlikely	Mild	Hospitalisation	Resolved: no residual effects
N01–164	Cambridge	Placebo	Reoperation owing to recollection of CSDH (same admission)	3 April 2016	3 April 2016	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N12–102	Imperial	Placebo	Worsening of CSDH	15 April 2016	19 April 2016	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N01–167	Cambridge	Placebo	Residual CSDH	29 April 2016	5 May 2016	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N35–112	Southampton	Placebo	Recollection of CSDH	1 May 2016	5 May 2016	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N48–101	Leeds	Placebo	Recollection of CSDH	23 May 2016	23 May 2016	Subdural haematoma	Nervous system disorders	Possibly	Moderate	Hospitalisation	Resolved: no residual effects

continued

TABLE 62 Listing of non-reportable SAEs (*continued*)

Participant ID	Site	Treatment arm	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N34–103	Sheffield	Placebo	Rebleed into CSDH (conservatively managed) and sub-arachnoid haemorrage	17 June 2016	20 June 2016	Subdural haematoma	Nervous system disorders	Possibly	Moderate	Hospitalisation	Resolved with residual effects
N01–188	Cambridge	Placebo	Residual CSDH (operated)	13 July 2016	15 July 2016	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N01–190	Cambridge	Placebo	Recurrent CSDH	3 August 2016	5 August 2016	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N01–198	Cambridge	Placebo	Residual CSDH	22 August 2016	23 August 2016	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N48–105	Leeds	Placebo	Recollection	12 September 2016	19 September 2016	Subdural haematoma	Nervous system disorders	Unlikely	Severe	Hospitalisation	Resolved: no residual effects
N01–210	Cambridge	Placebo	Recurrent CSDH	13 October 2016	15 October 2016	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N35–124	Southampton	Placebo	Recollection of CSDH	31 October 2016	7 November 2016	Subdural haematoma	Nervous system disorders	Unlikely	Severe	Hospitalisation	Resolved: no residual effects
N35–124	Southampton	Placebo	Seizure	9 November 2016	9 November 2016	Seizure	Nervous system disorders	Unlikely	Mild	Hospitalisation	Resolved: no residual effects
N01–218	Cambridge	Placebo	Reoperation owing to recollection of CSDH (same admission)	14 November 2016	14 November 2016	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N01–218	Cambridge	Placebo	Seizure	4 December 2016	5 December 2016	Seizure	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects

Participant ID	Site	Treatment arm	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N01–222	Cambridge	Placebo	Residual CSDH	8 December 2016	13 December 2016	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N01–228	Cambridge	Placebo	Recurrent CSDH	2 January 2017	3 January 2017	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N01–248	Cambridge	Placebo	Re-admission for recollection of CSDH	8 April 2017	8 April 2017	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N01–248	Cambridge	Placebo	Surgical site infection	8 April 2017	16 April 2017	Postoperative wound infection	Infections and infestations	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N34–112	Sheffield	Placebo	Recollection of CSDH	20 April 2017	23 April 2017	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N17–110	Plymouth	Placebo	Small rebleed	14 May 2017	16 May 2017	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved with residual effects
N31–105	Newcastle	Placebo	Evacuation of acute on chronic subdural haematoma	21 May 2017		Depressed level of consciousnesses	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Ongoing
N31–105	Newcastle	Placebo	Patient deterioration. Second recurrent haemorrhage	4 June 2017	22 June 2017	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved with residual effects
N07–113	Birmingham	Placebo	Late recollection of CSDH. No surgery required	9 June 2017	12 June 2017	Subdural haematoma	Nervous system disorders	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N08–110	Brighton	Placebo	Recurrence of CSDH	20 June 2017	21 June 2017	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects

continued

TABLE 62 Listing of non-reportable SAEs (*continued*)

Participant ID	Site	Treatment arm	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N31–105	Newcastle	Placebo	Re-admission: R Pupil 4, L Pupil 3, slurred speech, facial droop. Reopening of cranial wound, removal of infected bone flap and washout of empyema on 8 July 2017 and wound washout on 11 July 2017. R-sided facial weakness, dysphasia, evidence of collection and brain oedema on CT on 7 July 2017	4 July 2017		Brain empyema	Infections and infestations	Unrelated	Severe	Hospitalisation	Ongoing
N34–123	Sheffield	Placebo	Pneumocephalus	23 July 2017	25 July 2017	Pneumocephalus	Injury, poisoning and procedural complications	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N26–106	Hull	Placebo	Expansion CSDH	17 August 2017	18 August 2017	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N17–122	Plymouth	Placebo	Recollection of CSDH	24 August 2017	24 August 2017	Subdural haematoma	Nervous system disorders	Definitely	Severe	Hospitalisation	Resolved: no residual effects
N25–128	Glasgow	Placebo	Return to theatre for recollection of CSDH	29 August 2017	29 August 2017	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N07–117	Birmingham	Placebo	Seizure	5 October 2017	6 October 2017	Seizure	Nervous system disorders	Unlikely	Mild	Hospitalisation	Resolved with residual effects
N12–104	Imperial	Placebo	Repeat burr hole surgery	12 October 2017	12 October 2017	Subdural haematoma	Nervous system disorders	Unlikely	Moderate	Hospitalisation	Resolved: no residual effects
N33–107	Preston (Lancashire)	Placebo	Recollection of CSDH	20 October 2017	21 June 2018	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved with residual effects

Participant ID	Site	Treatment arm	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N26–108	Hull	Placebo	Left-sided weakness and residual bleeding	4 November 2017	18 November 2017	Subdural haematoma	Nervous system disorders	Unlikely	Mild	Considered medically significant by the investigator	Resolved: no residual effects
N23–104	Dundee	Placebo	Recurrent bilateral subdural haematoma (midline shift to right)	6 December 2017	14 December 2017	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved with residual effects
N01–328	Cambridge	Placebo	Recollection of CSDH with consequent reoperation	31 January 2018	31 January 2018	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N46–118	Stoke/North Staffs	Placebo	Recurrent L CSDH	17 February 2018	10 March 2018	Subdural haematoma	Nervous system disorders	Unlikely	Moderate	Hospitalisation	Resolved: no residual effects
N35–158	Southampton	Placebo	Frontal empyema (subdural)	23 February 2018	28 February 2018	Brain empyema	Infections and infestations	Unlikely	Moderate	Hospitalisation	Resolved: no residual effects
N34–134	Sheffield	Placebo	Subclinical seizures	24 March 2018		Seizure	Nervous system disorders	Unlikely	Severe	Hospitalisation	Ongoing
N35–161	Southampton	Placebo	Recollection of CSDH: right side	1 April 2018	3 April 2018	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N35–161	Southampton	Placebo	Recollection of CSDH: right side	9 April 2018	9 April 2018	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N18–108	Aberdeen	Placebo	Recollection of CSDH	14 April 2018	23 April 2018	Subdural haematoma	Nervous system disorders	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N26–111	Hull	Placebo	Post-surgery seizures/ epilepsy	22 April 2018	1 May 2018	Seizure	Nervous system disorders	Unlikely	Moderate	Hospitalisation	Resolved: no residual effects
N01–338	Cambridge	Placebo	Seizure post operation	16 May 2018	16 May 2018	Seizure	Nervous system disorders	Unrelated	Mild	Considered medically significant by the investigator	Resolved: no residual effects

continued

TABLE 62 Listing of non-reportable SAEs (*continued*)

Participant ID	Site	Treatment arm	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N26–111	Hull	Placebo	Rebleed causing subdural haematoma	22 May 2018	30 May 2018	Subdural haematoma	Nervous system disorders	Unlikely	Moderate	Hospitalisation	Resolved: no residual effects
N35–175	Southampton	Placebo	Recollection of left CSDH	15 August 2018	18 August 2018	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N48–148	Leeds	Placebo	Recollection of CSDH	18 September 2018	18 September 2018	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved with residual effects
N36–109	St George's	Placebo	Acute on chronic subdural haematoma (recurrence)	3 October 2018	10 October 2018	Subdural haematoma	Nervous system disorders	Unlikely	Severe	Hospitalisation	Worsening
N36–112	St George's	Placebo	Recollection of right CSDH	20 October 2018	25 October 2018	Subdural haematoma	Nervous system disorders	Unlikely	Moderate	Hospitalisation	Resolved with residual effects
N36–112	St George's	Placebo	Recollection of right CSDH	29 October 2018	12 November 2018	Subdural haematoma	Nervous system disorders	Unlikely	Severe	Hospitalisation	Resolved with residual effects
N36–112	St George's	Placebo	(Recurrent) acute plus chronic subdural haematoma	31 October 2018	12 November 2018	Subdural haematoma	Nervous system disorders	Unlikely	Severe	Hospitalisation	Resolved with residual effects
N36–112	St George's	Placebo	Residual collection of CSDH	9 November 2018	12 November 2018	Subdural haematoma	Nervous system disorders	Unlikely	Moderate	Hospitalisation	Resolved with residual effects
N31–109	Newcastle	Placebo	Recollection of CSDH	3 December 2018	14 December 2018	Subdural haematoma	Nervous system disorders	Unlikely	Moderate	Hospitalisation	Resolved: no residual effects
N14–105	Middlesbrough	Placebo	Tension pneumocephalus		15 July 2016	Pneumocephalus	Injury, poisoning and procedural complications	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N25–108	Glasgow	Placebo	Seizure		29 August 2016	Seizure	Nervous system disorders	Unrelated	Mild	Hospitalisation	Resolved: no residual effects

Participant ID	Site	Treatment arm	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N17–101	Plymouth	Dexamethasone	Seizure (post D/C)	7 November 2015	7 November 2015	Seizure	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N01–148	Cambridge	Dexamethasone	Recurrent CSDH	23 February 2016	1 March 2016	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N01–181	Cambridge	Dexamethasone	Re-admission reoperation for recollection	29 June 2016	1 July 2016	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N01–186	Cambridge	Dexamethasone	Expansion of contralateral CSDH	8 September 2016	11 September 2016	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N01–200	Cambridge	Dexamethasone	Seizures	9 September 2016	11 September 2016	Seizure	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N01–200	Cambridge	Dexamethasone	Recurrent CSDH	9 September 2016	11 September 2016	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N34–106	Sheffield	Dexamethasone	Residual CSDH	10 September 2016	11 September 2016	Subdural haematoma	Nervous system disorders	Unlikely	Mild	Hospitalisation	Resolved: no residual effects
N01–221	Cambridge	Dexamethasone	Residual CSDH	27 November 2016	1 December 2016	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N35–131	Southampton	Dexamethasone	Non-reportable recollection of CSDH	14 December 2016	6 January 2017	Subdural haematoma	Nervous system disorders	Probably	Moderate	Is life-threatening	Resolved with residual effects
N18–101	Aberdeen	Dexamethasone	Recollection of CSDH	7 January 2017	9 January 2017	Subdural haematoma	Nervous system disorders	Definitely	Moderate	Is life-threatening	Resolved with residual effects
N18–101	Aberdeen	Dexamethasone	Subdural empyema	7 January 2017	20 February 2017	Brain empyema	Infections and infestations	Possibly	Severe	Is life-threatening	Resolved: no residual effects
N18–101	Aberdeen	Dexamethasone	Seizures	7 January 2017	8 January 2017	Seizure	Nervous system disorders	Possibly	Moderate	Hospitalisation	Resolved: no residual effects

continued

TABLE 62 Listing of non-reportable SAEs (*continued*)

Participant ID	Site	Treatment arm	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N48–115	Leeds	Dexamethasone	Reaccumulation of haematoma (regarded as recollection of CSDH)	20 January 2017	31 January 2017	Subdural haematoma	Nervous system disorders	Unlikely	Severe	Hospitalisation	Resolved: no residual effects
N17–107	Plymouth	Dexamethasone	Subdural empyema	2 March 2017		Brain empyema	Infections and infestations	Unlikely	Severe	Hospitalisation	Ongoing
N01–244	Cambridge	Dexamethasone	Re-admission recurrence reoperation	16 April 2017	18 April 2017	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N01–244	Cambridge	Dexamethasone	Re-admission recurrence reoperation	25 April 2017	27 April 2017	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N34–117	Sheffield	Dexamethasone	Pneumocephalus	5 May 2017		Pneumocephalus	Injury, poisoning and procedural complications	Unrelated	Moderate	Hospitalisation	Ongoing
N01–260	Cambridge	Dexamethasone	Re-admission operation (recollection of CSDH)	1 June 2017	1 June 2017	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N16–103	Romford	Dexamethasone	Subdural empyema	6 July 2017		Brain empyema	Infections and infestations	Possibly	Severe	Hospitalisation	Ongoing
N01–268	Cambridge	Dexamethasone	Re-admission recurrence CSDH reoperation	7 July 2017	8 July 2017	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N01–279	Cambridge	Dexamethasone	Empyema	19 August 2017	20 August 2017	Brain empyema	Infections and infestations	Unrelated	Severe	Hospitalisation	Resolved with residual effects
N31–106	Newcastle	Dexamethasone	Surgical site infection	16 September 2017	17 October 2017	Postoperative wound infection	Infections and infestations	Probably	Severe	Is life-threatening	Resolved: no residual effects
N31–106	Newcastle	Dexamethasone	Seizures	16 September 2017	16 September 2017	Seizure	Nervous system disorders	Probably	Severe	Hospitalisation	Resolved: no residual effects

Participant ID	Site	Treatment arm	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N31–106	Newcastle	Dexamethasone	Surgical site infection	26 October 2017	21 November 2017	Postoperative wound infection	Infections and infestations	Probably	Moderate	Hospitalisation	Resolved: no residual effects
N34–127	Sheffield	Dexamethasone	Recurrence of CSDH requiring operation	14 December 2017	19 December 2017	Subdural haematoma	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N25–136	Glasgow	Dexamethasone	Drainage of left subdural empyema	27 January 2018	8 March 2018	Brain empyema	Infections and infestations	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N32–101	Oxford	Dexamethasone	Reaccumulation of CSDH	24 June 2018	26 June 2018	Subdural haematoma	Nervous system disorders	Unlikely	Mild	Hospitalisation	Resolved: no residual effects
N35–180	Southampton	Dexamethasone	Right CSDH	19 July 2018	7 September 2018	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N08–121	Brighton	Dexamethasone	CSDH residual (originally treated conservatively)	24 July 2018	26 July 2018	Subdural haematoma	Nervous system disorders	Unlikely	Moderate	Hospitalisation	Resolved: no residual effects
N01–347	Cambridge	Dexamethasone	Recollection of CSDH	29 August 2018	29 August 2018	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N01–347	Cambridge	Dexamethasone	Site infection surgical	29 August 2018	29 August 2018	Postoperative wound infection	Infections and infestations	Unlikely	Moderate	Hospitalisation	Resolved: no residual effects
N48–143	Leeds	Dexamethasone	Subdural empyema	20 September 2018	10 October 2018	Brain empyema	Infections and infestations	Possibly	Severe	Hospitalisation	Resolved: no residual effects
N48–151	Leeds	Dexamethasone	Symptomatic left CSDH	15 October 2018	22 October 2018	Subdural haematoma	Nervous system disorders	Unlikely	Severe	Hospitalisation	Resolved: no residual effects

D/C, discharge.

TABLE 63 Listing of reportable SAEs (pre-study day 30)

Participant ID	Site	Treatment arm	SAE reference number	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N25–105	Glasgow	Placebo	N25–105–01	Stroke	11 July 2016	21 July 2016	Cerebrovascular accident	Nervous system disorders	Unrelated	Severe	Death	Death
N14–108	Middlesbrough	Placebo	N14–108–01	Worsening of left acute subdural haematoma	28 July 2016		Subdural haematoma	Nervous system disorders	Unrelated	Severe	Is life-threatening	Ongoing
N01–190	Cambridge	Placebo	N01–190–01	Anaphylaxis related to flucloxacillin	2 August 2016	5 August 2016	Anaphylactic reaction	Immune system disorders	Unlikely	Severe	Is life-threatening	Resolved: no residual effects
N01–202	Cambridge	Placebo	N01–202–01	Laceration	23 September 2016	25 September 2016	Laceration	Injury, poisoning and procedural complications	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N14–114	Middlesbrough	Placebo	N14–114–01	Lethargy and feeling unwell	23 October 2016		Malaise	General disorders and administration site conditions	Unrelated	Moderate	Hospitalisation	Ongoing
N35–132	Southampton	Placebo	N35–132–01	Pyrexia from unknown origin	22 January 2017	25 January 2017	Pyrexia	General disorders and administration site conditions	Unrelated	Mild	Hospitalisation	Resolved with residual effects
N01–242	Cambridge	Placebo	N01–242–01	Fall	13 March 2017	14 March 2017	Fall	Injury, poisoning and procedural complications	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N25–120	Glasgow	Placebo	N25–120–01	Cardiac instability	7 June 2017	7 June 2017	Cardiac failure	Cardiac disorders	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N01–263	Cambridge	Placebo	N01–263–01	Deep-vein thrombosis	17 June 2017	24 June 2017	Deep-vein thrombosis	Vascular disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N46–108	Stoke/North Staffs	Placebo	N46–108–01	Hyponatremia	8 July 2017		Hyponatraemia	Metabolism and nutrition disorders	Unrelated	Mild	Hospitalisation	Ongoing
N34–123	Sheffield	Placebo	N34–123–01	Right anterior cerebral artery infarction	17 July 2017	19 July 2017	Cerebrovascular accident	Nervous system disorders	Unlikely	Severe	Hospitalisation	Resolved with residual effects
N01–291	Cambridge	Placebo	N01–291–01	Postoperative swelling	29 August 2017	13 September 2017	Brain oedema	Nervous system disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N34–129	Sheffield	Placebo	N34–129–01	Aspiration pneumonia	6 January 2018	14 January 2018	Pneumonia	Infections and infestations	Unlikely	Severe	Hospitalisation	Resolved: no residual effects
N48–127	Leeds	Placebo	N48–127–01	Reduced appetite and fluid intake	23 January 2018	26 January 2018	Hypophagia	Metabolism and nutrition disorders	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N34–132	Sheffield	Placebo	N34–132–01	Low platelets	21 March 2018		Thrombocytopenia	Blood and lymphatic system disorders	Unlikely	Mild	Hospitalisation	Ongoing

Participant ID	Site	Treatment arm	SAE reference number	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N26–111	Hull	Placebo	N26–111–01	Pneumonia	25 April 2018	30 April 2018	Pneumonia	Infections and infestations	Possibly	Moderate	Hospitalisation	Resolved: no residual effects
N26–111	Hull	Placebo	N26–111–02	Pulmonary embolism	10 May 2018	19 May 2018	Pulmonary embolism	Vascular disorders	Unlikely	Moderate	Hospitalisation	Resolved: no residual effects
N08–117	Brighton	Placebo	N08–117–01	Death discovered in retrospect. Cause of death reported by coroner as acute cardiac failure	11 May 2018	11 May 2018	Cardiac failure acute	Cardiac disorders	Unlikely	Severe	Death	Death
N46–120	Stoke/North Staffs	Placebo	N46–120–01	Attended A&E with neck/arm pain and tingling in tips of left hand	20 May 2018	20 May 2018	Cervical radiculopathy	Nervous system disorders	Unlikely	Mild	Considered medically significant by the investigator	Resolved: no residual effects
N34–143	Sheffield	Placebo	N26–143–01	Pneumonia	7 June 2018		Pneumonia	Infections and infestations	Possibly	Severe	Hospitalisation	Ongoing
N32–102	Oxford	Placebo	N01–102–01	Pyrexia of unknown origin	3 July 2018	4 July 2018	Pyrexia	General disorders and administration site conditions	Possibly	Moderate	Hospitalisation	Resolved: no residual effects
N26–113	Hull	Placebo	N48–113–01	Chest infection	4 August 2018	13 August 2018	Pneumonia	Infections and infestations	Unlikely	Mild	Considered medically significant by the investigator	Resolved: no residual effects
N01–346	Cambridge	Placebo	N25–346–01	Electrolyte imbalance	20 August 2018	22 August 2018	Electrolyte imbalance	Metabolism and nutrition disorders	Unlikely	Mild	Hospitalisation	Resolved: no residual effects
N48–148	Leeds	Placebo	N34–148–01	Worsened heart failure	29 September 2018	23 October 2018	Cardiac failure chronic	Cardiac disorders	Unrelated	Severe	Death	Death
N25–127	Glasgow	Placebo	N34–127–01	Collapse	[a]	[a]	Syncope	Vascular disorders	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N34–143	Sheffield	Placebo	N34–143–02	Slow ventricular response	[a]		Cardiac disorder	Cardiac disorders	Unlikely	Severe	Hospitalisation	Ongoing
N34–143	Sheffield	Placebo	N34–143–03	Gangrene in toes	[a]		Gangrene	Vascular disorders	Unlikely	Severe	Hospitalisation	Ongoing
N34–143	Sheffield	Placebo	N34–143–04	Delirium	[a]		Delirium	Psychiatric disorders	Possibly	Severe	Hospitalisation	Ongoing
N01–123	Cambridge	Dexamethasone	N01–123–01	General physical health deterioration	14 October 2015	24 October 2015	General physical health deterioration	General disorders and administration site conditions	Unrelated	Severe	Death	Death

continued

TABLE 63 Listing of reportable SAEs (pre-study day 30) (*continued*)

Participant ID	Site	Treatment arm	SAE reference number	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N01–130	Cambridge	Dexamethasone	N01–130–01	Aspiration bronchopneumonia	12 December 2015	1 January 2016	Pneumonia	Infections and infestations	Unrelated	Severe	Death	Death
N01–134	Cambridge	Dexamethasone	N01–134–01	Urinary tract infection	18 December 2015	20 December 2015	Urinary tract infection	Infections and infestations	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N12–101	Imperial	Dexamethasone	N12–101–01	Bowel perforation secondary to diverticulitis	15 March 2016	22 March 2016	Large intestinal perforation	Gastrointestinal disorders	Unlikely	Moderate	Hospitalisation	Resolved: no residual effects
N01–154	Cambridge	Dexamethasone	N01–154–01	Hyperparathyroidism	19 March 2016	13 April 2016	Hyperparathyroidism	Endocrine disorders	Unlikely	Moderate	Hospitalisation	Resolved with residual effects
N35–110	Southampton	Dexamethasone	N35–110–01	Stroke	31 March 2016	13 April 2016	Cerebrovascular accident	Nervous system disorders	Unrelated	Severe	Hospitalisation	Resolved with residual effects
N12–101	Imperial	Dexamethasone	N12–101–02	Traumatic subdural (acute)	4 April 2016	22 April 2016	Subdural haematoma	Nervous system disorders	Unlikely	Severe	Death	Death
N01–175	Cambridge	Dexamethasone	N01–175–01	Meningitis	13 May 2016	7 June 2016	Meningitis	Infections and infestations	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N34–101	Sheffield	Dexamethasone	N34–101–01	Fall	13 May 2016	17 May 2016	Fall	Injury, poisoning and procedural complications	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N07–102	Birmingham	Dexamethasone	N07–102–01	Infective endocarditis	12 June 2016	6 July 2016	Endocarditis	Infections and infestations	Unlikely	Moderate	Hospitalisation	Resolved: no residual effects
N25–101	Glasgow	Dexamethasone	N25–101–01	Chest pain	15 June 2016	22 June 2016	Non-cardiac chest pain	General disorders and administration site conditions	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N48–104	Leeds	Dexamethasone	N48–104–02	Delirium (multifactorial delirium with advanced dementia)	23 June 2016	2 July 2016	Senile dementia	Psychiatric disorders	Possibly	Mild	Hospitalisation	Resolved: no residual effects
N14–104	Middlesbrough	Dexamethasone	N14–104–01	*Clostridium difficile* infection	13 July 2016	1 August 2016	*Clostridium difficile* colitis	Infections and infestations	Unrelated	Severe	Hospitalisation	Resolved with residual effects
N25–106	Glasgow	Dexamethasone	N25–106–01	Pneumothorax	29 July 2016	8 August 2016	Pneumothorax spontaneous	Respiratory, thoracic and mediastinal disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N01–193	Cambridge	Dexamethasone	N01–193–02	Stroke	9 August 2016	14 August 2016	Cerebrovascular accident	Nervous system disorders	Unrelated	Severe	Death	Death
N25–106	Glasgow	Dexamethasone	N25–106–02	Deep-vein thrombosis	11 August 2016	12 August 2016	Deep-vein thrombosis	Vascular disorders	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N01–200	Cambridge	Dexamethasone	N01–200–01	Chest infection	21 August 2016	28 August 2016	Pneumonia	Infections and infestations	Unrelated	Severe	Hospitalisation	Resolved: no residual effects

Participant ID	Site	Treatment arm	SAE reference number	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N01–200	Cambridge	Dexamethasone	N01–200–02	Alcohol withdrawal	21 August 2016	27 August 2016	Alcohol withdrawal syndrome	Psychiatric disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N48–106	Leeds	Dexamethasone	N48–106–02	Shingles	21 August 2016	22 August 2016	Herpes zoster	Infections and infestations	Probably	Moderate	Hospitalisation	Resolved: no residual effects
N48–106	Leeds	Dexamethasone	N48–106–01	Pulmonary embolism	30 August 2016	2 September 2016	Pulmonary embolism	Vascular disorders	Unlikely	Severe	Hospitalisation	Resolved with residual effects
N14–111	Middlesbrough	Dexamethasone	N14–111–01	Acute kidney injury	2 September 2016	12 September 2016	Acute kidney injury	Renal and urinary disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N07–108	Birmingham	Dexamethasone	N07–108–01	Urosepsis with acute kidney injury	6 September 2016	11 September 2016	Urinary tract infection	Infections and infestations	Unlikely	Mild	Considered medically significant by the investigator	Resolved: no residual effects
N01–212	Cambridge	Dexamethasone	N01–212–01	Vomiting	2 November 2016	3 November 2016	Vomiting	Gastrointestinal disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N01–217	Cambridge	Dexamethasone	N01–217–01	Adrenal insufficiency	15 November 2016		Adrenal insufficiency	Endocrine disorders	Definitely	Moderate	Hospitalisation	Ongoing
N01–220	Cambridge	Dexamethasone	N01–220–01	Confusional state	21 November 2016		Confusional state	Psychiatric disorders	Unrelated	Severe	Hospitalisation	Ongoing
N25–117	Glasgow	Dexamethasone	N25–117–01	Aspiration pneumonia	24 November 2016	1 December 2016	Pneumonia	Infections and infestations	Unrelated	Severe	Death	Death
N18–101	Aberdeen	Dexamethasone	N18–101–01	Influenza A	8 December 2016	14 December 2016	Influenza	Infections and infestations	Unlikely	Mild	Hospitalisation	Resolved: no residual effects
N35–131	Southampton	Dexamethasone	N35–131–01	Urinary sepsis	14 December 2016	16 January 2017	Urinary tract infection	Infections and infestations	Possibly	Moderate	Hospitalisation	Resolved: no residual effects
N35–131	Southampton	Dexamethasone	N35–131–02	Hospital-acquired pneumonia	23 December 2016	2 January 2017	Pneumonia	Infections and infestations	Unlikely	Mild	Hospitalisation	Resolved with residual effects
N34–111	Sheffield	Dexamethasone	N34–111–01	Fall	22 February 2017	3 March 2017	Fall	Injury, poisoning and procedural complications	Unlikely	Mild	Hospitalisation	Resolved with residual effects
N08–105	Brighton	Dexamethasone	N08–105–01	Pseudo-obstruction	21 March 2017	30 March 2017	Intestinal pseudo-obstruction	Gastrointestinal disorders	Unlikely	Severe	Hospitalisation	Resolved: no residual effects
N18–103	Aberdeen	Dexamethasone	N18–103–01	Speech disturbance	26 March 2017	26 March 2017	Speech disorder	Nervous system disorders	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N17–111	Plymouth	Dexamethasone	N17–111–01	General decline	20 May 2017	15 June 2017	General physical health deterioration	General disorders and administration site conditions	Unrelated	Severe	Hospitalisation	Resolved: no residual effects

continued

TABLE 63 Listing of reportable SAEs (pre-study day 30) (*continued*)

Participant ID	Site	Treatment arm	SAE reference number	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N48–121	Leeds	Dexamethasone	N48–121–01	Fall	25 May 2017	8 June 2017	Fall	Injury, poisoning and procedural complications	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N34–117	Sheffield	Dexamethasone	N34–117–02	Death: cause – aspiration pneumonia, Alzheimer's. Prostate carcinoma present at death but not cause of death	30 May 2017	30 May 2017	Pneumonia	Infections and infestations	Unlikely	Severe	Death	Death
N25–125	Glasgow	Dexamethasone	N25–125–01	Mesenteric infarction	18 July 2017	19 July 2017	Intestinal infarction	Vascular disorders	Unrelated	Severe	Death	Death
N01–270	Cambridge	Dexamethasone	N01–270–01	Stroke	1 August 2017	1 August 2017	Cerebrovascular accident	Nervous system disorders	Unrelated	Severe	Death	Death
N01–276	Cambridge	Dexamethasone	N01–276–01	Deep-vein thrombosis	21 August 2017	25 August 2017	Deep-vein thrombosis	Vascular disorders	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N01–284	Cambridge	Dexamethasone	N01–284–01	Left facial swelling	30 August 2017	1 September 2017	Swelling face	Skin and subcutaneous tissue disorders	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N18–107	Aberdeen	Dexamethasone	N18–107–01	Stroke	19 September 2017	17 October 2017	Cerebrovascular accident	Nervous system disorders	Unlikely	Moderate	Hospitalisation	Ongoing
N18–107	Aberdeen	Dexamethasone	N18–107–02	Aspiration pneumonia	28 September 2017	17 October 2017	Pneumonia	Infections and infestations	Unlikely	Moderate	Death	Death
N35–146	Southampton	Dexamethasone	N35–146–01	Loss of consciousness	11 October 2017	12 October 2017	Syncope	Vascular disorders	Unlikely	Moderate	Hospitalisation	Resolved: no residual effects
N01–300	Cambridge	Dexamethasone	N01–300–01	Confusion	24 October 2017	26 October 2017	Confusional state	Psychiatric disorders	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N01–302	Cambridge	Dexamethasone	N01–302–01	Lower respiratory tract infection	28 October 2017	31 October 2017	Pneumonia	Infections and infestations	Possibly	Moderate	Hospitalisation	Resolved: no residual effects
N35–150	Southampton	Dexamethasone	N35–150–01	Cholangiocarcinoma	14 November 2017	29 November 2017	Cholangiocarcinoma	Neoplasms benign, malignant and unspecified (including cysts and polyps)	Unrelated	Severe	Death	Death
N34–127	Sheffield	Dexamethasone	N34–127–01	Bilateral axillary abscess	28 November 2017	14 December 2017	Subcutaneous abscess	Infections and infestations	Possibly	Moderate	Hospitalisation	Resolved: no residual effects

Participant ID	Site	Treatment arm	SAE reference number	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N34–126	Sheffield	Dexamethasone	N34–126–01	Chest infection	11 December 2017		Pneumonia	Infections and infestations	Possibly	Severe	Considered medically significant by the investigator	Ongoing
N17–125	Plymouth	Dexamethasone	N17–125–01	New acute subdural haemorrhage	21 December 2017	19 January 2018	Subdural haematoma	Nervous system disorders	Unrelated	Moderate	Considered medically significant by the investigator	Resolved with residual effects
N34–130	Sheffield	Dexamethasone	N34–130–01	Pneumonia	21 January 2018	8 February 2018	Pneumonia	Infections and infestations	Unlikely	Severe	Death	Death
N25–139	Glasgow	Dexamethasone	N25–139–02	(Suspected CSDH recurrence) Headache	21 February 2018	24 February 2018	Headache	Nervous system disorders	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N35–157	Southampton	Dexamethasone	N35–157–01	Pulmonary embolism	23 February 2018	1 March 2018	Pulmonary embolism	Vascular disorders	Unrelated	Severe	Hospitalisation	Resolved with residual effects
N25–139	Glasgow	Dexamethasone	N25–139–01	Intermittent back pain	11 March 2018	15 March 2018	Back pain	Musculoskeletal and connective tissue disorders	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N35–160	Southampton	Dexamethasone	N35–160–02	Head injury	25 March 2018	26 March 2018	Head injury	Injury, poisoning and procedural complications	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N35–160	Southampton	Dexamethasone	N35–160–01	Hospital-acquired pneumonia	25 March 2018	2 April 2018	Pneumonia	Infections and infestations	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N48–131	Leeds	Dexamethasone	N48–131–01	Dizziness and unsteadiness	25 March 2018	26 March 2018	Dizziness	Vascular disorders	Unlikely	Mild	Hospitalisation	Resolved: no residual effects
N34–136	Sheffield	Dexamethasone	N34–136–01	Chest infection	28 March 2018	17 April 2018	Infections and infestations	Infections and infestations	Possibly	[a]	Hospitalisation	Resolved: no residual effects
N48–131	Leeds	Dexamethasone	N48–131–02	Dizziness and unsteadiness	3 April 2018	4 April 2018	Dizziness	Vascular disorders	Unlikely	Mild	Hospitalisation	Resolved: no residual effects
N17–130	Plymouth	Dexamethasone	N17–130–01	Non-ST elevation myocardial infarction	10 May 2018	14 May 2018	Acute myocardial infarction	Cardiac disorders	Unrelated	Moderate	Is life- threatening	Resolved: no residual effects

continued

TABLE 63 Listing of reportable SAEs (pre-study day 30) (*continued*)

Participant ID	Site	Treatment arm	SAE reference number	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N07–123	Birmingham	Dexamethasone	N07–123–01	Acute bronchitis	10 July 2018	10 July 2018	Pneumonia	Infections and infestations	Unrelated	Severe	Death	Death
N35–171	Southampton	Dexamethasone	N35–171–01	Hyponatremia	12 July 2018	30 July 2018	Hyponatraemia	Metabolism and nutrition disorders	Unlikely	Moderate	Hospitalisation	Resolved: no residual effects
N25–151	Glasgow	Dexamethasone	N25–151–01	Frontal headache	15 July 2018	16 July 2018	Headache	Nervous system disorders	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N17–132	Plymouth	Dexamethasone	N17–132–01	Haematoma over right eye	20 July 2018		Periorbital haematoma	Injury, poisoning and procedural complications	Unlikely	Mild	Considered medically significant by the investigator	Ongoing
N23–105	Dundee	Dexamethasone	N23–105–01	Pneumonia	31 August 2018		Pneumonia	Infections and infestations	Possibly	Severe	Death	Death
N36–110	St George's	Dexamethasone	N36–110–01	Acute kidney injury	26 September 2018	4 October 2018	Acute kidney injury	Renal and urinary disorders	Unlikely	Mild	Hospitalisation	Resolved: no residual effects
N34–153	Sheffield	Dexamethasone	N34–153–01	Stroke	10 October 2018		Cerebrovascular accident	Nervous system disorders	Unlikely	Severe	Hospitalisation	Ongoing
N25–157	Glasgow	Dexamethasone	N25–157–01	Delirium, treated for UTI	12 October 2018	18 October 2018	Urinary tract infection	Infections and infestations	Unrelated	Mild	Hospitalisation	Resolved: no residual effects
N25–160	Glasgow	Dexamethasone	N25–160–01	Inferior myocardial infarction	15 October 2018	24 October 2018	Acute myocardial infarction	Cardiac disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N48–154	Leeds	Dexamethasone	N48–154–01	Sepsis	11 November 2018	3 December 2018	Sepsis	Infections and infestations	Probably	Severe	Hospitalisation	Resolved: no residual effects
N07–129	Birmingham	Dexamethasone	N07–129–01	Chest infection – hospital-acquired pneumonia	4 December 2018	29 January 2019	Pneumonia	Infections and infestations	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N34–117	Sheffield	Dexamethasone	N34–117–01	Swallowing difficulties	[a]		Dysphagia	Gastrointestinal disorders	Unrelated	[a]	Hospitalisation	Ongoing

a Values missing from final stats report.

TABLE 64 Listing of reportable SAEs (post-study day 30)

Participant ID	Site	Treatment arm	SAE reference number	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N17–105	Plymouth	Placebo	N17–105–01	Scalp laceration	28 April 2016	3 May 2016	Laceration	Injury, poisoning and procedural complications	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N01–183	Cambridge	Placebo	N01–183–01	Cardiac failure	15 July 2016	15 July 2016	Cardiac failure	Cardiac disorders	Unlikely	Severe	Death	Death
N34–103	Sheffield	Placebo	N34–103–01	Death: cause unknown	23 July 2016	23 July 2016	Death	General disorders and administration site conditions	Unlikely	Severe	Death	Death
N01–188	Cambridge	Placebo	N01–188–01	Intracerebral bleed	26 August 2016	16 September 2016	Cerebral haemorrhage	Nervous system disorders	Unrelated	Severe	Death	Death
N48–105	Leeds	Placebo	N48–105–01	Fall	15 September 2016	20 September 2016	Fall	Injury, poisoning and procedural complications	Unrelated	Severe	Hospitalisation	Resolved with residual effects
N07–101	Birmingham	Placebo	N07–101–01	Death (cause not known)	16 October 2016	16 October 2016	Death	General disorders and administration site conditions	Unlikely	Severe	Death	Death
N14–114	Middlesbrough	Placebo	N14–114–02	Death (cause unknown)	2 November 2016	2 November 2016	Death	General disorders and administration site conditions	Unrelated	Moderate	Death	Death
N25–104	Glasgow	Placebo	N25–104–01	Pneumonia	18 November 2016	22 November 2016	Pneumonia	Infections and infestations	Unrelated	Severe	Death	Death
N17–108	Plymouth	Placebo	N17–108–01	Hospitalisation	2 June 2017	8 June 2017	Cardiac failure	Cardiac disorders	Unlikely	Moderate	Hospitalisation	Resolved: no residual effects
N26–111	Hull	Placebo	N26–111–03	Heart failure	14 May 2018		Cardiac failure	Cardiac disorders	Unlikely	Moderate	Hospitalisation	Ongoing
N36–109	St George's	Placebo	N36–109–01	Bronchopneumonia	8 October 2018	10 October 2018	Pneumonia	Infections and infestations	Unlikely	Severe	Death	Death
N25–159	Glasgow	Placebo	N25–159–01	Acute kidney injury	27 October 2018	7 November 2018	Acute kidney injury	Renal and urinary disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N01–125	Cambridge	Dexamethasone	N01–125–01	Deep-vein thrombosis	20 November 2015	27 November 2015	Deep-vein thrombosis	Vascular disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects

continued

TABLE 64 Listing of reportable SAEs (post-study day 30) (*continued*)

Participant ID	Site	Treatment arm	SAE reference number	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Severity	Seriousness	Outcome
N01–111	Cambridge	Dexamethasone	N01–111–01	Acute subdural haematoma	23 November 2015	28 November 2015	Subdural haematoma	Injury, poisoning and procedural complications	Unrelated	Severe	Death	Death
N01–108	Cambridge	Dexamethasone	N01–108–01	Scalp laceration	11 March 2016	12 March 2016	Laceration	Injury, poisoning and procedural complications	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N01–142	Cambridge	Dexamethasone	N01–142-01	Fracture: left hip	3 May 2016	13 May 2016	Femur fracture	Injury, poisoning and procedural complications	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N01–135	Cambridge	Dexamethasone	N01–135-01	Incarcerated right groin hernia	6 June 2016	8 June 2016	Femoral hernia incarcerated	Gastrointestinal disorders	Unrelated	Moderate	Hospitalisation	Resolved: no residual effects
N01–174	Cambridge	Dexamethasone	N01–174-01	Pulmonary embolism	7 June 2016	26 July 2016	Pulmonary embolism	Vascular disorders	Unlikely	Moderate	Is life-threatening	Resolved: no residual effects
N35–111	Southampton	Dexamethasone	N35–111-01	Pulmonary embolism	7 July 2016	11 July 2016	Pulmonary embolism	Vascular disorders	Unrelated	Severe	Hospitalisation	Resolved with residual effects
N14–104	Middlesbrough	Dexamethasone	N14–104-02	Colitis (diffuse) secondary to *C. difficile infection*	1 September 2016	6 September 2016	Clostridial sepsis	Infections and infestations	Unrelated	Severe	Death	Death
N01–200	Cambridge	Dexamethasone	N01–200-03	*Clostridium difficile* diarrhoea	17 September 2016	10 November 2016	*Clostridium difficile* colitis	Infections and infestations	Unlikely	Severe	Hospitalisation	Resolved: no residual effects
N01–227	Cambridge	Dexamethasone	N01–227-01	Pulmonary embolism	17 January 2017	19 January 2017	Pulmonary embolism	Vascular disorders	Unrelated	Severe	Hospitalisation	Resolved: no residual effects
N01–320	Cambridge	Dexamethasone	N01–320-01	Transient ischaemic attack	24 January 2018	24 January 2018	Transient ischaemic attack	Nervous system disorders	Unrelated	Moderate	Considered medically significant by the investigator	Resolved: no residual effects

TABLE 65 Listing of AEs

Participant ID	Site	Treatment arm	Event	Onset date	Resolution date	MedDRA PT	MedDRA SOC	Causality	Outcome
N25–110	Glasgow	Placebo	Haematemesis	23 September 2016	23 September 2016	Haematemesis	Gastrointestinal disorders	Possibly	Resolved: no residual effects
N31–103	Newcastle	Placebo	Nausea	16 March 2017	16 March 2017	Nausea	Gastrointestinal disorders	Possibly	Resolved: no residual effects
N31–103	Newcastle	Placebo	Diarrhoea	19 March 2017	19 March 2017	Diarrhoea	Gastrointestinal disorders	Possibly	Resolved: no residual effects
N14–106	Middlesbrough	Dexamethasone	Agitation and aggressiveness	16 July 2016	16 July 2016	Agitation	Psychiatric disorders	Possibly	Resolved: no residual effects
N35–133	Southampton	Dexamethasone	Constipation	29 January 2017	31 January 2017	Constipation	Gastrointestinal disorders	Unrelated	Resolved: no residual effects
N35–123	Southampton	Dexamethasone	Appetite gain	[a]	[a]	Increased appetite	Metabolism and nutrition disorders	Possibly	[a]

a Values missing from final stats report.

Appendix 4 Missing data

In the case of the primary end point, 9% of values were missing, with an identical number of missing values in each arm. A similar proportion of values were missing in the case of the other secondary end points and visits, with the one exception being the GCS score at 6 months.

Thus, the incidence rate of missing values for the primary end point is below the threshold stated in the SAP at which further techniques beyond complete-case analysis are required, which assumes missing at random. The CONSORT diagram provides the most detailed view of reasons for missing values (see *Figure 1*).

A SA has been added below (*Figure 11*), in which missing not at random assumptions were quantified by two parameters (delta_pla and delta_dex) that assume that the missing values have a predicted response rate within each arm that differs from the observed values by the value of the parameter, on an absolute risk difference scale. The response rate (favourable outcome rate) in the control arm was near 90%, hence values for these two parameters are considered between −10% and +10% as being the limits of plausibility. MI techniques are applied and the results are as shown in *Figure 11*, leading to the original conclusion that the extent of missing data are too small to affect the conclusions.

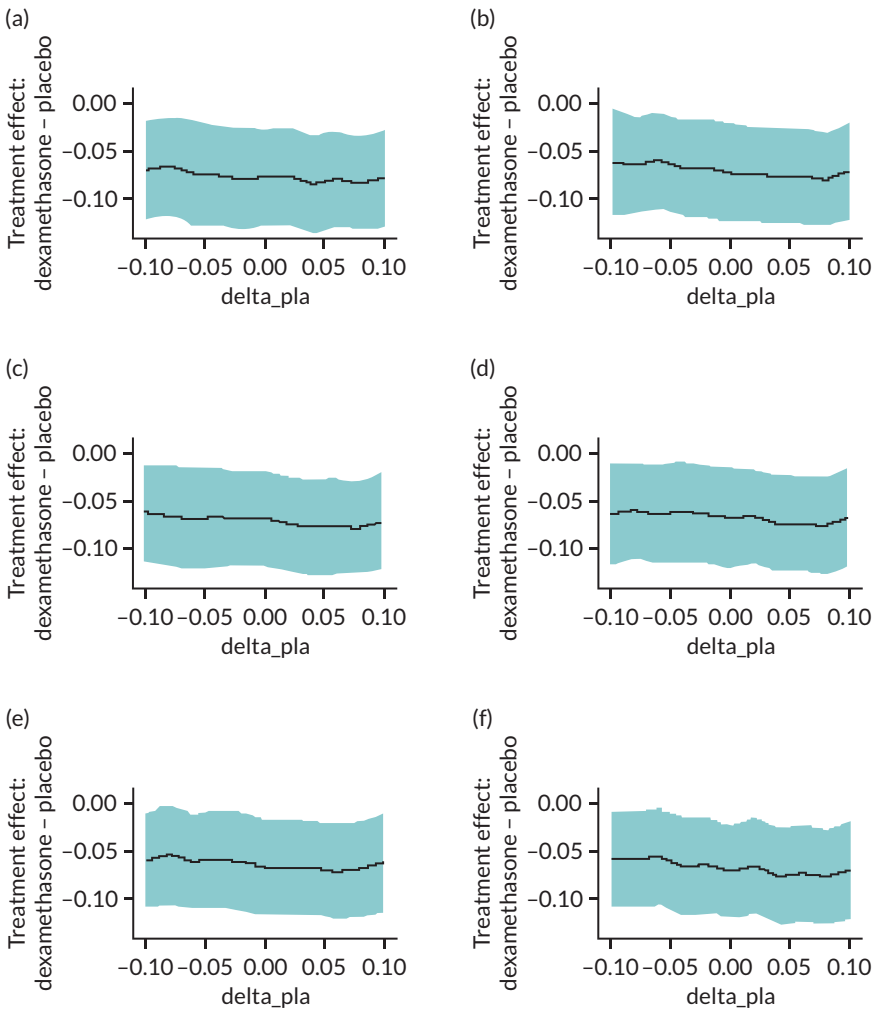

FIGURE 11 Sensitivity analysis. (a) delta_dex: −0.1; (b) delta_dex: −0.08; (c) delta_dex: −0.06; (d) delta_dex: −0.04; (e) delta_dex: −0.02; (f) delta_dex: 0; (g) delta_dex: 0.02; (h) delta_dex: 0.04; (i) delta_dex: 0.06; (j) delta_dex: 0.08; and (k) delta_dex: 0.1. (*continued*)

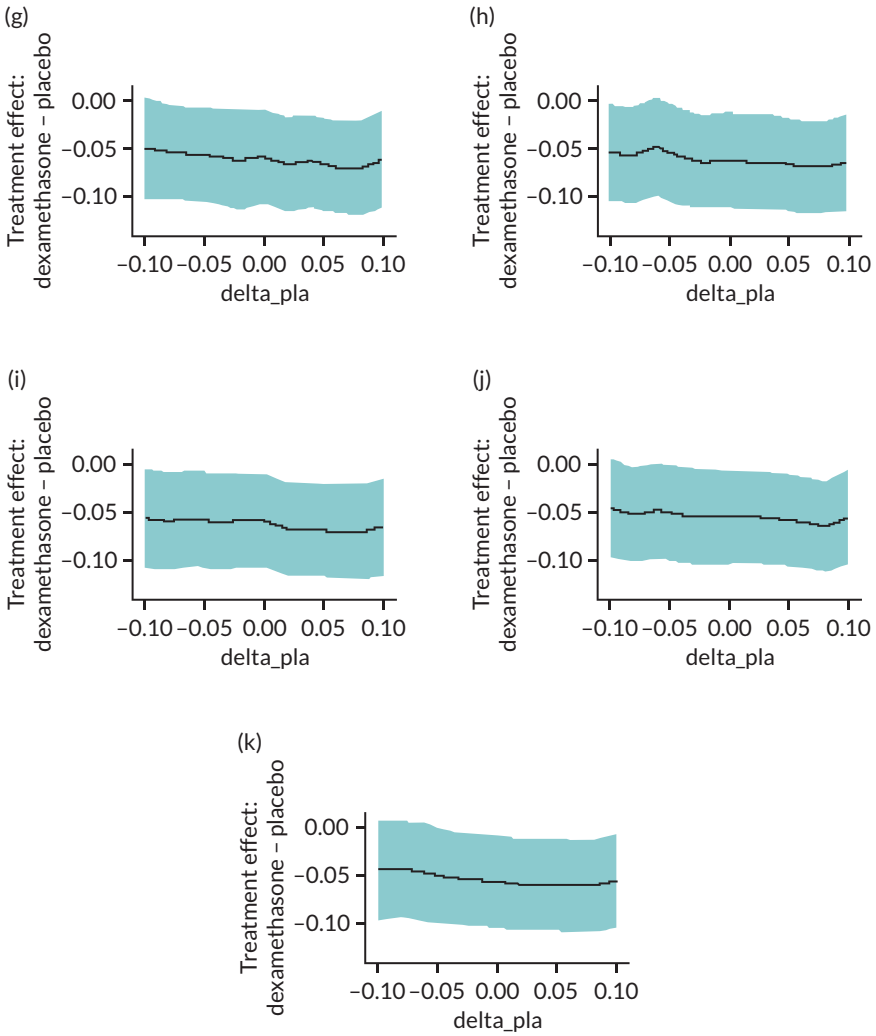

FIGURE 11 Sensitivity analysis. (a) delta_dex: −0.1; (b) delta_dex: −0.08; (c) delta_dex: −0.06; (d) delta_dex: −0.04; (e) delta_dex: −0.02; (f) delta_dex: 0; (g) delta_dex: 0.02; (h) delta_dex: 0.04; (i) delta_dex: 0.06; (j) delta_dex: 0.08; and (k) delta_dex: 0.1.

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