

**Clinical trial results:**

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

Summary

EudraCT number	2014-004948-35
Trial protocol	GB
Global end of trial date	29 August 2019

Results information

Result version number	v1 (current)
This version publication date	02 April 2021
First version publication date	02 April 2021
Summary attachment (see zip file)	Dex-CSDH Protocol v3 dated 27Apr17 (Dex-CSDH Protocol v3 27Apr17_final_signed.pdf) NEJM published paper (Hutchinson.pdf) NEJM published paper appendix (Hutchinson_appendix.pdf)

Trial information**Trial identification**

Sponsor protocol code	Dex-CSDH
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Additional study identifiers

ISRCTN number	ISRCTN80782810
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Cambridge University Hospitals NHS Foundation Trust
Sponsor organisation address	Box 401, Cambridge Clinical Trials Unit Level 6, Coton House, Cambridge, United Kingdom, CB20QQ
Public contact	Carrie Bayliss, Cambridge University Hospitals NHS Foundation Trust, +44 (0)1223348158, cctu@addenbrookes.nhs.uk
Scientific contact	Carrie Bayliss, Cambridge University Hospitals NHS Foundation Trust, +44 (0)1223 348158, cctu@addenbrookes.nhs.uk
Sponsor organisation name	University of Cambridge
Sponsor organisation address	Box 277, Addenbrooke's Hospital, Cambridge, United Kingdom, CB2 0QQ
Public contact	Steven Kelleher, Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge, +44 (0)1223 217418, research@addenbrookes.nhs.uk
Scientific contact	Stephen Kelleher, Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge, +44 (0)1223 217418, research@addenbrookes.nhs.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 February 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	29 August 2019
Global end of trial reached?	Yes
Global end of trial date	29 August 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate whether a two-week course of dexamethasone can improve the 6 month functional outcome of patients with symptomatic chronic Subdural Haematoma (CSDH) by reducing the rate of surgical intervention and the recurrence rate.

Protection of trial subjects:

The TSC (Trial Steering Committee) provided overall supervision with respect to the conduct of the study. Professor Tony Bell (St George's, University of London) was the independent chairman. The ethical and safety aspects of the trial were overseen by an independent DMC which was chaired by Professor Martin Smith (The National Hospital for Neurology and Neurosurgery, London). DMC meetings were timed so that reports could be fed into the TSC meetings.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 March 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 748
Worldwide total number of subjects	748
EEA total number of subjects	748

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	121
From 65 to 84 years	494
85 years and over	133

Subject disposition

Recruitment

Recruitment details:

All patients who had been admitted to the Neurosurgical Unit (NSU) of the participating sites with a confirmed CSDH could be screened for eligibility. A member of the clinical team assessed potential eligibility of these patients based on the protocol inclusion/exclusion criteria.

Pre-assignment

Screening details:

Where potential patients fulfilled the eligibility criteria, they were approached by a member of the research team who provided the patient with information about the study and offered the information sheet and clarified any information from the patient/relatives which may have precluded recruitment.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Dexamethasone
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use, Nasogastric use

Dosage and administration details:

The IMP is a two-week tapering course of either dexamethasone or matched placebo capsules. Route of administration: Oral or via nasogastric tube (see protocol section 9.4).

Day 1 = day of 1st dose

- 4 capsules in the morning and 4 at lunchtime for days 1, 2, 3
- 3 capsules in the morning and 3 at lunchtime for days 4, 5, 6
- 2 capsules in the morning and 2 at lunchtime for days 7, 8, 9
- 1 capsules in the morning and 1 at lunchtime for days 10, 11, 12
- 1 capsule once daily for days 13, 14
- Stop

Day 14 is the last day of treatment.

In the event of missing a dose of medication, these can be taken when remembered, but only up to the time of the next planned dose on the same day.

Dexamethasone IMP is supplied as over-encapsulated dexamethasone 2mg tablets. The capsules are size 00 gelatin capsules containing microcrystalline cellulose/magnesium stearate 1% as backfill; placebo capsules contain only microcrystalline cellulose/magnesium stearate 1%.

Arm title	Placebo
Arm description:	
Matched placebo capsules	
Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use, Nasogastric use

Dosage and administration details:

Trial medication administration schedule

Day 1 = day of first dose

Dexamethasone 2mg capsules or matched placebo capsules

Route of administration: Oral or via nasogastric tube (see protocol section 9.4)

- 4 capsules in the morning and 4 at lunchtime for days 1, 2, 3
- 3 capsules in the morning and 3 at lunchtime for days 4, 5, 6
- 2 capsules in the morning and 2 at lunchtime for days 7, 8, 9
- 1 capsules in the morning and 1 at lunchtime for days 10, 11, 12
- 1 capsule once daily for days 13, 14
- Stop

Day 14 is the last day of treatment.

Number of subjects in period 1	Dexamethasone	Placebo
Started	375	373
Completed	375	373

Period 2

Period 2 title	6 months Follow-Up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Dexamethasone
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Dexamethasone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Nasogastric use , Oral use

Dosage and administration details:

Trial medication administration schedule

Day 1 = day of first dose

Dexamethasone 2mg capsules or matched placebo capsules

Route of administration: Oral or via nasogastric tube (see protocol section 9.4)

- 4 capsules in the morning and 4 at lunchtime for days 1, 2, 3

- 3 capsules in the morning and 3 at lunchtime for days 4, 5, 6
 - 2 capsules in the morning and 2 at lunchtime for days 7, 8, 9
 - 1 capsules in the morning and 1 at lunchtime for days 10, 11, 12
 - 1 capsule once daily for days 13, 14
 - Stop
- Day 14 is the last day of treatment.

Arm title	Placebo
Arm description: -	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Nasogastric use , Oral use

Dosage and administration details:

Trial medication administration schedule

Day 1 = day of first dose

Dexamethasone 2mg capsules or matched placebo capsules

Route of administration: Oral or via nasogastric tube (see protocol section 9.4)

- 4 capsules in the morning and 4 at lunchtime for days 1, 2, 3
 - 3 capsules in the morning and 3 at lunchtime for days 4, 5, 6
 - 2 capsules in the morning and 2 at lunchtime for days 7, 8, 9
 - 1 capsules in the morning and 1 at lunchtime for days 10, 11, 12
 - 1 capsule once daily for days 13, 14
 - Stop
- Day 14 is the last day of treatment.

Number of subjects in period 2	Dexamethasone	Placebo
Started	375	373
Completed	341	339
Not completed	34	34
Consent withdrawn by subject	20	25
Lost to follow-up	14	9

Baseline characteristics

Reporting groups

Reporting group title	Dexamethasone
Reporting group description: -	
Reporting group title	Placebo
Reporting group description:	
Matched placebo capsules	

Reporting group values	Dexamethasone	Placebo	Total
Number of subjects	375	373	748
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	74.5	74.3	
standard deviation	± 11.8	± 11.0	-
Gender categorical			
Units: Subjects			
Female	107	87	194
Male	268	286	554

End points

End points reporting groups

Reporting group title	Dexamethasone
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: Matched placebo capsules	
Reporting group title	Dexamethasone
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Dichotomised Modified Rankin Scale - Favourable outcome

End point title	Dichotomised Modified Rankin Scale - Favourable outcome
End point description: modified Rankin Scale at 6-months which is dichotomised to favourable (0-3) vs unfavourable (4-6) . The counts and proportions will reflect patients achieving a favourable outcome	
End point type	Primary
End point timeframe: 6 Months Follow -up	

End point values	Dexamethason e	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	341	339		
Units: Patient	286	306		

Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description: The primary efficacy endpoint is mRS at 6 months which is dichotomised to favourable (0-3) vs unfavourable (4-6) The primary analysis will estimate the absolute difference between the two treatment arms (Dexamethasone - Placebo) in the proportions achieving a favourable outcome. A simple Normal approximation (ztest) will be used to produce a 95% confidence interval and two-sided P-value for the null hypothesis of zero difference	
Comparison groups	Dexamethasone v Placebo

Number of subjects included in analysis	680
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	z test
Parameter estimate	Risk difference (RD)
Point estimate	-0.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.11
upper limit	-0.014
Variability estimate	Standard error of the mean
Dispersion value	0.026

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 6 months initially. The AE reporting period was later reduced to stop at Day 30 after starting study medication. All observed events are included below.

Adverse event reporting additional description:

Non-reportable SAEs were: the initial index surgery, or those deemed due to complications of CSDH. When restricting the reporting period to day 30 the adverse events of special interest were 41/375 (10.9%) & 12/373 (3.2%), and for SAEs 60/375 (16.0%) & 24/373 (6.4%), for Dexamethasone and Placebo respectively.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Dexamethasone
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Dexamethasone	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	70 / 375 (18.67%)	34 / 373 (9.12%)	
number of deaths (all causes)	30	17	
number of deaths resulting from adverse events	15	10	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cholangiocarcinoma	Additional description: Cholangiocarcinoma		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vascular disorders			
Deep vein thrombosis	Additional description: Deep vein thrombosis		
subjects affected / exposed	3 / 375 (0.80%)	1 / 373 (0.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness	Additional description: Dizziness		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gangrene	Additional description: Gangrene		
	subjects affected / exposed	0 / 375 (0.00%)	1 / 373 (0.27%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Intestinal infarction	Additional description: Intestinal infarction		
	subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0
	deaths causally related to treatment / all	0 / 1	0 / 0
Pulmonary embolism	Additional description: Pulmonary embolism		
	subjects affected / exposed	5 / 375 (1.33%)	1 / 373 (0.27%)
	occurrences causally related to treatment / all	0 / 5	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Syncope	Additional description: Syncope		
	subjects affected / exposed	1 / 375 (0.27%)	1 / 373 (0.27%)
	occurrences causally related to treatment / all	0 / 1	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
General disorders and administration site conditions			
	Additional description: Death		
	subjects affected / exposed	0 / 375 (0.00%)	3 / 373 (0.80%)
	occurrences causally related to treatment / all	0 / 0	0 / 3
General physical health deterioration	Additional description: General physical health deterioration		
	subjects affected / exposed	2 / 375 (0.53%)	0 / 373 (0.00%)
	occurrences causally related to treatment / all	0 / 2	0 / 0
	deaths causally related to treatment / all	0 / 1	0 / 0
Malaise	Additional description: Malaise		
	subjects affected / exposed	0 / 375 (0.00%)	1 / 373 (0.27%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Non-cardiac chest pain	Additional description: Non-cardiac chest pain		
	subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0

Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	0 / 375 (0.00%)	2 / 373 (0.54%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction	Additional description: Anaphylactic reaction		
subjects affected / exposed	0 / 375 (0.00%)	1 / 373 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax spontaneous	Additional description: Pneumothorax spontaneous		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Alcohol withdrawal syndrome	Additional description: Alcohol withdrawal syndrome		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state	Additional description: Confusional state		
subjects affected / exposed	2 / 375 (0.53%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium	Additional description: Delirium		
subjects affected / exposed	0 / 375 (0.00%)	1 / 373 (0.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder	Additional description: Psychotic disorder		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Senile dementia	Additional description: Senile dementia		

subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fall	Additional description: Fall		
subjects affected / exposed	3 / 375 (0.80%)	2 / 373 (0.54%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture	Additional description: Femur fracture		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury	Additional description: Head injury		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periorbital haematoma	Additional description: Periorbital haematoma		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin laceration	Additional description: Skin laceration		
subjects affected / exposed	1 / 375 (0.27%)	2 / 373 (0.54%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma	Additional description: Subdural haematoma		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Acute myocardial infarction	Additional description: Acute myocardial infarction		
subjects affected / exposed	2 / 375 (0.53%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorder	Additional description: Cardiac disorder		
subjects affected / exposed	0 / 375 (0.00%)	1 / 373 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure	Additional description: Cardiac failure		
subjects affected / exposed	0 / 375 (0.00%)	4 / 373 (1.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute	Additional description: Cardiac failure acute		
subjects affected / exposed	0 / 375 (0.00%)	1 / 373 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure chronic	Additional description: Cardiac failure chronic		
subjects affected / exposed	0 / 375 (0.00%)	1 / 373 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Brain oedema	Additional description: Brain oedema		
subjects affected / exposed	0 / 375 (0.00%)	1 / 373 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage	Additional description: Cerebral haemorrhage		
subjects affected / exposed	0 / 375 (0.00%)	1 / 373 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular accident	Additional description: Cerebrovascular accident		
subjects affected / exposed	5 / 375 (1.33%)	2 / 373 (0.54%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Cervical radiculopathy	Additional description: Cervical radiculopathy		
subjects affected / exposed	0 / 375 (0.00%)	1 / 373 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache	Additional description: Headache		

subjects affected / exposed	2 / 375 (0.53%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Speech disorder	Additional description: Speech disorder		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma	Additional description: Subdural haematoma		
subjects affected / exposed	2 / 375 (0.53%)	1 / 373 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Transient ischaemic attack	Additional description: Transient ischaemic attack		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	0 / 375 (0.00%)	1 / 373 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia	Additional description: Dysphagia		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral hernia incarcerated	Additional description: Femoral hernia incarcerated		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction	Additional description: Intestinal obstruction		

subjects affected / exposed	0 / 375 (0.00%)	1 / 373 (0.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal pseudo-obstruction	Additional description: Intestinal pseudo-obstruction		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation	Additional description: Large intestine perforation		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Swelling face	Additional description: Swelling face		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	2 / 375 (0.53%)	1 / 373 (0.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency	Additional description: Adrenal insufficiency		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia	Additional description: Hyperglycaemia		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hyperparathyroidism	Additional description: Hyperparathyroidism		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain	Additional description: Back pain		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Clostridial sepsis	Additional description: Clostridial sepsis		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Clostridium difficile colitis	Additional description: Clostridium difficile colitis		
subjects affected / exposed	2 / 375 (0.53%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis	Additional description: Endocarditis		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster	Additional description: Herpes zoster		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza	Additional description: Influenza		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis	Additional description: Meningitis		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pneumonia	Additional description: Pneumonia		
	subjects affected / exposed	14 / 375 (3.73%)	6 / 373 (1.61%)
	occurrences causally related to treatment / all	4 / 14	2 / 6
	deaths causally related to treatment / all	1 / 7	0 / 2
Sepsis	Additional description: Sepsis		
	subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)
	occurrences causally related to treatment / all	1 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0
Subcutaneous abscess	Additional description: Subcutaneous abscess		
	subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)
	occurrences causally related to treatment / all	1 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0
Urinary tract infection	Additional description: Urinary tract infection		
	subjects affected / exposed	4 / 375 (1.07%)	0 / 373 (0.00%)
	occurrences causally related to treatment / all	1 / 4	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0
Metabolism and nutrition disorders			
	Additional description: Electrolyte imbalance		
	subjects affected / exposed	0 / 375 (0.00%)	1 / 373 (0.27%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
Hyponatraemia	Additional description: Hyponatraemia		
	subjects affected / exposed	1 / 375 (0.27%)	1 / 373 (0.27%)
	occurrences causally related to treatment / all	0 / 1	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Hypophagia	Additional description: Hypophagia		
	subjects affected / exposed	0 / 375 (0.00%)	1 / 373 (0.27%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Dexamethasone	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	44 / 375 (11.73%)	14 / 373 (3.75%)	
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences (all)	1	0	
Constipation	Additional description: Constipation		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences (all)	1	0	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	0 / 375 (0.00%)	1 / 373 (0.27%)	
occurrences (all)	0	1	
Dyspepsia	Additional description: Dyspepsia		
subjects affected / exposed	6 / 375 (1.60%)	2 / 373 (0.54%)	
occurrences (all)	6	2	
Gastrointestinal tract irritation	Additional description: Gastrointestinal tract irritation		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences (all)	1	0	
Haematemesis	Additional description: Haematemesis		
subjects affected / exposed	0 / 375 (0.00%)	1 / 373 (0.27%)	
occurrences (all)	0	1	
Melaena	Additional description: Melaena		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences (all)	1	0	
Nausea	Additional description: Nausea		
subjects affected / exposed	0 / 375 (0.00%)	2 / 373 (0.54%)	
occurrences (all)	0	2	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	2 / 375 (0.53%)	5 / 373 (1.34%)	
occurrences (all)	2	5	
Psychiatric disorders			
Acute psychosis	Additional description: Acute psychosis		
subjects affected / exposed	1 / 375 (0.27%)	1 / 373 (0.27%)	
occurrences (all)	1	1	
Agitation	Additional description: Agitation		

subjects affected / exposed	2 / 375 (0.53%)	0 / 373 (0.00%)	
occurrences (all)	2	0	
Delirium	Additional description: Delirium		
subjects affected / exposed	4 / 375 (1.07%)	0 / 373 (0.00%)	
occurrences (all)	4	0	
Euphoric mood	Additional description: Euphoric mood		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences (all)	1	0	
Hallucination	Additional description: Hallucination		
subjects affected / exposed	3 / 375 (0.80%)	1 / 373 (0.27%)	
occurrences (all)	3	1	
Psychotic disorder	Additional description: Psychotic disorder		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Hyperglycaemia	Additional description: Hyperglycaemia		
subjects affected / exposed	17 / 375 (4.53%)	3 / 373 (0.80%)	
occurrences (all)	19	3	
Type 2 diabetes mellitus	Additional description: Type 2 diabetes mellitus		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Increased appetite	Additional description: Increased appetite		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences (all)	1	0	
Type 2 diabetes mellitus	Additional description: Type 2 diabetes mellitus		
subjects affected / exposed	1 / 375 (0.27%)	0 / 373 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 September 2015	Amendment 2 (Substantial) was for the addition of new sites, and change of PI at 1 site. Approved 30Sep15 by ethics: N12 – Imperial, PI Mr Nandi N14 – James Cook, PI Prof Kane N34 – Sheffield, PI Mr Al-Tamimi N29 – Liverpool, PI Miss McMahon N48 – Leeds, PI Mr Timothy N08 – Brighton, PI Mr Critchley N46 – Stoke, PI Mr Tzerakis N18 – Aberdeen, PI Mr Bhatt N24 – Edinburgh, PI Mr Kandasamy N25 – Glasgow, PI Mr Suttner N30 – Salford, PI changed from Mr Holsgrove to Mr D’Urso
17 February 2016	Amendment 3 (Substantial) was for the addition of 5 new sites. Approved 17Feb16 by ethics: N36 – St George’s, PI Mr Papadopoulos N13 – Royal London, PI Mr Paraskevopoulos N03 – Cardiff, PI Mr Nannapaneni N23 –Dundee, PI Mr Hossain-Ibrahim N26 – Hull, PI Mr M Hussain
09 May 2016	Amendment 5 (Substantial) was for the change in PI at site N18 – Aberdeen, from Mr Bhatt to Mr Bodkin. Approved 09May16 by ethics.
15 June 2016	Amendment 4 (Substantial) was to update the protocol (to v2.0 dated 01Mar16). This was approved by ethics on 23Jun16, and the MHRA on 15Jun16. The study was also submitted for HRA approval (under the HRA “Lite” submission process for studies with pre-existing IRAS approval) and approval for the study was granted by the HRA on 21Oct16.
08 July 2016	Amendment 6 (Substantial) was for the change in PI at site N48 – Leeds, from Mr Timothy to Mr Thomson. Approved 08Jul16 by ethics.
02 December 2016	Amendment 9 (Substantial) to MHRA – Updated IMPD as 2nd manufacturing run was outsourced to Tio Pharma. Approved 02Dec16 by MHRA. This Amendment was also notified to the HRA and was categorised on 12Dec16.
05 December 2016	Amendment 8 (Substantial), was to add Queen’s Hospital, Romford as an additional participating site, and change the PI at the N13 Royal London Hospital from Mr Paraskevopoulos to Mr Ganesalingam Narenthiran. Approved 05Dec16 by ethics and the HRA confirmed on 09Jan17 that HRA assessment was not needed.
12 April 2017	Amendment 10 (Substantial), was to change the PI at the N13 Royal London Hospital from Mr Ganesalingam Narenthiran to Mr Dimitrios Paraskevopoulos. Approved and categorised on 12Apr17 by ethics and the REC confirmed on 12Apr17 that HRA assessment was not needed.

21 June 2017	Amendment 11 (Substantial) was to update the Protocol to v3.0 dated 27Apr17. Key protocol changes were as follows: 1. CHANGE TO ELIGIBILITY CRITERIA - only exclude patients on previous PO/IV GLUCOCORTICOID (other types of adrenocortcosteroids such as fludrocortisone are allowed). See list of steroids in protocol v3.0 page 23. 2. CHANGE TO CATAGORISATION OF AESI - now includes hyperglycaemia necessitating stopping of IMP (not necessarily requiring treatment). Please only report adverse events that fall specifically into one of these categories - see page 37 of protocol v3.0 3. CLARIFICATION ON REPORTING MEDICATION NON-COMPLIANCE - please report non-compliances for doses of medication that are given incorrectly or missed by ward staff or that you feel are clinically significant (if patient chooses not to take doses then this is not a non-compliance). This was submitted to ethics on 26May17 and classified as a Category A amendment, impacting all participating NHS organisations. The amendment was approved by ethics on 20Jun2017, and by the MHRA on 21Jun17. The study was also approved by the HRA on 27Jul17.
03 November 2017	Amendment 12 (Substantial), was to change the PI at the N03 Queen's Medical Centre, Nottingham, from Mr Stuart Smith to Mr Simon Howarth and to add the John Radcliffe Hospital, Oxford, as an additional site (PI Mr Patel). This was a Category B amendment, and was approved on 03Nov17 by ethics and the HRA.
19 April 2018	Amendment 13 (Substantial) to MHRA - This was to register updated RSI (Reference Safety Information) from the SmPC for Aspen dexamethasone (Date of revision of text 23Jan18, Updated in Electronic Medicines Compendium 26Jan18) – Approved by MHRA on 19Apr18. This Amendment was also notified to the REC for information only and was categorised (Category C) on 03Apr18. No REC validation or HRA approval was required, as this was an MHRA only approval.
23 July 2018	Amendment 14 (Non-Substantial) to HRA only - This was to register an extension in recruitment period from 28Feb18 to 28Feb19, following approval by the funder to extend the funding and duration of recruitment. Submitted 19Jul18 and approved by HRA on 23Jul18. However, the initial approval notification was not received, so was re-sent on 23Aug18.
15 October 2018	**Amendment 15 – This application was voided, and was not applicable due to a change in circumstances. Please see details below** This Substantial amendment (to REC and MHRA) was initially planned and submitted to the REC and MHRA on 26Sep18, as a substantial amendment, to increase the number of participants to up to 1000 patients, in-case this was mandated by our interim analysis results. This would have updated the Protocol to v4.0 dated 17Sep18. REC approval was granted on 15Oct18, but there was a delay in receiving MHRA approval. When the MHRA approval was chased, it was found that the application was in-valid and would need to be resubmitted. Initially we were going to re-submit the Amendment 15 but in the meantime, our Interim Analysis result had since confirmed (on 12Oct18) that we did not need to recruit above 750 patients. As the MHRA submission had never been granted, we notified REC on 11Dec18 that we would not be proceeding with implementation of Amendment 15. Therefore, the Protocol in use remains unchanged as the Protocol v3.0 dated 27Apr17.

29 August 2019	Amendment 16 (Substantial) to ethics only – This amendment approved a thank you card for patients or their surviving next of kin, and a GP treatment unblinding notification letter, advising which treatment the patient received during the trial, which will also be enclosed for patients when the thank you cards are issued. A patient friendly summary of the trial results will also be included in the card pack when sent out. In this amendment, changes to the methods of dissemination of trial information were also made, and a patient permission letter to request specific permission from 4 patients to use their questionnaire data were approved also. (In this submission, ethics were also notified for information only, of the GDPR letter that had been sent to ongoing patients in the trial, which was deemed a non-notifiable document). Approved by HRA 02Jan20. (Approval date listed as EOT date above as true date not accepted)
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33326713>