Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Hutchinson PJ, Edlmann E, Bulters D, et al. Trial of dexamethasone for chronic subdural hematoma. N Engl J Med. DOI: 10.1056/NEJMoa2020473

APPENDIX – Dex-CSDH trial

S1. Investigators and trial sites

Dex-CSDH trial collaborators *(to be indexed on PubMed)*:

- Daniela Georgieva - Southampton University Hospital, UK
- Carol Dalton - Queen Elizabeth University Hospital, Glasgow, UK
- Mary Kambafwile - Leeds General Infirmary, UK
- Charlotte Eglington - Derriford Hospital, Plymouth, UK
- Giles Critchley, Laura Ortiz-Ruiz De Gordoa - Royal Sussex County Hospital, Brighton, UK
- Manjunath Prasad, Philip Kane, Emanuel Cirstea - James Cook University Hospital, Middlesbrough, UK
- Nikolaos Tzerakis - Royal Stoke University Hospital, UK
- Marios C. Papadopoulos - St.George's Hospital, London, UK
- Jothy Kandasamy - Western General Hospital, Edinburgh, UK
- Masood Hussain - Hull Royal Infirmary, UK
- Dimitrios Paraskevopoulos, Chris Uff - Royal London Hospital, UK
- Peter Bodkin - Aberdeen Royal Infirmary, UK
- Damian Holliman - Royal Victoria Infirmary, Newcastle, UK
- Nihal Gurusinghe, Taha Lilo, Terrie Louise Cromie - Royal Preston Hospital, UK
- Jash Patel - John Radcliffe Hospital, Oxford, UK
- Nick Haliasos – Queen's Hospital, Romford, UK
- Kismet Hossain-Ibrahim - Ninewells Hospital, Dundee, UK
- Dipankar Nandi, Kevin Tsang - Charing Cross Hospital, London, UK
- Ravindra Nannapaneni - University Hospital of Wales, Cardiff, UK
- Pietro D'Urso - Salford Royal Hospital, Salford, Greater Manchester, UK

BNTRC trial collaborators *(to be indexed on PubMed)*:

- Taiwo Akhigbe - Southampton University Hospital, UK
- Michael Canty, Paul Fivey, Isaac Phang - Queen Elizabeth University Hospital, Glasgow, UK
- Oliver Richards, Fozia Saeed, Chris Akhunbay-Fudge - Leeds General Infirmary, UK
- Adam Wahba, Dan Gatt, Arif Zafar, Stuart Stokes - Royal Hallamshire Hospital, Sheffield, UK
- Boh Sofela, Sam Jeffrey - Derriford Hospital, Plymouth, UK
- Kamal M Yakoub, Emma Toman - Queen Elizabeth Hospital, Birmingham, UK
- Marian Vintu - Royal Sussex County Hospital, Brighton, UK
- Mathew Gallagher, Florence Hogg – St George's Hospital, London, UK
- Hamza Solieman, Julie Woodfield - Western General Hospital, Edinburgh, UK
- Adam Razak - Hull Royal Infirmary, UK
- Shumaila Hasan - Royal London Hospital, UK
- Anthony Wiggins, Aimun Jamjoom - Aberdeen Royal Infirmary, UK
- Ian Coulter, Venetia Giannakaki - Royal Victoria Infirmary, Newcastle, UK
- James Manfield - Royal Preston Hospital, UK
- Rory Piper - John Radcliffe Hospital, Oxford, UK
- Khaled Badran - Ninewells Hospital, Dundee, UK
- Edward Dyson - Charing Cross Hospital, London UK
- Malik Zaben - University Hospital of Wales, Cardiff, UK

- John Hanrahan – Addenbrooke's Hospital, Cambridge, UK

Trial co-applicants *(to be indexed on PubMed)*:
Thais Minett, Patrick Mitchell, Carol Brayne, Andrew Gardner

Trial Steering Committee members *(to be indexed on PubMed)*:
Anthony Bell, Allison Hirst, Laurence Watkins, Peter McCabe

Independent Data Monitoring and Ethics Committee members *(to be indexed on PubMed)*:
Martin Smith, Joan Grieve, Jonathan Cook.

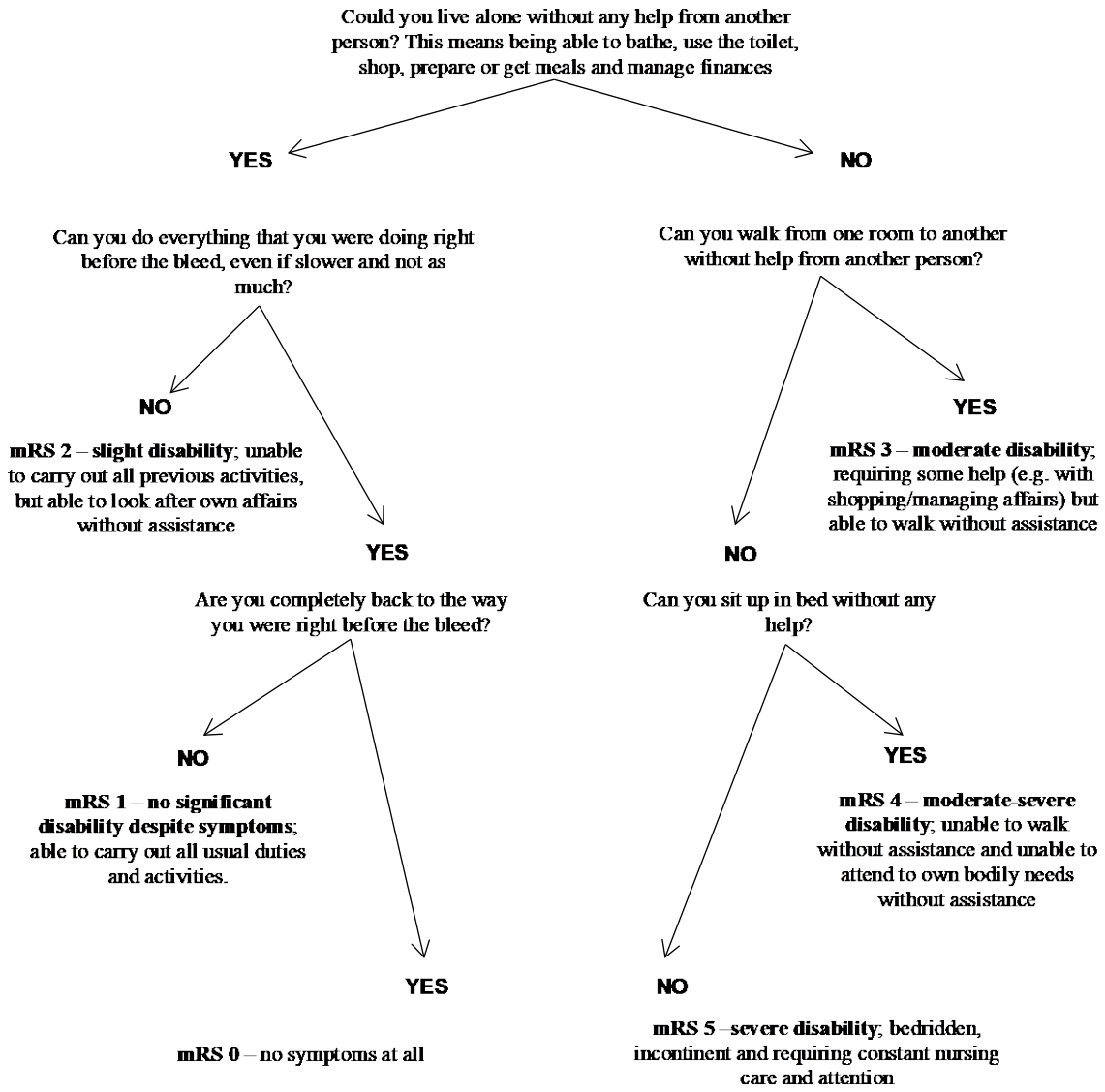
Trial Sites

Site	Patients randomised
Addenbrooke's Hospital, Cambridge	247
Southampton University Hospital, Southampton	84
Queen Elizabeth University Hospital, Glasgow	61
Leeds General Infirmary, Leeds	59
Royal Hallamshire Hospital, Sheffield	57
Derriford Hospital, Plymouth	33
Queen Elizabeth Hospital Birmingham, Birmingham	29
Royal Sussex County Hospital, Brighton	26
James Cook University Hospital, Middlesbrough	23
Royal Stoke University Hospital, Stoke	20
St George's Hospital, London	15
Western General Hospital, Edinburgh	15
Hull Royal Infirmary, Hull	15
Royal London Hospital, London	12
Aberdeen Royal Infirmary, Aberdeen	10
Royal Victoria Infirmary, Newcastle	9
Royal Preston Hospital, Preston	8
John Radcliffe Hospital, Oxford	7
Queen's Hospital, Romford	7
Ninewells Hospital, Dundee	6
Charing Cross Hospital, London	5
Salford Royal Hospital, Manchester	1
University Hospital of Wales, Cardiff	1
	750

S2. Adverse events of special interest (potentially related to dexamethasone) and expected serious adverse events (related to surgical intervention)

Adverse Events of Special Interest	**Expected Serious Adverse Events**
METABOLIC - Hyperglycemia necessitating treatment or stopping of trial medication - New onset diabetes necessitating on-going medical treatment at day 30 follow-up - Hyperosmolar hyperglycemic state	PERI-OPERATIVE - Re-bleeding into cavity forming ASDH - Tension Pneumocephalus - Intracerebral Haemorrhage - Residual CSDH exerting mass effect - Seizures - Neurological worsening - Anaesthetic complications
PSYCHIATRIC - New onset psychosis	EARLY - Residual CSDH - Expansion of contralateral CSDH - Seizures
GASTRIC - Upper gastrointestinal side (e.g. heartburn, vomiting) - Peptic ulceration and gastro-intestinal bleeding	INTERMEDIATE and LATE - Recollection of CSDH - Wound complications - Surgical site infection and subdural empyema - Epilepsy

S3. Modified Rankin Scale patient self-assessment questions, algorithm and descriptors



S4. Additional patient baseline data

	Placebo (373)	**Dexamethasone** (375)
Residence prior to CSDH diagnosis; *no./total no. (%)*		
Independent at home	328/372 (88.2)	327/374 (87.4)
Carers at home	30/372 (8.1)	24/374 (6.4)
Residential home	1/372 (0.3)	3/374 (0.8)
Nursing home	4/372 (1.1)	6/374 (1.6)
Other	9/372 (2.4)	14/374 (3.7)
Mobility prior to CSDH diagnosis; *no./total no. (%)*		
Independent	307/372 (82.5)	294/375 (78.4)
Stick	40/372 (10.8)	43/375 (11.5)
Walking frame	20/372 (5.4)	17/375 (4.5)
Wheelchair	1/372 (0.3)	3/375 (0.8)
Bed bound	0/372 (0)	5/375 (1.3)
Other	4/372 (1)	13/375 (3.5)
mRS at premorbid baseline *no./total no. (%)*		
0 – no symptoms	182/373 (48.8%)	178/373 (47.7%)
1 – no significant disability	53/373 (14.2%)	55/373 (14.7%)
2 – slight disability	40/373 (10.7%)	36/373 (9.7%)
3 – moderate disability	29/373 (7.8%)	30/373 (8%)
4 – moderately severe disability	14/373 (3.8%)	20/373 (5.4%)
5 – severe disability	0/373 (0%)	3/373 (0.8%)
Not available	55/373 (14.7%)	51/373 (13.7%)
mRS at admission *no./total no. (%)*		
1 – no significant disability	48/373 (12.9%)	48/373 (12.9%)
2 – slight disability	70/373 (18.8%)	61/373 (16.4%)
3 – moderate disability	64/373 (17.2%)	77/373 (20.6%)
4 – moderately severe disability	99/373 (26.5%)	100/373 (26.8%)
5 – severe disability	23/373 (6.2%)	24/373 (6.4%)
Not available	69/373 (18.5%)	63/373 (16.9%)
Other presenting symptoms for CSDH;* *no.*		
Nausea and vomiting	17	14
In-coordination	11	14
Dizziness	8	10
Visual symptoms	9	6
Lethargy	7	6

Numbness/paraesthesia	7	4
Incontinence	6	2
Dysphagia	2	2
Neck pain/stiffness	2	0
Tinnitus	2	0
Time interval from head trauma to admission, *no./total no. (%)*		
< 2 weeks	56/267 (21)	59/253 (23.3)
2 to 4 weeks	77/267 (28.8)	72/253 (28.5)
1 to 3 months	110/267 (41.2)	94/253 (37.2)
4 to 6 months	10/267 (3.8)	17/253 (6.7)
> 6 months	6/267 (2.2)	1/253 (0.4)
Not known/reported	8/267 (3)	10/253 (3.9)
Time interval from CSDH symptom onset to admission; *no./total no. (%)*		
<7 days	133/373 (35.7%)	140/373 (37.5%)
7-14 days	116/373 (31.1%)	100/373 (26.8%)
15– 28 days	75/373 (20.1%)	64/373 (17.2%)
29–42 days	22/373 (5.9%)	26/373 (7%)
>42 days	19/373 (5.1%)	35/373 (9.4%)
Not available	8/373 (2.1%)	8/373 (2.1%)
Co-morbidities, *no./total no. (%)*		
Diabetes	54/373 (14.5%)	55/375 (14.7%)
Ischaemic heart disease	50/373 (13.4%)	58/375 (15.5%)
Atrial fibrillation	68/373 (18.2%)	88/375 (23.5%)
Metallic heart valve	7/373 (1.9%)	9/375 (2.4%)
DVT/PE	19/373 (5.1%)	24/375 (6.4%)
Stroke	39/373 (10.5%)	34/375 (9.1%)
Previous CSDH	5/373 (1.3%)	9/375 (2.4%)
Epilepsy	11/373 (2.9%)	15/375 (4%)
Dementia	21/373 (5.6%)	19/375 (5.1%)
COPD	25/373 (6.7%)	33/375 (8.8%)
Liver disease	9/373 (2.4%)	9/375 (2.4%)
Current malignancy	16/373 (4.3%)	13/375 (3.5%)
Other	284/373 (76.1%)	273/375 (72.8%)

Any anti-thrombotic, *no./total no. (%)*	166/368 (45.1)	178/370 (48.1)
Aspirin only	57/368 (15.5)	63/370 (17.1)
Clopidogrel only	18/368 (4.9)	16/370 (4.3)
Warfarin only	52/368 (14.1)	77/370 (20.8)
Other single anti-thrombotic	21/368 (5.7)	17/370 (4.6)
Combination treatment	18/368 (4.9)	5/370 (1.4)
Other medications, *no./total no. (%)*		
Antacid or proton pump inhibitor	102/368 (27.7)	115/371 (31)
ACE inhibitors	91/368 (24.7)	75/371 (20.2)
Diuretics	52/368 (14.1)	53/371 (14.3)
NSAIDs	22/368 (6)	30/371 (8.1)
Immunosuppressants	7/368 (1.9)	3/371 (0.8)
Bilateral CSDH, *no./total no. (%)*	80/373 (21.4)	89/373 (23.9)
No. of bilateral operations	73/373 (19.6)	82/373 (22)
Density of CSDH on CT, *no./total no. (%)*		
Hypodense	89/355 (25.1)	111/361 (30.7)
Isodense	96/355 (27)	73/361 (20.2)
Mixed density	170/355 (47.9)	177/361 (49)

ACE = angiotensin converting enzyme, COPD = chronic obstructive pulmonary disease, DVT = deep vein thrombosis, NSAID = non-steroid anti-inflammatory drug, PE = pulmonary embolism.

* numbers equal more than total as some patients reported more than one “other” symptom.

S5. Trial intervention data

	Placebo (373)	**Dexamethasone** (375)
Primary surgery, *no./total no. of primary surgeries (%)****		
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)
Post-operative drain, *no./total no. of primary surgeries (%)*†		
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)
Anesthesia used, *no./total no. of primary surgeries (%)*		
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, *no./total no. of patients with primary surgery (%)*		
Burr hole(s) (total);	**304/350 (86.8)**	**302/349 (86.5)**
One burr hole	78/304	63/302
Two burr hole	217/304	232/302
Three burr hole	1/304	0/302
Unknown no. burr holes	1/304	0/302
Combination of one/two (in bilateral cases)	7/304	6/302
Mini-craniotomy	**44/350 (12.6)**	**40/349 (11.5)**
Other	**2/350 (0.6)**	**7/349 (2)**
Bilateral surgery with combination of BH and MC	1/2	4/7
Re-opening of old BH or MC from previous surgery	1/2	2/7
craniectomy	0/2	1/7
Recurrent surgery, *no./total no. of recurrent surgeries (%)*‡		
New burr hole/s	3/28 (10.7)	1/14 (7.1)
Mini-craniotomy	5/28 (17.8)	2/14 (14.3)
Previous burr holes re-opened	21/28 (75)	9/14 (64.3)
Previous burr holes extended to min-craniotomy	6/28 (21.4)	3/14 (21.4)
Subdural/subgaleal drain	27/28 (96.4)	14/14 (100)
Compliance with assigned treatment, *mean percentage of tablets taken from full course across all patients*§	89%	87%
Confirmed Nasogastric (NG) route of drug administration	4/373	6/375

Concomitant treatments, *no./total no. (%)*		
Vitamin K only	6/373 (1.6%)	13/374 (3.5%)
Prothrombin Complex Concentrate only	5/373 (1.3%)	7/374 (1.9%)
Platelets only	36/373 (9.7%)	28/374 (7.5%)
Fresh frozen plasma only	0/373 (0%)	1/374 (0.3%)
PRBCs only	0/373 (0%)	1/374 (0.3%)
Combination of above	32/373 (8.6%)	43/374 (11.5%)
Other only	1/373 (0.3%)	3/374 (0.8%)

BH = burr holes, MC = mini-craniotomy.

* 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 6 patients due to early withdrawal). Six percent of all patients (43/742) were managed without any surgery during the trial period (n = 20, 5.4% in placebo group and n=23, 6.1% in dexamethasone group).

† One patient in the placebo group had both a subgaleal and subdural drain inserted.

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

§ Compliance with assigned treatment was assessed by a combination of reviewing medication administration records and a trial medication diary, which was completed by patients if discharged home prior to the end of the two-week course. Figures include patients who were withdrawn/stopped receiving assigned medication but remained in the trial for follow-up purposes, if data was available. Treatment compliance data was available for 723 patients. The compliance analyses (complier average causal effect and instrumental variables) demonstrated less favorable outcome with increased dexamethasone compliance (see appendix S10).

S6. Sub-group analyses

Exploratory analyses examined treatment interaction effect on the primary outcome for a number of pre-specified subgroups (study site, patient age, timing of head trauma, use of anti-thrombotics, GCS score on admission and unilateral versus bilateral chronic subdural hematoma). Analysis of baseline subgroups showed that only side of hematoma (bilateral versus unilateral) had a significant interaction with treatment, with OR of a favorable outcome in unilateral chronic subdural hematoma treated with dexamethasone compared to placebo of 0.422 (95% CI 0.244 to 0.711, P=0.001), whilst bilateral chronic subdural hematoma showed no significant difference between groups (OR 1.55, 95% CI 0.574 to 4.29, P=0.388).

Summary statistics (frequency and percentage for the primary outcome) were produced for pre-specified, post-randomization subgroups as part of an exploratory analysis. These included: > 1 operations during all admissions, conservatively managed chronic subdural hematoma, trial of conservative management (surgery more than seven days after randomization), surgery within seven days of randomization, type of surgical intervention during primary surgery (burr hole or mini-craniotomy), and drain versus no-drain during primary surgery

	Placebo (373)	**Dexamethasone** (375)
CSDH > 1 operation	25/28 (89.3)	9/15 (60)
Conservative management (no surgery on any admission)	16/16 (100)	18/22 (82)
Trial of conservative management (surgery > 7 days after randomization)	10/10 (100)	4/6 (67)
Surgery within 7 days of randomization	280/313 (89)	264/313 (84)
Primary surgical intervention		
Burr Hole(s)	249/278 (89.6)	229/274 (83.6)
Craniectomy	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)

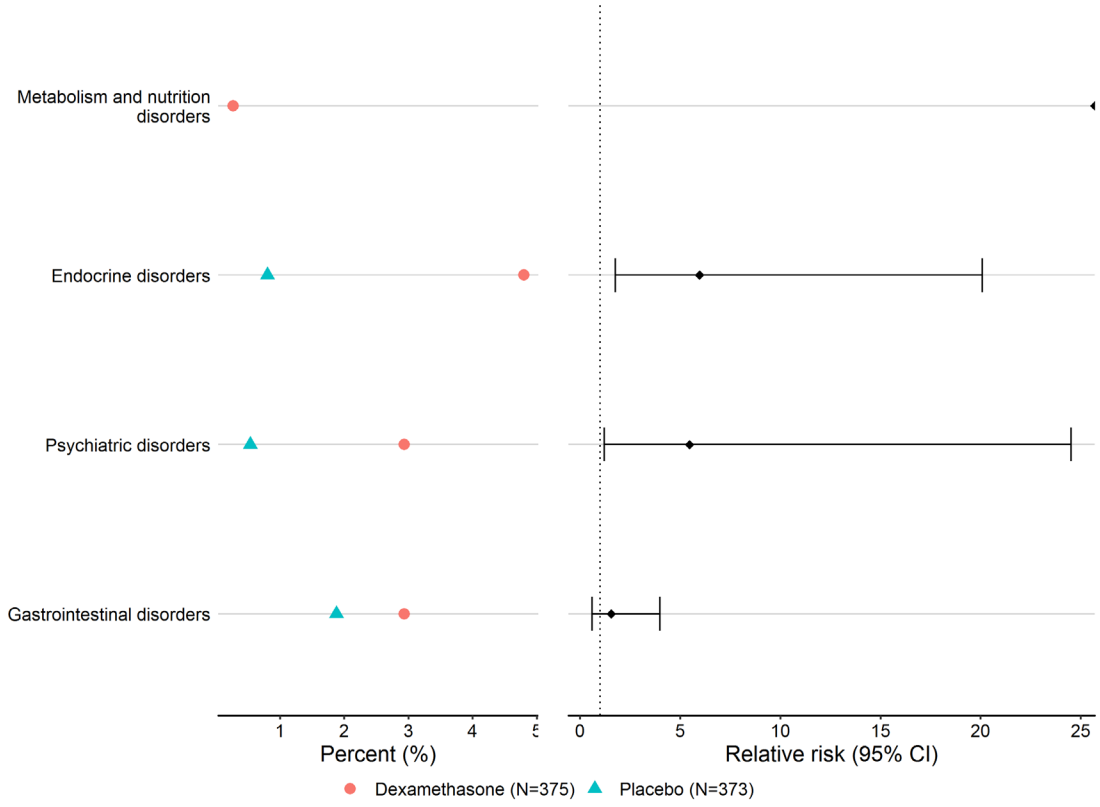
S7. Additional secondary outcome data

Analysis of secondary outcomes was performed using negative binomial regression for length of stay, logistic regression for discharge destination, linear regression for Barthel Index, and a Poisson regression for chronic subdural hematoma-related surgical interventions. No regression analyses were performed on the GCS outcomes due to a) majority of subjects receiving a score of 15 at discharge, and b) limited data at 6-months. Because of the lack of a prespecified plan for adjusting confidence intervals for multiple comparisons, no definite conclusions can be drawn from secondary outcome data in the trial.

Variable	**Placebo (373)**	**Dexamethasone (375)**	**Estimate (95% CI)**
Length of stay (days)	Mean (SD)	Mean (SD)	
NSU	9.03 (8)	9.3 (8.4)	1.03 (0.93 to 1.14)
Secondary care	13.7 (23)	13.0 (17)	0.95 (0.85 to 1.09)
Discharge destination	n (%)	n (%)	
Home	253/362 (69.9%)	239/361 (66.2%)	1.18 (0.867, 1.62)*
Carers at home	13/362 (3.6%)	6/361 (1.7%)	
Local Hospital	66/362 (18.2%)	84/361 (23.3%)	
Rehabilitation Center	8/362 (2.2%)	8/361 (2.2%)	
Residential Home	1/362 (0.3%)	1/361 (0.3%)	
Nursing Home	2/362 (0.6%)	5/361 (1.4%)	
Other	19/362 (5.2%)	18/361 (5%)	
GCS at discharge, *no. (%)*			
9 to 12	1/356 (0.3)	3/354 (0.8)	NA
13 to 15	355/356 (99.7)	351/354 (99.2)	
Barthel Index	Mean (SD)	Mean (SD)	
3-months	89.4 (20)	86.7 (24)	-2.68 (-6.16, 0.8)
6-months	90.3 (19)	88.1 (23)	-2.29 (-5.57, 0.995)
No operations during index admission, no./total no. (%)‡	29/370 (7.8)	30/372 (8.1)	-
1 operation during index admission, no./total no. (%)	330/370 (89.2)	341/372 (91.7)	0.97 (0.83 to 1.12)
>1 operations during index admission, no./total no. (%)	11/370 (3)	1/372 (0.2)	-

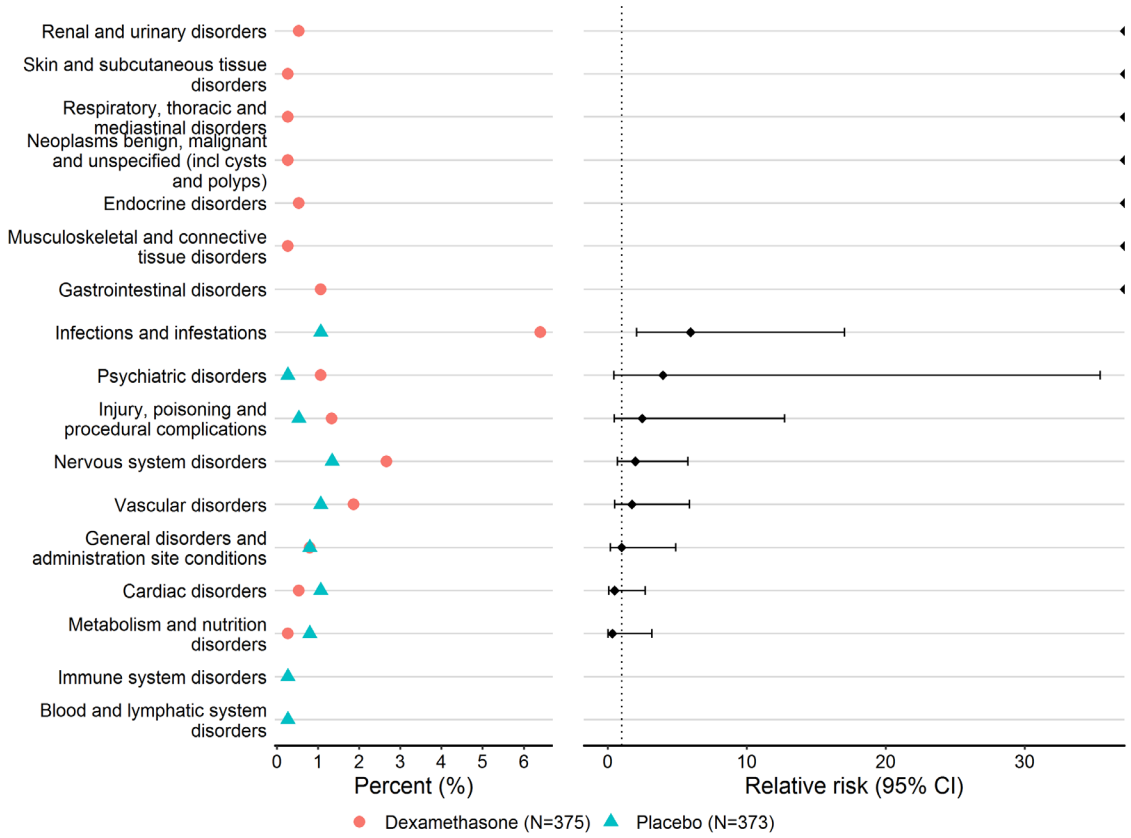
*Result for logistic regression analysis on "home" compared to all other categories (caregivers at home, local hospital, rehabilitation centre, residential home, nursing home and other). *Secondary care = NSU + self-reported length of stay in hospital or health care facility from patient 6-month questionnaire.*

S8. Incidence and relative risk of adverse events of special interest (up to day 30) by treatment group



Each row shows statistics for a particular adverse event, or group of events. On the left side are the absolute incidence rates with a symbol for each arm, or no symbol if the event was not observed in an arm. On the right are estimates and 95% confidence intervals for the relative risk comparing the arms; a value towards the right indicates a higher incidence in the dexamethasone arm. Given the large number of comparisons, care should be taken not to over-interpret confidence intervals that slightly exclude a relative risk of 1.

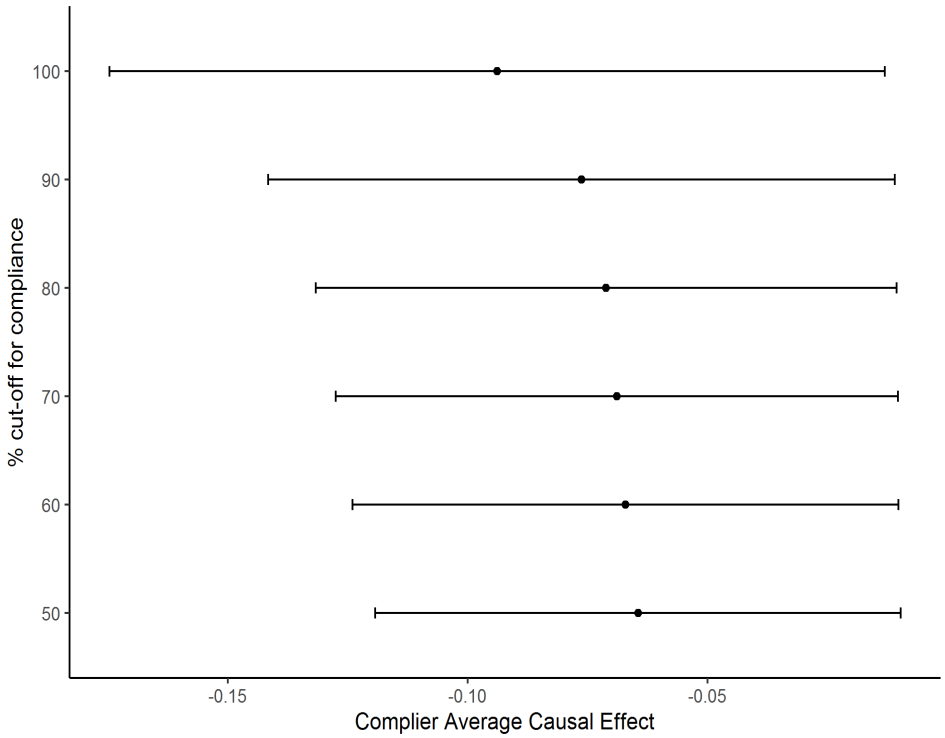
S9. Incidence and relative risk of serious adverse events (up to day 30) by treatment group.



Each row shows statistics for a particular adverse event, or group of events. On the left side are the absolute incidence rates with a symbol for each arm, or no symbol if the event was not observed in an arm. On the right are estimates and 95% confidence intervals for the relative risk comparing the arms; a value towards the right indicates a higher incidence in the dexamethasone arm. Given the large number of comparisons, care should be taken not to over-interpret confidence intervals that slightly exclude a relative risk of 1.

S10. Complier Average Causal Effect (CACE) analysis for 50-100% compliance

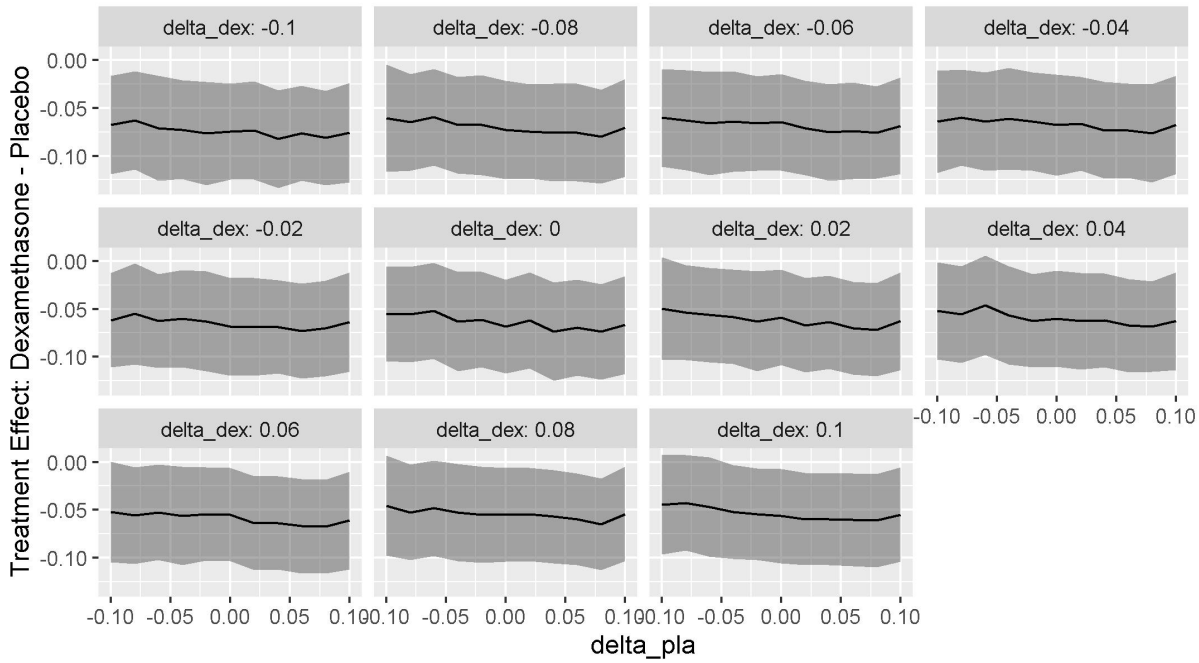
The effect of receiving, as opposed to assignment to, treatment on the primary outcome was estimated with a complier average causal effect (CACE) analysis, whereby a patient was dichotomized as a complier or non-complier if their proportion of tablets taken was above a threshold or not, and assuming the treatment has no effect in the non-compliant subset; the threshold for compliance was varied in sensitivity analyses from >50% to 100% in increments of 10%. A complimentary instrumental variables analysis avoided dichotomization by assuming compliance has a continuous, linear effect on the size of the treatment effect, and estimated the change in treatment effect per unit change in compliance. At an 80% cut-off for compliance the CACE is a reduction in the proportion achieving a favorable outcome at six months of 7% (95% CI 1%, 13%) in the dexamethasone group. The instrumental variables analysis gave an OR of 0.942 (95% CI 0.891, 0.994) of achieving a favorable outcome at six months for every 10 percent increase in medication taken.

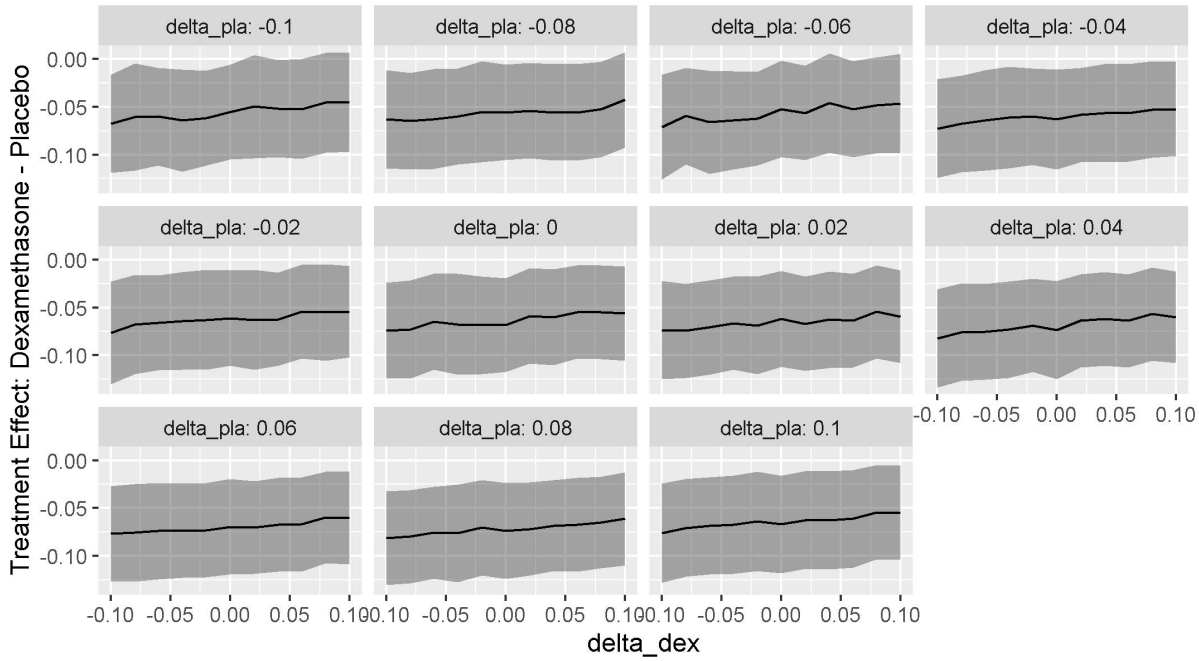


S11. Missing data

The primary endpoint had 9% missing values, with an identical number in each arm. A similar amount of missing values is present for the other secondary endpoints and visits; the one exception being the GCS at 6 months.

A sensitivity analysis has been added below, for which missing not at random assumptions are quantified by 2 parameters (delta_pla & 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 2 parameters are considered between -10% to +10%, as being the limits of plausibility. Multiple imputation techniques are applied, and the results are as shown in the two figures below, leading to the original conclusion that the extent of missing data is too small to affect the conclusions.

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delta_pla: -0.06
delta_pla: -0.04
delta_pla: -0.02
delta_pla: 0
delta_pla: 0.02
delta_pla: 0.04
delta_pla: 0.06
delta_pla: 0.08
delta_pla: 0.1
Treatment Effect: Dexamethasone - Placebo
0.00
-0.05
-0.10
-0.10 -0.05 0.00 0.05 0.10
delta_dex