National Institute for Health and Care Excellence

Final

Adrenal insufficiency: identification and management

Evidence review G: Routine pharmacological management of secondary and tertiary adrenal insufficiency

NICE guideline NG243

Evidence review underpinning recommendations 1.3.1 to 1.3.4 and recommendation for research 4 in the NICE guideline

August 2024

Final

This evidence review was developed by NICE

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1.1. Review question:

What is the clinical and cost effectiveness of glucocorticoids for the routine management of secondary and tertiary adrenal insufficiency?

1.1.1. Introduction

People with secondary and tertiary adrenal Insufficiency are dependent on glucocorticoids for survival because the pituitary and hypothalamus do not send the hormone signals to the adrenal glands to make cortisol and require daily replacement of the missing hormone, cortisol.

In current practice, glucocorticoid replacement therapy is usually given as either oral hydrocortisone or prednisolone. Hydrocortisone is typically administered in two to four divided doses, with a higher dose often administered in the morning in an attempt to mimic the natural circadian rhythm. Novel formulations of modified-release hydrocortisone allow for less frequent dosing, although their place in standard therapy is still not clear. Prednisolone has a longer duration of action and may be given once daily. There is considerable variation in the use of glucocorticoids in clinical practice and no current consensus on the optimum replacement therapy.

Both under and over-replacement of glucocorticoids may contribute to comorbidities and long-term complications. Appropriate glucocorticoid replacement therapy is therefore required to reduce these risks, maintain well-being, and improve outcomes.

Babies, children, and young people with AI go through a period of rapid growth and change requiring different doses and dosing schedules to adult patients and frequent adjustment to their doses to optimise growth and well-being.

In this chapter, we review the different glucocorticoid therapies to establish which is the most clinically and cost-effective pharmacological treatment for patients with a diagnosis of secondary or tertiary adrenal insufficiency.

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	People with adrenal insufficiency (secondary or tertiary) who are diagnosed or suspected of having an adrenal crisis including the following groups: • Adults (aged ≥16 years). • Children aged ≥5 up to 16 years. • Infants aged 1-5 years (because of more frequent dosing). • Infants aged <1 year including neonates.
Intervention(s)	**Glucocorticoids:** • Hydrocortisone including:

	○ Oral ○ Modified release hydrocortisone ○ Injected forms (sub cut and iv) • Prednisolone • Dexamethasone *Be aware some are not licensed for children Note: weight-based regimens should also be included **Exclusions:** • Hydrocortisone acetate • Long-acting methylprednisolone • Prednisone (not used in the UK)
Comparison(s)	**For glucocorticoids:** Glucocorticoids compared to each other including different doses, routes of administration and preparations (e.g., modified release compared to standard, crushed tablets compared to whole tablets or oral suspensions) **For all:** Comparisons to standard care as defined by authors.
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Mortality • Health-related quality of life, for example EQ-5D, SF-36 • Complications of adrenal insufficiency Fatigue as measured using specific fatigue scales such as National Fatigue Index (NFI), fatigue Severity Scale (FSS) • Incidence of adrenal crisis (as defined by authors) • Complications of adrenal crisis • Admission to hospital and/or ITU • Readmission to hospital • Length of hospital stay. • Treatment-related adverse events • Activities of daily living **Follow up:** Any time point as this will be different for different variables. Most will be short term (within 30 days) except for weight or growth-related outcomes, QoL and activities of daily living. We will prioritise data from similar timepoints in order to increase the possibility of conducting a meta-analysis (if appropriate)
Study design	Systematic reviews of RCTs and RCTs will be considered for inclusion.

Cross-over trials will also be considered for inclusion regardless of washout period as it is unsafe for patients to be completely free of background medication especially glucocorticoids.

If insufficient RCT evidence is available, a search for non-randomised studies will be conducted. Studies will only be considered for inclusion if they have conducted a multivariate analysis adjusting for at least 3-4 of the following key confounders: age, sex, weight / BMI, smoking, Type 1 diabetes, thyroid disease.

Published NMAs and IPDs will be considered for inclusion.

1.1.3. Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

This evidence review includes evidence relating to use of glucocorticoids for routine management of secondary and tertiary adrenal insufficiency.

1.1.4. Effectiveness evidence

1.1.4.1. Included studies

Four randomised crossover controlled trials (RCTs, 6 papers) were included in the review[1-4, 6, 8, 9]; these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

See also the study selection flow chart in Appendix C, study evidence tables in Appendix D, forest plots in Appendix E and GRADE tables in Appendix F.

The studies compared different doses of oral hydrocortisone. These studies included the following comparisons:

- Hydrocortisone: 5mg 2x daily vs. 10mg 2x daily[1], 1 week follow-up
- Hydrocortisone: Dose A (20 mg 0800 h, 10 mg 1600 h) vs Dose B (10 mg 0800 h and 1600 h) vs Dose C (10 mg 0800 h and 5 mg 1600 h)[2, 3], 6-week follow-up
- Hydrocortisone: Dose A [10mg/5mg HC] vs Dose B [10mg/5mg/5mg HC][4], 4-week follow-up
- Hydrocortisone: Low dose [0.2-0.3 mg/kg] vs High dose [0.4-0.6 mg/kg][8, 9], 10-week follow-up
- Hydrocortisone: Once-daily modified-release tablets (MR-HC) vs. standard glucocorticoid[6]

These studies all included adult patients with secondary adrenal insufficiency (SAI). SAI was defined in all studies based on cortisol levels. However, different criteria were used to classify patients across the studies:

- Agha 2004: Included patients with partial adrenocorticotropic hormone (ACTH) deficiency, defined as fasting 08·00 h total serum cortisol exceeding 200 nmol/l with a stimulated peak value of less than 500 nmol/L
- Behan 2011, Behan 2016: Included patients with severe ACTH deficiency, defined as fasting morning total serum cortisol concentration <100 nmol/l and a stimulated peak

value of <400 nmol/L. All patients in these studies had been diagnosed with and treated for pituitary tumours 3-18 years prior to study enrolment.
- Benson 2012: Included patients with SAI, defined as peak cortisol =< 450 nmol/L
- Wermeus Buning 2015, Wermeus Buning 2016: Included patients who had been diagnosed with adrenal insufficiency in adulthood. Fasting morning cortisol levels used to define SAI are not specified.

One study (Isidori 2018) included a mixed population of adults with primary AI (n=44 Addison's disease) or SAI (n=45). Results were presented together so it was not possible to separate the data. These outcomes have been downgraded for population indirectness. Fasting morning cortisol levels used to define SAI are not specified. This study has been included in this review and also in the evidence review 4.1 for primary AI. Any data extracted has been included in both reviews.

Two of the studies (Agha, 2004; Behan 2011; Behan 2016) excluded female subjects due to the potential effect of oestrogen status on corticosteroid-binding globulin (CBG) levels.

Due to heterogeneity in the interventions, comparators, and outcomes across the studies, it was not possible to generate meta-analyses.

No studies including children or people with tertiary AI were identified in this review.

1.1.4.2. Excluded studies.

See the excluded studies list in Appendix J.

1.1.5. Summary of studies included in the effectiveness evidence.

Table 2: Summary of studies included in the evidence review.

Study	Intervention and comparison	Population	Relevant outcomes	Comments
Agha 2004[1] Crossover RCT Conducted in Ireland	Group 1: Conventional full-dose hydrocortisone - 10mg twice daily Group 2: Half dose hydrocortisone - 5mg twice daily Follow-up: 1 weeks After 1 week, patients switched groups	n=10 male adults with partial ACTH deficiency, defined as a fasting 08·00 h total serum cortisol exceeding 200 nmol/l with a stimulated peak value of less than 500 nmol/l Mean age 43.9 (range 23 -60 years) Female subjects were excluded because of the potential effect of oestrogen status on corticosteroid-binding globulin (CBG) levels.	Peak cortisol Trough cortisol Systolic BP Diastolic BP Plasma sodium	
Behan 2011[3]	Oral hydrocortisone administered in the	n=10 male adults with severe ACTH	SF-36 scores	

Study	Intervention and comparison	Population	Relevant outcomes	Comments
Crossover RCT Conducted in Ireland	following dose regimens: Dose A (20 mg 0800 h, 10 mg 1600 h), Dose B (10 mg 0800h and 1600h), Dose C (10 mg 0800 h and 5 mg 1600 h) for 6 weeks of each dose regimen Follow-up: 6 weeks After 6 weeks, patients switched groups.	deficiency, defined by a fasting morning total serum cortisol concentration <100 nmol/l and a stimulated peak cortisol in response to insulin-induced hypoglycaemia of <400 nmol/l Mean age 46 (range 26-65 years) Female subjects were excluded because of the potential effect of oestrogen status on corticosteroid-binding globulin (CBG) levels.	Nottingham Health Profile (NHP) scores	
Behan 2016[2] Crossover RCT Conducted in Ireland *Secondary publication of Behan 2011*	*See above*	*See above*	Systolic BP (24-hr ambulatory) Diastolic BP (24-hr ambulatory)	
Benson 2012[4]	Oral hydrocortisone administered in the following dose regimens: Dose A: 10mg at 0700, 5mg at 1500 Dose B: 10mg at 0700, 5mg at 1200, 5mg at 1800 Follow-up:	N=18 patients with secondary adrenal insufficiency, defined as peak cortisol =< 450 nmol/L Mean age 52 years (SD 10.3)	SF-36 score. BSI Global Severity Index Stanford Sleepiness Score	

Study	Intervention and comparison	Population	Relevant outcomes	Comments
	After 6 weeks, patients switched groups			
Isidori 2018[6] Normal RCT Single-blind Conducted in Italy	Intervention: Once-daily (MR-HC). Patients were instructed to take the dose on waking. Patients previously on multiple doses of hydrocortisone a day received the same total daily dose, whereas patients previously on cortisone received 0·8 mg of hydrocortisone per 1 mg of cortisone. Intermediate doses were rounded up to the nearest 5 mg (e.g. 22·5 mg to 25·0 mg) to avoid any potential dangerous reduction in total daily dose. Dose of MR-HC was equivalent to standard care. Comparison: Standard care (continue standard glucocorticoid therapy) Follow-up: 24 weeks	89 adults with primary AI (n=44 Addison's disease) or secondary (n=45) Mean age 48, IQR 43-54	BMI Bodyweight HbA1c AddiQoL Infections (flu or flu-like events in 6 months) Total cholesterol Serious adverse	Patients were on a stable hydrocortisone dose (for at least 3 months before entering the study), which was kept constant throughout the study. Prior to study enrolment, baseline HC equivalent dose adjusted for body surface area (mg/m2 per day) in the intervention group was 16 (95%CI 14-18) and 18 (95%CI 15-21) in the control group. Study included a mixed population of primary and secondary AI
Wermeus Buning 2015[8] Crossover RCT Conducted in the Netherlands	Oral hydrocortisone administered TID in the following dose regimens: Low dose: 0.2-0.3mg/kg body weight. Total daily HC doses ranged from 15mg (for people 50-74kg), 17.5 mg (75-84kg) to 20mg (85-100kg).	N=47 people with secondary adrenal insufficiency (SAI) who receive glucocorticoid replacement therapy Median age (IQR): 55 (43-61) 38% female	Numbers of patients showing impaired scores in the following dimensions: Immediate memory, Short-term memory, Delayed memory, Recognition, Divided attention, Visual scanning, Fluency Working memory, Cognitive	

Study	Intervention and comparison	Population	Relevant outcomes	Comments
	High dose: 0.4-0.6mg/kg body weight. Total daily HC doses ranged from 30mg (for people 50-74kg), 35 mg (75-84kg) to 40mg (85-100kg). Follow-up: 10 weeks After 10 weeks, patients switched groups		flexibility, Social cognition, Psychomotor speed	
Wermeus Buning 2016[9] Secondary publication of Wermeus Buning 2015 *See above*	*See above*	*See above*	Systolic BP Diastolic BP BMI Plasma sodium	

See Appendix D for full evidence tables.

1.1.6. Summary of the effectiveness evidence

See Appendix F for full GRADE tables.

Table 3: Clinical evidence summary: 5mg HC 2x daily vs 10 mg HC 2x daily

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 10 mg 2x daily	Risk difference with 5mg 2x daily
Peak cortisol (nmol/L) follow-up: 1 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean peak cortisol (nmol/L) was **508.6** nmol/L	MD **84.2 nmol/L lower** (163.12 lower to 5.28 lower)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 10 mg 2x daily	Risk difference with 5mg 2x daily
Trough cortisol (nmol/L) follow-up: 1 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean trough cortisol (nmol/L) was **149.8** nmol/L	MD **15.8 nmol/L higher** (38.06 lower to 69.66 higher)
Systolic BP (mmHg) follow-up: 1 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean systolic BP (mmHg) was **129.5** mmHg	MD **4.8 mmHg higher** (7.03 lower to 16.63 higher)
Diastolic BP (mmHg) follow-up: 1 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,f]	-	The mean diastolic BP (mmHg) was **83.4** mmHg	MD **0.3 mmHg higher** (8.25 lower to 8.85 higher)
Plasma sodium (nmol/L) follow-up: 1 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,g]	-	The mean plasma sodium (nmol/L) was **140.5** mmol/L	MD **0.3 mmol/L lower** (1.79 lower to 1.19 higher)

Explanations

a. Downgraded by 2 increment due to very high risk of bias arising from the randomisation process

b. Downgraded by 1 increment as population includes males only [Female subjects were excluded because of the potential effect of oestrogen status on corticosteroid-binding globulin (CBG) levels]

c. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 43)

d. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 24.55)

e. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 6.2)

f. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 4.35)

g. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 0.85)

Table 4: Clinical evidence summary: Dose A (20 mg 0800 h, 10 mg 1600 h) vs Dose B (10 mg 0800 h and 1600 h) vs Dose C (10 mg 0800 h and 5 mg 1600 h) – SF-36 Outcomes

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with comparator	Risk difference with intervention
SF36 - Physical functioning - A vs B Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF36 - Physical functioning - A vs B was **79.5** points	MD **9 points higher** (9.74 lower to 27.74 higher)
SF36 - Physical functioning - A vs C Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF36 - Physical functioning - A vs C was **80.5** points	MD **8 points higher** (10.99 lower to 26.99 higher)
SF36 - Physical functioning - B vs C Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF36 - Physical functioning - B vs C was **80.5** points	MD **1 points lower** (22.26 lower to 20.26 higher)
SF36 - Role Physical – A vs B Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF36 - Role Physical - A vs B was **62.5** points	MD **15 points higher** (17.36 lower to 47.36 higher)
SF36 - Role Physical - A vs C Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF36 - Role Physical - A vs C was **55** points	MD **22.5 points higher** (14.15 lower to 59.15 higher)
SF36 - Role Physical - B vs C Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF36 - Role Physical - B vs C was **55** points	MD **7.5 points higher** (28.29 lower to 43.29 higher)
SF36 - Bodily pain - A vs B Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF36 - Bodily pain - A vs B was **82.5** points	MD **2.6 points higher** (16.67 lower to 21.87 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with comparator	Risk difference with intervention
SF36 - Bodily pain - A vs C Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF36 - Bodily pain - A vs C was **76.5** points	MD **8.6 points higher** (10.2 lower to 27.4 higher)
SF36 - Bodily pain - B vs C Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF36 - Bodily pain - B vs C was **76.5** points	MD **6 points higher** (14.43 lower to 26.43 higher)
SF36 - General health - A vs B Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean SF36 - General health - A vs B was **61.8** points	MD **1 points higher** (13.06 lower to 15.06 higher)
SF36 - General health - A vs C Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean SF36 - General health - A vs C was **59.8** points	MD **3 points higher** (11.81 lower to 17.81 higher)
SF36 - General health - B vs C Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean SF36 - General health - B vs C was **59.8** points	MD **2 points higher** (10.3 lower to 14.3 higher)
SF36 - Vitality - A vs B Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean SF36 - Vitality - A vs B was **47.5** points	MD **15 points higher** (6.14 lower to 36.14 higher)
SF36 - Vitality - A vs C Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean SF36 - Vitality - A vs C was **44** points	MD **18.5 points higher** (3.15 lower to 40.15 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with comparator	Risk difference with intervention
SF36 - Vitality - B vs C Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean SF36 - Vitality - B vs C was **44** points	MD **3.5 points higher** (17.46 lower to 24.46 higher)
SF36 - Social functioning - A vs B Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF36 - Social functioning - A vs B was **92.5** points	MD **2.5 points lower** (16.11 lower to 11.11 higher)
SF36 - Social functioning - A vs C Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF36 - Social functioning - A vs C was **85** points	MD **7.5 points higher** (6.61 lower to 21.61 higher)
SF36 - Social functioning - B vs C Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF36 - Social functioning - B vs C was **85** points	MD **7.5 points higher** (6.61 lower to 21.61 higher)
SF36 - Role emotional - A vs B Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean SF36 - Role emotional - A vs B was **66.6** points	MD **16.7 points higher** (17.35 lower to 50.75 higher)
SF36 - Role emotional - A vs C Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean SF36 - Role emotional - A vs C was **73.3** points	MD **10 points higher** (23.77 lower to 43.77 higher)
SF36 - Role emotional - B vs C Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean SF36 - Role emotional - B vs C was **73.3** points	MD **6.7 points lower** (42.81 lower to 29.41 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with comparator	Risk difference with intervention
SF36 - Mental health - A vs B Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF36 - Mental health - A vs B was **80** points	MD **0.4 points lower** (16.49 lower to 15.69 higher)
SF36 - Mental health - A vs C Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF36 - Mental health - A vs C was **80** points	MD **0.4 points lower** (15.83 lower to 15.03 higher)
SF36 - Mental health - B vs C Scale from: 0 to 100 follow-up: 6 weeks (higher is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean SF36 - Mental health - B vs C was **80** points	MD **0 points** (15.92 lower to 15.92 higher)

Explanations

a. Downgraded by 2 increments due to very serious risk of bias: Study authors do not provide necessary details around recruitment and randomisation so outcomes are at very high risk of selection bias..

b. Downgraded by 1 increment as population includes males only [Female subjects were excluded because of the potential effect of oestrogen status on corticosteroid-binding globulin (CBG) levels]

c. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 3)

d. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 2)

e. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 4)

Table 5: Clinical evidence summary: Dose A (20 mg 0800 h, 10 mg 1600 h) vs Dose B (10 mg 0800 h and 1600 h) vs Dose C (10 mg 0800 h and 5 mg 1600 h) – Nottingham Health Profile (NHP) Outcomes

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with comparator	Risk difference with intervention
NHP - Energy level - A vs B Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean NHP - Energy level - A vs B was **35.1** points	MD **1.2 points higher** (36.54 lower to 38.94 higher)
NHP - Energy level - A vs C Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean NHP - Energy level - A vs C was **41.3** points	MD **5 points lower** (40.56 lower to 30.56 higher)
NHP - Energy level - B vs C Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean NHP - Energy level - B vs C was **41.3** points	MD **6.2 points lower** (41.25 lower to 28.85 higher)
NHP - Pain - A vs B Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean NHP - Pain - A vs B was **7** points	MD **1.1 points higher** (15.72 lower to 17.92 higher)
NHP - Pain - A vs C Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,f]	-	The mean NHP - Pain - A vs C was **10.6** points	MD **2.5 points lower** (21.7 lower to 16.7 higher)
NHP - Pain - B vs C Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,f]	-	The mean NHP - Pain - B vs C was **10.6** points	MD **3.6 points lower** (20.11 lower to 12.91 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with comparator	Risk difference with intervention
NHP - Emotional reaction - A vs B Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⨁◯◯◯ Very low[a,b,g]	-	The mean NHP - Emotional reaction - A vs B was **7.3** points	MD **1.2 points higher** (10.33 lower to 12.73 higher)
NHP - Emotional reaction - A vs C Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⨁◯◯◯ Very low[a,b,h]	-	The mean NHP - Emotional reaction - A vs C was **8.6** points	MD **0.1 points lower** (12.47 lower to 12.27 higher)
NHP - Emotional reaction - B vs C Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⨁◯◯◯ Very low[a,b,h]	-	The mean NHP - Emotional reaction - B vs C was **8.6** points	MD **1.3 points lower** (15.6 lower to 13 higher)
NHP - Sleep - A vs B Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⨁◯◯◯ Very low[a,b,i]	-	The mean NHP - Sleep - A vs B was **15.3** points	MD **5.4 points higher** (18.3 lower to 29.1 higher)
NHP - Sleep - A vs C Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⨁◯◯◯ Very low[a,b,j]	-	The mean NHP - Sleep - A vs C was **10.9** points	MD **9.8 points higher** (8.29 lower to 27.89 higher)
NHP - Sleep - B vs C Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⨁◯◯◯ Very low[a,b,k]	-	The mean NHP - Sleep - B vs C was **10.9** points	MD **4.4 points higher** (17.4 lower to 26.2 higher)
NHP - Social isolation - A vs B Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⨁◯◯◯ Very low[a,b,l]	-	The mean NHP - Social isolation - A vs B was **7.5** points	MD **1 points higher** (14.2 lower to 16.2 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with comparator	Risk difference with intervention
NHP - Social isolation - A vs C Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,m]	-	The mean NHP - Social isolation - A vs C was **0** points	MD **0 points** (0 to 0)
NHP - Social isolation - B vs C Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,m]	-	The mean NHP - Social isolation - B vs C was **0** points	MD **0 points** (0 to 0)
NHP - Physical abilities - A vs B Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,n]	-	The mean NHP - Physical abilities - A vs B was **13.1** points	MD **4.2 points lower** (20.78 lower to 12.38 higher)
NHP - Physical abilities - A vs C Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,o]	-	The mean NHP - Physical abilities - A vs C was **14.4** points	MD **5.5 points lower** (21.43 lower to 10.43 higher)
NHP - Physical abilities - B vs C Scale from: 0 to 100 follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,o]	-	The mean NHP - Physical abilities - B vs C was **14.4** points	MD **1.3 points lower** (19.85 lower to 17.25 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with comparator	Risk difference with intervention

a. Downgraded by 2 increments due to very serious risk of bias: Study authors do not provide necessary details around recruitment and randomisation so outcomes are at risk of selection bias. Study authors also do not provide details around blinding so outcomes are at risk of measurement bias.

b. Downgraded by 1 increment as population includes males only [Female subjects were excluded because of the potential effect of oestrogen status on corticosteroid-binding globulin (CBG) levels]

c. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 21.25)

d. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 18.65)

e. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 7.8)

f. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 10.8)

g. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 7.75)

h. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 8.55)

i. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 15.2)

j. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 8.85)

k. Downgraded by 1 increment as confidence interval crossed both MIDs (+/- 8.85)

l. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 6.65)

m. Downgraded by 2 increments because comparator value was not captured

n. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 10.9)

o. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 10.25)

Table 6: Clinical evidence summary: Dose A (20 mg 0800 h, 10 mg 1600 h) vs Dose B (10 mg 0800 h and 1600 h) vs Dose C (10 mg 0800 h and 5 mg 1600 h) – Blood pressure (BP) outcomes

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with comparator	Risk difference with intervention
24h ambulatory systolic BP - A vs B follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean 24h ambulatory systolic BP - A vs B was **117** mmHg	MD **2 mmHg lower** (12.52 lower to 8.52 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with comparator	Risk difference with intervention
24h ambulatory systolic BP - A vs C follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean 24h ambulatory systolic BP - A vs C was **115** mmHg	MD **0 mmHg** (10.97 lower to 10.97 higher)
24h ambulatory systolic BP - B vs C follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean 24h ambulatory systolic BP - B vs C was **115** mmHg	MD **2 mmHg higher** (8.97 lower to 12.97 higher)
24h ambulatory diastolic BP - A vs B follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean 24h ambulatory diastolic BP - A vs B was **68** mmHg	MD **2 mmHg higher** (5.01 lower to 9.01 higher)
24h ambulatory diastolic BP - B vs C follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,f]	-	The mean 24h ambulatory diastolic BP - B vs C was **68** mmHg	MD **2 mmHg higher** (4.59 lower to 8.59 higher)
24h ambulatory diastolic BP - A vs C follow-up: 6 weeks (lower is better)	10 (1 RCT)	⊕◯◯◯ Very low[a,b,f]	-	The mean 24h ambulatory diastolic BP - A vs C was **68** mmHg	MD **0 mmHg** (6.59 lower to 6.59 higher)

Explanations

a. Downgraded by 2 increments due to very serious risk of bias: Study authors do not provide necessary details around recruitment and randomisation so outcomes are at risk of selection bias. Study authors also do not provide details around blinding, so outcomes are at risk of measurement bias.

b. Downgraded by 1 increment as population includes males only [Female subjects were excluded because of the potential effect of oestrogen status on corticosteroid-binding globulin (CBG) levels]

c. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 6)

d. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 6.5)

e. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 4)

f. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 3.5)

Table 7: Clinical evidence summary: Dose A [10mg/5mg HC] vs Dose B [10mg/5mg/5mg HC]

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Dose B [10mg/5mg/5mg HC]	Risk difference with Dose A [10mg/5mg HC]
SF-36 - Physical sum scale Scale from: 0 to 100 follow-up: 4 weeks (higher is better)	18 (1 RCT)	⊕◯◯◯ Very low[a,b]	-	The mean SF-36 - Physical sum scale was **40.7** points	MD **3.2 points higher** (4.66 lower to 11.06 higher)
SF-36 - Psychological sum scale Scale from: 0 to 100 follow-up: 4 weeks (higher is better)	18 (1 RCT)	⊕◯◯◯ Very low[a,c]	-	The mean SF-36 - Psychological sum scale was **46.4** points	MD **0.1 points lower** (7 lower to 6.8 higher)
BSI Global Severity Index Scale from: 0 to 100 follow-up: 4 weeks (lower is better)	18 (1 RCT)	⊕◯◯◯ Very low[a,d]	-	The mean BSI Global Severity Index was **58.1** points	MD **0.2 points lower** (8.15 lower to 7.75 higher)
Satisfaction with medication assessed with: 100 mm visual analog scale Scale from: 0 to 100 follow-up: 4 weeks (lower is better)	18 (1 RCT)	⊕◯◯◯ Very low[a,e]	-	The mean satisfaction with medication was **56.6** points	MD **5.4 points lower** (25.22 lower to 14.42 higher)
Sleepiness score 0700 assessed with: Stanford Sleepiness Scale Scale from: 0 to 7 follow-up: 4 weeks (lower is better)	18 (1 RCT)	⊕◯◯◯ Very low[a,f]	-	The mean sleepiness score 0700 was **2.3** points	MD **0.2 points higher** (0.02 lower to 0.42 higher)
Sleepiness score 1200 assessed with: Stanford Sleepiness Scale Scale from: 0 to 7 follow-up: 4 weeks (lower is better)	18 (1 RCT)	⊕◯◯◯ Very low[a,g]	-	The mean sleepiness score 1200 was **1.7** points	MD **0 points** (0.17 lower to 0.17 higher)
Sleepiness score 1500 assessed with: Stanford Sleepiness Scale Scale from: 0 to 7 follow-up: 4 weeks (lower is better)	18 (1 RCT)	⊕◯◯◯ Very low[a,h]	-	The mean sleepiness score 1500 was **1.8** points	MD **0 points** (0.17 lower to 0.17 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Dose B [10mg/5mg/5mg HC]	Risk difference with Dose A [10mg/5mg HC]
Sleepiness score 1800 assessed with: Stanford Sleepiness Scale Scale from: 0 to 7 follow-up: 4 weeks (lower is better)	18 (1 RCT)	⊕⊕◯◯ low[a,i]	-	The mean sleepiness score 1800 was **2.1** points	MD **0.4 points lower** (0.57 lower to 0.23 lower)
Sleepiness score 2200 assessed with: Stanford Sleepiness Scale Scale from: 0 to 7 follow-up: 4 weeks (lower is better)	18 (1 RCT)	⊕⊕◯◯ low[a,j]	-	The mean sleepiness score 2200 was **3.4** points	MD **0.7 points lower** (0.99 lower to 0.41 lower)

Explanations

a. Downgraded by 2 increments for risk of bias (potential for measurement bias in patient-reported outcome, little information provided on deviations from intended interventions).

b. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 2)

c. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 3)

d. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 6.45)

e. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 13.65)

f. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 0.16)

g. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 0.145)

h. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 0.12)

i. no imprecision MID (+/- 0.15)

j. no imprecision MID (+/- 0.25)

Table 8: Clinical evidence summary: Low dose HC (0.2-0.3 mg/kg) vs High dose HC (0.4-0.6 mg/kg)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with high dose HC (0.4-0.6 mg/kg)	Risk difference with low dose HC (0.2-0.3 mg/kg)
Systolic BP follow-up: 10 weeks (lower is better)	47 (1 RCT)	⊕◯◯◯ Very low[a,b]	-	The mean systolic BP was **138** mmHg	MD **5 mmHg lower** (11.08 lower to 1.08 higher)
Diastolic BP follow-up: 10 weeks (lower is better)	47 (1 RCT)	⊕◯◯◯ Very low[a,c]	-	The mean diastolic BP was **78** mmHg	MD **2 mmHg lower** (5.85 lower to 1.85 higher)
BMI follow-up: 10 weeks (lower is better)	47 (1 RCT)	⊕⊕◯◯ low[a]	-	The mean BMI was **27.1** kg/m2	MD **0.2 kg/m2 lower** (1.82 lower to 1.42 higher)
Number of patients with impaired memory: immediate memory follow-up: 10 weeks (lower is better)	47 (1 RCT)	⊕◯◯◯ Very low[a,e]	**RR 0.87** (0.46 to 1.62)	319 per 1,000	**41 fewer per 1,000** (172 fewer to 198 more)
Number of patients with impaired memory: short-term memory follow-up: 10 weeks (lower is better)	47 (1 RCT)	⊕◯◯◯ Very low[a,e]	**RR 0.75** (0.18 to 3.17)	85 per 1,000	**21 fewer per 1,000** (70 fewer to 185 more)
Number of patients with impaired memory: delayed memory follow-up: 10 weeks (lower is better)	47 (1 RCT)	⊕◯◯◯ Very low[a,e]	**RR 1.00** (0.41 to 2.44)	170 per 1,000	**0 fewer per 1,000** (100 fewer to 245 more)
Number of patients with impaired memory: recognition follow-up: 10 weeks (lower is better)	47 (1 RCT)	⊕◯◯◯ Very low[a,e]	**RR 2.00** (0.53 to 7.53)	64 per 1,000	**64 more per 1,000** (30 fewer to 417 more)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with high dose HC (0.4-0.6 mg/kg)	Risk difference with low dose HC (0.2-0.3 mg/kg)
Number of patients with impaired attention: divided attention errors follow-up: 10 weeks (lower is better)	47 (1 RCT)	⊕◯◯◯ Very low[a,e]	**RR 0.86** (0.31 to 2.36)	149 per 1,000	**21 fewer per 1,000** (103 fewer to 203 more)
Number of patients with impaired attention: visual scanning errors follow-up: 10 weeks (lower is better)	47 (1 RCT)	⊕◯◯◯ Very low[a,e]	**RR 1.00** (0.31 to 3.23)	106 per 1,000	**0 fewer per 1,000** (73 fewer to 237 more)
Number of patients with impaired executive function: fluency follow-up: 10 weeks (lower is better)	47 (1 RCT)	⊕◯◯◯ Very low[a,e]	**RR 1.00** (0.31 to 3.23)	106 per 1,000	**0 fewer per 1,000** (73 fewer to 237 more)
Number of patients with impaired executive function: working memory follow-up: 10 weeks (lower is better)	47 (1 RCT)	⊕◯◯◯ Very low[a,e]	**RR 0.75** (0.18 to 3.17)	85 per 1,000	**21 fewer per 1,000** (70 fewer to 185 more)
Number of patients with impaired executive function: cognitive flexibility follow-up: 10 weeks (lower is better)	47 (1 RCT)	⊕◯◯◯ Very low[a,e]	**RR 1.00** (0.35 to 2.88)	128 per 1,000	**0 fewer per 1,000** (83 fewer to 240 more)
Number of patients with impaired social cognition follow-up: 10 weeks (lower is better)	47 (1 RCT)	⊕◯◯◯ Very low[a,f]	**RR 1.64** (0.87 to 3.08)	234 per 1,000	**150 more per 1,000** (30 fewer to 487 more)
Number of patients with impaired psychomotor speed follow-up: 10 weeks (lower is better)	47 (1 RCT)	⊕◯◯◯ Very low[a,f]	**RR 0.71** (0.44 to 1.14)	511 per 1,000	**148 fewer per 1,000** (286 fewer to 71 more)

Explanations

a. Downgraded by 2 increments for risk of bias due to missing outcome data.

b. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 8)

c. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 4.5)

d. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 2)

e. Downgraded by 2 increments as confidence interval crossed 2 MIDs (0.8, 1.25)

f. Downgraded by 1 increment as confidence interval crossed 1 MID (0.8, 1.25)

Table 9: Modified-Release HC tablet vs Standard Glucocorticoid

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard glucocorticoid	Risk difference with MR-HC
Change in BMI from baseline At 24 weeks (lower is better)	78 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean change in BMI from baseline was **0.7** kg/m2	MD **1.6 kg/m2 lower** (2.7 lower to 0.5 lower)
Change in bodyweight from baseline At 24 weeks (lower is better)	78 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean change in bodyweight from baseline was **1.9** kg	MD **4 kg lower** (6.64 lower to 1.36 lower)
Change in HbA1c from baseline At 24 weeks (lower is better)	78 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean change in HbA1c from baseline was **0.1** %	MD **0.3 % lower** (0.44 lower to 0.16 lower)
Change in AddiQoL from baseline At 24 weeks (higher is better)	78 (1 RCT)	⊕◯◯◯ Very low[b,f,g]	-	The mean change in AddiQoL from baseline was **2** out of 10 (AddiQoL score).	MD **5 out of 10 (AddiQoL score) higher** (0.89 higher to 9.11 higher)
Change in infections [flu or flu-like events in 6 mos] from baseline At 24 weeks (lower is better)	78 (1 RCT)	⊕◯◯◯ Very low[a,b,h]	-	The mean change in infections [flu or flu-like events in 6 mos] from baseline was **-0.4** flu or flu-like events.	MD **0.8 flu or flu-like events. lower** (1.52 lower to 0.08 lower)
Change in total cholesterol from baseline At 24 weeks (lower is better)	78 (1 RCT)	⊕◯◯◯ Very low[a,b,i]	-	The mean change in total cholesterol from baseline was **0** mg/dL	MD **1 mg/dL lower** (14.76 lower to 12.76 higher)
Serious adverse events At 24 weeks (lower is better)	78 (1 RCT)	⊕◯◯◯ Very low[a,b,j]	**OR 0.10** (0.01 to 1.73)	57 per 1,000	**51 fewer per 1,000** (57 fewer to 38 more)

Footnotes

a. Downgraded by 1 increment as the majority of evidence was of high risk of bias due to bias arising from the randomisation process [single-blind study design, allocation not concealed from patients].

b. Downgraded by 1 increment because of population indirectness. Population includes people with both primary and secondary AI [50% of population have secondary AI]

c. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 1.165)

d. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 2.91)

e. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 0.145)

f. Downgraded by 2 increments as the majority of evidence was of high risk of bias due to bias arising from the randomisation process [single-blind study design, allocation not concealed from patients] and measurement of the outcome [risk of measurement bias in patient-reported outcome].

g. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 4.365)

h. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 0.8)

i. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 13.1)

j. Downgraded by 2 increments as the confidence interval crossed two MIDS (0.8 to 1.25 default MID)

1.1.7. Economic evidence

1. Included studies.

No health economic studies were included.

1.1.7.1. Excluded studies.

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in 0.

1.1.8. Unit costs

Relevant unit costs are provided below to aid the consideration of cost-effectiveness. Unit costs for children are presented in Table 10 (combination hydrocortisone is a combination of standard release and Alkindi granules in capsules) and unit costs for adults are presented in Table 11.

Table 10: Unit costs for children for the routine pharmacological management of secondary and tertiary adrenal insufficiency

Resource[(a)]	Dose per day	Cost per day	Cost per year
Hydrocortisone	***8mg/m² - 15 mg/m²***		
Neonate	2mg – 2.5mg		
Standard release	2mg – 2.5mg[(b)]	£0.29	£104.15
Alkindi	2mg – 2.5mg	£2.70 - £3.38	£985.50 - £1,231.88
Combination	n/a		
1 year	3.5mg – 4.5mg		
Standard release	3.5mg – 4.5mg[(b)]	£0.29	£104.15
Alkindi	3.5mg – 4.5mg	£4.73 - £6.08	£1,724.63 - £2,217.38
Combination	3.5mg – 4.5mg[(c)]	£2.04 - £3.39	£744.24 - £1,236.99
2 years	4.5mg – 5.5mg		

Resource[a]	Dose per day	Cost per day	Cost per year
Standard release	4.5mg – 5.5mg[b]	£0.29	£104.15
Alkindi	n/a		
Combination	4.5mg – 5.5mg[d]	£3.39 - £4.74	£1,236.99 - £1,729.74
5 years	6mg – 7.5mg		
Standard release	6mg – 7.5mg[b]	£0.21	£78.11
Alkindi	n/a		
Combination	6mg – 7.5mg[e]	£5.41 - £4.75	£1,976.11 - £1,734.85
10 years	9mg – 11mg		
Standard release	9mg – 11mg[f]	£0.21 - £2.17	£78.11 - £793.15
Alkindi	n/a		
Combination	9mg – 11mg[g]	£3.51 - £3.52	£1,280.79 - £1,285.90
12 years	9.5mg – 12mg		
Standard release	9.5mg – 12mg[f]	£0.21 - £2.17	£78.11 - £793.15
Combination	9.5mg – 12mg[h]	£4.18 - £4.87	£1,527.16 - £1,778.65
14 years	12mg – 15mg		
Standard release	12mg – 15mg[i]	£0.21 - £2.97	£78.11 - £1,083.32
Combination	12mg[j]	£4.87	£1,778.65
16 years	13mg – 17mg		
Standard release	13mg – 17mg[i]	£0.21 - £2.97	£78.11 - £1,083.32
Combination	13mg – 17mg[k]	£3.54 - £3.57	£1,291.01 - £1,301.78

(a) Source of costs from The British National Formulary (BNF).[5] Dosage based committee expert opinion. For children over 1 year assumed the largest dose is given in the morning and the smallest in the evening, mimicking the normal daily rhythm of cortisol secretion.
(b) One 10mg tablet used for each dose, assuming four doses daily until age 4 and three doses daily from age 5. Each tablet is crushed and dissolved in water allowing for correct dose to be drawn up and administered. For older children tablets can be split to make up doses. Assumes drug wastage.
(c) 3.5mg costed as one 2.5mg standard release tablet and 1mg Alkindi granules in capsules; 4.5mg costs as one 2.5mg standard release tablet and 2 mg Alkindi granules in capsules.
(d) 4.5mg costs as one 2.5mg standard release tablet and 2mg Alkindi granules in capsules;5.5mg costed as one 2.5mg standard release tablet and 3mg Alkindi granules in capsules.
(e) 6mg costs as one 2.5mg standard release tablet and 3.5mg Alkindi granules in capsules;7.5mg costed as two 2.5mg standard release tablets and 2.5mg Alkindi granules in capsules.
(f) Either one 10mg tablet used for each dose, assuming three doses daily, tablets can be split to make up doses or 10mg costed as one 5mg and two 2.5mg standard release tablets.
(g) 9mg costs as one 2.5mg and one 5mg standard release tablets and 1.5mg Alkindi granules in capsules;11mg costed as one 5mg and two 2.5mg standard release tablets and 1mg Alkindi granules in capsules.
(h) 9.5mg costs as one 2.5mg and one 5mg standard release tablets and 2mg Alkindi granules in capsules;12mg costed as one 5mg and two 2.5mg standard release tablets and 2mg Alkindi granules in capsules.
(i) Either one 10mg tablet used for each dose, assuming three doses daily, tablets can be split to make up doses or 15mg costed as two 5mg and two 2.5mg standard release tablets.
(j) Costed as one 5mg and two 2.5mg standard release tablets and 2mg Alkindi granules in capsules.
(k) 13mg costs as three 2.5mg and one 5mg standard release tablets and 0.5mg Alkindi granules in capsules;17mg costed as one 10mg and one 5mg standard release tablets and 2mg Alkindi granules in capsules.

Table 11: Unit costs for adults for the routine pharmacological management of secondary and tertiary adrenal insufficiency

Resource[a]	Dose per day	Cost per day [b]	Cost per year[b]
Hydrocortisone	***15mg – 25mg***		
Prescribed as one and a half 10mg tablets a day	15mg	£0.11	£39.06
Prescribed as two 10mg tablets a day	15mg – 20mg[c]	£0.14	£52.07

Resource[a]	Dose per day	Cost per day [b]	Cost per year[b]
Prescribed as one 10mg tablet and one 15mg tablet a day	25mg	£1.19	£434.72
Prescribed as three 10mg tablets a day	15-mg – 25mg	£0.21	£78.11
Modified release hydrocortisone (Plenadren)	***15mg – 25mg***		
Prescribed as three 5mg tablets a day	15mg	£14.55	£5,310.75
Prescribed as four 5mg tablets a day	20mg	£19.40	£7,081.00
Prescribed as one 20mg tablet a day	20mg	£8.00	£2,920.00
Prescribed as one 5mg tablet and one 20mg tablet a day	25mg	£12.85	£4,690.25
Prednisolone	***3mg – 6mg***		
Prescribed as three 1mg capsules a day	3mg	£0.08	£30.11
Prescribed as one 1mg capsule and one 5mg capsule a day	6mg	£0.06	£22.29
Dexamethasone			
Dexamethasone	0.25mg – 0.5mg[d]	£0.05 - £0.10	£19.10 - £39.19

(a) Source of costs from The British National Formulary (BNF).[5]
(b) Standard release hydrocortisone is taken either 2 or 3 times daily.
(c) For a 15mg dose of hydrocortisone this calculation assumes the additional 5mg is wasted.
(d) Cost available in the BNF is for 0.5mg per day. The cost for 0.25mg a day assumes people take half a 0.5mg tablet daily and there is no drug wastage.

1.2. The committee's discussion and interpretation of the evidence

1.2.1. The outcomes that matter most

The committee considered all outcomes listed in the protocol to be critical and of equal importance in decision-making. These outcomes included mortality, Health-related Quality of Life, complications of adrenal insufficiency, fatigue, incidence or complications of adrenal crisis, admission to hospital or ITU, length of hospital stay, treatment-related adverse events and activities of daily living.

1.2.2. The quality of the evidence

The clinical evidence for all outcomes was graded very low. This was largely due to imprecision and risk of bias. Imprecision arose from confidence intervals crossing one of MIDs and the risk of bias was mainly due to the lack of details on the randomisation process. Some studies were also downgraded for indirectness as the study population included only men.

All trials were cross-over RCTs that used oral glucocorticoid replacement therapies. Total daily doses ranged from 10 mg to 40 mg and were administered at different daily schedules. Outcomes were varied and included quality of life measures, cortisol levels and blood pressure. The variability in the interventions, comparators and outcomes meant that a meta-analysis of the data was not possible.

No studies including children or people with tertiary AI were identified in this review.

1.2.3. Benefits and harms

Adults

The committee noted that the evidence did not show any clinically important differences in metabolic measures (blood pressure and plasma sodium) when using 10 mg hydrocortisone (HC) twice daily compared to 5 mg twice daily. There was a clinically important difference in the peak cortisol levels at the higher dose. However, since there was no clinically important difference in the trough cortisol levels, the committee found this evidence inconclusive.

In discussing the evidence from a study comparing 3 different doses of hydrocortisone (Dose A [20mg/10mg] vs Dose B [10mg/10mg] vs Dose C [10mg/5mg], the committee noted that for most outcomes there were no clinically important differences between the treatment arms (SF-36 scores for mental health and all Nottingham Health Profile scores). For several outcomes where there were clinically important differences, the committee agreed that the evidence indicated that higher doses were better: for example, the SF-36 scores for role physical, bodily pain, vitality, social functioning, and role emotional. However, the committee acknowledged the very low quality rating of these outcomes and particularly the imprecision around the effect estimate which reduced the committees confidence in these findings. Ultimately, they did not take these benefits into account in their decision making.

In one study comparing Dose A (10/5mg HC) vs Dose B (10/5/5 mg HC) there was a clinically important benefit from treatment with Dose A (10/5 mg HC) compared to Dose B (10/5/5 mg HC) for the physical sum score of the SF-36 scale. Additionally, for the Stanford Sleepiness Scale outcomes, the evidence indicated a clinically important benefit from treatment with Dose A [10/5 mg] later in the day (18:00 and 22:00) compared to Dose B [10/5/5 mg]. However, the committee considered that these outcomes were downgraded twice for risk of bias and imprecision and consequently reduced their certainty in the results. There was also a clinically important harm for treatment with Dose A at 07:00 on the Stanford sleepiness scale, but at 12:00 and 15:00 there were no clinically important differences. Therefore, the committee did not use these outcomes to aid their decision making.There was no clinically important difference between the two treatments for the psychological sum score of the SF-36 scale, nor any difference for the BSI Global Severity Index or patient satisfaction with medication.

The committee noted that in a study comparing low-dose HC (0.2-0.3 mg/kg) vs. high-dose HC (0.4-0.6 mg/kg), there were no clinically important differences between the treatment arms for the majority of outcomes in this study: including metabolic outcomes (systolic/diastolic BP and BMI) and assessments of memory, attention and executive function. The only outcomes where clinically important differences were noted were social cognition, where the evidence indicated a clinically important harm from low-dose HC; and psychomotor speed, where the evidence indicated a clinically important benefit from low-dose HC. The committee noted that assessments of memory, attention, executive function, social cognition and psychomotor speed used in this study were based on a battery of tests as opposed to a single method of assessment. As a result, the committee found these assessments inconclusive as the results did not give a clear indication of which intervention was most beneficial.

In discussing the evidence from one study (Isidori 2018[6]) comparing once-daily modified-release hydrocortisone tablet to standard glucocorticoid therapy, the committee noted clinically important benefits for bodyweight, HbA1c %, AddiQOL and serious adverse events. A further two outcomes (infections in the last 6 months and BMI) just reached the threshold for a clinically important benefit of modified-release hydrocortisone tablets. Cholesterol showed no clinically important difference.

The committee acknowledged the benefits of modified-release hydrocortisone formulations but advised that they are not currently used as part of standard practice for the management of adrenal insufficiency in the UK, due to their high prices relative to standard oral hydrocortisone tablets. Furthermore, the committee noted that although there was some evidence of clinical benefit from the use of modified-release hydrocortisone tablets compared to standard glucocorticoid therapy, the magnitude of benefit was not significant enough to change standard practice.

Overall, the committee concluded that despite the disparities and the low certainty in the evidence, it mostly indicated that, for people with secondary adrenal insufficiency, total daily doses of hydrocortisone between 15-25 mg in divided doses were safe to use. This was also in line with their clinical expertise and reflected current practice. The committee was not able to determine the optimal dosage or timing of doses based on the evidence included in this review. They agreed for multiple daily doses, it would be usual to have the larger dose in the morning and the smaller in the evening, mimicking the normal diurnal rhythm of cortisol secretion. The committee also emphasised that as the maximum follow-up in these studies was 10 weeks, longer-term data would be needed to accurately assess the cumulative benefits and/or potential harms of daily treatment with hydrocortisone for people with secondary and tertiary adrenal insufficiency.

No clinical evidence was identified comparing prednisolone or dexamethasone to HC or to each other. Dexamethasone is not prescribed to adults in current practice due to the high risk of side effects such as cushingoid side effects. Prednisolone is known to have growth hampering effects. Therefore, it should only be used in people who have stopped growing and is a reasonable alternative to hydrocortisone for people who have difficulty taking hydrocortisone multiple times a day.

Children and young people

No evidence was identified in children. Therefore, the committee made recommendations based on their clinical experience and current practice. For children between 1 and 16 years old 8-10 mg/m2 of hydrocortisone in 3-4 divided doses would be prescribed. The committee agreed a reduced dose of prednisolone would be considered in children under age 16 who have reached final adult height when adherence to their replacement medication is a concern.

Based on clinical experience, the committee noted that adherence to glucocorticoid therapy is often an issue for patients with adrenal insufficiency since standard care typically involves 2 (BID) or 3 (TID) daily oral doses of hydrocortisone tablets. They noted that younger patients in particular younger adults, can often forget or choose to skip doses.

The committee suggested that a 1- or 2-dose regimen may likely have better acceptability among patients compared to a 3- to 4-dose regimen. Both prednisolone and modified release hydrocortisone tablets were considered alternatives due to their less frequent daily doses where adherence was a concern in young people. Prednisolone is only an option when the person has stopped growing. For modified release hydrocortsion tablets this was only an option if over 12 years and they have stopped growing. The committee noted the latter is off-label as it is only currently licensed in adults.

For infants under 1 year old a daily replacement dose of 8-10 mg/m2 hydrocortisone in 3- 4 equally divided doses would be prescribed. The committee did note that there would be a potential benefit in terms of adherence to therapy for a once-daily therapy compared to standard GC therapy.

Tertiary AI

No evidence was identified for tertiary AI. However, the committee agreed that although the underlying causes of tertiary and secondary adrenal Insufficiency are different, treatment is the same in both cases. The aim being, to adequately replace the missing cortisol through glucocorticoid replacement as cortisol is essential for life. Therefore, the committee agreed that the recommendations for tertiary adrenal insufficiency should be the same as those for secondary adrenal insufficiency.

The committee agreed that research evidence comparing different preparations of glucocorticoids (hydrocortisone, prednisolone and modified release hydrocortisone) for secondary and tertiary adrenal insufficiency is needed. This would determine the benefits of one pharmacological treatment over another in regard to improved clinical effectiveness. Therefore, the committee made a research recommendation (see Appendix K).

1.2.4. Cost effectiveness and resource use

No economic evaluations were identified for this review question; therefore, unit costs were presented to aid the committee's consideration of cost-effectiveness.

For children, the costing was done using the unit costs of immediate-release tablets, alkindi granules and a combination of the two. The latter approach was to allow for smaller doses without splitting or dispersing tablets. The committee noted that current practice is variable in terms of which type of immediate-release hydrocortisone is used in children. The least expensive option was to use 10mg immediate-release hydrocortisone tablets, where one is used for each dose, with three to four a day needed. These tablets are either crushed and dispersed in water or split to make up the correct dose. Using alkindi granules alone or in combination with 2.5mg, 5mg or 10mg immediate-release hydrocortisone tablets is more expensive. The committee noted that dispersing tablets is not a licenced usage of immediate release hydrocortisone and therefore for young children who struggle to swallow tablets, the only licenced option is alkindi granules. In addition, the benefit of alkindi granules is more accurate dosing and ease of administration for parents and carers. It was also noted that no clinical evidence in children was identified comparing the alternative formulations, as such the committee did not specify which approach to take in the recommendation.

Similarly, to primary adrenal insufficiency, immediate release hydrocortisone was considered the first-choice glucocorticoid. The committee recommended prednisolone as an alternative glucocorticoid to immediate release hydrocortisone in those who have stopped growing and with adherence difficulties with immediate-release hydrocortisone. Due to the modified-release tablet preparation costing significantly more with similar efficacy, the committee recommended its use as an alternative glucocorticoid to be considered when immediate-release hydrocortisone and prednisolone are not suitable. Of note the latter only applied to adults and children over the age of 12 who had stopped growing.

The committee discussed the clinical evidence and costs presented and subsequently made recommendations reflective of current practice. Therefore, these recommendations will not result in a significant resource impact.

1.2.5. Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.1 – 1.3.4 and the recommendation for research on the clinical and cost-effectiveness of pharmacological treatments for the routine management of secondary and tertiary adrenal insufficiency.

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Appendices

Appendix A Review protocols

A.1 Review protocol for 4.2: pharmacological management of secondary and tertiary adrenal hyperplasia

Table 12: Clinical review protocol

ID	Field	Content
1.	Review title	Routine pharmacological management of secondary and tertiary adrenal insufficiency
2.	Review question	What is the clinical and cost effectiveness of pharmacological treatments for the routine management of secondary and tertiary adrenal insufficiency?
3.	Objective	To determine the clinical effectiveness of pharmacological treatments for routine management of secondary adrenal insufficiency
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies

		The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Secondary and tertiary adrenal insufficiency
6.	Population	Inclusion: People with adrenal insufficiency (secondary or tertiary) who are diagnosed or suspected of having an adrenal crisis including the following groups: • Adults (aged ≥16 years). • Children aged ≥5 up to 16 years. • Infants aged 1-5 years (because of more frequent dosing). • Infants aged <1 year including neonates. Exclusion: None specified

7.	Intervention /	Any preparation, any dose and any route of administration of the following:
		Glucocorticoids:
		• Hydrocortisone including:
		  ○ Oral (where possible, note oral granules, oral suspension, or crushed tablets) Modified release hydrocortisone (separate to normal release hydrocortisone)
		  ○ Injected forms
		• Prednisolone
		• Dexamethasone
		Androgen replacement (in women only):

		DHEA replacement (unlicensed) may be prescribed in certain circumstances (such as persistent fatigue). Usually prescribed for adults and sometimes teenagers. Note: Weight-based regimens should also be included. Be aware that some of these interventions may not be licensed for this indication. Exclusions: Hydrocortisone acetate Long-acting methylprednisolone Prednisone (not used in the UK)
8.	Comparator	**For glucocorticoids:** Glucocorticoids compared to each other including different doses, routes of administration and preparations (e.g., modified release compared to standard, crushed tablets compared to whole tablets or oral suspensions) **For DHEA:** Comparisons of different DHEA regimens including doses and routes of administration **For all:** Comparisons to standard care as defined by authors
9.	Types of study to be included	Systematic reviews of RCTs and RCTs will be considered for inclusion. Cross-over trials will also be considered for inclusion regardless of washout period as it is unsafe for patients to be completely free of background medication especially glucocorticoids. If insufficient RCT evidence is available, a search for non-randomised studies will be considered if they have conducted a multivariate analysis adjusting for at least 3-4 of the following key confounders: - Age - Sex

		- Weight / BMI - Type 2 diabetes (small numbers) - Hypothalamic syndrome or associated symptoms - Hypertension - Lipids - Smoking - Growth hormone - Testosterone or oestrogen replacement, desmopressin, thyroid hormone replacement - Other treatments for underlying diseases such as radiotherapy brain or pituitary - Neurosurgery related e.g., craniotomy. - Neurocognitive issues - Hydrocephalus - Ventricular shunt - Steroid doses for underlying conditions - Underlying conditions e.g., RA Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Studies comparing glucocorticoids and DHEAs to each other as each type of drug is given for different indications and therefore a patient would not be prescribed one drug or the other. Comparisons of glucocorticoids or mineralocorticoids to placebo or no treatment Non comparative cohort studies Before and after studies Non-English language studies.

		Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
11.	Context	-
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • **Mortality** • **Health-related quality of life, for example EQ-5D, SF-36** • **Complications of adrenal insufficiency** – growth related issues in children – Low blood sugar/ hypoglycaemia – Early satiety • **Fatigue** as measured using specific fatigue scales such as National Fatigue Index (NFI), fatigue Severity Scale (FSS) • **Incidence of adrenal crisis** (as defined by authors) • **Complications of adrenal crisis**- for example neurological complications, psychological, hypoglycaemia, shock, acute kidney injury may be as part of shock and related to hypovolaemia. • **Admission to hospital and/or ITU** • **Readmission to hospital** • **Length of hospital stay.** • **Treatment-related adverse events:** – Hypertension – Obesity/weight gain – Osteoporosis – Fracture

		– Heart disease/CVS – Cushingoid features: e.g., stretch marks. – Diabetes – Impact on sleep- poor sleep due to overnight high cortisol levels – stunted growth in children – Hb1ac – Psychological effects (depression, anxiety) – Fluid retention – Increased risk of glaucoma/high pressure in the eyes – Effects on concentration – Specific to subcutaneous routes: sites reactions, infections, pumps breaking. – Stomach ulcers • **Activities of daily living** – Social participation – Participation in education (School/university) – Participation in physical activity (measured by any validated scale such as Barthel Index, the Katz Index, or the Functional Independence Measure). Note: there is some overlap between outcomes. For example, hypoglycaemia may be due to either complications of AI or be a complication of adrenal crisis. We will note which outcome these relate to. **Follow up:**

		Any time point as this will be different for different variables. Most will be short term (within 30 days) except for weight or growth-related outcomes, QoL and activities of daily living. We will prioritise data from similar timepoints in order to increase the possibility of conducting a meta-analysis (if appropriate)
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately. • a sample of the data extractions • correct methods are used to synthesise data. • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non-randomised studies, including cohort studies: Cochrane ROBINS-I

15.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency, and imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. WinBUGS will be used for network meta-analysis, if possible, given the data identified.	
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Patients on exogenous steroids for underlying condition – may have been on bigger doses before studies	
17.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)

18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date	June 2022		
21.	Anticipated completion date	April 2024		
22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
23.	Named contact	5a. Named contact Guideline Development Team NGC 5b Named contact e-mail Hypoadrenalism@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
24.	Review team members	From NICE: Sharon Swain [Guideline lead]		

		Saoussen Ftouh [Senior systematic reviewer] Meena Tafazzoli [Systematic reviewer] Alexandra Bannon [Health economist] Stephen Deed [Information specialist] Madelaine Zucker [Technical analyst]
25.	Funding sources/sponsor	Development of this systematic review is being funded by NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10237.
28.	Other registration details	-
29.	Reference/URL for published protocol	-
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.

31.	Keywords	Hypoadrenalism, adrenal insufficiency, glucocorticoids, pharmacological management, DHEA, androgen replacement, hydrocortisone, dexamethasone, prednisolone	
32.	Details of existing review of same topic by same authors	-	
33.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	-	
35.	Details of final publication	www.nice.org.uk	

A.2 Health economic review protocol

Table 13: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions, and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2007, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[7] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:*

	• UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland). • Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2007 or later but that depend on unit costs and resource data entirely or predominantly from before 2007 will be rated as 'Not applicable'. • Studies published before 2007 be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual. [7]

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies as these concepts may not be indexed or described in the title or abstract and are therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 14: Database parameters, filters and limits applied.

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 September 2023	Randomised controlled trials. Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 26 September 2023	Randomised controlled trials. Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 9 of 12, 26 September 2023 Cochrane Central Register of Controlled Trials to Issue 9 of 12, 26 September 2023	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 26 September 2023	Systematic review Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	exp Adrenal Insufficiency/
2.	Adrenal Hyperplasia, Congenital/
3.	(addison* disease or addisonian*).ti,ab,kf.

4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.
6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	or/1-13
15.	letter/
16.	editorial/
17.	news/
18.	exp historical article/
19.	Anecdotes as Topic/
20.	comment/
21.	case reports/
22.	(letter or comment*).ti.
23.	or/15-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animals/ not humans/
27.	exp Animals, Laboratory/
28.	exp Animal Experimentation/
29.	exp Models, Animal/
30.	exp Rodentia/
31.	(rat or rats or mouse or mice or rodent*).ti.
32.	or/25-31
33.	14 not 32
34.	limit 33 to English language
35.	Glucocorticoids/
36.	((glucocorticoid* or glucocorticosteroid* or steroid* or corticosteroid* or cortisone) adj3 (replace* or treat* or therap* or supplement* or regimen* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or intra muscular* or intramuscular* or exogenous* or subcutaneous*)).ti,ab,kf.
37.	Hydrocortisone/ or Dexamethasone/ or Prednisolone/
38.	(hydrocortisone* or prednisolone* or methylprednisolone* or dexamethasone*).ti,ab,kf.
39.	(Solu-Cortef or Hydventia or Plenadren or Neofordex or Glensoludex or Martapan or Deltacortril or Deltastab or Dilacort or Pevanti).ti,ab,kf.

40.	Mineralocorticoids/
41.	(mineralocorticoid* adj3 (replace* or treat* or therap* or supplement* or regimen* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or intra muscular* or intramuscular* or exogenous* or subcutaneous*)).ti,ab,kf.
42.	Fludrocortisone/
43.	fludrocortisone*.ti,ab,kf.
44.	Florinef.ti,ab,kf.
45.	Androgens/
46.	Hormone Replacement Therapy/
47.	((androgen* or hormon*) adj4 (replace* or treat* or therap* or supplement*)).ti,ab,kf.
48.	exp Dehydroepiandrosterone/
49.	(dehydroepiandrosterone or dehydro epiandrosterone or DHEA).ti,ab,kf.
50.	prosterone*.ti,ab,kf.
51.	Sodium Chloride/
52.	((sodium or saline or salt*) adj3 (replace* or treat* or therap* or solution* or supplement* or regimen* or intake* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or IV)).ti,ab,kf.
53.	Glucose/
54.	((glucose or dextrose) adj3 (replace* or treat* or therap* or solution* or supplement* or regimen* or intake* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or IV)).ti,ab,kf.
55.	HypoGel.ti,ab,kf.
56.	or/35-55
57.	34 and 56
58.	randomized controlled trial.pt.
59.	controlled clinical trial.pt.
60.	randomi#ed.ab.
61.	placebo.ab.
62.	randomly.ab.
63.	clinical trials as topic.sh.
64.	trial.ti.
65.	cross-over studies/
66.	(crossover or "cross over").ti,ab.
67.	or/58-66
68.	Meta-Analysis/
69.	Meta-Analysis as Topic/
70.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
71.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
72.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
73.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
74.	(search* adj4 literature).ab.
75.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
76.	cochrane.jw.
77.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
78.	or/68-77
79.	57 and (67 or 78)

Embase (Ovid) search terms

1.	exp Adrenal cortex insufficiency/
2.	Congenital adrenal hyperplasia/
3.	(addison* disease or addisonian*).ti,ab,kf.
4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.
6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	or/1-13
15.	letter.pt. or letter/
16.	note.pt.
17.	editorial.pt.
18.	case report/ or case study/
19.	(letter or comment*).ti.
20.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
21.	or/15-20
22.	randomized controlled trial/ or random*.ti,ab.
23.	21 not 22
24.	animal/ not human/
25.	nonhuman/
26.	exp Animal Experiment/
27.	exp Experimental Animal/
28.	animal model/
29.	exp Rodent/
30.	(rat or rats or mouse or mice or rodent*).ti.
31.	or/23-30
32.	14 not 31
33.	limit 32 to English language
34.	glucocorticoid/
35.	((glucocorticoid* or glucocorticosteroid* or steroid* or corticosteroid* or cortisone) adj3 (replace* or treat* or therap* or supplement* or regimen* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous or intra*muscular or exogenous* or subcutaneous*)).ti,ab,kf.
36.	hydrocortisone/ or dexamethasone/ or prednisolone/

37.	(hydrocortisone* or prednisolone* or methylprednisolone* or dexamethasone*).ti,ab,kf.
38.	(Solu-Cortef or Hydventia or Plenadren or Neofordex or Glensoludex or Martapan or Deltacortril or Deltastab or Dilacort or Pevanti).ti,ab,kf.
39.	mineralocorticoid/
40.	(mineralocorticoid* adj3 (replace* or treat* or therap* or supplement* or regimen* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous or intra*muscular or exogenous* or subcutaneous*)).ti,ab,kf.
41.	fludrocortisone/
42.	fludrocortisone*.ti,ab,kf.
43.	Florinef.ti,ab,kf.
44.	androgen therapy/
45.	hormone substitution/
46.	((androgen* or hormon*) adj4 (replace* or treat* or therap* or supplement*)).ti,ab,kf.
47.	(dehydroepiandrosterone or dehydro epiandrosterone or DHEA).ti,ab,kf.
48.	prosterone*.ti,ab,kf.
49.	sodium chloride/
50.	((sodium or saline or salt*) adj3 (replace* or treat* or therap* or solution* or supplement* or regimen* or intake* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or IV)).ti,ab,kf.
51.	glucose/
52.	((glucose or dextrose) adj3 (replace* or treat* or therap* or solution* or supplement* or regimen* or intake* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or IV)).ti,ab,kf.
53.	HypoGel.ti,ab,kf.
54.	or/34-53
55.	33 and 54
56.	random*.ti,ab.
57.	factorial*.ti,ab.
58.	(crossover* or cross over*).ti,ab.
59.	((doubl* or singl*) adj blind*).ti,ab.
60.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
61.	crossover procedure/
62.	single blind procedure/
63.	randomized controlled trial/
64.	double blind procedure/
65.	or/56-64
66.	Systematic Review/
67.	Meta-Analysis/
68.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
69.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
70.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
71.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
72.	(search* adj4 literature).ab.
73.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
74.	cochrane.jw.
75.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.

76.	or/66-75
77.	55 and (65 or 76)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Adrenal Insufficiency] explode all trees
#2.	MeSH descriptor: [Adrenal Hyperplasia, Congenital] this term only
#3.	((addison* NEXT disease) or addisonian*):ti,ab,kw
#4.	((adrenal* or adrenocort* or adreno-cort*) near/3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)):ti,ab,kw
#5.	((cortisol or aldosterone or adrenocorticotrop* or adreno-corticotrop* or ACTH or (corticotropi* NEXT releas*) or (corticotrophi* NEXT releas*) or corticoliberin or CRH) near/3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)):ti,ab,kw
#6.	(hypoadrenal* or hypo-adrenal* or hypoadrenocorticism or "hypo adrenocorticism" or adrenoleukodystrophy or "adreno leukodystrophy" or adrenomyeloneuropathy or "adreno myeloneuropathy" or hypoaldosteronism or "hypo aldosteronism"):ti,ab,kw
#7.	((adrenogenital or "adreno genital") near/1 (syndrome or disorder*)):ti,ab,kw
#8.	((haemorrhag* or hemorrhag* or bleed*) near/3 adrenal*):ti,ab,kw
#9.	((Bronze NEXT Schilder*) or "Melanodermic Leukodystrophy" or (Schilder NEXT Addison*) or (Siemerling NEXT Creutzfeldt*)):ti,ab,kw
#10.	((Allgrove or 3A or TripleA or AAA) near/1 syndrome):ti,ab,kw
#11.	(CAH or X-ALD):ti,ab
#12.	((Waterhouse NEXT Friderichsen*) or "antiphospholipid syndrome"):ti,ab,kw
#13.	Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy:ti,ab,kw
#14.	(or #1-#13)
#15.	conference:pt or (clinicaltrials or trialsearch):so
#16.	#14 not #15
#17.	MeSH descriptor: [Glucocorticoids] this term only
#18.	((glucocorticoid* or glucocorticosteroid* or steroid* or corticosteroid* or cortisone) near/3 (replace* or treat* or therap* or supplement* or regimen* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or intra-muscular* or intramuscular* or exogenous* or subcutaneous*)):ti,ab,kw
#19.	MeSH descriptor: [Hydrocortisone] this term only
#20.	MeSH descriptor: [Dexamethasone] this term only
#21.	MeSH descriptor: [Prednisolone] this term only
#22.	(hydrocortisone* or prednisolone* or methylprednisolone* or dexamethasone*):ti,ab,kw
#23.	(Solu-Cortef or Hydventia or Plenadren or Neofordex or Glensoludex or Martapan or Deltacortril or Deltastab or Dilacort or Pevanti):ti,ab,kw
#24.	MeSH descriptor: [Mineralocorticoids] this term only
#25.	(mineralocorticoid* near/3 (replace* or treat* or therap* or supplement* or regimen* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or intra muscular* or intramuscular* or exogenous* or subcutaneous*)):ti,ab,kw
#26.	MeSH descriptor: [Fludrocortisone] this term only
#27.	fludrocortisone*:ti,ab,kw
#28.	Florinef:ti,ab,kw
#29.	MeSH descriptor: [Androgens] this term only
#30.	MeSH descriptor: [Hormone Replacement Therapy] this term only
#31.	((androgen* or hormon*) near/4 (replace* or treat* or therap* or supplement*)):ti,ab,kw

#32.	MeSH descriptor: [Dehydroepiandrosterone] explode all trees
#33.	(dehydroepiandrosterone or dehydro-epiandrosterone or DHEA):ti,ab,kw
#34.	prosterone*:ti,ab,kw
#35.	MeSH descriptor: [Sodium Chloride] this term only
#36.	((sodium or saline or salt*) near/3 (replace* or treat* or therap* or solution* or supplement* or regimen* or intake* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or IV)):ti,ab,kw
#37.	MeSH descriptor: [Glucose] this term only
#38.	((glucose or dextrose) near/3 (replace* or treat* or therap* or solution* or supplement* or regimen* or intake* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or IV)):ti,ab,kw
#39.	HypoGel:ti,ab,kw
#40.	(or #17-#39)
#41.	#16 and #40

Epistemonikos search terms

1.	(title:((title:("adrenal insufficiency" OR "adrenal inadequacy" OR "adrenal deficiency" OR "adrenal suppression" OR "adrenal hypofunction" OR "adrenal disorder" OR "adrenal underactivity" OR "adrenal dysfunction" OR "adrenal crisis" OR "adrenal crises" OR "adrenal hypoplasia" OR "adrenal congenital hyperplasia" OR "addison disease" OR "addisons disease" OR "addison's disease" OR addisonian* OR hypoadrenal* OR "hypo adrenalism" OR hypoadrenocorticism OR "hypo adrenocorticism" OR adrenoleukodystrophy OR "adreno leukodystrophy" OR adrenomyeloneuropathy OR "adreno myeloneuropathy" OR hypoaldosteronism OR "hypo aldosteronism") OR abstract:("adrenal insufficiency" OR "adrenal inadequacy" OR "adrenal deficiency" OR "adrenal suppression" OR "adrenal hypofunction" OR "adrenal disorder" OR "adrenal underactivity" OR "adrenal dysfunction" OR "adrenal crisis" OR "adrenal crises" OR "adrenal hypoplasia" OR "adrenal congenital hyperplasia" OR "addison disease" OR "addisons disease" OR "addison's disease" OR addisonian* OR hypoadrenal* OR "hypo adrenalism" OR hypoadrenocorticism OR "hypo adrenocorticism" OR adrenoleukodystrophy OR "adreno leukodystrophy" OR adrenomyeloneuropathy OR "adreno myeloneuropathy" OR hypoaldosteronism OR "hypo aldosteronism")) AND (title:(((glucocorticoid* OR glucocorticosteroid* OR steroid* OR corticosteroid* OR mineralocorticoid* OR sodium OR saline OR salt OR dextrose OR glucose OR androgen* OR hormon*) AND (replace* OR treat* OR therap* OR supplement*)) OR hydrocortisone* OR prednisolone* OR methylprednisolone* OR dexamethasone* OR "Solu-Cortef" OR Hydventia OR Plenadren OR Neofordex OR Glensoludex OR Martapan OR Deltacortril OR Deltastab OR Dilacort OR Pevanti OR fludrocortisone* OR Florinefv OR dehydroepiandrosterone OR "dehydro epiandrosterone" OR DHEA OR prosterone* OR hypogel) OR abstract:(((glucocorticoid* OR glucocorticosteroid* OR steroid* OR corticosteroid* OR mineralocorticoid* OR sodium OR saline OR salt OR dextrose OR glucose OR androgen* OR hormon*) AND (replace* OR treat* OR therap* OR supplement*)) OR hydrocortisone* OR prednisolone* OR methylprednisolone* OR dexamethasone* OR "Solu-Cortef" OR Hydventia OR Plenadren OR Neofordex OR Glensoludex OR Martapan OR Deltacortril OR Deltastab OR Dilacort OR Pevanti OR fludrocortisone* OR Florinefv OR dehydroepiandrosterone OR "dehydro epiandrosterone" OR DHEA OR prosterone* OR hypogel))) OR abstract:((title:("adrenal insufficiency" OR "adrenal inadequacy" OR "adrenal deficiency" OR "adrenal suppression" OR "adrenal hypofunction" OR "adrenal disorder" OR "adrenal underactivity" OR "adrenal dysfunction" OR "adrenal crisis" OR "adrenal crises" OR "adrenal hypoplasia" OR "adrenal congenital hyperplasia" OR "addison disease" OR "addisons disease" OR "addison's disease" OR addisonian* OR hypoadrenal* OR "hypo adrenalism" OR hypoadrenocorticism OR "hypo adrenocorticism" OR adrenoleukodystrophy OR "adreno leukodystrophy" OR adrenomyeloneuropathy OR "adreno myeloneuropathy" OR hypoaldosteronism OR "hypo aldosteronism") OR abstract:("adrenal insufficiency" OR "adrenal inadequacy" OR "adrenal deficiency" OR "adrenal suppression" OR "adrenal hypofunction" OR "adrenal disorder" OR "adrenal underactivity" OR "adrenal

	dysfunction" OR "adrenal crisis" OR "adrenal crises" OR "adrenal hypoplasia" OR "adrenal congenital hyperplasia" OR "addison disease" OR "addisons disease" OR "addison's disease" OR addisonian* OR hypoadrenal* OR "hypo adrenalism" OR hypoadrenocorticism OR "hypo adrenocorticism" OR adrenoleukodystrophy OR "adreno leukodystrophy" OR adrenomyeloneuropathy OR "adreno myeloneuropathy" OR hypoaldosteronism OR "hypo aldosteronism")) AND (title:(((glucocorticoid* OR glucocorticosteroid* OR steroid* OR corticosteroid* OR mineralocorticoid* OR sodium OR saline OR salt OR dextrose OR glucose OR androgen* OR hormon*) AND (replace* OR treat* OR therap* OR supplement*)) OR hydrocortisone* OR prednisolone* OR methylprednisolone* OR dexamethasone* OR "Solu-Cortef" OR Hydventia OR Plenadren OR Neofordex OR Glensoludex OR Martapan OR Deltacortril OR Deltastab OR Dilacort OR Pevanti OR fludrocortisone* OR Florinefv OR dehydroepiandrosterone OR "dehydro epiandrosterone" OR DHEA OR prosterone* OR hypogel) OR abstract:(((glucocorticoid* OR glucocorticosteroid* OR steroid* OR corticosteroid* OR mineralocorticoid* OR sodium OR saline OR salt OR dextrose OR glucose OR androgen* OR hormon*) AND (replace* OR treat* OR therap* OR supplement*)) OR hydrocortisone* OR prednisolone* OR methylprednisolone* OR dexamethasone* OR "Solu-Cortef" OR Hydventia OR Plenadren OR Neofordex OR Glensoludex OR Martapan OR Deltacortril OR Deltastab OR Dilacort OR Pevanti OR fludrocortisone* OR Florinefv OR dehydroepiandrosterone OR "dehydro epiandrosterone" OR DHEA OR prosterone* OR hypogel))))

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Adrenal Insufficiency population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards.

Table 15: Database parameters, filters and limits applied.

Database	Dates searched	Search filters and limits applied
Medline (OVID)	1 January 2014 – 26 September 2023	Health economics studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1 January 2014 – 26 September 2023	Health economics studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	

Database	Dates searched	Search filters and limits applied
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 26 September 2023	English language

Medline (Ovid) search terms

1.	exp Adrenal Insufficiency/
2.	Adrenal Hyperplasia, Congenital/
3.	(addison* disease or addisonian*).ti,ab,kf.
4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.
6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	or/1-13
15.	letter/
16.	editorial/
17.	news/
18.	exp historical article/
19.	Anecdotes as Topic/
20.	comment/
21.	case reports/
22.	(letter or comment*).ti.
23.	or/15-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24

26.	animals/ not humans/
27.	exp Animals, Laboratory/
28.	exp Animal Experimentation/
29.	exp Models, Animal/
30.	exp Rodentia/
31.	(rat or rats or mouse or mice or rodent*).ti.
32.	or/25-31
33.	14 not 32
34.	limit 33 to English language
35.	Economics/
36.	Value of life/
37.	exp "Costs and Cost Analysis"/
38.	exp Economics, Hospital/
39.	exp Economics, Medical/
40.	Economics, Nursing/
41.	Economics, Pharmaceutical/
42.	exp "Fees and Charges"/
43.	exp Budgets/
44.	budget*.ti,ab.
45.	cost*.ti.
46.	(economic* or pharmaco?economic*).ti.
47.	(price* or pricing*).ti,ab.
48.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
49.	(financ* or fee or fees).ti,ab.
50.	(value adj2 (money or monetary)).ti,ab.
51.	or/35-50
52.	34 and 51
53.	limit 52 to yr="2014 -Current"

Embase (Ovid) search terms

1.	exp Adrenal cortex insufficiency/
2.	Congenital adrenal hyperplasia/
3.	(addison* disease or addisonian*).ti,ab,kf.
4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.
6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.

7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	or/1-13
15.	letter.pt. or letter/
16.	note.pt.
17.	editorial.pt.
18.	case report/ or case study/
19.	(letter or comment*).ti.
20.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
21.	or/15-20
22.	randomized controlled trial/ or random*.ti,ab.
23.	21 not 22
24.	animal/ not human/
25.	nonhuman/
26.	exp Animal Experiment/
27.	exp Experimental Animal/
28.	animal model/
29.	exp Rodent/
30.	(rat or rats or mouse or mice or rodent*).ti.
31.	or/23-30
32.	14 not 31
33.	limit 32 to English language
34.	health economics/
35.	exp economic evaluation/
36.	exp health care cost/
37.	exp fee/
38.	budget/
39.	funding/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/34-46
48.	33 and 47
49.	limit 48 to yr="2014 -Current"

NHS EED and HTA (CRD) search terms

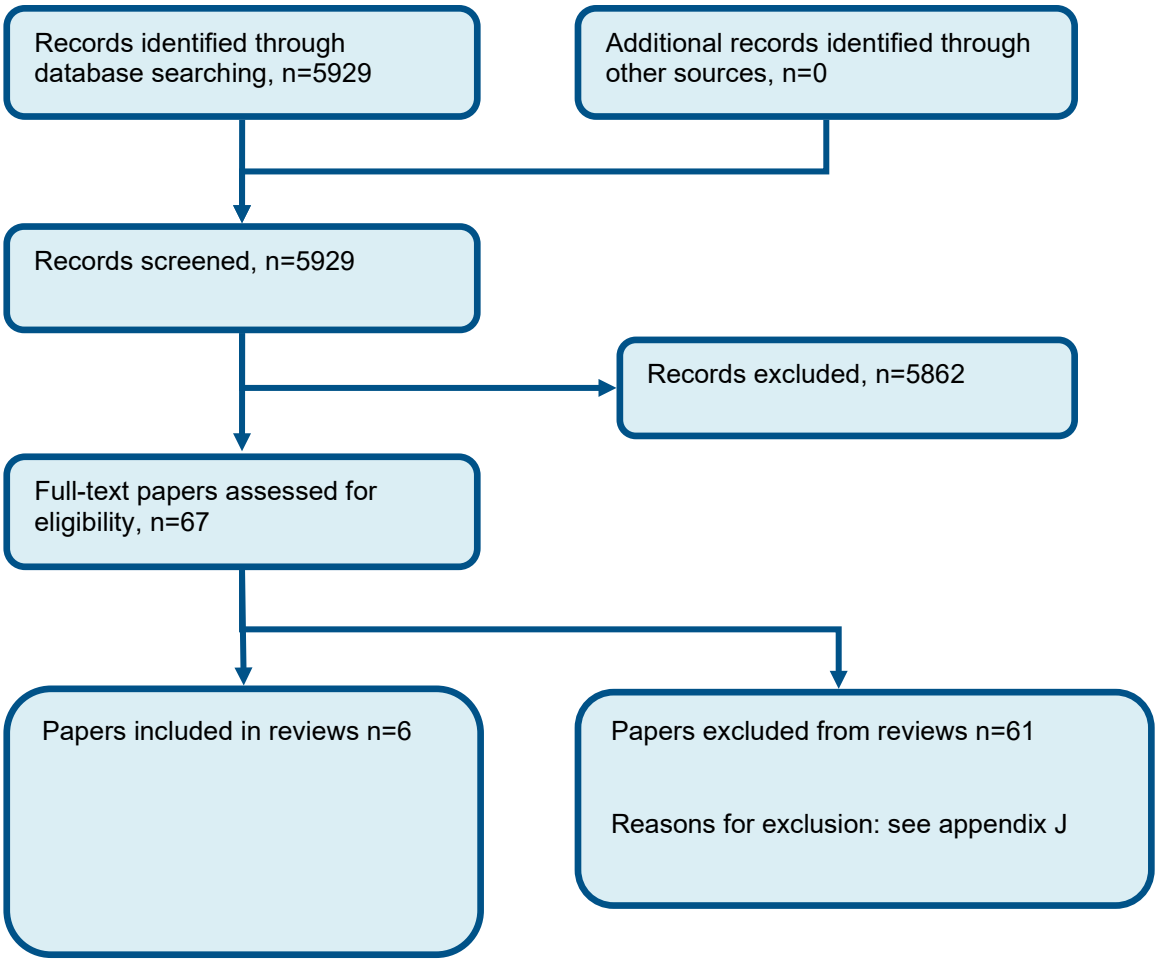
#1.	MeSH DESCRIPTOR Adrenal Insufficiency EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Adrenal Hyperplasia, Congenital EXPLODE ALL TREES
#3.	(addison* disease or addisonian)
#4.	(adrenal*) AND (insufficien* or inadequa* or deficien* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed)
#5.	(cortisol or aldosterone or adrenocortical or adrenocorticotropi* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) AND (insufficien* or inadequac* or deficien* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or produc* or limited)
#6.	(hypoadrenalism or hypoadrenocorticism or adrenoleukodystrophy or adrenomyeloneuropathy or hypoaldosteronism)
#7.	((Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease))
#8.	(Allgrove or 3A or TripleA or AAA) AND (syndrome)
#9.	(X-ALD)
#10.	((Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome))
#11.	((Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy))
#12.	(adrenogenital or adreno genital) AND (syndrome)
#13.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12

INAHTA search terms

1.	(("Adrenal Insufficiency"[mhe]) OR (hypoadrenalism) OR (addison*) OR (adrenal insufficiency) OR (adrenal crisis))

Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of routine pharmacological management of secondary and tertiary AI



Appendix D Effectiveness evidence

Agha, 2004

Bibliographic Reference	Agha, A.; Liew, A.; Finucane, F.; Baker, L.; O'Kelly, P.; Tormey, W.; Thompson, C. J.; Conventional glucocorticoid replacement overtreats adult hypopituitary patients with partial ACTH deficiency; Clinical Endocrinology; 2004; vol. 60 (no. 6); 688-93

Study details

Secondary publication of another included study- see primary study for details	No
Other publications associated with this study included in review	None
Trial name / registration number	Not reported
Study type	Randomised controlled trial (RCT)
Study location	Ireland
Study setting	Department of Endocrinology, Beaumont Hospital, Ireland
Study dates	Not reported
Sources of funding	Unclear "We would like to thank Professor Dermot Kenny and the staff of the RCSI Clinical Research Centre, Dublin, Ireland where the study was conducted. We are indebted to Dr Jamie Zadeh of Charing Cross Hospital, London, UK who performed the CBG assays. Dr Agha was in receipt of a Pharmacia International Research Fellowship."
Inclusion criteria	Male adult hypopituitary patients with partial ACTH deficiency, defined as a fasting 08·00 h total serum cortisol exceeding 200 nmol/l with a stimulated peak value of less than 500 nmol/l, ACTH reserves were assessed fewer than 6 months before the start of the study in all patients. Because glucagon stimulation is associated with subnormal cortisol responses in about 8% of healthy subjects (Rao & Spathis, 1987), patients whose ACTH deficiency was defined by abnormal response to GST were only included if they also had both significant GH deficiency (stimulated peak < 3 ng/ml and IGF-1 below age-specified reference range) and gonadotrophin deficiency, in order to exclude those with false negative responses to glucagon.
Exclusion criteria	Patients with severe cardiac or respiratory disease

	patients with terminal illness Patients on antiepileptic therapy or other medications which interfere with hydrocortisone metabolism. Female subjects were excluded because of the potential effect of oestrogen status on corticosteroid-binding globulin (CBG) level
Recruitment / selection of participants	"Identified from the Beaumont Hospital Pituitary Database" "We identified 14 patients who fulfilled the criteria,10 agreed to participate"
Intervention(s)	Conventional full-dose hydrocortisone - 10mg twice daily for 1 week Half dose hydrocortisone - 5mg twice daily for 1 week
Population subgroups	None
Comparator	No hydrocortisone treatment for 1 week Note: not a placebo
Number of participants	10
Duration of follow-up	3 weeks total - 1 week per treatment crossover
Additional comments	Analysis of variance (anova) models were used to compare serum cortisol results of patients on full-dose, half-dose and no hydrocortisone treatments, and controls at various time periods and also to compare peak and trough cortisol values between patients and controls. Multiple comparison tests using a Bonferroni correction factor was used to determine if results reach significance at the 5% level. The Student's t-test was used to compare body mass index (BMI), PR, BP, plasma sodium and CBG levels between patients and control groups. P-values less than 0·05 were taken as significant.

Study arms

No treatment (N = 10)

5mg hydrocortisone twice daily for 1 week (N = 10)

10mg hydrocortisone twice daily for 1 week (N = 10)

Characteristics

Study-level characteristics

Characteristic	Study (N = 10)
% Female No of events	n = 0 ; % = 0
Mean age (SD) Mean (SD)	43.9 (10.8)
BMI (kg/m²)	31.1 (4.5)

Characteristic	Study (N = 10)
Mean (SD)	

Outcomes

Study timepoints

1 week

Clinical parameters and cortisol

Outcome	No treatment, 1 week, N = 10	5mg hydrocortisone twice daily for 1 week, 1 week, N = 10	10mg hydrocortisone twice daily for 1 week, 1 week, N = 10
Peak cortisol (nmol/L) Mean (SD)	323 (74.2)	424.4 (93.9)	508.6 (86)
Trough cortisol (nmol/L) Mean (SD)	180.5 (64.1)	165.6 (71.7)	149.8 (49.1)
Pulse rate (beats per minute) Mean (SD)	67.9 (2.4)	66.6 (3.1)	68.2 (3.4)
Systolic blood pressure (mmHg) Mean (SD)	131.1 (9.6)	134.3 (14.5)	129.5 (12.4)
Diastolic blood pressure (mmHg) Mean (SD)	79.1 (11.6)	83.7 (10.7)	83.4 (8.7)
Plasma sodium (mmol/L) Mean (SD)	141.2 (2.2)	140.2 (1.7)	140.5 (1.7)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial.

Cortisol levels

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of clarity around blinding)*
Overall bias and Directness	Overall Directness	Partially applicable

Pulse rate

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of clarity around blinding)*
Overall bias and Directness	Overall Directness	Directly applicable

Blood pressure

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of clarity around blinding)*
Overall bias and Directness	Overall Directness	Directly applicable

Plasma sodium

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Lack of clarity around blinding)*
Overall bias and Directness	Overall Directness	Directly applicable

Behan, 2016

Bibliographic Reference	Behan, L. A.; Carmody, D.; Rogers, B.; Hannon, M. J.; Davenport, C.; Tormey, W.; Smith, D.; Thompson, C. J.; Stanton, A.; Agha, A.; Low-dose hydrocortisone replacement is associated with improved arterial stiffness index and blood pressure dynamics in severely adrenocorticotrophin-deficient hypopituitary male patients; European Journal of Endocrinology; 2016; vol. 174 (no. 6); 791-9

Study details

Secondary publication of another included study- see primary study for details	Behan 2011
Other publications associated with this study included in review	Behan 2011 [Optimizing glucocorticoid replacement therapy in severely adrenocorticotropin-deficient hypopituitary male patients]
Trial name / registration number	Irish Medicines Board Clinical Trial Number–CT900/459/1 EudraCT Number–2007-005018-37 [Same as Behan 2011]
Study type	Randomised controlled trial (RCT)

Study location	RCSI Clinical Research Centre, Dublin, Ireland
Study setting	Clinic
Study dates	Not stated
Sources of funding	An unrestricted educational grant from Pfizer Endocrine Care
Inclusion criteria	[Same as Behan 2011] Adults Known severe ACTH deficiency defined by a fasting morning total serum cortisol concentration <100 nmol/l and a stimulated peak cortisol in response to insulin-induced hypoglycaemia of <400 nmol/l
Exclusion criteria	Aged less than 18 years, Patients with acute medical or surgical illness, patients with advanced cardiac/pulmonary disease, patients with a terminal illness, patients on glucocorticoids for purposes other than ACTH deficiency and those on agents that interfere with corticosteroid metabolism. Female patients [excluded because of the unpredictable effects of oestrogen status on corticosteroid binding globulin (CBG) levels and thus total cortisol concentration and also free cortisol kinetics]
Recruitment / selection of participants	Not stated
Intervention(s)	Hydrocortisone oral: Dose A (20 mg 0800 h, 10 mg 1600 h), Dose B (10 mg 0800 h and 1600 h) Dose C (10 mg 0800 h and 5 mg 1600 h) 6 weeks of each dose regimen
Population subgroups	N/A
Comparator	See "Intervention(s)"
Number of participants	n=10 intervention, n=10 control
Duration of follow-up	6 weeks for each treatment arm
Indirectness	N/A
Additional comments	Not stated, likely ITT

Study arms

Dose A [20 mg 0800 h, 10 mg 1600 h] (N = 10)

Dose B [10 mg 0800 h and 1600 h] (N = 10)

Dose C [10 mg 0800 h and 5 mg 1600 h (N = 10)

Control (N = 10)

Healthy matched controls

Outcomes

24h Ambulatory Blood Pressure levels

Outcome	Dose A [20 mg 0800 h, 10 mg 1600 h], , N = 10	Dose B [10 mg 0800 h and 1600 h], , N = 10	Dose C [10 mg 0800 h and 5 mg 1600 h, , N = 10	Control, , N = 10
24h systolic BP (mmHg) Mean (SD)	115 (12)	117 (12)	115 (13)	121 (10)
24h diastolic BP Mean (SD)	70 (8)	68 (8)	68 (7)	73 (8)

At the end of each 6-week treatment regimen, schedule patients were admitted for 28 h to the clinical research centre to undergo metabolic investigations, which included a 24-h ambulatory BP measurement (24-h ABPM). On each admission, between 0730 and 0800 h, patients were fitted with validated oscillometric devices to record 24-h ambulatory blood pressure (SpaceLabs 90202 or 90207), programmed to obtain BP readings at 30-min intervals for 24 h throughout each 28-h admission period.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial.

24h Ambulatory BP

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Partially applicable *(Study only includes male patients and therefore may not be generalisable to women with secondary and tertiary adrenal insufficiency)*

Behan, 2011

Bibliographic Reference	Behan, L. A.; Rogers, B.; Hannon, M. J.; O'Kelly, P.; Tormey, W.; Smith, D.; Thompson, C. J.; Agha, A.; Optimizing glucocorticoid replacement therapy in

severely adrenocorticotropin-deficient hypopituitary male patients; Clinical Endocrinology; 2011; vol. 75 (no. 4); 505-13

Study details

Other publications associated with this study included in review	Behan 2016 [Low-dose hydrocortisone replacement is associated with improved arterial stiffness index and blood pressure dynamics in severely adrenocorticotrophin-deficient hypopituitary male patients]
Trial name / registration number	Irish Medicines Board Clinical Trial Number–CT900/459/1 EudraCT Number–2007-005018-37 [Same as Behan 2016]
Study type	Randomised controlled trial (RCT)
Study location	RCSI Clinical Research Centre, Dublin, Ireland
Study setting	Clinic
Study dates	Not stated
Sources of funding	An unrestricted educational grant from Pfizer Endocrine Care and Sanofi Aventis Pharmaceuticals
Inclusion criteria	Adults Known severe ACTH deficiency defined by a fasting morning total serum cortisol concentration <100 nmol/l and a stimulated peak cortisol in response to insulin-induced hypoglycaemia of <400 nmol/L
Exclusion criteria	Aged less than 18 years, Patients with acute medical or surgical illness, patients with advanced cardiac/pulmonary disease, patients with a terminal illness, patients on glucocorticoids for purposes other than ACTH deficiency and those on agents that interfere with corticosteroid metabolism. Female patients [excluded because of the unpredictable effects of oestrogen status on corticosteroid binding globulin (CBG) levels and thus total cortisol concentration and also free cortisol kinetics]
Recruitment / selection of participants	Not stated
Intervention(s)	Hydrocortisone oral: Dose A (20 mg 0800 h, 10 mg 1600 h), Dose B (10 mg 0800 h and 1600 h) Dose C (10 mg 0800 h and 5 mg 1600 h)

	6 weeks of each dose regimen
Population subgroups	N/A
Comparator	See Intervention(s)
Number of participants	n=10 intervention, n=10 control
Duration of follow-up	6 weeks for each treatment arm
Indirectness	N/A
Additional comments	Not stated, likely ITT

Study arms

Dose A (20 mg 0800 h, 10 mg 1600 h) (N = 10)

Dose B (10 mg 0800 h and 1600 h) (N = 10)

Dose C (10 mg 0800 h and 5 mg 1600 h) (N = 10)

Control (N = 10)

Healthy matched controls

Characteristics

Study-level characteristics

Characteristic	**Study (N = 10)**
% Female Nominal	0
Mean age (SD) Mean (SD)	46 (15)
BMI (kg/m2) Mean (SD)	29.8 (5.3)
Basal cortisol (nmol/L) Mean (SD)	76.8 (6.5)
Basal testosterone (pmol/L) Mean (SD)	14.2 (4.1)

Outcomes

Raw quality of life scores

Outcome	Dose A (20 mg 0800 h, 10 mg 1600 h), , N = 10	Dose B (10 mg 0800 h and 1600 h), , N = 10	Dose C (10 mg 0800 h and 5 mg 1600 h), , N = 10	Control, , N = 10
SF-36 physical functioning Mean (SD)	88.5 (18.4)	79.5 (24)	80.5 (24.5)	92.9 (13.4)
SF-36 Role Physical Mean (SD)	77.5 (38)	62.5 (35.8)	55 (45.3)	95.8 (12)
SF-36 bodily pain Mean (SD)	85.1 (20)	82.5 (23.8)	76.5 (22.8)	81 (21.2)
SF-36 general health Mean (SD)	62.8 (18.6)	61.8 (13)	59.8 (15)	77 (12.7)
SF-36 vitality Mean (SD)	62.5 (24.9)	47.5 (23.3)	44 (24.5)	70 (13.3)
SF-36 social functioning Mean (SD)	90 (17.4)	92.5 (13.4)	85 (18.4)	91 (14.5)
SF-36 Role Emotional Mean (SD)	83.3 (36)	66.6 (41.5)	73.3 (40.9)	91.6 (20.2)
SF-36 Mental Health Mean (SD)	79.6 (17.8)	80 (18.9)	80 (17.4)	78.8 (13.1)
NHP Energy level Mean (SD)	36.3 (43.6)	35.1 (42.5)	41.3 (37.3)	3.2 (11.1)
NHP Pain Mean (SD)	8.1 (22.2)	7 (15.6)	10.6 (21.6)	2.1 (4.4)
NHP Emotional reaction Mean (SD)	8.5 (10.3)	7.3 (15.5)	8.6 (17.1)	8.9 (13.4)
NHP Sleep Mean (SD)	20.7 (23.2)	15.3 (30.4)	10.9 (17.7)	11.2 (18.4)

Outcome	Dose A (20 mg 0800 h, 10 mg 1600 h), , N = 10	Dose B (10 mg 0800 h and 1600 h), , N = 10	Dose C (10 mg 0800 h and 5 mg 1600 h), , N = 10	Control, , N = 10
NHP Social Isolation Mean (SD)	8.5 (20.6)	7.5 (13.3)	0 (0)	4.4 (13.6)
NHP Physical abilities Mean (SD)	8.9 (15.5)	13.1 (21.8)	14.4 (20.5)	2.2 (5.6)

- SF-36 physical functioning - Polarity - Higher values are better.
- SF-36 Role Physical - Polarity - Higher values are better.
- SF-36 bodily pain - Polarity - Higher values are better.
- SF-36 general health - Polarity - Higher values are better.
- SF-36 vitality - Polarity - Higher values are better.
- SF-36 social functioning - Polarity - Higher values are better.
- SF-36 Role Emotional - Polarity - Higher values are better.
- SF-36 Mental Health - Polarity - Higher values are better.
- NHP Energy level - Polarity - Lower values are better.
- NHP Pain - Polarity - Lower values are better.
- NHP Emotional reaction - Polarity - Lower values are better.
- NHP Sleep - Polarity - Lower values are better.
- NHP Social Isolation - Polarity - Lower values are better.
- NHP Physical abilities - Polarity - Lower values are better.
- Following 6 weeks of each regimen patients underwent 24 h serum cortisol sampling and QoL assessment with the Short Form 36 (SF36) and the Nottingham Health Profile (NHP) questionnaires.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial.

SF-36 scores.

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Very serious risk of bias as details on recruitment, randomisation, and blinding not provided)*
Overall bias and Directness	Overall Directness	Partially applicable *(Study only includes male patients and therefore may not be generalisable to women with secondary and tertiary adrenal insufficiency)*

NHP Scores

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Very serious risk of bias as details on recruitment, randomisation, and blinding not provided)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Partially applicable *(Study only includes male patients and therefore may not be generalisable to women with secondary and tertiary adrenal insufficiency)*

Benson, 2012

Bibliographic Reference	Benson, S.; Neumann, P.; Unger, N.; Schedlowski, M.; Mann, K.; Elsenbruch, S.; Petersenn, S.; Effects of standard glucocorticoid replacement therapies on subjective well-being: a randomized, double-blind, crossover study in patients with secondary adrenal insufficiency; European Journal of Endocrinology; 2012; vol. 167 (no. 5); 679-85

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	None
Trial name / registration number	No trial registration reported. "The study was approved by the Local Ethics Committee (permit no. 03-2279)"
Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	University Hospital of Essen, Germany
Study dates	Not reported
Sources of funding	"This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector."
Inclusion criteria	Inclusion criteria were age 18–75 years and stable substitution therapy of all pituitary axes (if necessary) for at least 3 months.
Exclusion criteria	Patients were excluded if Beck Depression Inventory score exceeded the cutoff indicating moderate-to-severe depressive symptoms. Pregnancy and a previous history of hypercortisolism also led to exclusion from the study. A peak cortisol of more than 500 nmol/l during the insulin tolerance test was used to categorize the patients as adrenal sufficient (patient controls (PC)) and a peak cortisol of <450 nmol/l to diagnose SAI. Owing to difficulties in establishing a clear diagnosis, patients with peak cortisol levels between 450 and 500 nmol/l were excluded from the study.

Recruitment / selection of participants	Medical records from n=248 patients who had undergone pituitary surgery at the University Hospital of Essen, Germany, and evaluation of the adrenal function within the previous 12 months were screened Ninety-three patients met all inclusion criteria, of those 43 (n=23 SAI, n=20 PC) agreed to participate. Three SAI patients dropped out after initial consent but before treatment, and two SAI patients were excluded during the study for noncompliance, resulting in 18 SAI patients and 20 PC that completed the study protocol.
Intervention(s)	three different established glucocorticoid replacement therapies (i.e., treatment A, hydrocortisone 10 mg-placebo-5 mg-placebo; treatment B, hydrocortisone 10 mg-5 mg-placebo-5 mg; and treatment C, prednisone 5 mg-placebo-placebo-placebo) for 4-week periods. Identically looking capsules containing either medication or placebo were prepared by the pharmacy of the University Hospital Essen. Capsules were designed to be completely resolved within 30 min; hence, an effect of capsules on the pharmacokinetics of the active drugs can be excluded. Capsules were administered at distinct time points (i.e., 0700, 1200, 1500, and 1800 h). Given that a wash out period is not feasible in adrenal insufficient patients, questionnaires were completed at the end of each 4-week treatment regimen.
Population subgroups	None
Comparator	See intervention - 3 different treatment regimes
Number of participants	18
Duration of follow-up	12 weeks total - 4 weeks per treatment crossover
Indirectness	
Additional comments	Effects of replacement regimens on psychological parameters within SAI patients were assessed with repeated measures analysis of covariance (ANCOVA) controlling for disease duration. In case of significant ANCOVA treatment effects, post hoc paired t-tests were computed. For variables that were measured over the course of the study days (i.e., current well-being and alertness), two-way ANCOVAs with the repeated factors replacement treatment and time were computed.

Study arms

Treatment A hydrocortisone 10mg-placebo-5mg-placebo daily for 4 weeks (N = 18)

Treatment B hydrocortisone 10mg-5mg-placebo-5mg daily for 4 weeks (N = 18)

Treatment C prednisone 5mg-placebo-placebo-placebo daily for 4 weeks (N = 18)

Excluded in protocol as prednisone not used in UK - included for info only.

Characteristics

Study-level characteristics

Characteristic	Study (N = 18)
% Female No of events	n = 10; % = 55.6
Mean age (SD) Mean (SD)	52 (10.3)
BMI (kg/m²) Mean (SD)	27 (7.4)

Outcomes

Study timepoints

- 4 weeks

HRQoL, emotional distress, alertness

Outcome	Treatment A hydrocortisone 10mg-placebo-5mg-placebo daily for 4 weeks, 4-week, N = 18	Treatment B hydrocortisone 10mg-5mg-placebo-5mg daily for 4 weeks, 4-week, N = 18	Treatment C prednisone 5mg-placebo-placebo-placebo daily for 4 weeks, 4-week, N = 18
SF-36 physical sum scale Mean (SD)	43.9 (10.5)	40.7 (13.4)	42.8 (12.2)
SF36 psychological sum scale Mean (SD)	46.3 (7.7)	46.4 (12.8)	46.5 (12.7)
BSI Global symptom severity Mean (SD)	57.9 (11.4)	58.1 (12.9)	58.2 (13.5)

Outcome	Treatment A hydrocortisone 10mg-placebo-5mg-placebo daily for 4 weeks, 4-week, N = 18	Treatment B hydrocortisone 10mg-5mg-placebo-5mg daily for 4 weeks, 4-week, N = 18	Treatment C prednisone 5mg-placebo-placebo-placebo daily for 4 weeks, 4-week, N = 18
0700h Mean (SD)	2.5 (0.35)	2.3 (0.32)	2.4 (0.33)
1200h Mean (SD)	1.7 (0.24)	1.7 (0.29)	1.7 (0.19)
1500h Mean (SD)	1.8 (0.27)	1.8 (0.24)	2 (0.39)
1800h Mean (SD)	1.7 (0.21)	2.1 (0.3)	1.8 (0.27)
2200 Mean (SD)	2.7 (0.39)	3.4 (0.5)	3.3 (0.48)
Satisfaction with medication (100mm visual analog scale) Mean (SD)	51.2 (33.1)	56.6 (27.3)	62.1 (28.5)

- SF-36 physical sum scale - Polarity - Higher values are better.
- SF36 psychological sum scale - Polarity - Higher values are better.
- BSI Global symptom severity - Polarity - Lower values are better.
- Stanford Sleepiness Scale - Polarity - Lower values are better.
- Satisfaction with medication (100mm visual analogue scale) - Polarity - Higher values are better.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial.

SF-36 Score

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

BSI Global Symptom Severity

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Stanford Sleepiness Scale

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Satisfaction with medication

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Isidori, 2018

Bibliographic Reference	Isidori, A. M.; Venneri, M. A.; Graziadio, C.; Simeoli, C.; Fiore, D.; Hasenmajer, V.; Sbardella, E.; Gianfrilli, D.; Pozza, C.; Pasqualetti, P.; Morrone, S.; Santoni, A.; Naro, F.; Colao, A.; Pivonello, R.; Lenzi, A.; Effect of once-daily, modified-release hydrocortisone versus standard glucocorticoid therapy on metabolism and innate immunity in patients with adrenal insufficiency (DREAM): a single-blind, randomised controlled trial; The Lancet Diabetes & Endocrinology; 2018; vol. 6 (no. 3); 173-185

Study details

Trial name / registration number	NCT02277587
Study type	Randomised controlled trial (RCT)
Study location	Italy
Study setting	Academic hospital
Study dates	March 1, 2014, to June 30, 2016
Sources of funding	Italian Ministry of University and Research No pharma sponsor. "The funder of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or in the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication."
Inclusion criteria	Eligible patients were aged 18–80 years, had primary or secondary adrenal insufficiency, were taking conventional glucocorticoid therapy (hydrocortisone or cortisone two or three times a day plus daily doses of fludrocortisone as needed), had been stable for at least 3 months before enrolment, and were willing to change their regimen according to random allocation.
Exclusion criteria	Not specified
Recruitment / selection of participants	Methods not specified
Intervention(s)	Once-daily modified-release hydrocortisone tablet. Patients allocated to once daily, modified-release hydrocortisone were instructed to take the dose on waking, before

	leaving their bed. Patients previously on multiple doses of hydrocortisone a day received the same total daily dose, whereas patients previously on cortisone received 0·8 mg of hydrocortisone per 1 mg of cortisone, as recommended by the European Medicines Agency drug fact sheet.
Population subgroups	• Primary AI (n=44) • Secondary AI (n=45) • Female (n=47) • Male (n=42)
Comparator	Standard glucocorticoid therapy. Patients assigned to continue standard therapy were instructed to take the first dose on waking before leaving their bed and subsequent doses according to their established schedule (two or three times a day), but with the last dose no later than 1700 h.
Number of participants	n= 89
Duration of follow-up	24 weeks
Indirectness	No concerns
Additional comments	Efficacy analyses included data from all patients who had received at least one dose of study drug. Authors assessed normality of distribution for all interventions at all timepoints using the Shapiro-Wilk's test (p>0·05). Log transformation or reciprocal transformation was used to correct for skewed data and a mixed-model analysis to assess changes in outcomes with accommodation for repeated measurements. In the mixed-model analysis, the patient was a random effect and treatment, time, and treatment-by-time interaction were fixed effects. The differences in change from baseline to week 12 and week 24 were analysed between the groups using an ANCOVA model that included baseline outcome as a covariate and treatment as a fixed effect and used the last observation- carried-forward principle.

Study arms

MR-HC (N = 46)

Standard glucocorticoid (N = 43)

Characteristics

Arm-level characteristics

Characteristic	MR-HC (N = 46)	Standard glucocorticoid (N = 43)
Female No of events	n = 25; % = 54	n = 22; % = 51
Primary AI No of events	n = 22; % = 48	n = 22; % = 51
Secondary AI No of events	n = 24; % = 52	n = 21; % = 49
Other autoimmune disorder No of events	n = 12; % = 26	n = 12; % = 28

Characteristic	MR-HC (N = 46)	Standard glucocorticoid (N = 43)
Pituitary tumor or surgery No of events	n = 22; % = 48	n = 20; % = 47
Other hypothalmic-pituitary failure No of events	n = 2; % = 4	n = 1; % = 2
Adrenalectomy No of events	n = 2; % = 4	n = 2; % = 5
Use of hydrocortisone at baseline No of events	n = 20; % = 43	n = 17; % = 40
Use of cortisone at baseline No of events	n = 26; % = 57	n = 26; % = 60
Baseline HC equivalent dose Mean (95% CI)	16 (14 to 18)	18 (15 to 21)
Diabetes No of events	n = 8; % = 17	n = 7; % = 16
BMI (kg/m2) Mean (95% CI)	27 (25 to 28)	26 (24 to 27)
Bodyweight (kg) Mean (95% CI)	75 (69 to 81)	70 (63 to 76)
Fasting blood glucose (mg/dL) Mean (95% CI)	89 (80 to 98)	79 (74 to 84)
Insulin (mU/ml) Mean (95% CI)	10 (8 to 12)	9 (7 to 12)
Total cholesterol (mg/dL) Mean (95% CI)	-1 (-11 to 10)	0 (-9 to 9)
HBA1C (%) Mean (95% CI)	5.2 (4.9 to 5.4)	5.5 (5.2 to 5.8)
Age Mean (95% CI)	48 (43 to 52)	49 (44 to 54)
Duration of adrenal insufficiency (Months) Median (IQR)	42 (24 to 108)	48 (24 to 132)
Fludrocortisone No of events	n = 21; % = 46	n = 20; % = 47

Characteristic	MR-HC (N = 46)	Standard glucocorticoid (N = 43)
AddiQoL Mean (95% CI)	82 (78 to 86)	83 (76 to 89)

Outcomes

Difference from baseline at 24 weeks

Outcome	MR-HC, , N = 43	Standard glucocorticoid, , N = 35
BMI (kg/m2) Mean (95% CI)	-0.9 (-1.7 to -0.1)	0.7 (-0.1 to 1.5)
Bodyweight (kg) Mean (95% CI)	-2.1 (-4 to -0.3)	1.9 (-0.1 to 3.9)
Fasting blood glucose (mg/dL) Mean (95% CI)	7 (3 to 10)	5 (0 to 11)
Insulin (mU/ml) Mean (95% CI)	0 (-2 to 2)	0 (-3 to 3)
Total cholesterol (mg/dL) Mean (95% CI)	-1 (-11 to 10)	0 (-9 to 9)
HbA1c (%) Mean (95% CI)	-0.2 (-0.3 to -0.1)	0.1 (0 to 0.2)
AddiQoL Total score, Addison's disease specific QoL Mean (95% CI)	7 (4 to 10)	2 (-1 to 5)
Flu or flu-like events in 6 mos Mean (95% CI)	-1.2 (-1.7 to -0.7)	-0.4 (-0.9 to 0.2)

Anthropometric measures [BMI, bodyweight] adjusted for age, sex, type of adrenal insufficiency, diabetes mellitus, smoking, and outcome at baseline. All other outcomes [HbA1c, fasting blood glucose, insulin, total cholesterol, flu-like events, AddiQoL] adjusted for age, sex, BMI, type of adrenal insufficiency, diabetes, smoking, and outcome at baseline.

Treatment-related difference at 24 weeks

Outcome	MR-HC vs Standard glucocorticoid, , N2 = 43, N1 = 35
BMI (kg/m2) Mean (95% CI)	-1.7 (-3 to -0.5)
BMI (kg/m2) Mean (p value)	-1.7 (0.008)
Bodyweight (kg) Mean (95% CI)	-4 (-6.9 to -1.1)

Outcome	MR-HC vs Standard glucocorticoid, , N2 = 43, N1 = 35
Bodyweight (kg) Mean (p value)	-4 (0.008)
HbA1c (%) Mean (95% CI)	-0.3 (-0.5 to -0.1)
HbA1c (%) Mean (p value)	-0.3 (0.001)
Fasting blood glucose (mg/dL) Mean (95% CI)	3 (-2 to 9)
Fasting blood glucose (mg/dL) Mean (p value)	3 (0.24)
Insulin (mU/ml) Mean (95% CI)	0 (-4 to 4)
Insulin (mU/ml) Mean (p value)	0 (0.99)
Total cholesterol (mg/dL) Mean (95% CI)	0 (-16 to 15)
Total cholesterol (mg/dL) Mean (p value)	0 (0.96)
AddiQoL Mean (95% CI)	5 (1 to 9)
AddiQoL Mean (p value)	5 (0.027)
Flu or flu-like events in 6 mos Mean (95% CI)	-1 (-1.6 to -0.4)
Flu or flu-like events in 6 mos Mean (p value)	-1.7 (0.0002)

Anthropometric measures [BMI, bodyweight] adjusted for age, sex, type of adrenal insufficiency, diabetes mellitus, smoking, and outcome at baseline. All other outcomes [HbA1c, fasting blood glucose, insulin, total cholesterol, flu-like events, AddiQol] adjusted for age, sex, BMI, type of adrenal insufficiency, diabetes, smoking, and outcome at baseline.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Normal RCT

BMI

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

AddiQoL

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Outcome data available for all patients and unlikely to be subject to measurement bias. However, there is no information re: non-protocol interventions being balanced between the treatment and intervention groups. Also, risk of measurement bias in patient-reported outcomes.)*
Overall bias and Directness	Overall Directness	Directly applicable

Bodyweight

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable

Cholesterol

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Outcome data available for all patients and unlikely to be subject to measurement bias. However, there is no information re: non-protocol interventions being balanced between the treatment and intervention groups.)*
Overall bias and Directness	Overall Directness	Directly applicable

HbA1c

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Outcome data available for all patients and unlikely to be subject to measurement bias. However, there is no information re: non-protocol interventions being balanced between the treatment and intervention groups.)*
Overall bias and Directness	Overall Directness	Directly applicable

Illness

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Outcome data available for all patients and unlikely to be subject to measurement bias. However, there is no information re: non-protocol interventions being balanced between the treatment and intervention groups.)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Werumeus Buning, 2015

Bibliographic Reference	Werumeus Buning, J.; Brummelman, P.; Koerts, J.; Dullaart, R. P.; van den Berg, G.; van der Klauw, M. M.; Tucha, O.; Wolffenbuttel, B. H.; van Beek, A. P.; The effects of two different doses of hydrocortisone on cognition in patients with secondary adrenal insufficiency--results from a randomized controlled trial; Psychoneuroendocrinology; 2015; vol. 55; 36-47

Study details

Secondary publication of another included study- see primary study for details	This is the primary report for trial registration NCT01546922
Other publications associated with this study included in review	Primary report for trial registration NCT01546922 Further outcomes reported in: Buning (2016) Effects of hydrocortisone on the regulation of blood pressure: results from a randomized controlled trial Buning (2016) Hydrocortisone dose influences pain, depressive symptoms and perceived health and adrenal insufficiency: a randomized controlled trial
Trial name / registration number	NCT01546922
Study type	Randomised controlled trial (RCT) "Randomized double-blind cross-over study" "Patients were randomly assigned to either group 1 or group 2 by the research pharmacy with a block size of 4."
Study location	Netherlands
Study setting	"Patients were recruited for participation at the endocrine outpatient clinic of the University Medical Center Groningen (UMCG), a tertiary referral center for pituitary surgery in the Netherlands."
Study dates	"All patients were tested in the period between May 2012 and June 2013."
Sources of funding	"This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector."
Inclusion criteria	All patients had SAI for which they received GC substitution therapy.

	To avoid effects of switching to a different type of GCs, all patients on CA were converted to treatment with HC in a bioequivalent dose (i.e., CA dose (in mg) times 0.8 when compared to HC dose (mg)) during a four-week run-in phase. The diagnosis of SAI was based on internationally accepted biochemical criteria, principally early morning (0800—0900 h) serum cortisol measurements and, if necessary, an insulin tolerance test. Early morning cut-off cortisol levels for adrenal insufficiency in our center were validated for patients with hypothalamic—pituitary disorders as previously published (Dullaart et al., 1999). Thyroid hormone deficiency was based on a low serum free thyroxine concentration (<11.0 pmol/l). Growth hormone (GH) deficiency was based on a low insulin-like growth factor 1 (IGF-1) Z-score (less than 2 SD) and/or an insufficient peak GH concentration (<10 mU/l) in response to insulin-induced hypoglycaemia or a peak growth hormone <18 mU/l during an arginine-GHRH test. Insufficiency of the pituitary—gonadal axis was defined in men as a testosterone concentration below 10 nmol/l, in premenopausal women (aged < 50 years) as loss of menses and in postmenopausal women (aged > 50 years) as LH and FSH concentrations below 15 mU/l. Diabetes insipidus was defined as the incapacity to properly concentrate urine (increased urine volume with low urine osmolality) in the face of a high plasma osmolality (and sodium) and/or current treatment with desmopressin. Biochemical control of adequacy of hormonal substitution treatment was judged by the physicians that were responsible for the care of the participating patients using free thyroxine, IGF-1 and testosterone levels where necessary. Other inclusion criteria were age 18—75 years, body weight of 50—100 kg at screening, time interval of at least one year between study entry and tumor treatment with surgery and/or radiotherapy, and adequate replacement of all other pituitary hormone deficiencies for at least six months prior to entry of the study.
Exclusion criteria	Main exclusion criteria were inability of legal consent, documented major cognitive impairment (MMSE < 24) (Lezak et al., 2004), drug abuse or dependence, current psychiatric disorders, treatment for a malignancy, shift work, previous Cushing's disease, hospital admission during the study, diabetes mellitus with medication known to be able to induce hypoglycemia (e.g., sulfonylurea derivatives and insulin) and a history of frequent episodes of clinical hypocortisolism. The concomitant use of other corticosteroids and drugs known to interfere with HC metabolism, e.g., anti-epileptics, was not allowed either.
Recruitment / selection of participants	In this randomized double-blind cross-over study, patients were recruited for participation at the endocrine outpatient clinic of the University Medical Center Groningen (UMCG), a tertiary referral center for pituitary surgery in the Netherlands. A total of 63 patients were included in this study, of whom 60 patients completed the run-in phase and the baseline measurement (mean (SD) age, 52 (13), range 19—73, 35 males, 25 females).
Intervention(s)	Group 1 first received a physiological low dose of HC for 10 weeks, followed by a physiological high dose for another 10 weeks. Group 2 first received a physiological high dose for 10 weeks, followed by a physiological low dose. Patients were treated with oral tablets containing either 5 mg HC (low dose) or 10 mg HC (high dose). Only the research pharmacy knew which dose was administered in each period. In the low dose condition, patients received a cumulative daily dose of 0.2-0.3 mg HC per kg body weight in three divided doses (before breakfast, before lunch, before diner). In the high dose condition, patients received the double amount, 0.4-0.6 mg HC per kg body weight. In cases of intercurrent illness or fever, patients were allowed to double or triple their HC dose. Because the study aimed to investigate two different dosing schemes, increasing the dose of HC was allowed for a maximum of 7 days (i.e., 10% of the study time and of the cumulative HC dose) but not in the week preceding the second

	and the third visit. Compliance with the study medication was assessed in several ways. Firstly, by patient reports in daily diaries: patients were instructed to daily report if they had forgotten and/or doubled their medication and if so, how many doses they had forgotten or doubled. Secondly, the tablets returned by the patients after each study period were counted. Lastly, cortisol concentrations in plasma between the two study periods were compared.
Population subgroups	None reported
Comparator	See intervention - High v Low dose HC
Number of participants	47 included in analyses. (63 randomised - 60 completed run-in phase - 60 started first 10-week treatment period, 53 completed - 53 started second 10-week treatment period, 47 completed)
Duration of follow-up	20 weeks overall - 10 weeks per treatment
Indirectness	NA
Additional comments	Because of the absence of relevant data from literature, we performed a power analysis. A study with 2 arms, each with 25 patients (total number of patients of 50) is able to detect an effect size of 0.4 (two-sided alpha = 0.05 and beta = 0.80) in test results even when between test correlations are poor (0.50). An effect size of 0.4 was chosen because it was considered a relevant change with a small to medium size effect. To allow for a drop-out rate of ±20% a total number of ±60 patients were needed. Cognitive performance data were presented as mean Z-score (SD). Higher Z-scores represent better cognitive performance compared to healthy subject of the same age, sex and educational level. Normality of data was analyzed using Q—Q plots. Since not all data were normally distributed, non-parametric tests for paired samples were used. To compare the cognitive performances at baseline of group 1 and group 2, the Mann—Whitney U-test was used. The cognitive performance which was obtained while on a low dose of HC was compared to the performance on cognitive tests while on a high dose of HC by using the Wilcoxon Signed Rank Test. In addition, Cohen's d effect sizes were calculated to give a measure of the magnitude of the difference. An effect size of d = 0.2 is considered a small effect, d = 0.5 a moderate effect and d = 0.8 a large effect.

Study arms

Low dose (0.2-0.3mg/kg body weight) hydrocortisone for 10 weeks (N = 47)

High dose (0.4-0.6mg/kg body weight) hydrocortisone for 10 weeks (N = 47)

Characteristics

Study-level characteristics

Characteristic	Study (N = 47)
% Female Sample size	n = 18; % = 38.3
Mean age (SD) Median (IQR)	55 (43 to 61)

Characteristic	Study (N = 47)
BMI (kg/m²) Median (IQR)	26.6 (24.5 to 29.4)

Outcomes

Study timepoints

10 week

Comparison of impaired scores between the low dose and high dose hydrocortisone

Outcome	Low dose (0.2-0.3mg/kg body weight) hydrocortisone for 10 weeks, 10-week, N = 47	High dose (0.4-0.6mg/kg body weight) hydrocortisone for 10 weeks, 10-week, N = 47
Immediate memory No of events	n = 13; % = 27.7	n = 15; % = 31.9
Short-term memory No of events	n = 3; % = 6.4	n = 4; % = 8.5
Delayed memory No of events	n = 8; % = 17	n = 8; % = 17
Recognition No of events	n = 6; % = 12.8	n = 3; % = 6.4
Divided attention errors No of events	n = 6; % = 12.8	n = 7; % = 14.9
Visual scanning errors No of events	n = 5; % = 10.6	n = 5; % = 10.6
Fluency No of events	n = 10; % = 21.3	n = 10; % = 21.3
Working memory No of events	n = 3; % = 6.4	n = 4; % = 8.5
Cognitive flexibility No of events	n = 6; % = 12.8	n = 6; % = 12.8
Social cognition (Number of patients showing impaired score) No of events	n = 18; % = 38.3	n = 11; % = 23.4

Outcome	Low dose (0.2-0.3mg/kg body weight) hydrocortisone for 10 weeks, 10-week, N = 47	High dose (0.4-0.6mg/kg body weight) hydrocortisone for 10 weeks, 10-week, N = 47
Psychomotor speed (Number of patients showing impaired score) No of events	n = 17; % = 36.2	n = 24; % = 51.1

Data also available for all tests as mean Z scores in Table 4 of article.

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial.

Memory test

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable

Attention scores.

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable

Executive function

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Indirectly applicable

Werumeus Buning, 2016

Bibliographic Reference	Werumeus Buning, J.; van Faassen, M.; Brummelman, P.; Dullaart, R. P.; van den Berg, G.; van der Klauw, M. M.; Kerstens, M. N.; Stegeman, C. A.; Muller Kobold, A. C.; Kema, I. P.; Wolffenbuttel, B. H.; van Beek, A. P.; Effects of Hydrocortisone on the Regulation of Blood Pressure: Results From a Randomized Controlled Trial; Journal of Clinical Endocrinology & Metabolism; 2016; vol. 101 (no. 10); 3691-3699

Study details

Secondary publication of another included study- see	Primary report: Buning (2015) The effects of two different doses of hydrocortisone on cognition in patients with secondary adrenal insufficiency - results from a randomized controlled trial.

primary study for details	
Other publications associated with this study included in review	Further outcomes: Buning (2016) Hydrocortisone dose influences pain, depressive symptoms and perceived health in adrenal insufficiency: a randomized controlled trial Also: Sorgdrager (2018) Hydrocortisone affects fatigue and physical functioning through metabolism of tryptophan: a randomized controlled trial
Trial name / registration number	NCT01546922
Study type	Randomised controlled trial (RCT)
Study location	See Buning (2015)
Study setting	See Buning (2015)
Study dates	See Buning (2015)
Sources of funding	See Buning (2015)
Inclusion criteria	See Buning (2015)
Exclusion criteria	See Buning (2015)
Recruitment / selection of participants	See Buning (2015)
Intervention(s)	See Buning (2015)
Population subgroups	See Buning (2015)
Comparator	See Buning (2015)
Number of participants	47
Duration of follow-up	20 weeks total - 10 weeks per treatment crossover
Additional comments	Normally distributed data were presented as mean (SD), non-normally distributed data were presented as median [interquartile range], and categorical data were presented as number or percentage. Normality of data was analysed by visual inspection of Q-Q plots and histograms. To test for period and carryover effects, the procedure developed by Altman was used (32). In this procedure, to test for a carryover effect, the average response to both treatments (i.e., of the low dose and high dose combined) was compared between the two treatment groups. If these average responses were not different between the treatment groups, the effect of the treatment was considered the same irrespective of the order in which the treatments were administered (32). All variables were compared using the Wilcoxon signed rank test for paired observations. Statistical significance was set at $P < 0.05$.

Study arms

Low dose (0.2-0.3mg/kg body weight) hydrocortisone for 10 weeks (N = 47)

High dose (0.4-0.6mg/kg body weight) hydrocortisone for 10 weeks (N = 47)

Outcomes

Study timepoints

10 weeks

Anthropometric measures and biochemical and hormonal analysis

Outcome	Low dose (0.2-0.3mg/kg body weight) hydrocortisone for 10 weeks, 10-week, N = 47	High dose (0.4-0.6mg/kg body weight) hydrocortisone for 10 weeks, 10-week, N = 47
Systolic blood pressure (mmHg) Mean (SD)	133 (14)	138 (16)
Diastolic blood pressure (mmHg) Mean (SD)	76 (10)	78 (9)
Weight (kg) Standardised Mean (SD)	82.8 (14)	83.3 (14.3)
BMI (kg/m2) Mean (SD)	26.9 (4)	27.1 (4)
Plasma sodium (mmol/L) Median (IQR)	142 (141 to 143)	142 (141 to 143)
Plasma potassium (mmol/L) Median (IQR)	3.9 (3.7 to 4)	3.8 (3.6 to 4)
Plasma creatinine (micromol/L) Median (IQR)	82 (66 to 88)	80 (68 to 89)
Serum corticosteroid binding globulin (CBG) (microg/ml) Median (IQR)	53.2 (49.1 to 63)	56.5 (49 to 62.5)
Plasma renin concentration (pg/mL) Median (IQR)	11.6 (6.7 to 17.3)	8.6 (5.9 to 14.9)

Outcome	Low dose (0.2-0.3mg/kg body weight) hydrocortisone for 10 weeks, 10-week, N = 47	High dose (0.4-0.6mg/kg body weight) hydrocortisone for 10 weeks, 10-week, N = 47
Serum aldosterone (pmol/L) Median (IQR)	150 (77 to 256)	107 (43 to 235)
Aldosterone to renin ratio (pmol/ng) Median (IQR)	13.8 (7.3 to 21.3)	11 (6.1 to 19.8)
Transtubular potassium gradient Median (IQR)	7.42 (6.12 to 9.48)	7.47 (6 to 9.18)
Plasma copeptin (pmol/L) Median (IQR)	3.7 (2.5 to 5)	3.4 (2.5 to 4.9)
Urine sodium (mmol/24hour) Median (IQR)	142 (119 to 206)	161 (112 to 200)
Urine potassium (mmol/24hour) Median (IQR)	77 (64 to 96)	83 (69 to 103)
Creatinine clearance calculated (ml/min) Mean (SD)	117 (37)	117 (29)

Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) Cross-over trial

Blood pressure

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to missing outcome data)*
Overall bias and Directness	Overall Directness	Directly applicable

BMI

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to missing outcome data)*
Overall bias and Directness	Overall Directness	Directly applicable

Plasma sodium

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to missing outcome data)*
Overall bias and Directness	Overall Directness	Directly applicable

Appendix E Forest plots

E.1.1.1 Comparison 1: 5mg HC 2x daily vs 10 mg HC 2x daily

Figure 2: Peak Cortisol (nmol/L) (lower is better)

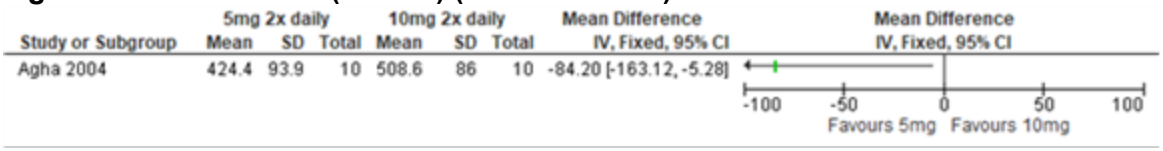


Figure 3: Trough Cortisol (nmol/L) (lower is better)

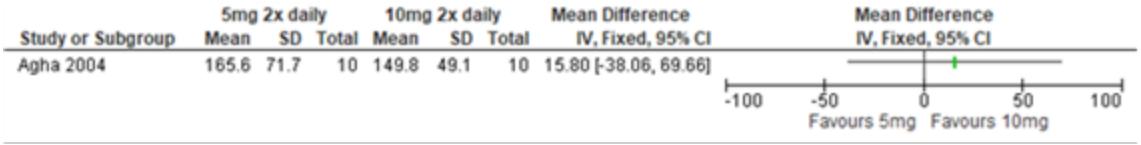


Figure 4: Systolic BP (mmHg) (lower is better)

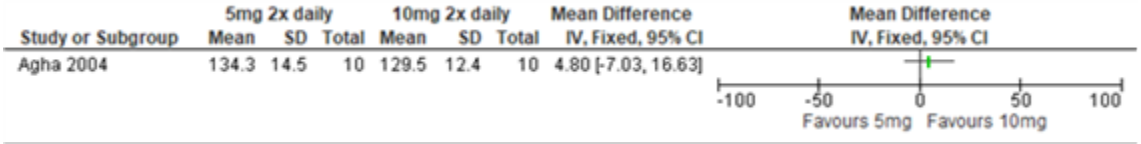


Figure 5: Diastolic BP (mmHg) (lower is better)

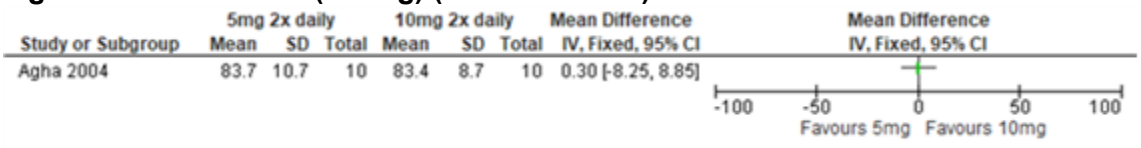
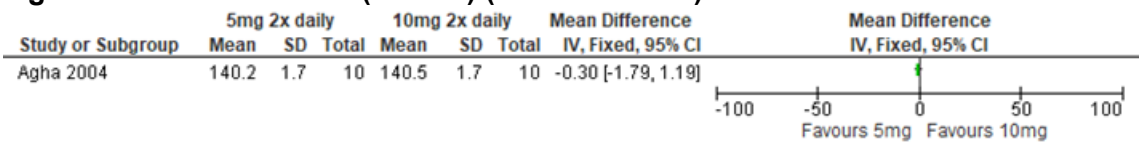


Figure 6: Plasma Sodium (nmol/L) (lower is better)



E.1.1.2 Comparison 2: Dose A [20mg/10mg] vs Dose B [10mg/10mg] vs Dose C [10mg/5mg] – SF-36 Outcomes

Figure 7: SF-36 – Physical Functioning (higher is better)
A: 20mg HC 0800h, 10mg HC 1600h
B: 10mg HC 0800h, 10mg HC 1600 h
C: 10mg HC 0800h, 5mg HC 1600 h

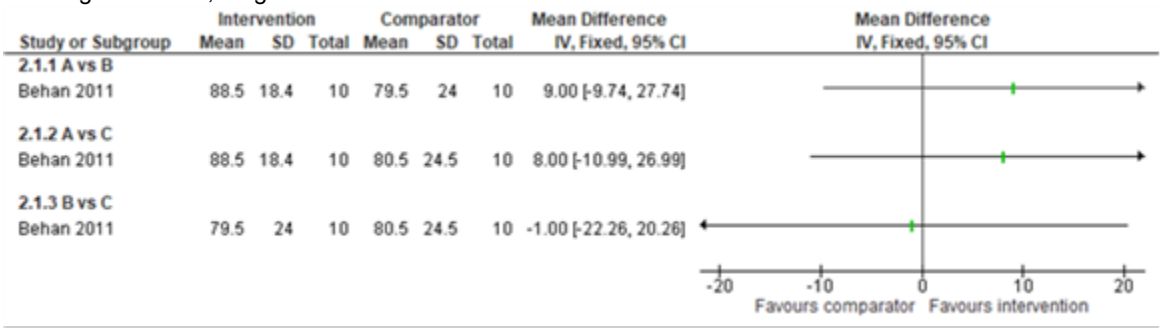


Figure 8: SF-36 – Role Physical (higher is better)
A: 20mg HC 0800h, 10mg HC 1600h
B: 10mg HC 0800h, 10mg HC 1600 h
C: 10mg HC 0800h, 5mg HC 1600 h

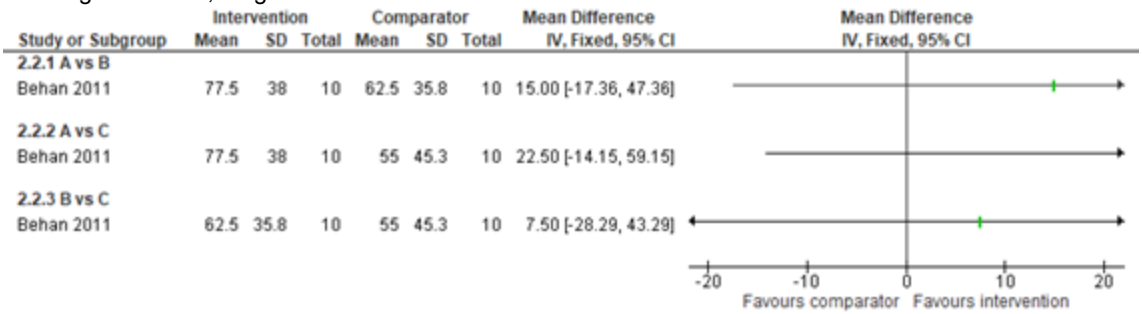


Figure 9: SF-36 – Bodily Pain (higher is better)
A: 20mg HC 0800h, 10mg HC 1600h
B: 10mg HC 0800h, 10mg HC 1600 h
C: 10mg HC 0800h, 5mg HC 1600 h

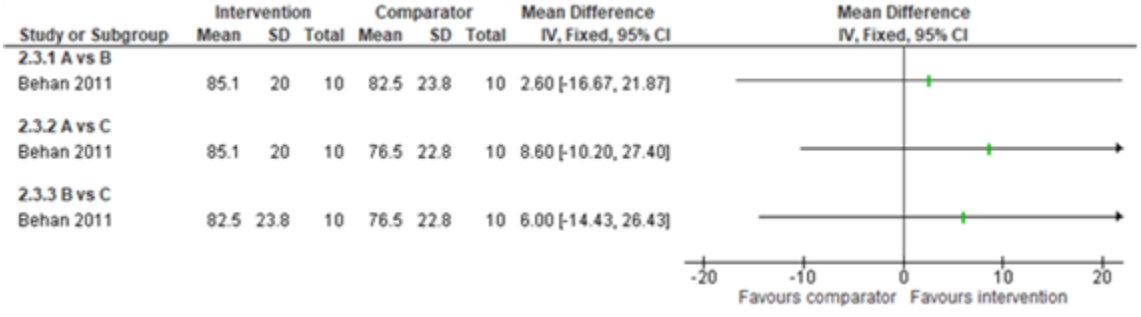


Figure 10: SF-36 – General Health (higher is better)
A: 20mg HC 0800h, 10mg HC 1600h
B: 10mg HC 0800h, 10mg HC 1600 h
C: 10mg HC 0800h, 5mg HC 1600 h

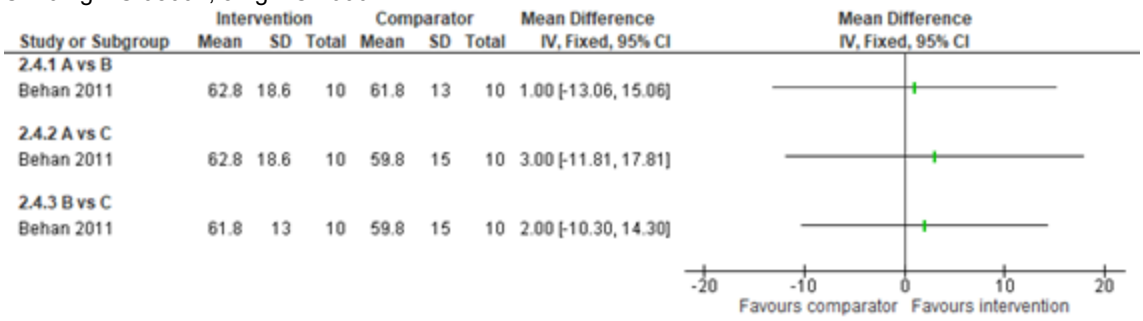


Figure 11: SF-36 – Vitality (higher is better)
A: 20mg HC 0800h, 10mg HC 1600h
B: 10mg HC 0800h, 10mg HC 1600 h
C: 10mg HC 0800h, 5mg HC 1600 h

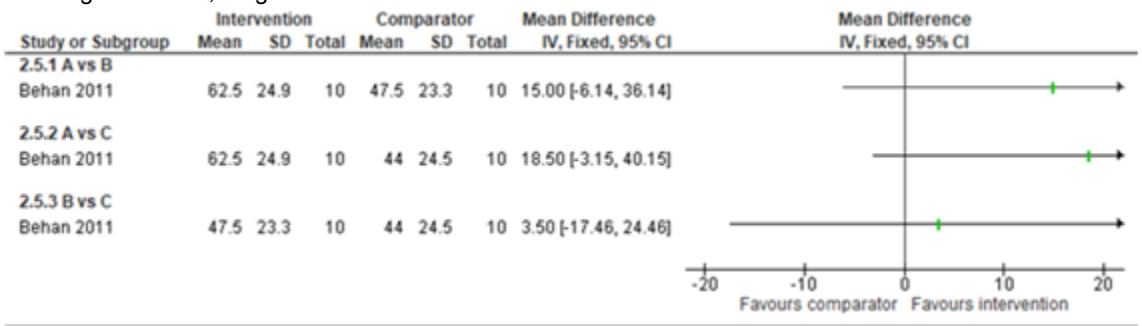


Figure 12: SF-36 – Social functioning (higher is better)
A: 20mg HC 0800h, 10mg HC 1600h
B: 10mg HC 0800h, 10mg HC 1600 h
C: 10mg HC 0800h, 5mg HC 1600 h

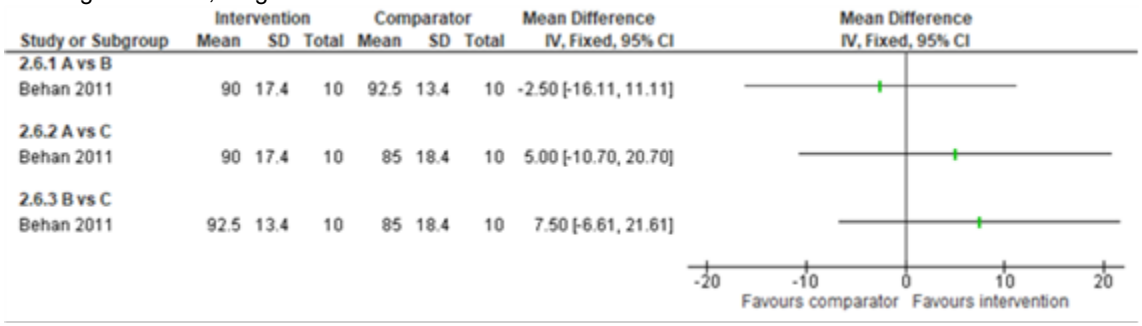


Figure 13: SF-36 – Role emotional (higher is better)
A: 20mg HC 0800h, 10mg HC 1600h
B: 10mg HC 0800h, 10mg HC 1600 h
C: 10mg HC 0800h, 5mg HC 1600 h

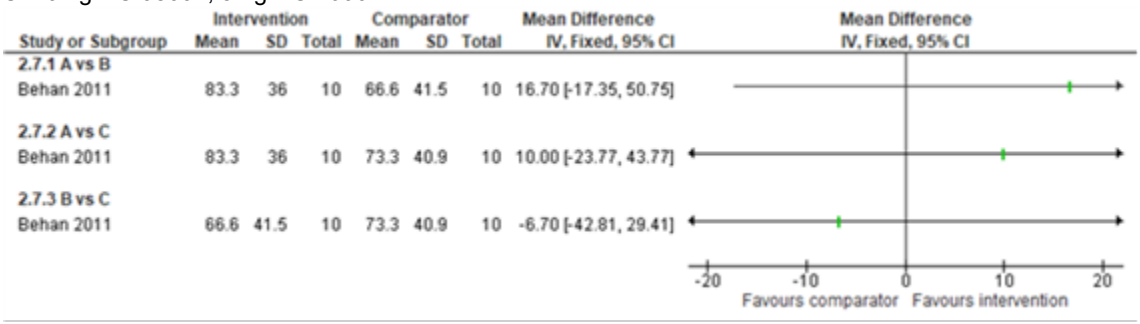
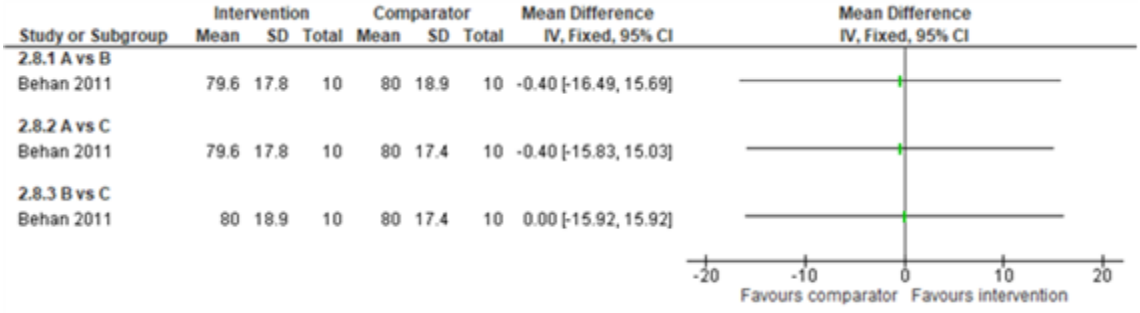


Figure 14: SF-36 – Mental health (higher is better)
A: 20mg HC 0800h, 10mg HC 1600h
B: 10mg HC 0800h, 10mg HC 1600 h
C: 10mg HC 0800h, 5mg HC 1600 h



E.1.1.3 Comparison 3: Dose A [20mg/10mg] vs Dose B [10mg/10mg] vs Dose C [10mg/5mg] – Nottingham health profile (NHP) Outcomes

Figure 15: NHP – Energy Levels (lower is better)
A: 20mg HC 0800h, 10mg HC 1600h
B: 10mg HC 0800h, 10mg HC 1600 h
C: 10mg HC 0800h, 5mg HC 1600 h

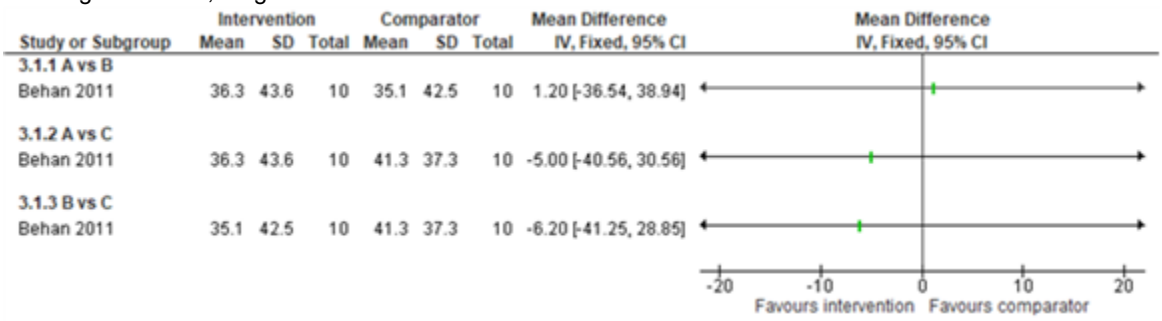


Figure 16: NHP – Pain (lower is better)
A: 20mg HC 0800h, 10mg HC 1600h
B: 10mg HC 0800h, 10mg HC 1600 h
C: 10mg HC 0800h, 5mg HC 1600 h

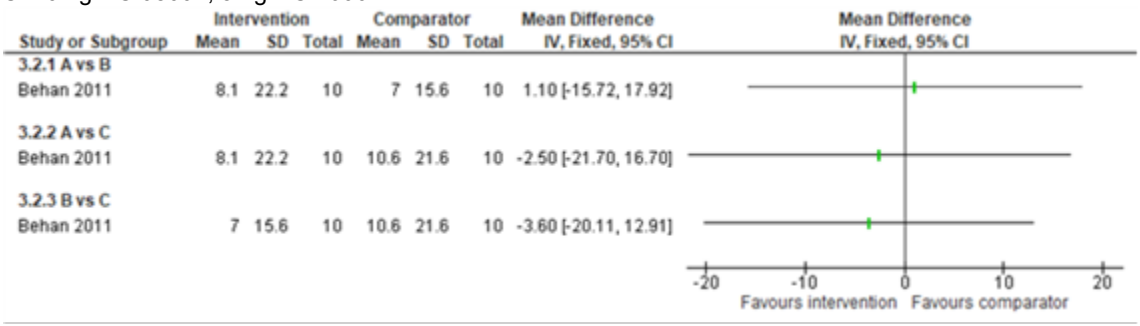


Figure 17: NHP – Emotional reaction (lower is better)

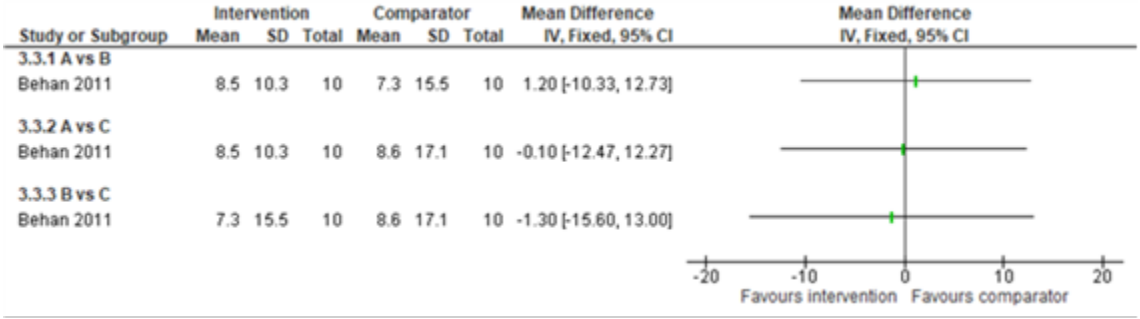


Figure 18: NHP – Sleep (lower is better)
A: 20mg HC 0800h, 10mg HC 1600h
B: 10mg HC 0800h, 10mg HC 1600 h
C: 10mg HC 0800h, 5mg HC 1600 h

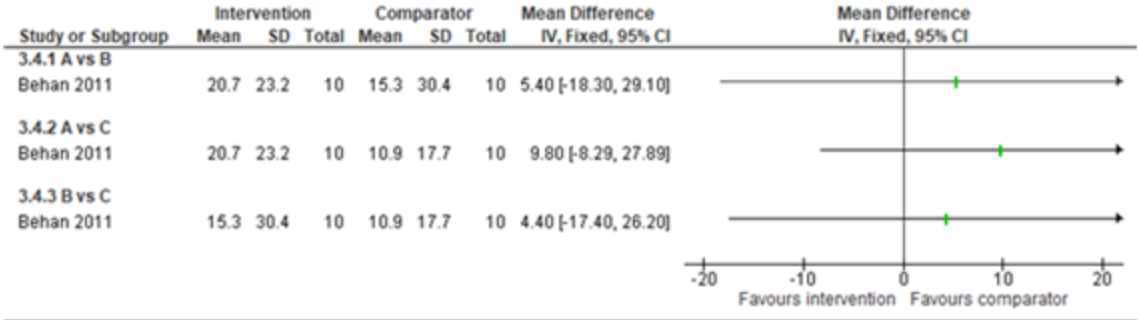


Figure 19: NHP – Social isolation (lower is better)

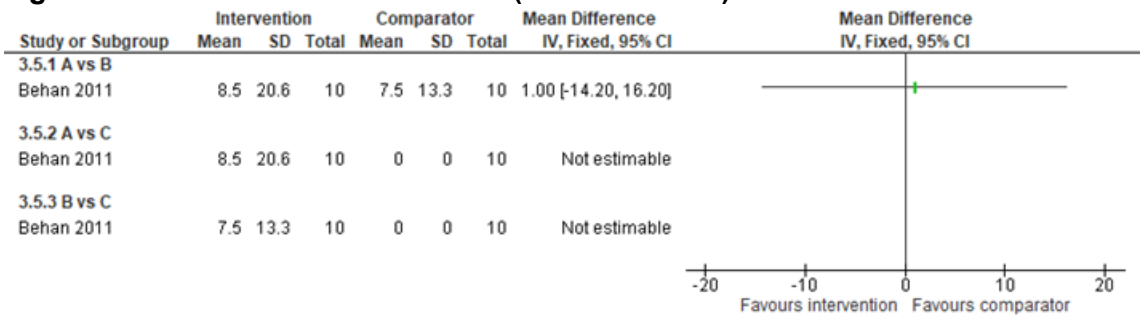
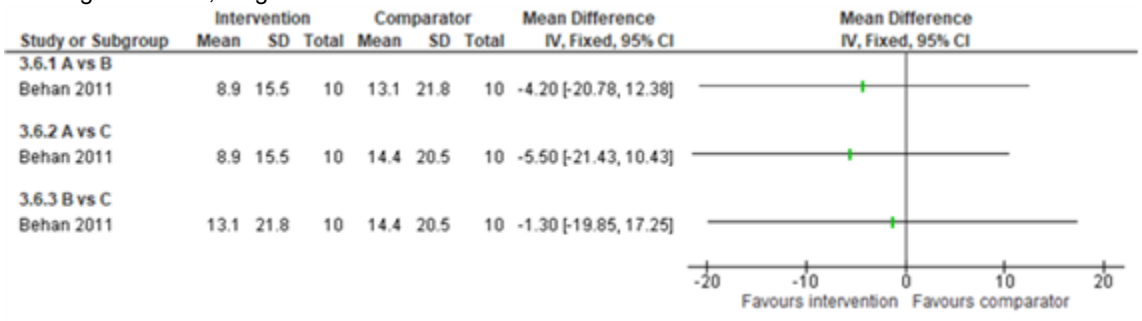


Figure 20: NHP – Physical abilities (lower is better)

A: 20mg HC 0800h, 10mg HC 1600h
B: 10mg HC 0800h, 10mg HC 1600 h
C: 10mg HC 0800h, 5mg HC 1600 h



E.1.1.4 Comparison 4: Dose A [20mg/10mg] vs Dose B [10mg/10mg] vs Dose C [10mg/5mg] – Blood Pressure Outcomes

Figure 21: Nottingham Health Profile (NHP) – 24hr Ambulatory Systolic BP (lower is better)

A: 20mg HC 0800h, 10mg HC 1600h
B: 10mg HC 0800h, 10mg HC 1600 h
C: 10mg HC 0800h, 5mg HC 1600 h

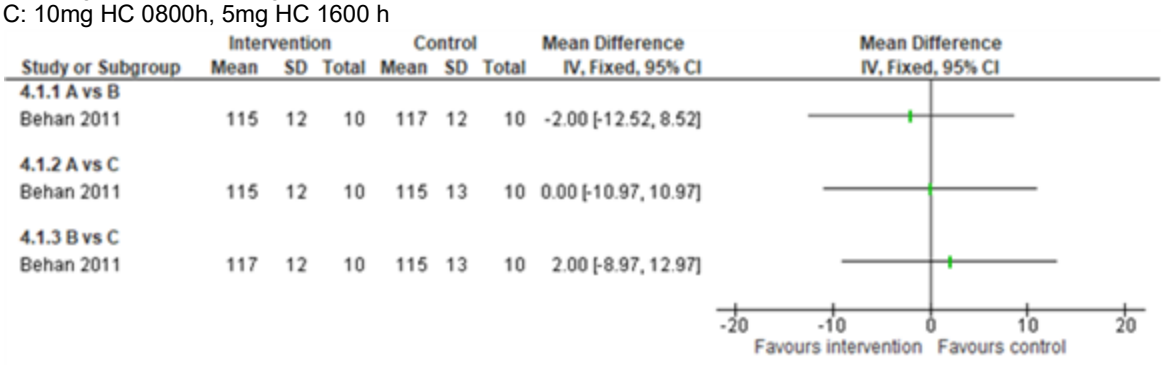
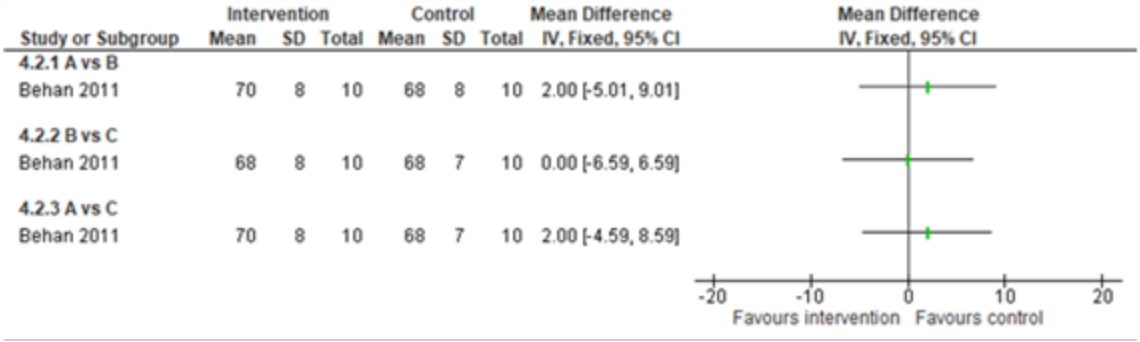


Figure 22: Nottingham Health Profile (NHP) – 24hr Ambulatory Diastolic BP (lower is better)

A: 20mg HC 0800h, 10mg HC 1600h
B: 10mg HC 0800h, 10mg HC 1600 h
C: 10mg HC 0800h, 5mg HC 1600 h



E.1.1.5 Comparison 5: Dose A [10mg/5mg HC] vs Dose B [10mg/5mg/5mg HC]

Figure 23: SF-36 – Physical sum scale (higher is better)

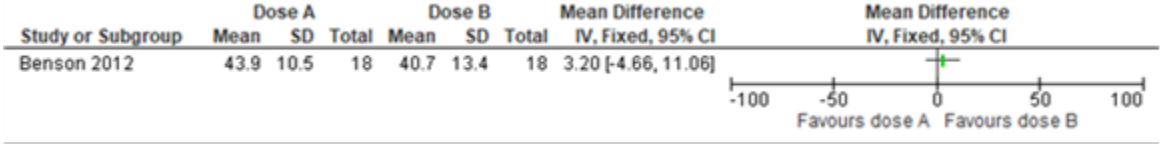


Figure 24: SF-36 – Psychological sum scale (higher is better)

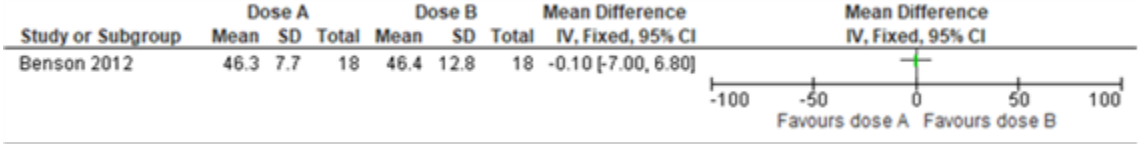


Figure 25: BSI Global Severity Index (lower is better)

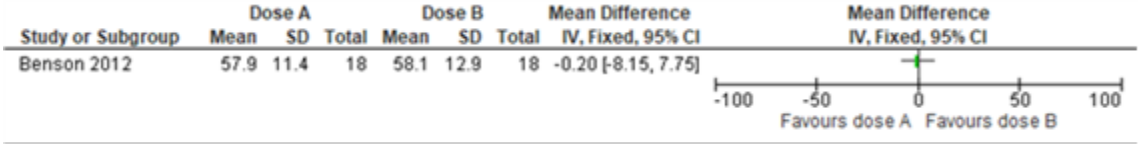


Figure 26: Sleepiness score 0700 (lower is better)

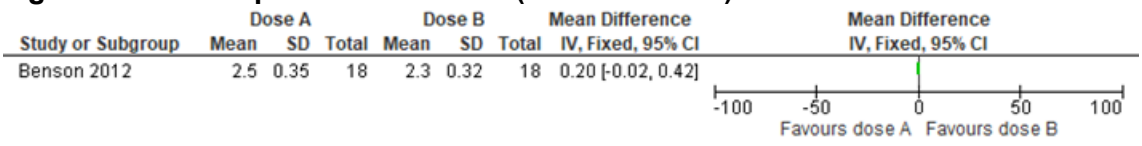


Figure 27: Sleepiness score 1200 (lower is better)

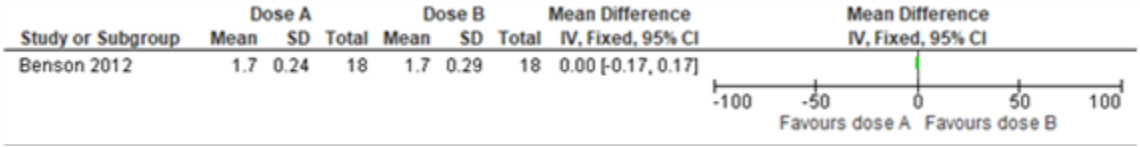


Figure 28: Sleepiness score 1500 (lower is better)

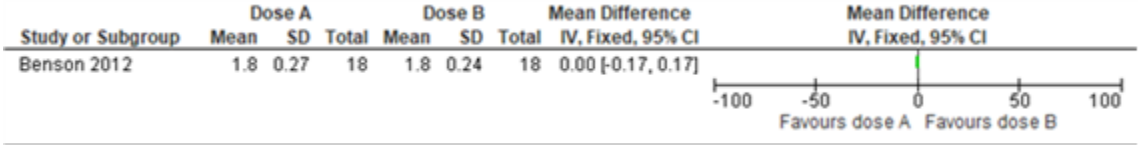


Figure 29: Sleepiness score 1800 (lower is better)

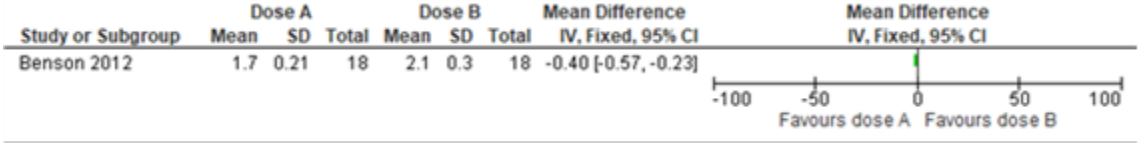


Figure 30: Sleepiness score 2200 (lower is better)

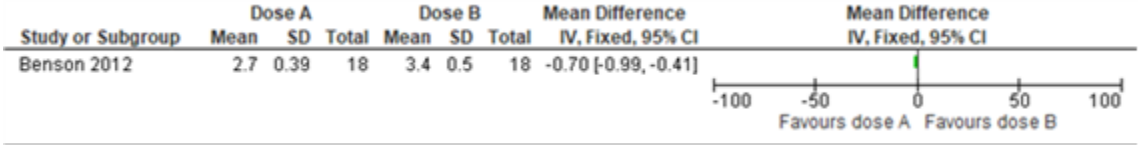
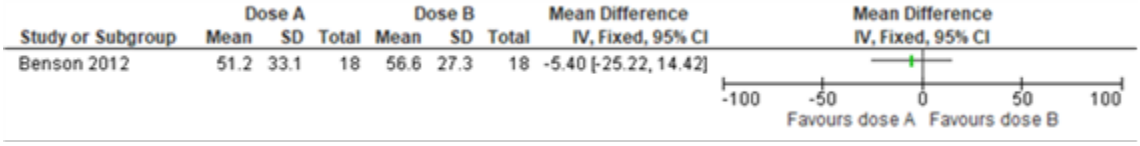


Figure 31: Satisfaction with medication (lower is better)



E.1.1.6 Comparison 6: Low dose HC [0.2-0.3 mg/kg] vs High dose HC [0.4-0.6 mg/kg]

Figure 32: Systolic BP (lower is better)

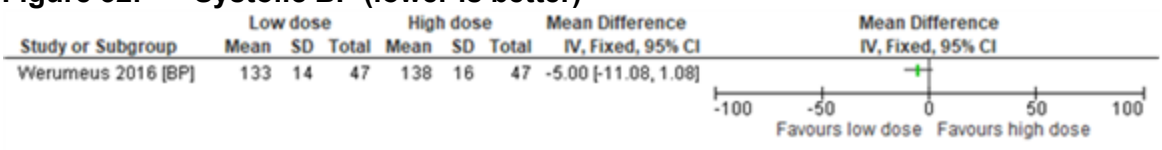


Figure 33: Diastolic BP (lower is better)

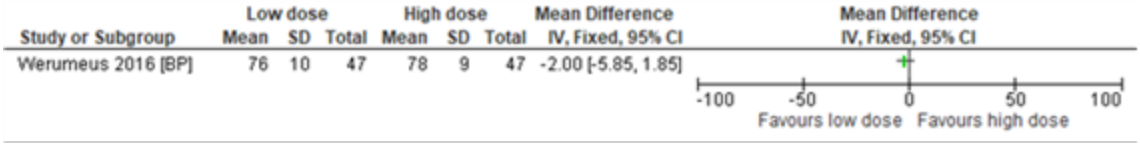


Figure 34: BMI (lower is better)

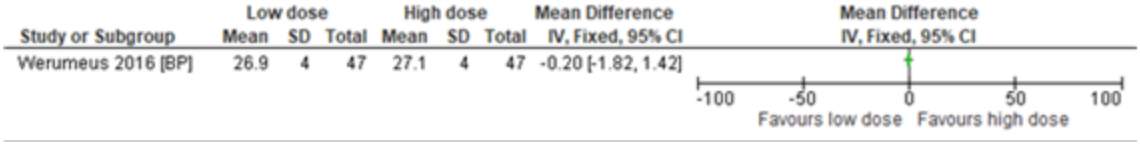


Figure 35: Number of patients with impaired memory: immediate memory (lower is better)

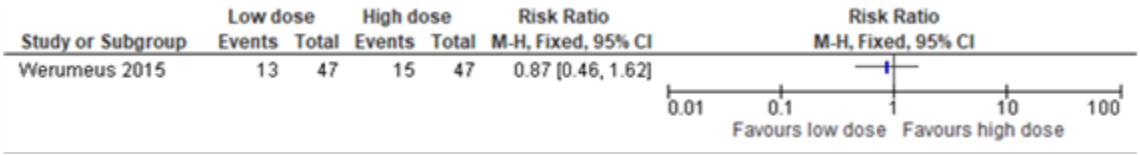


Figure 36: Number of patients with impaired memory: short-term memory (lower is better)

Figure 37: Number of patients with impaired memory: delayed memory (lower is better)

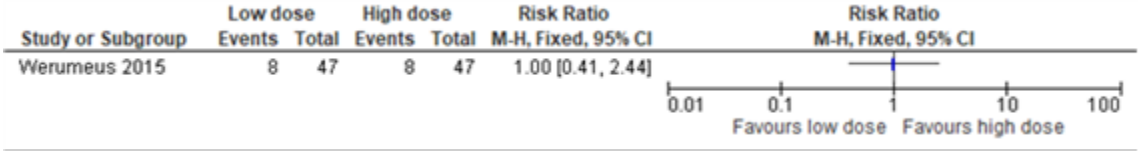


Figure 38: Number of patients with impaired memory: recognition (lower is better)

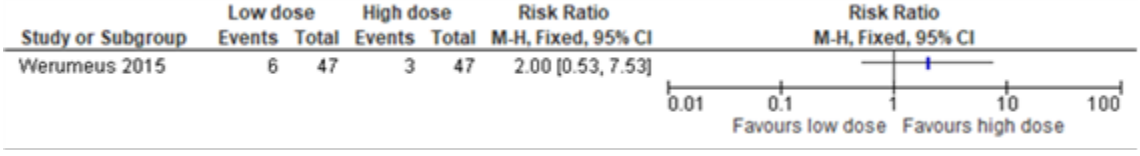


Figure 39: Number of patients with impaired attention: divided attention errors (lower is better)

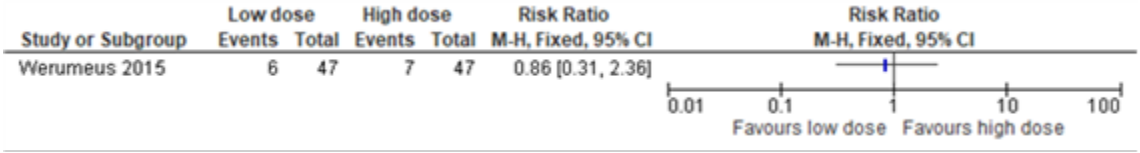


Figure 40: Number of patients with impaired attention: visual scanning errors (lower is better)

Figure 41: Number of patients with impaired executive function: fluency (lower is better)

Figure 42: Number of patients with impaired executive function: working memory (lower is better)

Figure 43: Number of patients with impaired executive function: cognitive flexibility (lower is better)

Figure 44: Number of patients with impaired social cognition (lower is better)

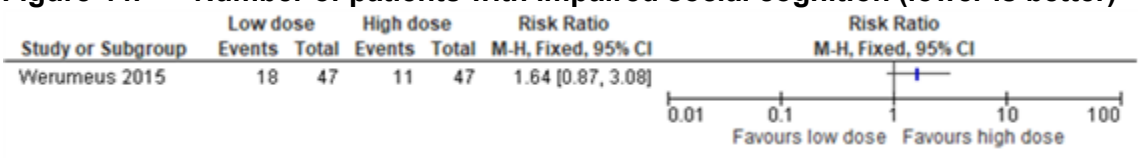


Figure 45: Number of patients with impaired psychomotor speed (lower is better)

E.1.1.7 Modified-Release HC tablet vs Standard Glucocorticoid [Isidori 2018]

Figure 46: Change in BMI from baseline (kg/m2) (lower is better)

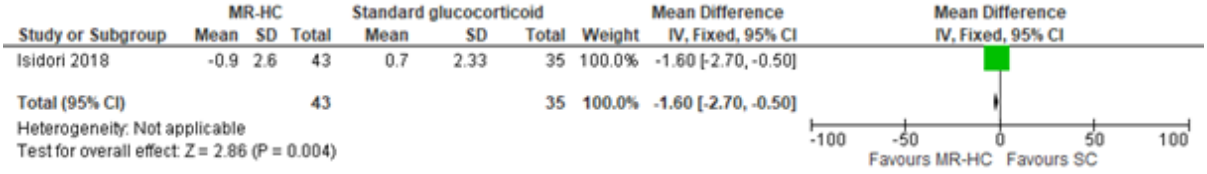


Figure 47: Change in bodyweight from baseline (kg) (lower is better)

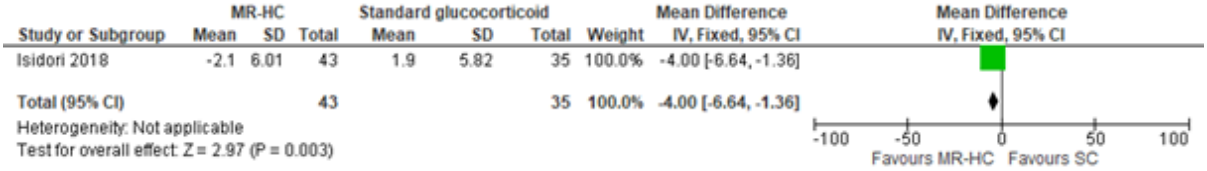


Figure 48: Change in HbA1c (%) from baseline (lower is better)

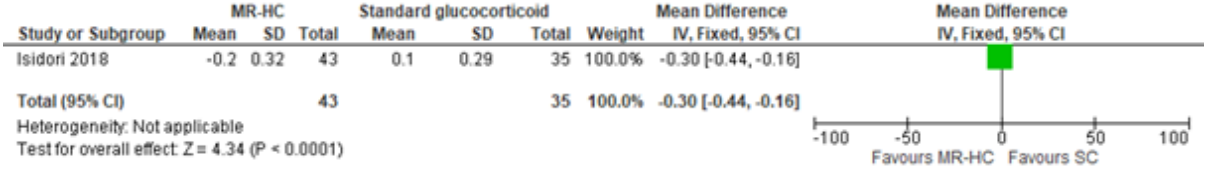


Figure 49: AddiQoL (higher is better)

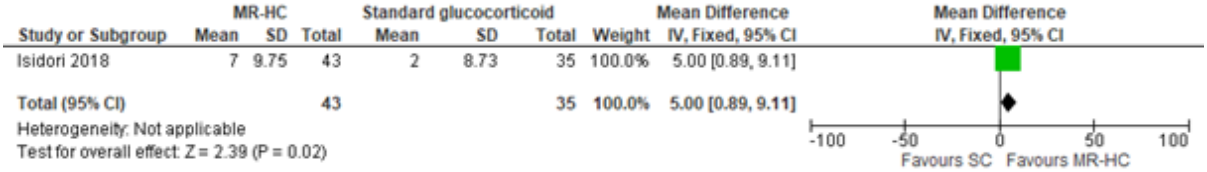


Figure 50: Flu or flu-like events in 6 months (lower is better)

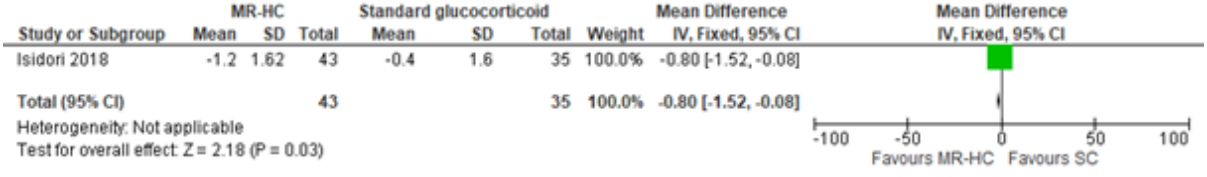


Figure 51: Change in total cholesterol (mg/dL) from baseline (lower is better)

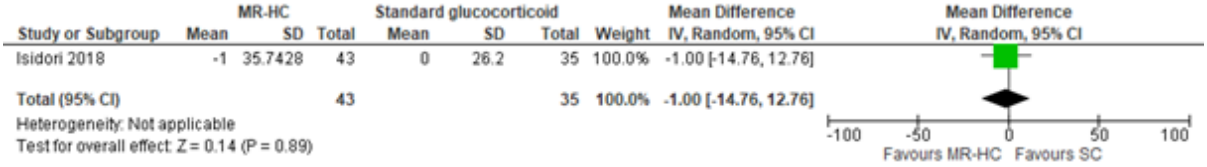
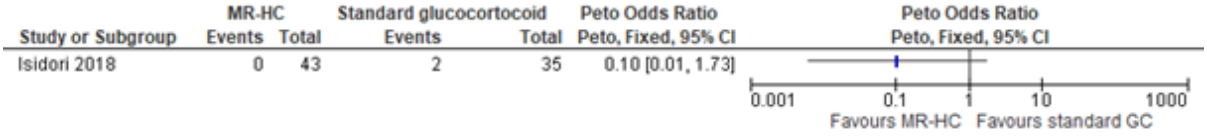


Figure 52: Serious adverse events (lower is better)



Appendix F GRADE tables

Table 16: Clinical evidence profile: 5mg HC 2x daily vs 10 mg HC 2x daily

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With 10mg HC 2x daily	With 5mg HC 2x daily		Risk with 10mg HC 2x daily	Risk difference with 5mg HC 2x daily
Peak cortisol (nmol/L) (follow-up: 1 weeks)											
10 (1 RCT)	Very serious[a]	not serious	serious[b]	serious[c]	none	⨁◯◯◯ Very low	10	10	-	The mean peak cortisol (nmol/L) was **508.6** nmol/L	MD **84.2 nmol/L lower** (163.12 lower to 5.28 lower)
Trough cortisol (nmol/L) (follow-up: 1 weeks)											
10 (1 RCT)	Very serious[a]	not serious	serious[b]	very serious[d]	none	⨁◯◯◯ Very low	10	10	-	The mean trough cortisol (nmol/L) was **149.8** nmol/L	MD **15.8 nmol/L higher** (38.06 lower to 69.66 higher)
Systolic BP (mmHg) (follow-up: 1 weeks)											

Certainty assessment							Summary of findings				
10 (1 RCT)	Very serious[a]	not serious	serious[b]	Very serious[e]	none	⊕◯◯◯ Very low	10	10	-	The mean systolic BP (mmHg) was **129.5** mmHg	MD **4.8 mmHg higher** (7.03 lower to 16.63 higher)
Diastolic BP (mmHg) (follow-up: 1 weeks)											
10 (1 RCT)	Very serious[a]	not serious	serious[b]	Very serious[f]	none	⊕◯◯◯ Very low	10	10	-	The mean diastolic BP (mmHg) was **83.4** mmHg	MD **0.3 mmHg higher** (8.25 lower to 8.85 higher)
Plasma sodium (nmol/L) (follow-up: 1 weeks)											
10 (1 RCT)	Very serious[a]	not serious	serious[b]	Very serious[g]	none	⊕◯◯◯ Very low	10	10	-	The mean plasma sodium (nmol/L) was **140.5** mmol/L	MD **0.3 mmol/L lower** (1.79 lower to 1.19 higher)

Explanations

a. Downgraded by 2 increment due to very high risk of bias arising from the randomisation process
b. Downgraded by 1 increment as population includes males only [Female subjects were excluded because of the potential effect of oestrogen status on corticosteroid-binding globulin (CBG) levels]
c. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 43)
d. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 24.55)
e. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 6.2)
f. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 4.35)
g. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 0.85)

Table 17: Clinical evidence profile: Dose A (20 mg 0800 h, 10 mg 1600 h) vs Dose B (10 mg 0800 h and 1600 h) vs Dose C (10 mg 0800 h and 5 mg 1600 h) for secondary and tertiary adrenal insufficiency [SF-36 Outcomes]

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With comparator	With intervention		Risk with comparator	Risk difference with intervention
SF36 - Physical functioning - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[c]	none	⨁◯◯◯ Very low	10	10	-	The mean SF36 - Physical functioning - A vs B was **79.5** points	MD **9 points higher** (9.74 lower to 27.74 higher)
SF36 - Physical functioning - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[c]	none	⨁◯◯◯ Very low	10	10	-	The mean SF36 - Physical functioning - A vs C was **80.5** points	MD **8 points higher** (10.99 lower to 26.99 higher)
SF36 - Physical functioning - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[c]	none	⨁◯◯◯ Very low	10	10	-	The mean SF36 - Physical functioning - B vs C was **80.5** points	MD **1 points lower** (22.26 lower to 20.26 higher)
SF36 - Role Physical - A vs B (follow-up: 6 weeks)											

Certainty assessment							Summary of findings				
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[c]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Role Physical - A vs B was **62.5** points	MD **15 points higher** (17.36 lower to 47.36 higher)
SF36 - Role Physical - A vs C (follow-up: 6 weeks)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[c]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Role Physical - A vs C was **55** points	MD **22.5 points higher** (14.15 lower to 59.15 higher)
SF36 - Role Physical - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[c]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Role Physical - B vs C was **55** points	MD **7.5 points higher** (28.29 lower to 43.29 higher)
SF36 - Bodily pain - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[c]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Bodily pain - A vs B was **82.5** points	MD **2.6 points higher** (16.67 lower to 21.87 higher)
SF36 - Bodily pain - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)											

Certainty assessment							Summary of findings				
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[c]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Bodily pain - A vs C was **76.5** points	MD **8.6 points higher** (10.2 lower to 27.4 higher)
SF36 - Bodily pain - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[c]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Bodily pain - B vs C was **76.5** points	MD **6 points higher** (14.43 lower to 26.43 higher)
SF36 - General health - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[d]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - General health - A vs B was **61.8** points	MD **1 points higher** (13.06 lower to 15.06 higher)
SF36 - General health - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[d]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - General health - A vs C was **59.8** points	MD **3 points higher** (11.81 lower to 17.81 higher)
SF36 - General health - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)											

Certainty assessment							Summary of findings				
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[d]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - General health - B vs C was **59.8** points	MD **2 points higher** (10.3 lower to 14.3 higher)
SF36 - Vitality - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[d]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Vitality - A vs B was **47.5** points	MD **15 points higher** (6.14 lower to 36.14 higher)
SF36 - Vitality - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[d]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Vitality - A vs C was **44** points	MD **18.5 points higher** (3.15 lower to 40.15 higher)
SF36 - Vitality - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[d]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Vitality - B vs C was **44** points	MD **3.5 points higher** (17.46 lower to 24.46 higher)
SF36 - Social functioning - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)											

Certainty assessment							Summary of findings				
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[c]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Social functioning - A vs B was **92.5** points	MD **2.5 points lower** (16.11 lower to 11.11 higher)
SF36 - Social functioning - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[c]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Social functioning - A vs C was **85** points	MD **7.5 points higher** (6.61 lower to 21.61 higher)
SF36 - Social functioning - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[c]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Social functioning - B vs C was **85** points	MD **7.5 points higher** (6.61 lower to 21.61 higher)
SF36 - Role emotional - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[e]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Role emotional - A vs B was **66.6** points	MD **16.7 points higher** (17.35 lower to 50.75 higher)
SF36 - Role emotional - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)											

Certainty assessment							Summary of findings				
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[e]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Role emotional - A vs C was **73.3** points	MD **10 points higher** (23.77 lower to 43.77 higher)
SF36 - Role emotional - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[e]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Role emotional - B vs C was **73.3** points	MD **6.7 points lower** (42.81 lower to 29.41 higher)
SF36 - Mental health - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[c]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Mental health - A vs B was **80** points	MD **0.4 points lower** (16.49 lower to 15.69 higher)
SF36 - Mental health - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[c]	none	⊕◯◯◯ Very low	10	10	-	The mean SF36 - Mental health - A vs C was **80** points	MD **0.4 points lower** (15.83 lower to 15.03 higher)
SF36 - Mental health - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)											

Certainty assessment							Summary of findings				
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[c]	none	⨁◯◯◯ Very low	10	10	-	The mean SF36 - Mental health - B vs C was **80** points	MD **0 points** (15.92 lower to 15.92 higher)

Explanations

a. Downgraded by 2 increments due to very serious risk of bias: Study authors do not provide necessary details around recruitment and randomisation so outcomes are at risk of selection bias.
b. Downgraded by 1 increment as population includes males only [Female subjects were excluded because of the potential effect of oestrogen status on corticosteroid-binding globulin (CBG) levels]
c. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 3)
d. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 2)
e. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 4)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparator	Relative (95% CI)	Absolute (95% CI)		
NHP - Energy level - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[c]	none	10	10	-	MD **1.2 points higher** (36.54 lower to 38.94 higher)	⨁◯◯◯ Very low	
NHP - Energy level - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[d]	none	10	10	-	MD **5 points lower** (40.56 lower to 30.56 higher)	⨁◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparator	Relative (95% CI)	Absolute (95% CI)		
NHP - Energy level - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[d]	none	10	10	-	MD **6.2 points lower** (41.25 lower to 28.85 higher)	⨁◯◯◯ Very low	
NHP - Pain - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[e]	none	10	10	-	MD **1.1 points higher** (15.72 lower to 17.92 higher)	⨁◯◯◯ Very low	
NHP - Pain - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[f]	none	10	10	-	MD **2.5 points lower** (21.7 lower to 16.7 higher)	⨁◯◯◯ Very low	
NHP - Pain - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[f]	none	10	10	-	MD **3.6 points lower** (20.11 lower to 12.91 higher)	⨁◯◯◯ Very low	
NHP - Emotional reaction - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)												
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[g]	none	10	10	-	MD **1.2 points higher** (10.33 lower to 12.73 higher)	⨁◯◯◯ Very low	
NHP - Emotional reaction - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparator	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[h]	none	10	10	-	MD **0.1 points lower** (12.47 lower to 12.27 higher)	⨁◯◯◯ Very low	

NHP - Emotional reaction - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	serious[b]	very serious[h]	none	10	10	-	MD **1.3 points lower** (15.6 lower to 13 higher)	⨁◯◯◯ Very low	

NHP - Sleep - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	serious[b]	very serious[i]	none	10	10	-	MD **5.4 points higher** (18.3 lower to 29.1 higher)	⨁◯◯◯ Very low	

NHP - Sleep - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	serious[b]	serious[i]	none	10	10	-	MD **9.8 points higher** (8.29 lower to 27.89 higher)	⨁◯◯◯ Very low	

NHP - Sleep - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	serious[b]	very serious[k]	none	10	10	-	MD **4.4 points higher** (17.4 lower to 26.2 higher)	⨁◯◯◯ Very low	

NHP - Social isolation - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	intervention	comparator	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	serious[b]	very serious[l]	none	10	10	-	MD **1 points higher** (14.2 lower to 16.2 higher)	⨁◯◯◯ Very low	

NHP - Social isolation - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	serious[b]	extremely serious[m]	none	10	10	-	MD **0 points** (0 to 0)	⨁◯◯◯ Very low	

NHP - Social isolation - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	serious[b]	extremely serious[m]	none	10	10	-	MD **0 points** (0 to 0)	⨁◯◯◯ Very low	

NHP - Physical abilities - A vs B (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	serious[b]	very serious[n]	none	10	10	-	MD **4.2 points lower** (20.78 lower to 12.38 higher)	⨁◯◯◯ Very low	

NHP - Physical abilities - A vs C (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	serious[b]	very serious[o]	none	10	10	-	MD **5.5 points lower** (21.43 lower to 10.43 higher)	⨁◯◯◯ Very low	

NHP - Physical abilities - B vs C (follow-up: 6 weeks; Scale from: 0 to 100)

1	randomised trials	very serious[a]	not serious	serious[b]	very serious[o]	none	10	10	-	MD **1.3 points lower** (19.85 lower to 17.25 higher)	⨁◯◯◯ Very low	

a. Downgraded by 2 increments due to very serious risk of bias: Study authors do not provide necessary details around recruitment and randomisation so outcomes are at risk of selection bias. Study authors also do not provide details around blinding so outcomes are at risk of measurement bias.

b. Downgraded by 1 increment as population includes males only [Female subjects were excluded because of the potential effect of oestrogen status on corticosteroid-binding globulin (CBG) levels]

c. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 21.25)

d. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 18.65)

e. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 7.8)

f. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 10.8)

g. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 7.75)

h. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 8.55)

i. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 15.2)

j. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 8.85)

k. Downgraded by 1 increment as confidence interval crossed both MIDs (+/- 8.85)

l. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 6.65)

m. Downgraded by 2 increments because comparator value was not captured

n. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 10.9)

o. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 10.25)

Table 18: Clinical evidence profile: Dose A (20 mg 0800 h, 10 mg 1600 h) vs Dose B (10 mg 0800 h and 1600 h) vs Dose C (10 mg 0800 h and 5 mg 1600 h) for secondary and tertiary adrenal insufficiency [Blood Pressure Outcomes]

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With comparator	With intervention		Risk with comparator	Risk difference with intervention
24h ambulatory systolic BP - A vs B (follow-up: 6 weeks)											

Certainty assessment							Summary of findings				
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[c]	none	⊕◯◯◯ Very low	10	10	-	The mean 24h ambulatory systolic BP - A vs B was **117** mmHg	MD **2 mmHg lower** (12.52 lower to 8.52 higher)
24h ambulatory systolic BP - A vs C (follow-up: 6 weeks)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[d]	none	⊕◯◯◯ Very low	10	10	-	The mean 24h ambulatory systolic BP - A vs C was **115** mmHg	MD **0 mmHg** (10.97 lower to 10.97 higher)
24h ambulatory systolic BP - B vs C (follow-up: 6 weeks)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[d]	none	⊕◯◯◯ Very low	10	10	-	The mean 24h ambulatory systolic BP - B vs C was **115** mmHg	MD **2 mmHg higher** (8.97 lower to 12.97 higher)
24h ambulatory diastolic BP - A vs B (follow-up: 6 weeks)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[e]	none	⊕◯◯◯ Very low	10	10	-	The mean 24h ambulatory diastolic BP - A vs B was **68** mmHg	MD **2 mmHg higher** (5.01 lower to 9.01 higher)
24h ambulatory diastolic BP - B vs C (follow-up: 6 weeks)											

Certainty assessment							Summary of findings				
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[f]	none	⊕◯◯◯ Very low	10	10	-	The mean 24h ambulatory diastolic BP - B vs C was **68** mmHg	MD **2 mmHg higher** (4.59 lower to 8.59 higher)
24h ambulatory diastolic BP - A vs C (follow-up: 6 weeks)											
10 (1 RCT)	very serious[a]	not serious	serious[b]	very serious[f]	none	⊕◯◯◯ Very low	10	10	-	The mean 24h ambulatory diastolic BP - A vs C was **68** mmHg	MD **0 mmHg** (6.59 lower to 6.59 higher)

Explanations

a. Downgraded by 2 increments due to very serious risk of bias: Study authors do not provide necessary details around recruitment and randomisation so outcomes are at risk of selection bias.
b. Downgraded by 1 increment as population includes males only [Female subjects were excluded because of the potential effect of oestrogen status on corticosteroid-binding globulin (CBG) levels]
c. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 6)
d. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 6.5)
e. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 4)
f. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 3.5)

Table 19: Clinical evidence profile: Dose A [10mg/5mg HC] vs Dose B [10mg/5mg/5mg HC]

Certainty assessment							Summary of findings		
		Inconsistency	Indirectness	Imprecision			Study event rates (%)		Anticipated absolute effects

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias				Publication bias	Overall certainty of evidence	With Dose B [10mg/5mg/5mg HC]	With Dose A [10mg/5mg HC]	Relative effect (95% CI)	Risk with Dose B [10mg/5mg/5mg HC]	Risk difference with Dose A [10mg/5mg HC]
SF-36 - Physical sum scale (follow-up: 4 weeks; Scale from: 0 to 100)											
18 (1 RCT)	very serious[a]	not serious	not serious	very serious[b]	none	⨁◯◯◯ Very low	18	18	-	The mean SF-36 - Physical sum scale was **40.7** points	MD **3.2 points higher** (4.66 lower to 11.06 higher)
SF-36 - Psychological sum scale (follow-up: 4 weeks; Scale from: 0 to 100)											
18 (1 RCT)	very serious[a]	not serious	not serious	very serious[c]	none	⨁◯◯◯ Very low	18	18	-	The mean SF-36 - Psychological sum scale was **46.4** points	MD **0.1 points lower** (7 lower to 6.8 higher)
BSI Global Severity Index (follow-up: 4 weeks; Scale from: 0 to 100)											
18 (1 RCT)	very serious[a]	not serious	not serious	very serious[d]	none	⨁◯◯◯ Very low	18	18	-	The mean BSI Global Severity Index was **58.1** points	MD **0.2 points lower** (8.15 lower to 7.75 higher)
Satisfaction with medication (follow-up: 4 weeks; assessed with: 100 mm visual analog scale; Scale from: 0 to 100)											
18 (1 RCT)	very serious[a]	not serious	not serious	very serious[e]	none	⨁◯◯◯ Very low	18	18	-	The mean satisfaction with medication was **56.6** points	MD **5.4 points lower** (25.22 lower to 14.42 higher)
Sleepiness score 0700 (follow-up: 4 weeks; assessed with: Stanford Sleepiness Scale; Scale from: 0 to 7)											

Certainty assessment							Summary of findings				
18 (1 RCT)	very serious[a]	not serious	not serious	serious[f]	none	⊕◯◯◯ Very low	18	18	-	The mean sleepiness score 0700 was **2.3** points	MD **0.2 points higher** (0.02 lower to 0.42 higher)
Sleepiness score 1200 (follow-up: 4 weeks; assessed with: Stanford Sleepiness Scale; Scale from: 0 to 7)											
18 (1 RCT)	very serious[a]	not serious	not serious	very serious[g]	none	⊕◯◯◯ Very low	18	18	-	The mean sleepiness score 1200 was **1.7** points	MD **0 points** (0.17 lower to 0.17 higher)
Sleepiness score 1500 (follow-up: 4 weeks; assessed with: Stanford Sleepiness Scale; Scale from: 0 to 7)											
18 (1 RCT)	very serious[a]	not serious	not serious	very serious[h]	none	⊕◯◯◯ Very low	18	18	-	The mean sleepiness score 1500 was **1.8** points	MD **0 points** (0.17 lower to 0.17 higher)
Sleepiness score 1800 (follow-up: 4 weeks; assessed with: Stanford Sleepiness Scale; Scale from: 0 to 7)											
18 (1 RCT)	very serious[a]	not serious	not serious	not serious[i]	none	⊕⊕◯◯ Low	18	18	-	The mean sleepiness score 1800 was **2.1** points	MD **0.4 points lower** (0.57 lower to 0.23 lower)
Sleepiness score 2200 (follow-up: 4 weeks; assessed with: Stanford Sleepiness Scale; Scale from: 0 to 7)											
18 (1 RCT)	very serious[a]	not serious	not serious	not serious[j]	none	⊕◯◯◯ Very low	18	18	-	The mean sleepiness score 2200 was **3.4** points	MD **0.7 points lower** (0.99 lower to 0.41 lower)

Explanations

a. Downgraded by 2 increments for risk of bias (potential for measurement bias in patient-reported outcome, little information provided on deviations from intended interventions).
b. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 2)
c. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 3)
d. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 6.45)
e. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 13.65)
f. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 0.16)
g. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 0.145)
h. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 0.12)
i. No imprecision MID (+/- 0.15)
j. No imprecision MID (+/- 0.25)

Table 20: Clinical evidence profile: Low dose HC [0.2-0.3 mg/kg] vs High dose HC [0.4-0.6mg/kg]

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With high dose HC (0.4-0.6 mg/kg)	With low dose HC (0.2-0.3 mg/kg)	Relative effect (95% CI)	Risk with high dose HC (0.4-0.6 mg/kg)	Risk difference with low dose HC (0.2-0.3 mg/kg)
Systolic BP (follow-up: 10 weeks)											
47 (1 RCT)	very serious[a]	not serious	not serious	serious[b]	none	⨁◯◯◯ Very low	47	47	-	The mean systolic BP was **138** mmHg	MD **5 mmHg lower** (11.08 lower to 1.08 higher)
Diastolic BP (follow-up: 10 weeks)											

Certainty assessment							Summary of findings				
47 (1 RCT)	very serious[a]	not serious	not serious	serious[c]	none	⊕◯◯◯ Very low	47	47	-	The mean diastolic BP was **78** mmHg	MD **2 mmHg lower** (5.85 lower to 1.85 higher)
BMI (follow-up: 10 weeks)											
47 (1 RCT)	very serious[a]	not serious	not serious	not serious	none	⊕⊕◯◯ Low	47	47	-	The mean BMI was **27.1** kg/m2	MD **0.2 kg/m2 lower** (1.82 lower to 1.42 higher)
Number of patients with impaired memory: immediate memory (follow-up: 10 weeks)											
47 (1 RCT)	very serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ Very low	15/47 (31.9%)	13/47 (27.7%)	**RR 0.87** (0.46 to 1.62)	319 per 1,000	**41 fewer per 1,000** (from 172 fewer to 198 more)
Number of patients with impaired memory: short-term memory (follow-up: 10 weeks)											
47 (1 RCT)	very serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ Very low	4/47 (8.5%)	3/47 (6.4%)	**RR 0.75** (0.18 to 3.17)	85 per 1,000	**21 fewer per 1,000** (from 70 fewer to 185 more)
Number of patients with impaired memory: delayed memory (follow-up: 10 weeks)											
47 (1 RCT)	very serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ Very low	8/47 (17.0%)	8/47 (17.0%)	**RR 1.00** (0.41 to 2.44)	170 per 1,000	**0 fewer per 1,000** (from 100 fewer to 245 more)

Certainty assessment							Summary of findings				
Number of patients with impaired memory: recognition (follow-up: 10 weeks)											
47 (1 RCT)	very serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ Very low	3/47 (6.4%)	6/47 (12.8%)	**RR 2.00** (0.53 to 7.53)	64 per 1,000	**64 more per 1,000** (from 30 fewer to 417 more)
Number of patients with impaired attention: divided attention errors (follow-up: 10 weeks)											
47 (1 RCT)	very serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ Very low	7/47 (14.9%)	6/47 (12.8%)	**RR 0.86** (0.31 to 2.36)	149 per 1,000	**21 fewer per 1,000** (from 103 fewer to 203 more)
Number of patients with impaired attention: visual scanning errors (follow-up: 10 weeks)											
47 (1 RCT)	very serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ Very low	5/47 (10.6%)	5/47 (10.6%)	**RR 1.00** (0.31 to 3.23)	106 per 1,000	**0 fewer per 1,000** (from 73 fewer to 237 more)
Number of patients with impaired executive function: fluency (follow-up: 10 weeks)											
47 (1 RCT)	very serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ Very low	5/47 (10.6%)	5/47 (10.6%)	**RR 1.00** (0.31 to 3.23)	106 per 1,000	**0 fewer per 1,000** (from 73 fewer to 237 more)
Number of patients with impaired executive function: working memory (follow-up: 10 weeks)											
47 (1 RCT)	very serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ Very low	4/47 (8.5%)	3/47 (6.4%)	**RR 0.75** (0.18 to 3.17)	85 per 1,000	**21 fewer per 1,000** (from 70 fewer to 185 more)

Certainty assessment							Summary of findings				
Number of patients with impaired executive function: cognitive flexibility (follow-up: 10 weeks)											
47 (1 RCT)	very serious[a]	not serious	not serious	very serious[e]	none	⊕◯◯◯ Very low	6/47 (12.8%)	6/47 (12.8%)	**RR 1.00** (0.35 to 2.88)	128 per 1,000	**0 fewer per 1,000** (from 83 fewer to 240 more)
Number of patients with impaired social cognition (follow-up: 10 weeks)											
47 (1 RCT)	very serious[a]	not serious	not serious	serious[f]	none	⊕◯◯◯ Very low	11/47 (23.4%)	18/47 (38.3%)	**RR 1.64** (0.87 to 3.08)	234 per 1,000	**150 more per 1,000** (from 30 fewer to 487 more)
Number of patients with impaired psychomotor speed (follow-up: 10 weeks)											
47 (1 RCT)	very serious[a]	not serious	not serious	serious[f]	none	⊕◯◯◯ Very low	24/47 (51.1%)	17/47 (36.2%)	**RR 0.71** (0.44 to 1.14)	511 per 1,000	**148 fewer per 1,000** (from 286 fewer to 71 more)

Explanations

a. Downgraded by 2 increments for risk of bias due to missing outcome data.
b. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 8)
c. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 4.5)
d. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 2)
e. Downgraded by 2 increments as confidence interval crossed both MIDs (0.8, 1.25)
f. Downgraded by 1 increment as confidence interval crossed one MIDs (0.8, 1.25)

Table 21: Modified-Release HC tablet vs Standard Glucocorticoid

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Isidori/Mixed] Modified-Release hydrocortisone	standard glucocorticoid	Relative (95% CI)	Absolute (95% CI)		
Change in BMI from baseline												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c]	none	43	35	-	MD **1.6 kg/m2 lower** (2.7 lower to 0.5 lower)	⊕◯◯◯ Very low	CRITICAL
Change in bodyweight from baseline												
1	randomised trials	serious[a]	not serious	serious[b]	serious[d]	none	43	35	-	MD **4 kg lower** (6.64 lower to 1.36 lower)	⊕◯◯◯ Very low	CRITICAL
Change in HbA1c from baseline												
1	randomised trials	serious[a]	not serious	serious[b]	serious[e]	none	43	35	-	MD **0.3 % lower** (0.44 lower to 0.16 lower)	⊕◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[Isidori/Mixed] Modified-Release hydrocortisone**	**standard glucocorticoid**	**Relative (95% CI)**	**Absolute (95% CI)**		
Change in AddiQoL from baseline												
1	randomised trials	very serious[f]	not serious	serious[b]	serious[g]	none	43	35	-	MD **5 out of 10 (AddiQoL score). higher** (0.89 higher to 9.11 higher)	⨁◯◯◯ Very low	CRITICAL
Change in infections [flu or flu-like events in 6 months] from baseline												
1	randomised trials	serious[a]	not serious	serious[b]	serious[h]	none	43	35	-	MD **0.8 flu or flu-like events. lower** (1.52 lower to 0.08 lower)	⨁◯◯◯ Very low	CRITICAL
Change in total cholesterol from baseline												

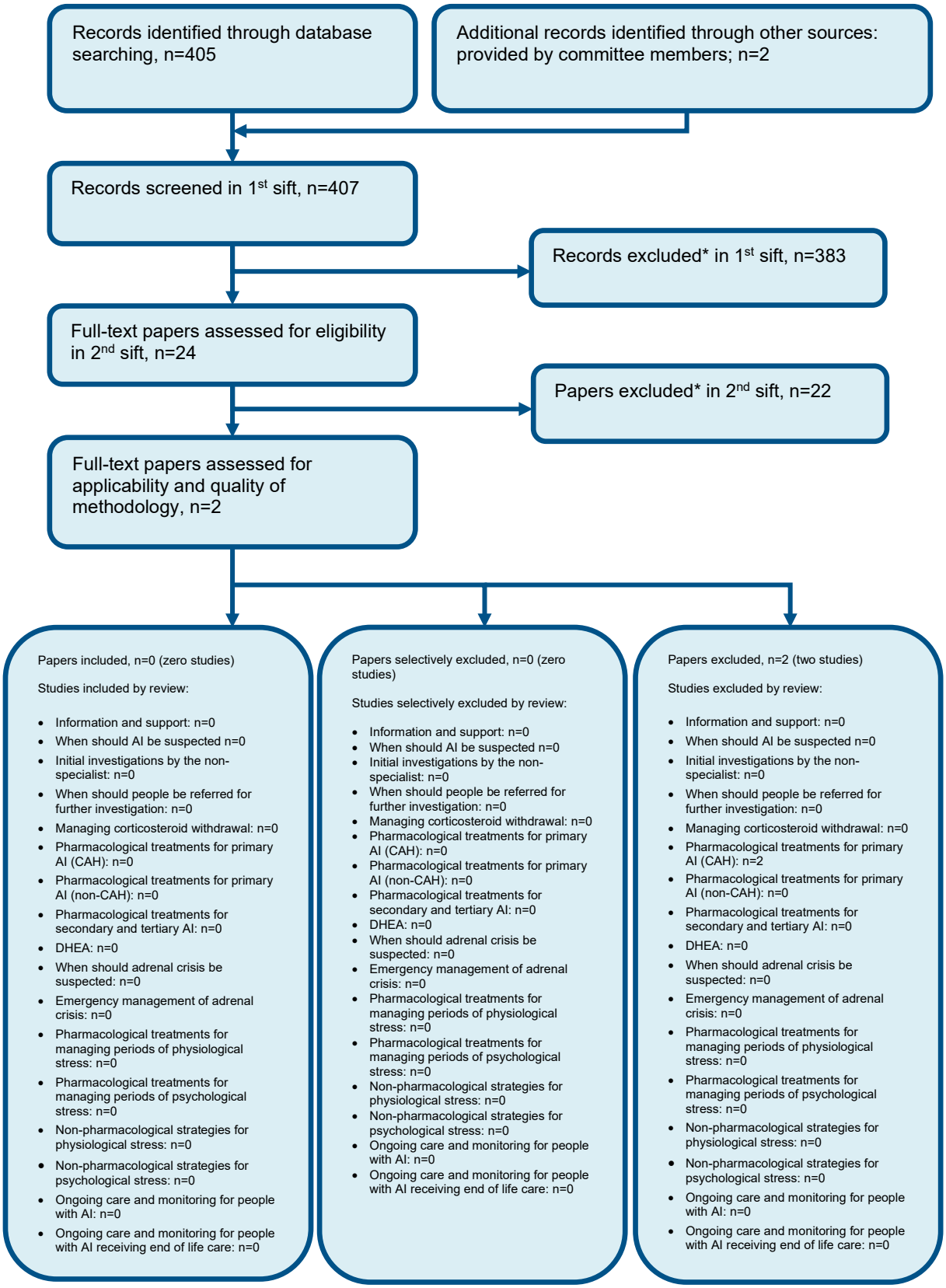
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Isidori/Mixed] Modified-Release hydrocortisone	standard glucocorticoid	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	serious[b]	serious[i]	none	43	35	-	MD **1 mg/dL lower** (14.76 lower to 12.76 higher)	⊕◯◯◯ Very low	CRITICAL
Serious adverse events												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[j]	none	0/43 (0.0%)	2/35 (5.7%)	**OR 0.10** (0.01 to 1.73)	**51 fewer per 1,000** (from 57 fewer to 38 more)	⊕◯◯◯ Very low	CRITICAL

Explanations

a. Downgraded by 1 increment as the majority of evidence was of high risk of bias due to bias arising from the randomisation process [single-blind study design, allocation not concealed from patients].
b. Downgraded by 1 increment because of population indirectness. Population includes people with both primary and secondary AI [50% of population have secondary AI]
c. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 1.165)
d. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 2.91)
e. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 0.145)

f. Downgraded by 2 increments as the majority of evidence was of high risk of bias due to bias arising from the randomisation process [single-blind study design, allocation not concealed from patients] and measurement of the outcome [risk of measurement bias in patient-reported outcome].
g. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 4.365)
h. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 0.8)
i. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 13.1)
j. Downgraded by 2 increments as the confidence interval crossed two MIDS (0.8 to 1.25 default MID)

Appendix G Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H Economic evidence tables

None

Appendix I Health economic model

No health economic model undertaken.

Appendix J Excluded studies

J.1 Clinical studies

Table 22: Studies excluded from the clinical review

Study	Reasons for exclusion
Al Nofal, A., Bancos, I., Benkhadra, K. et al. (2017) Glucocorticoid Replacement Regimens in Chronic Adrenal Insufficiency: A Systematic Review and Meta-Analysis. Endocrine Practice 23(1): 17-31	- Systematic review used as source of primary studies
Alkatib, A. A., Cosma, M., Elamin, M. B. et al. (2009) A systematic review and meta-analysis of randomized placebo-controlled trials of DHEA treatment effects on quality of life in women with adrenal insufficiency. Journal of Clinical Endocrinology & Metabolism 94(10): 3676-81	- Systematic review used as source of primary studies
Arlt, W. (2004) Dehydroepiandrosterone replacement therapy. Seminars in Reproductive Medicine 22(4): 379-88	- Review article but not a systematic review
Arlt, W. (2006) Dehydroepiandrosterone replacement therapy. Current Opinion in Endocrinology and Diabetes 13(3): 291-305	- Review article but not a systematic review
Arlt, W., Callies, F., van Vlijmen, J. C. et al. (1999) Dehydroepiandrosterone replacement in women with adrenal insufficiency. New England Journal of Medicine 341(14): 1013-20	- Intervention not relevant to this review protocol (DHEAS)
Arlt, W.; Callies, F.; Allolio, B. (2000) DHEA replacement in women with adrenal insufficiency--pharmacokinetics, bioconversion and clinical effects on well-being, sexuality and cognition. Endocrine Research 26(4): 505-11	- Intervention not relevant to this review protocol (DHEAS)
Bannon, C. A., Gallacher, D., Hanson, P. et al. (2020) Systematic review and meta-analysis of the metabolic effects of modified-release hydrocortisone versus standard glucocorticoid replacement therapy in adults with adrenal insufficiency. Clinical Endocrinology 93(6): 637-651	- Systematic review used as source of primary studies
Behan, L. A., Kelleher, G., Hannon, M. J. et al. (2014) Low-dose hydrocortisone replacement therapy is associated with improved bone remodelling balance in hypopituitary male patients. European Journal of Endocrinology 170(1): 141-50	- Outcomes do not meet review protocol
Bennett, G.; Cussen, L.; O'Reilly, M. W. (2022) The role for long-term use of dehydroepiandrosterone in adrenal	- Review article but not a systematic review *Non-systematic review, NRS included, no MA*

Study	Reasons for exclusion
insufficiency. Current Opinion in Endocrinology, Diabetes & Obesity 29(3): 284-293	
Bilger, M., Speraw, S., LaFranchi, S. H. et al. (2005) Androgen replacement in adolescents and young women with hypopituitarism. Journal of Pediatric Endocrinology & Metabolism 18(4): 355-62	- Intervention not relevant to this review protocol (DHEAS)
Binder, G., Weber, S., Ehrismann, M. et al. (2009) Effects of dehydroepiandrosterone therapy on pubic hair growth and psychological well-being in adolescent girls and young women with central adrenal insufficiency: a double-blind, randomized, placebo-controlled phase III trial. Journal of Clinical Endocrinology & Metabolism 94(4): 1182-90	- Intervention not relevant to this review protocol (DHEAS)
Boesen, Vb, Borresen, Sw, Christoffersen, T et al. (2021) The effect of dual-release versus conventional hydrocortisone on fatigue, measured by ecological momentary assessments. Endocrine 71(2): 467-475	- Non-randomised - no multivariate analysis
Brooke, A. M., Kalingag, L. A., Miraki-Moud, F. et al. (2006) Dehydroepiandrosterone improves psychological well-being in male and female hypopituitary patients on maintenance growth hormone replacement. Journal of Clinical Endocrinology & Metabolism 91(10): 3773-9	- Population not relevant to this review protocol
Callies, F., Fassnacht, M., van Vlijmen, J. C. et al. (2001) Dehydroepiandrosterone replacement in women with adrenal insufficiency: effects on body composition, serum leptin, bone turnover, and exercise capacity. Journal of Clinical Endocrinology & Metabolism 86(5): 1968-72	- Intervention not relevant to this review protocol (DHEAS)
Cameron, D. R. and Braunstein, G. D. (2005) The use of dehydroepiandrosterone therapy in clinical practice. Treatments in Endocrinology 4(2): 95-114	- Review article but not a systematic review
Ceccato, F. and Scaroni, C. (2019) Central adrenal insufficiency: open issues regarding diagnosis and glucocorticoid treatment. Clinical Chemistry & Laboratory Medicine 57(8): 1125-1135	- Review article but not a systematic review
Christiansen, J. J., Andersen, N. H., Sorensen, K. E. et al. (2007) Dehydroepiandrosterone substitution in female adrenal failure: no impact on endothelial function and cardiovascular parameters despite normalization of androgen status. Clinical Endocrinology 66(3): 426-33	- Intervention not relevant to this review protocol (DHEAS)
Christiansen, J. J., Bruun, J. M., Christiansen, J. S. et al. (2011) Long-term DHEA substitution in	- Intervention not relevant to this review protocol (DHEAS)

Study	Reasons for exclusion
female adrenocortical failure, body composition, muscle function, and bone metabolism: a randomized trial. European Journal of Endocrinology 165(2): 293-300	
Christiansen, J. J., Gravholt, C. H., Fisker, S. et al. (2005) Very short term dehydroepiandrosterone treatment in female adrenal failure: impact on carbohydrate, lipid and protein metabolism. European Journal of Endocrinology 152(1): 77-85	- Data not reported in an extractable format or a format that can be analysed *Outcomes*
Christiansen, J. J., Gravholt, C. H., Fisker, S. et al. (2004) Dehydroepiandrosterone supplementation in women with adrenal failure: impact on twenty-four hour GH secretion and IGF-related parameters. Clinical Endocrinology 60(4): 461-9	- Data not reported in an extractable format or a format that can be analysed
Crowley, R. K., Argese, N., Tomlinson, J. W. et al. (2014) Central hypoadrenalism. Journal of Clinical Endocrinology & Metabolism 99(11): 4027-36	- Review article but not a systematic review
Dhatariya, K. K., Greenlund, L. J., Bigelow, M. L. et al. (2008) Dehydroepiandrosterone replacement therapy in hypoadrenal women: protein anabolism and skeletal muscle function. Mayo Clinic Proceedings 83(11): 1218-25	- Population not relevant to this review protocol
Dhatariya, K.; Bigelow, M. L.; Nair, K. S. (2005) Effect of dehydroepiandrosterone replacement on insulin sensitivity and lipids in hypoadrenal women. Diabetes 54(3): 765-9	- Population not relevant to this review protocol
Dineen, R., Behan, L. A., Kelleher, G. et al. (2020) The contribution of serum cortisone and glucocorticoid metabolites to detrimental bone health in patients receiving hydrocortisone therapy. BMC Endocrine Disorders 20(1): 154	- Outcomes do not meet review protocol
Dineen, R., Martin-Grace, J., Ahmed, K. M. S. et al. (2021) Cardiometabolic and psychological effects of dual-release hydrocortisone: A cross-over study. European Journal of Endocrinology 184(2): 253-265	- Non-randomised - no multivariate analysis *No control group. Study authors do not make it clear if participants were randomized and if baseline characteristics in treatment groups are comparable*
Gagliardi, L., Nenke, M. A., Thynne, T. R. et al. (2014) Continuous subcutaneous hydrocortisone infusion therapy in Addison's disease: a randomized, placebo-controlled clinical trial. Journal of Clinical Endocrinology & Metabolism 99(11): 4149-57	- Population not relevant to this review protocol
Grossman, A. B. (2010) Clinical Review#: The diagnosis and management of central hypoadrenalism. Journal of Clinical Endocrinology & Metabolism 95(11): 4855-63	- Review article but not a systematic review *Only 1 database searched*

Study	Reasons for exclusion
Groves, R. W., Toms, G. C., Houghton, B. J. et al. (1988) Corticosteroid replacement therapy: twice or thrice daily?. Journal of the Royal Society of Medicine 81(9): 514-6	- Population not relevant to this review protocol
Gruber, L. M. and Bancos, I. (2022) Secondary Adrenal Insufficiency: Recent Updates and New Directions for Diagnosis and Management. Endocrine Practice 28(1): 110-117	- Review article but not a systematic review
Hahner, S. and Allolio, B. (2005) Management of adrenal insufficiency in different clinical settings. Expert Opinion on Pharmacotherapy 6(14): 2407-17	- Review article but not a systematic review
Hayashi, R., Tamada, D., Murata, M. et al. (2019) Glucocorticoid Replacement Affects Serum Adiponectin Levels and HDL-C in Patients With Secondary Adrenal Insufficiency. Journal of Clinical Endocrinology & Metabolism 104(12): 5814-5822	- Data not reported in an extractable format or a format that can be analysed
Hayes, A. G.; Rushworth, R. L.; Torpy, D. J. (2022) Risk assessment, diagnosis, and treatment of cancer treatment-related adrenal insufficiency. Expert Review of Endocrinology and Metabolism 17(1): 21-33	- Review article but not a systematic review
Ho, W. and Druce, M. (2018) Quality of life in patients with adrenal disease: A systematic review. Clinical Endocrinology 89(2): 119-128	- Systematic review used as source of primary studies
Libe, R., Barbetta, L., Dall'Asta, C. et al. (2004) Effects of dehydroepiandrosterone (DHEA) supplementation on hormonal, metabolic and behavioral status in patients with hypoadrenalism. Journal of Endocrinological Investigation 27(8): 736-41	- Intervention not relevant to this review protocol (DHEAS)
Lovas, K., Gebre-Medhin, G., Trovik, T. S. et al. (2003) Replacement of dehydroepiandrosterone in adrenal failure: no benefit for subjective health status and sexuality in a 9-month, randomized, parallel group clinical trial. Journal of Clinical Endocrinology & Metabolism 88(3): 1112-8	- Intervention not relevant to this review protocol (DHEAS)
Johannsson, G., Skrtic, S., Lennernas, H. et al. (2014) Improving outcomes in patients with adrenal insufficiency: a review of current and future treatments. Current Medical Research & Opinion 30(9): 1833-47	- Review article but not a systematic review
Joseph, R. M., Hunter, A. L., Ray, D. W. et al. (2016) Systemic glucocorticoid therapy and adrenal insufficiency in adults: A systematic review. Seminars in Arthritis & Rheumatism 46(1): 133-41	- Study does not contain an intervention relevant to this review protocol

Study	Reasons for exclusion
Joseph, R. M., Hunter, L., Ray, D. W. et al. (2015) Shocking? A systematic review of adrenal insufficiency in adults on oral steroids. Arthritis and Rheumatology. Conference: American College of Rheumatology/Association of Rheumatology Health Professionals Annual Scientific Meeting, ACR/ARHP 67(suppl10)	- Study does not contain an intervention relevant to this review protocol
Lee, K. H., Lee, H., Lee, C. H. et al. (2019) Adrenal insufficiency in systematic lupus erythematosus (SLE) and antiphospholipid syndrome (APS): A systematic review. Autoimmunity Reviews 18(1): 1-8	- Population not relevant to this review protocol *Only included case reviews*
McHenry, C. M., Bell, P. M., Hunter, S. J. et al. (2012) Effects of dehydroepiandrosterone sulphate (DHEAS) replacement on insulin action and quality of life in hypopituitary females: a double-blind, placebo-controlled study. Clinical Endocrinology 77(3): 423-9	- Intervention not relevant to this review protocol (DHEAS)
Mifsud, S., Gauci, Z., Gruppetta, M. et al. (2021) Adrenal insufficiency in HIV/AIDS: a review. Expert Review of Endocrinology & Metabolism 16(6): 351-362	- Review article but not a systematic review
Mongioi, L. M., Condorelli, R. A., Barbagallo, F. et al. (2020) Dual-release hydrocortisone for treatment of adrenal insufficiency: a systematic review. Endocrine 67(3): 507-515	- Systematic review used as source of primary studies
Panjari, M. and Davis, S. R. (2007) DHEA therapy for women: effect on sexual function and wellbeing. Human Reproduction Update 13(3): 239-48	- Systematic review used as source of primary studies
Peixoto, C., Devicari Cheda, J. N., Nardi, A. E. et al. (2014) The effects of dehydroepiandrosterone (DHEA) in the treatment of depression and depressive symptoms in other psychiatric and medical illnesses: a systematic review. Current Drug Targets 15(9): 901-14	- Systematic review used as source of primary studies
Quinkler, M., Beuschlein, F., Hahner, S. et al. (2013) Adrenal cortical insufficiency--a life threatening illness with multiple etiologies. Deutsches Arzteblatt International 110(5152): 882-8	- Review article but not a systematic review
Rice, S. P., Agarwal, N., Bolusani, H. et al. (2009) Effects of dehydroepiandrosterone replacement on vascular function in primary and secondary adrenal insufficiency: a randomized crossover trial. Journal of Clinical Endocrinology & Metabolism 94(6): 1966-72	- Intervention not relevant to this review protocol (DHEAS)

Study	Reasons for exclusion
Sorgdrager, F. J. H., Werumeus Buning, J., Bos, E. H. et al. (2018) Hydrocortisone Affects Fatigue and Physical Functioning Through Metabolism of Tryptophan: A Randomized Controlled Trial. Journal of Clinical Endocrinology & Metabolism 103(9): 3411-3419	- Secondary publication of an included study that does not provide any additional relevant information
Srinivasan, M., Irving, B. A., Dhatariya, K. et al. (2009) Effect of dehydroepiandrosterone replacement on lipoprotein profile in hypoadrenal women. Journal of Clinical Endocrinology & Metabolism 94(3): 761-4	- Population not relevant to this review protocol
Stacey, M.; Gifford, R. M.; Woods, D. (2021) Safer care for patients with adrenal insufficiency: Weighing the evidence, balancing risks and acknowledging uncertainties. Clinical Medicine, Journal of the Royal College of Physicians of London 21(5): e541-e542	- Review article but not a systematic review
van Thiel, S. W., Romijn, J. A., Pereira, A. M. et al. (2005) Effects of dehydroepiandrostenedione, superimposed on growth hormone substitution, on quality of life and insulin-like growth factor I in patients with secondary adrenal insufficiency: a randomized, placebo-controlled, cross-over trial. Journal of Clinical Endocrinology & Metabolism 90(6): 3295-303	- Intervention not relevant to this review protocol (DHEAS)
Vu, T.; Vallabh, M.; Laine, G. (2020) Adrenal Insufficiency and Response to Stress Dose Hydrocortisone in Patients With Cirrhosis and Vasopressor Dependency Using Cirrhosis-Specific Cortisol Thresholds. Annals of Pharmacotherapy 54(8): 742-749	- Non-randomised - no multivariate analysis
Vulto, A., Bergthorsdottir, R., van Faassen, M. et al. (2019) Residual endogenous corticosteroid production in patients with adrenal insufficiency. Clinical Endocrinology 91(3): 383-390	- Study design not relevant to this review protocol *comparing case control of primary with an RCT of secondary*
Vulto, A., van Faassen, M., Kerstens, M. N. et al. (2022) Susceptibility to Adrenal Crisis Is Associated With Differences in Cortisol Excretion in Patients With Secondary Adrenal Insufficiency. Frontiers in Endocrinology 13: 849188	- Study design not relevant to this review protocol *looking back at people who've had an adrenal crisis - not from a perspective of managing the condition*
Werumeus Buning, J., Dimova, L. G., Perton, F. G. et al. (2017) Downregulation of cholesteryl ester transfer protein by glucocorticoids: a randomised study on HDL. European Journal of Clinical Investigation 47(7): 494-503	- Secondary publication of an included study that does not provide any additional relevant information *genetic/biochem outcomes only*
Werumeus Buning, J., Konopka, K. H., Brummelman, P. et al. (2017) Somatosensory function in patients with secondary adrenal	- Secondary publication of an included study that does not provide any additional relevant information

Study	Reasons for exclusion
insufficiency treated with two different doses of hydrocortisone-Results from a randomized controlled trial. PLoS ONE [Electronic Resource] 12(7): e0180326	*Genetic/biochem outcomes only*
Werumeus Buning, J., Kootstra-Ros, J. E., Brummelman, P. et al. (2016) Higher hydrocortisone dose increases bilirubin in hypopituitary patients- results from an RCT. European Journal of Clinical Investigation 46(5): 475-80	- Secondary publication of an included study that does not provide any additional relevant information *genetic/biochem outcomes only*
Werumeus Buning, J., Brummelman, P., Koerts, J. et al. (2016) Hydrocortisone Dose Influences Pain, Depressive Symptoms and Perceived Health in Adrenal Insufficiency: A Randomized Controlled Trial. Neuroendocrinology 103(6): 771-8	- Data not reported in an extractable format or a format that can be analysed
Wichers, M., Springer, W., Bidlingmaier, F. et al. (1999) The influence of hydrocortisone substitution on the quality of life and parameters of bone metabolism in patients with secondary hypocortisolism. Clinical Endocrinology 50(6): 759-765	- No useable outcome data
Wierman, M. E., Arlt, W., Basson, R. et al. (2014) Androgen therapy in women: a reappraisal: an Endocrine Society clinical practice guideline. Journal of Clinical Endocrinology & Metabolism 99(10): 3489-510	- Systematic review used as source of primary studies

J.2 Health Economic studies

None.

Appendix K Recommendation for research

K.1 Research question:

What is the clinical and cost effectiveness of pharmacological treatments for the routine management of secondary and tertiary adrenal insufficiency?

K.1.1 Why this is important

Prednisolone and hydrocortisone are recommended as alternative pharmacological treatments in this guideline on the basis of current evidence. However, there are as yet no data directly comparing outcomes between these preparations, or with modified-release hydrocortisone, in this specific group. Gaining such evidence is important as there may be benefits of one pharmacological treatment over another. Restoration of a physiological circadian cortisol replacement schedule using modified-release hydrocortisone may reduce body mass index and improve glucose metabolism in patients with primary or secondary adrenal insufficiency, albeit that the number of patients previously studied is small. Conversely, prednisolone binds longer to the glucocorticoid receptor than hydrocortisone, which might lead to a prolonged clinical effect, improved adherence and reduced risk of adrenal crisis. Whether these theoretical differences lead to different clinical outcomes is unknown. Research to understand which glucocorticoid preparation is the more clinically effective in this population is therefore required. The health economic implications should also be addressed.

K.1.2 Rationale for research recommendation

Importance to 'patients' or the population	This may provide evidence to change current care by recommending prednisolone, hydrocortisone or modified-release hydrocortisone as first-line treatment to people with secondary or tertiary adrenal insufficiency if one is proven to improve outcomes more than the other. This may improve outcomes and quality of life.
Relevance to NICE guidance	This question would potentially change guidance in terms of which corticosteroid preparation should be offered first-line in patients with secondary and tertiary adrenal insufficiency.
Relevance to the NHS	Potential impacts on the NHS include on service delivery in prehospital and hospital settings.
National priorities	None.
Current evidence base	
Equality considerations	In addition to the broader group of patients this research recommendation highlights the need for understanding corticosteroid use in specific subgroups (including but not exclusive to) people < 16 years of age.

K.1.3 Modified PICO table

Population	Inclusion: All adults and young people (>16 yrs) with established secondary or tertiary adrenal insufficiency. Stratified by: Aetiology • Adrenal insufficiency secondary to hypothalamic/pituitary disease • Adrenal insufficiency secondary to previous corticosteroid or opiate use On stable hydrocortisone replacement for at least 4 months

	On stable additional hormone replacement (thyroid hormone, oestrogen or testosterone, growth hormone) for at least 4 months Willing and able to provide written informed consent. Exclusion: Unable or unwilling to provide written informed consent. Pregnancy or breastfeeding
Intervention	Oral prednisolone and/or modified-release hydrocortisone
Comparison	Oral hydrocortisone
Outcomes	Disease-specific Quality of Life questionnaire (AddiQOL) Short Form-36 questionnaire EQ-5D Body weight Weight circumference Blood pressure Heart rate HbA1c Lipid profile Bone turnover markers Incidence of adrenal crises, infections and need for hospitalisation. Adverse events Outcomes measured at 1, 3 and 6 months.
Study design	RCT (potentially using a crossover design)
Timeframe	Medium term – in time for the next update
Additional information	None