National Institute for Health and Care Excellence

1

Draft

Adrenal Insufficiency: identification and management

Evidence review F: Routine pharmacological management of primary adrenal insufficiency

NICE guideline <number

Evidence reviews underpinning recommendations 1.3.1 – 1.3.6 in the NICE guideline

March 2024

Draft for Consultation

This evidence review was developed by NICE

1

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN:

Contents

1. Routine pharmacological management of primary Adrenal Insufficiency

1.1. Review question

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

1.1.1. Introduction

People with Primary Adrenal Insufficiency (PAI) are dependent on different steroid hormone replacement for survival. Those with a confirmed diagnosis of PAI require daily replacement of their missing adrenal hormones, cortisol, and aldosterone. 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.

People with Congenital Adrenal Hyperplasia CAH may also have dose adjustment of glucocorticoids to manage control of excess androgen production. The majority of people with primary adrenal insufficiency, also require the replacement of mineralocorticoids and this is given in the form of daily fludrocortisone. Sodium chloride supplements may also be necessary.

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

In this chapter, we review the different glucocorticoid regimens to establish which is the most clinically and cost-effective pharmacological treatment for patients, and optimum management of mineralocorticoid replacement for patients with a diagnosis of primary 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	**Babies, children, young people and adults with suspected and diagnosed primary adrenal insufficiency including those with Addison's disease and congenital adrenal hyperplasia (CAH) stratified as follows:** • Adults (aged ≥16 years) – All adults with primary adrenal insufficiency including Addison's disease and CAH. • Children aged ≥1 up to 16 years with CAH. • Children aged ≥1 to <16 years with no CAH.

	• Infants aged <1 year including neonates (up to 28 days) with CAH. • Infants aged <1 year including neonates (up to 28 days) with no CAH

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
	
	Mineralocorticoid:
	Fludrocortisone
	
	Sodium chloride (specific to infants with CAH)
	
	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, regimens and preparations (e.g., modified release compared to standard) **For mineralocorticoid:** Comparisons of different mineralocorticoid doses and regimens (twice vs once a day) **For sodium chloride:** Comparisons of different doses and regimens **For all:** Comparisons to standard care as defined by authors may also be included
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- for example neurological complications, psychological, hypoglycaemia, shock, acute kidney injury may be as part of shock and related to hypovolaemia. • Androgen normalisation (specific to CAH) determined by biochemical parameters such as 17 OHP, androstenedione, testosterone and DHEAS).

	• Admission to hospital and/or ITU. • Readmission to hospital. • Length of stay at hospital or ITU. • Treatment-related adverse events. • Activities of daily living. 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 QoL and activities of daily living.
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 • Childhood onset vs adult onset for Autoimmune polyglandular syndrome type 1 (APS-1) as this may affect mortality in Addison's. 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.

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 primary adrenal insufficiency among people who do not have congenital adrenal hyperplasia.

All primary adrenal insufficiency

1.1.4. Effectiveness evidence

1.1.4.1. Included studies

Five randomised controlled trials (RCTs) were included in the review;[4, 6, 7, 12, 13] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Tables 3-7).

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.

These studies included the following comparisons:

- Once-daily modified-release hydrocortisone (MR-HC) vs. standard glucocorticoid[6]
- Once-daily dual-release hydrocortisone (DR-HC) vs. three times daily (TID) hydrocortisone[7, 12]
- Twice-daily (BID) hydrocortisone vs. 4-times-daily hydrocortisone[4]
- Continuous subcutaneous hydrocortisone vs. standard care[13]

Follow-up periods for these studies ranged between 4 weeks and 24 weeks.

Four of these 5 studies were crossover RCTs[4, 7, 12, 13], only the Isidori 2019 study was a parallel RCT.

Four of these 5 studies included only people with primary adrenal insufficiency[4, 7, 12, 13]. One study (Isidori 2018[6]), included a mixed population where half of the participants had primary adrenal insufficiency and half had secondary or tertiary adrenal insufficiency. This study was therefore downgraded for indirectness of the population.

All studies included adults only.

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

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
Ekman 2012[4] Crossover RCT Double-blind Conducted in Sweden	Total daily dose of 30 mg hydrocortisone for in the following schedule: Intervention: 2 daily doses (20 mg 12:00, 10mg 16:00) Comparison: 4 daily doses 10mg 07:00,	15 adults with primary AI Mean age 44.6 (range 21 -74 years); 40% female	Bodyweight BMI Systolic BP Diastolic BP SF-36: Physical function, role function, bodily pain, general health, vitality, social function,	Prior to study enrolment, n=9 participants used hydrocortisone (mean (SD) daily dose: 30mg (5mg), and n=6 participants used cortisone acetate 43.75mg (6.85mg).

Study	Intervention and comparison	Population	Relevant outcomes	Comments
	10mg 12:00, 5 mg 16:00, 5mg 20:00) Follow-up: 4 weeks After 4 weeks, patients switched groups (no washout period).		mental health	
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 potentially 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	Bodyweight reduction Blood glucose HbA1c	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.
Johannsson 2012[7] Crossover RCT Conducted in Sweden	Equivalent total daily dose of hydrocortisone in the following schedule: Intervention: Once-daily (OD) Dual release hydrocortisone (DR-HC). The dual-release tablets (20 and 5 mg) were administered orally OD in the fasting state in the morning (at 0800 h).	64 adults with primary AI Mean age 47 (range 19 -71 years); 41% female	Bodyweight BMI HbA1c Adverse events Total cholesterol Blood pressure	Patients were on a stable hydrocortisone dose (for at least 3 months before entering the study), which was kept constant throughout the study. The most common dose of hydrocortisone was 30 mg/d (58.7%), and 45% had a

Study	Intervention and comparison	Population	Relevant outcomes	Comments
	Comparison: Hydrocortisone TID. The reference drug was a hydrocortisone 10-mg tablet administered TID (at 0800, 1200, and 1600 h). Follow-up: 12 weeks After 12 weeks, patients switched groups (no washout period).			TID regimen before the study.
Nilsson 2014[12] Crossover RCT Conducted in Sweden (Secondary paper of Johannsson 2012[7])	Equivalent total daily dose of hydrocortisone in the following schedule: Intervention: Once-daily dual-release hydrocortisone (DR-HC) Comparison: Hydrocortisone TID (0800, 1200, and 1600h) Follow-up: 12 weeks After 12 weeks, patients switched groups (no washout period).	N=64 adults with primary AI Mean age 47.2 +/- 13.6; 42% female	Periods of intercurrent illness	It is likely this study is a post-hoc analysis of data from the Johannsson 2012 RCT (above) but this is not able to be confirmed based on trial numbers. Only data from the first phase of trial have been extracted and included
Oksnes 2014[13] Crossover RCT Open label Conducted in Sweden	Intervention: Hydrocortisone, continuous SC (CSHI): Mean dose 0.31 mg/kg, administered via insulin pump Comparison: Hydrocortisone TID: Mean dose 0.26 mg/kg via 5-mg tablet administered 4 hours apart.	n=33 adults with autoimmune Addison's Disease Mean age 48 +/- 12; 75.8% female	HbA1c Cholesterol BMI Weight HRQOL Adverse events Treatment-related adverse events Serious adverse events	3 participants were screened out prior to randomisation due to technical difficulty with pump gear and 1 was screened out due to plaster allergy. After randomisation, 3 patients withdrew consent [1 due to plaster allergy, 1 due to technical issues with pump, 1 due to lack of time for the study] Mean (SD) hydrocortisone-equivalent pretrial

Study	Intervention and comparison	Population	Relevant outcomes	Comments
				dose was 0.36 mg/kg*d (0.07)

See Appendix D for full evidence tables.

1.1.6. Summary of the effectiveness evidence

Table 3: Hydrocortisone 2 dose vs. 4 dose

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 4 doses	Risk difference with 2 doses
Bodyweight at 4 weeks (lower is better)	15 (1 RCT)	⊕⊕◯◯ Low[a]	-	The mean bodyweight was **74.9** kg	MD **0.2 kg higher** (9.96 lower to 10.36 higher)
BMI at 4 weeks (lower is better)	15 (1 RCT)	⊕⊕◯◯ Low[b]	-	The mean BMI was **24.0** kg	MD **0.3 kg higher** (2.06 lower to 2.66 higher)
SF-36 Physical function at 4 weeks (Higher is better)	15 (1 RCT)	⊕◯◯◯ Very low[c,d]	-	The mean SF-36 Physical function was **92.3** out of 100 (SF-36 score).	MD **1 out of 100 (SF-36 score) lower** (8.55 lower to 6.55 higher)
SF-36 Role function at 4 weeks (higher is better)	15 (1 RCT)	⊕◯◯◯ Very low[c,d]	-	The mean SF-36 Role function was **91.7** out of 100 (SF-36 score).	MD **15 out of 100 (SF-36 score) lower** (38.48 lower to 8.48 higher)
SF-36 Bodily pain follow-up at 4 weeks (higher is better)	15 (1 RCT)	⊕◯◯◯ Very low[c,d]	-	The mean SF-36 Bodily pain was **85.6** out of 100 (SF-36 score).	MD **8.5 out of 100 (SF-36 score) lower** (25.53 lower to 8.53 higher)
SF-36 General health follow-up at 4 weeks (higher is better)	15 (1 RCT)	⊕◯◯◯ Very low[c,e]	-	The mean SF-36 General health was **81.7** out of 100 (SF-36 score).	MD **2.1 out of 100 (SF-36 score) lower** (12.66 lower to 8.46 higher)
SF-36 Vitality follow-up at 4 weeks (higher is better)	15 (1 RCT)	⊕◯◯◯ Very low[c,e]	-	The mean SF-36 Vitality was **77.3** out of 100 (SF-36 score).	MD **6.1 out of 100 (SF-36 score). lower** (20.09 lower to 7.89 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 4 doses	Risk difference with 2 doses
SF-36 Social function follow-up at 4 weeks (higher is better)	15 (1 RCT)	⊕⊕◯◯ Low[c,f]	-	The mean SF-36 Social function was **98.3** out of 100 (SF-36 score).	MD **3.3 out of 100 (SF-36 score). lower** (8.46 lower to 1.86 higher)
SF-36 Mental Health follow-up at 4 weeks (higher is better)	15 (1 RCT)	⊕◯◯◯ Very low[c,d]	-	The mean SF-36 Mental Health was **89.3** out of 100 (SF-36 score).	MD **4.2 out of 100 (SF-36 score). lower** (15.32 lower to 6.92 higher)
Systolic BP follow-up at 4 weeks (lower is better)	15 (1 RCT)	⊕⊕◯◯ Low[g]	-	The mean systolic BP was **124** mmHg	MD **1 mmHg higher** (9.12 lower to 11.12 higher)
Diastolic BP follow-up at 4 weeks (lower is better)	15 (1 RCT)	⊕⊕◯◯ Low[h]	-	The mean diastolic BP was **79** mmHg	MD **2 mmHg lower** (7.21 lower to 3.21 higher)

Explanations

a. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 7.1)

b. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 1.6)

c. Downgraded by 1 increment due to risk of measurement bias in patient-reported outcomes.

d. Downgraded by 2 increments for imprecision as confidence interval crossed both thresholds for established MID (+/- 3)

e. Downgraded by 2 increments for imprecision as confidence interval crossed both thresholds for established MID (+/- 2)

f. Downgraded by 1 increment for imprecision as confidence interval crossed the established MID (+/- 3)

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

h. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 2.5)

Table 4: Modified-Release HC 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)

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 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 months] 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 (lower is better) At 24 weeks	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)

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)

Table 5: Dual-release OD Hydrocortisone vs. Hydrocortisone TID

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with hydrocortisone TID	Risk difference with DR-HC
Adverse event (any) At 12 weeks (lower is better)	64 (1 RCT)	⊕⊕◯◯ Low[a,b]	**RR 1.12** (0.89 to 1.41)	656 per 1,000	**79 more per 1,000** (72 fewer to 269 more)
Serious AE/Hospitalisation At 12 weeks (lower is better)	64 (1 RCT)	⊕⊕◯◯ Low[c]	**RR 3.00** (0.63 to 14.31)	31 per 1,000	**63 more per 1,000** (12 fewer to 416 more)
AE: Fatigue At 12 weeks (lower is better)	64 (1 RCT)	⊕◯◯◯ Very low[a,c]	**RR 2.67** (0.74 to 9.60)	47 per 1,000	**78 more per 1,000** (12 fewer to 403 more)
Change in HbA1c% from baseline At 12 weeks (lower is better)	64 (1 RCT)	⊕⊕⊕◯ Moderate[d,f]	-	The mean change in HbA1c% from baseline was **5.0** %	MD **0.1 % lower** (0.46 lower to 0.26 higher)
Change in total cholesterol from baseline At 12 weeks (lower is better)	64 (1 RCT)	⊕⊕⊕◯ Moderate[d,f]	-	The mean change in total cholesterol from baseline was **5.3** nmol/L	MD **0.1 nmol/L lower** (0.45 lower to 0.25 higher)

Explanations

a. Downgraded by 1 increments as the majority of evidence was of high risk of bias due to bias arising from measurement of the outcome [risk of measurement bias in patient-reported outcome].

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

c. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 0.8, 1.25)

d. Downgraded by 1 increment as the majority of evidence was of high risk of bias due to bias arising from incomplete outcome data: results are only reported for a subset of the ITT population, study authors do not make it clear why the outcome data is missing.

e. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 0.55)

f. No imprecision (+/- 0.45)

Table 6: Dual-release HC vs. Hydrocortisone TID

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with hydrocortisone TID	Risk difference with DR-HC
Illness episodes per patient within 3 months (lower is better)	64 (1 RCT)	⊕◯◯◯ Very low[a,b]	-	The mean illness episodes per patient within 3 months was **1.82** episodes	MD **0.33 episodes higher** (0.28 lower to 0.94 higher)
Number of days per illness episode at 12 weeks (lower is better)	64 (1 RCT)	⊕◯◯◯ Very low[a,c]	-	The mean number of days per illness episode was **3.30** days	MD **0.86 days lower** (2.02 lower to 0.3 higher)
Additional hydrocortisone dose per illness episode (mg) at 12 weeks (lower is better)	64 (1 RCT)	⊕◯◯◯ Very low[a,d]	-	The mean additional hydrocortisone dose per illness episode (mg) was **17.65** mg	MD **5.19 mg higher** (1.1 higher to 9.28 higher)

Explanations

a. Downgraded by 2 increments as the majority of evidence was of very high risk of bias due to bias arising from the randomisation process and in measurement of the outcome [open-label study design, allocation not concealed from patients or outcome assessors].

b. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 0.935)

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

d. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 4.91)

Table 7: Continuous SC hydrocortisone vs. standard hydrocortisone [Oksnes 2014]

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard HC	Risk difference with continuous SC HC
HbA1c at 12 weeks (lower is better	14 (1 RCT)	⊕◯◯◯ Very low[a,b]	-	The mean hbA1c was **5.1** %	MD **0.1 % higher** (0.03 lower to 0.23 higher)
BMI At 12 weeks (lower is better	33 (1 RCT)	⊕◯◯◯ Very low[a,c]	-	The mean BMI was **25.3** kg/m2	MD **0.5 kg/m2 higher** (1.34 lower to 2.34 higher)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with standard HC	Risk difference with continuous SC HC
Weight at 12 weeks (lower is better)	33 (1 RCT)	⊕◯◯◯ Very low[a,d]	-	The mean weight was **73.9** kg	MD **1.9 kg higher** (4.56 lower to 8.36 higher)
Systolic BP at 12 weeks (lower is better)	33 (1 RCT)	⊕◯◯◯ Very low[a,e]	-	The mean systolic BP was **115.5** mmHg	MD **0.9 mmHg lower** (5.87 lower to 4.07 higher)
Diastolic BP at 12 weeks (lower is better)	33 (1 RCT)	⊕◯◯◯ Very low[a,f]	-	The mean diastolic BP was **75.7** mmHg	MD **0.5 mmHg lower** (3.36 lower to 2.36 higher)
Total cholesterol at 12 weeks (lower is better)	33 (1 RCT)	⊕◯◯◯ Very low[a,g]	-	The mean total cholesterol was **5.3** nmol/L	MD **0.2 nmol/L higher** (0.21 lower to 0.61 higher)
Any AE at 12 weeks (lower is better)	33 (1 RCT)	⊕◯◯◯ Very low[h,i]	**RR 1.13** (0.82 to 1.54)	667 per 1,000	**87 more per 1,000** (120 fewer to 360 more)
Treatment-related AE at 12 weeks (lower is better)	33 (1 RCT)	⊕◯◯◯ Very low[h,j]	**RR 0.82** (0.24 to 2.80)	152 per 1,000	**27 fewer per 1,000** (115 fewer to 273 more)
Serious AE/Hospitalisation at 12 weeks (lower is better)	33 (1 RCT)	⊕◯◯◯ Very low[h,k]	**OR 0.14** (0.00 to 7.03)	30 per 1,000	**26 fewer per 1,000** (30 fewer to 150 more)

Explanations

a. Downgraded by 2 increments as the majority of evidence was of high risk of bias due to bias arising from missing outcome data [outcome not reported for entire ITT population] and open-label trial design.

b. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 0.085)

c. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 1.83)

d. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 6.485)

e. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 4.935)

f. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 2.96)

g. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 0.42)

h. Downgraded by 2 increments as the majority of evidence was of very high risk of bias due to risk of bias from measurement of the outcome [study authors do not state how adverse events are identified] and open-label trial design.

i. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 1.25)

j. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 0.8, 1.25)

k. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 0.8, 1.25)

1.1.7. Economic evidence

1.1.7.1. Included studies

No health economic studies were included.

1.1.7.2. 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 F.2.1.

1.1.8. Economic model

This area was not prioritised for new cost-effectiveness analysis.

1.1.9. Unit costs

Relevant unit costs are provided below to aid the consideration of cost-effectiveness. Combination hydrocortisone in children is a combination of standard release and Alkindi granules in capsules.

Table 8: Unit costs for children for the routine pharmacological management of Addison's disease

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		
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

Resource[a]	Dose per day	Cost per day	Cost per year
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
Fludrocortisone			
Fludrocortisone	50mcg – 200mcg[l]	£0.10 - £0.42	£37.90 - £151.60
Sodium chloride			
Sodium chloride	17mmol – 34mmol	£0.66-£1.33	£242.62 - £485.23

(a) Source of costs from The British National Formulary (BNF).[2] 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.

(l) Cost available in the BNF is for 100mcg per day. The cost for 50mcg a day assumes people take half a 100mcg tablet daily and there is no drug wastage.

.

Table 9: Unit costs for adults for the routine pharmacological management of Addison's disease

Resource[a]	Dose per day	Cost per day	Cost per year
Hydrocortisone	***15mg – 25mg[b]***		
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	Cost per year
Prescribed as one 10mg tablet and one 15mg tablet a day	25mg	£1.19	£434.72
Prescribed as three 10mg tablets a day	15mg – 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 tablets a day	3mg	£0.08	£30.11
Prescribed as one 1mg tablet and one 5mg tablet a day	6mg	£0.06	£22.29
Dexamethasone			
Dexamethasone	0.25mg – 0.5mg[d]	£0.05 - £0.10	£19.10 - £39.19
Fludrocortisone			
Fludrocortisone	50mcg – 300mcg[e]	£0.10 - £0.62	£37.90 - £227.40

(a) Source of costs from The British National Formulary (BNF).[2]
(b) Standard release hydrocortisone is taken either 2 or 3 times a day.
(c) For a 15mg dose of hydrocortisone 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.
(e) Cost available in the BNF is for 100mcg per day. The cost for 50mcg a day assumes people take half a 100mcg tablet daily and there is no drug wastage.

Primary adrenal insufficiency due to Congenital Adrenal hyperplasia (CAH)

1.1.10. Effectiveness evidence

1.1.10.1. Included studies

Five randomised controlled trials that investigated the effect of glucocorticoids in the management of congenital adrenal hyperplasia (CAH) were included in the review;[3,German, #91,Merke, 2021 #100,Nebesio, 2016 #101,Silva, 1997 #109]. Four were included in a published Cochrane review, Ng, 2020[11] and one [8] was identified through a literature search. The included studies are summarised in Table 2 below. The Cochrane review was referenced in the assessments of risk of bias and certainty of the evidence (GRADE) for the studies included in it and the RevMan file was used to generate forest plots. One study, Winterer 1985[16] was included in the Cochrane review in a narrative summary but excluded from this review due to the results not being in an extractable format and only presented graphically. Some results were presented in the Cochrane review as median value, IQR and P values. These have been presented in this review but no further analyses of these outcomes using RevMan or GRADE were possible.

All studies evaluated oral glucocorticoid replacement therapies including hydrocortisone, prednisolone and dexamethasone at different daily doses and schedules:

- One study (Caldato 2004[3]) compared once-daily prednisolone to 3 times daily (TID) hydrocortisone in prepubertal and pubertal participants (parallel RCT)
- One study (German 2008[5]) compared a high morning dose of TID hydrocortisone to a high evening dose in children (cross-over RCT)
- One study (Merke 2021[8]) compared modified-release hydrocortisone to standard glucocorticoid in adult participants.
- One study (Nebesio 2016[10]) compared hydrocortisone 15mg daily in 3 doses to prednisolone 3mg/day and dexamethasone 0.3mg/m2/day in pubertal and prepubertal children (cross-over RCT)
- One study (Silva 1997[15]) compared hydrocortisone 15 mg/m2/day vs. 25 mg/m2/day administered in 3 daily doses in children (cross over RCT)

All studies included male and female participants with a confirmed diagnosis of CAH. Two of the 5 studies included children and adults and three studies included children only. There was no evidence available to inform the stratum of children <1-year-old (including neonates) and 1 study (Caldato 2004[3]) included a study population of children and adults so did not fit directly into one stratum.

Evidence was available for the following outcomes: Health-related quality of life (EQ-5D-5L, SF-36), complications of adrenal insufficiency (growth-related issues in children), fatigue, incidence of adrenal crisis and androgen normalisation. Androgen normalisation determined by biochemical parameters such as 17 OHP, androstenedione, testosterone and DHEAS was the most commonly reported outcome across the studies. Outcome data for growth-related issues in children were not always directly reported by the papers. Therefore, bone age (BA) to chronological age (CA) ratio, height velocity and final adult height were used as surrogate markers. since under-treatment and the resulting excess production of androgens causes accelerated growth, advanced skeletal maturation and early epiphyseal fusion leading to reduced final adult height.

Follow-up periods for these studies ranged between 4 weeks and 1 year.

Due to these important differences in the interventions, methodologies, and reporting of outcomes in the trials a meta-analysis could not be conducted.

Evidence from these studies are summarised in the clinical evidence summary tables below (Tables 10-15).

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.

1.1.10.2. Excluded studies.

See the excluded studies list in Appendix J.

1.1.11. Summary of studies included in the effectiveness evidence.

Table 10: Summary of studies included in the evidence review.

Study	Intervention and comparison	Population	Outcomes	Comments
Caldato 2004[3] Parallel RCT Conducted in Brazil	Intervention: (n= 23) Prednisolone phosphate (single morning oral dose). Doses of daily prednisolone were between 2.4 - 3.75 mg/m2. Comparison: (n=21) Hydrocortisone (3 times daily): 50% of total daily dose in the morning, 25% at midday and 25% in the evening. daily dose of hydrocortisone was between 10-15 mg/m2. Concomitant therapy: All patients also received 0.1 mg fludrocortisone daily in the morning. Follow-up: 1 year	44 pre-pubertal and pubertal people with CAH due to 21-hydroloxase deficiency. Mean age: 9 (range 1 -21 years) Male female ratio: 10:34	Final adult height 17OHP Androstenedione Testosterone	
German 2008[5] Cross over RCT Conducted in Israel	Intervention: (high AM dose) Hydrocortisone: 50% of total daily dose in the morning, 25% at midday and 25% in the evening for 2 weeks. All participants also received a daily dose of fludrocortisone. The total HC dose ranged from 13.5 - 15.5 mg/m2/day. Comparison: (high PM dose) Hydrocortisone: 25% of total daily dose in the morning, 25% at midday and 50% in the evening for 2 weeks. All participants also received a daily dose of fludrocortisone. The total HC dose ranged from 13.5 - 15.5 mg/m2/day. Concomitant therapy: All patients also received a daily dose of fludrocortisone.	15 Children with CAH. Mean Age: 10 (range 7.5 - 14.5 years) Male female ratio: 9:6	17OHP Testosterone Androstenedione DHEAS	

Study	Intervention and comparison	Population	Outcomes	Comments
	Follow-up: 4 weeks. Two weeks for each treatment. Washout period not stated.			
Merke 2021[8] Parallel RCT Conducted in USA	Intervention: (n= 61) Modified-release hydrocortisone. Starting doses of modified-release hydrocortisone (MR-HC) varied based on patient's baseline therapy and were titrated by blinded physicians at 4 and 12 weeks. The median starting dose of daily MR-HC was 25 mg, and at 24 weeks the median dose was 30mg. Comparison: (n= 61) Standard glucocorticoid. Starting doses varied based on patient's baseline therapy and were titrated by blinded physicians at 4 and 12 weeks. By 24 weeks the median dose was 31mg. Follow up: 24 weeks	122 adults with CAH. Age: Range 19-68 years Male female ratio: 44:78 female	17OHP Androstenedione Adrenal crisis Weight HbA1c Fatigue	After 24 weeks, 91 patients continued in a safety extension study for an additional year. Outcomes from the first 24 weeks only are presented in this review.
Nebesio 2016[10] Cross over RCT Conducted in USA	Intervention group 1: (n= 9) Hydrocortisone (HC) 15mg daily in 3 doses Intervention group 2: (n= 9) Prednisolone (PD) 3mg/day Comparison: (n= 9) Dexamethasone (DX) 0.3mg/m2/day Follow-up: 18 weeks. Each treatment schedule lasted 6 weeks before switching to another one. No washout periods.	27 children with CAH Age: range 4.8 - 11.6 years Male female ratio: 4:5	Androstenedione 17OHP	
Silva 1997[15] Cross over RCT Conducted in Brazil	Intervention: Hydrocortisone 15 mg/m2 1x daily and Fludrocortisone 0.1 mg/day for 6 months Comparison: Hydrocortisone 25 mg/m2 1x daily and Fludrocortisone 0.1 mg/day for 6 months	26 children with CAH due to 21-hydroxylase deficiency Mean age: 3.8 (range 3.6 months to 15 years) Male female ratio: 8:18	17OHP Androstenedione Testosterone Final adult height	Outcomes were presented separately for prepubertal (n= 22) vs. pubertal (n = 4).

Study	Intervention and comparison	Population	Outcomes	Comments
	6 months per treatment arm, but washout period was not stated in the paper. Patients were followed up for 1 year.			

1 See Appendix D for full evidence tables.

2

1.1.12. Summary of the effectiveness evidence

See Appendix F for full GRADE tables.

Clinical evidence summaries:

Table 11: Prednisolone (1x daily) compared to hydrocortisone (3 x daily) in pubertal and prepubertal people with congenital adrenal hyperplasia

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Hydrocortisone (3x daily)	Risk difference with prednisolone (1x daily)
Mean level 17OHP (17OHP) assessed with: nmol/L follow-up: 1 years (lower is better)	44 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	-	The mean level 17OHP was 2833 nmol/L	MD 1189.1 nmol/L higher (51.08 lower to 2429.28 higher)
Mean level androstenedione (Androstenedione) assessed with: nmol/L follow-up: 1 years (lower is better)	44 (1 RCT)	⊕◯◯◯ Very low[a,b,d]	-	The mean level androstenedione was 183.2 nmol/L	MD 57.75 nmol/L lower (11.19 lower to 104.31 lower)
Mean level testosterone (Testosterone) assessed with: nmol/L follow-up: 1 years (lower is better)	44 (1 RCT)	⊕◯◯◯ Very low[a,b,e]	-	The mean level testosterone was 118.7 nmol/L	MD 38.55 nmol/L higher (6.48 lower to 83.58 higher)
Mean growth velocity follow-up: 1 years (higher is better)	44 (1 RCT)	⊕◯◯◯ Very low[a,b,f]	-	The mean growth velocity was 1.38	MD 0.26 higher (0.82 lower to 1.34 higher)
Height (Standard deviation scores) assessed with: Bone age follow-up: 1 years (higher is better)	32 (1 RCT)	⊕◯◯◯ Very low[a,b,g]	-	The mean height (Standard deviation scores) was -0.98	MD 0.81 lower (1.47 lower to 0.15 lower)

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Hydrocortisone (3x daily)	Risk difference with prednisolone (1x daily)
Height (Standard deviation scores) assessed with: chronological age follow-up: 1 years (higher is better)	32 (1 RCT)	⊕◯◯◯ Very low[a,b,h]	-	The mean height (Standard deviation scores) was 0.43	MD 0.14 lower (0.99 lower to 0.71 higher)
Ratio BA/CA - at 1 year assessed with: bone age/chronological age ratio (lower is better)	34 (1 RCT)	⊕◯◯◯ Very low[a,b,i]	-	The mean ratio BA/CA - at 1 year was 1.29	MD 0.15 lower (0.03 lower to 0.33 higher)
Height cm - At 1 year follow-up: 1 years (higher is better)	32 (1 RCT)	⊕◯◯◯ Very low[a,b,j]	-	-	SMD 0.17 lower (0.87 lower to 0.52 higher)

Explanations

a. Downgraded by 2 increments as the majority of the evidence was at very high risk of bias (Risk of bias due to performance/measurement bias: Reporting bias: not all outcome measures listed in the methods section were fully reported in results and Study attrition rate not reported).

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs as per the MIDs below

c. Downgraded by 1 interval - MID = 1236 (0.5 x control group SD for final value as vales taken from a published Cochrane review)

d. Downgraded by 1 interval - MID = 47.9 (0.5 x control group SD for final value as vales taken from a published Cochrane review)

e. Downgraded by 1 interval - MID = 44.6 (0.5 x control group SD for final value as vales taken from a published Cochrane review)

f. Downgraded by 2 intervals - MID = 0.53 (0.5 x control group SD for final value as vales taken from a published Cochrane review)

g. Downgraded by 1 interval - MID = 0.37 (0.5 x control group SD for final value as vales taken from a published Cochrane review)

h. Downgraded by 2 intervals - MID = 0.53 (0.5 x control group SD for final value as vales taken from a published Cochrane review)

i. Downgraded by 1 interval - MID = 0.08 (0.5 x control group SD for final value as vales taken from a published Cochrane review)

j. Downgraded by 2 intervals MID = 0.5 (SMD)

Table 12: Hydrocortisone (TID, high morning dose) compared to hydrocortisone (TID, high evening dose) in children with congenital adrenal hyperplasia

Outcomes	No of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Impact
Median 17OHP (17OHP - morning) assessed with: nmol/L follow-up: 4 weeks (lower is better)	15 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	Results for 17 OHP are presented as medians (IQR); 44 (16 to 116) for the high morning dose (n=5) compared to 33 (15 to 76) for the high evening dose (n=6).
Median testosterone (Testosterone) assessed with: nmol/L follow-up: 4 weeks (lower is better)	15 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	Median testosterone was 0.70 nmol/L (IQR 0.30 - 2.30) for those in the high morning dose group (n=5) compared to 1.1 nmol/L (IQR 0.60 to 2.70) for those in the high evening dose group (n=6).
Median androstenedione (Androstenedione) assessed with: nmol/L follow-up: 4 weeks (lower is better)	15 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	Median androstenedione was 1.80 nmol/L (IQR 1.00 – 3.00) for those in the high morning dose group compared to 1.90 nmol/L (IQR 1.20 to 6.50) for those in the high evening dose group.
Median DHEAS (DHEAS) assessed with: nmol/L follow-up: 4 weeks (lower is better)	15 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	Median DHEAS was 0.20 nmol/L (IQR 0.20 - 0.60) for those in the high morning dose group compared to 0.40 nmol/L (IQR 0.20 to 0.70) for those in the high evening dose group.

Explanations

a. Downgraded by 2 increments as the majority of the evidence was at very high risk of bias (Risk of bias due to due to missing outcome data for 4 patients, attrition rate not reported).

b. Downgraded due to uncertainty: small sample size and wide IQR (taken directly from published Cochrane review).

c. Data taken directly from a published Cochrane review. Reported as median values so unable to perform additional analyses.

Table 13: Modified-release hydrocortisone compared to standard glucocorticoid in adults with congenital adrenal hyperplasia

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 from baseline 17OHP 24-hour profile at 24 weeks follow-up: 24 weeks (lower is better)	105 (1 RCT)	⊕◯◯◯ Very low[a,b,c,d]	-	The mean change from baseline 17OHP 24-hour profile at 24 weeks was -0.17	MD 0.23 lower (0.54 lower to 0.08 higher)
Change from baseline 17OHP 7am-3pm profile at 24 weeks follow-up: 24 weeks (lower is better)	105 (1 RCT)	⊕◯◯◯ Very low[a,b,c,d]	-	The mean change from baseline 17OHP 7am-3pm profile at 24 weeks was -0.21	MD 0.48 lower (0.82 lower to 0.14 lower)
Incidence of adrenal crisis (number of patients %) follow-up: 24 weeks (lower is better)	122 (1 RCT)	⊕◯◯◯ Very low[a,b,c,f]	OR 0.13 (0.01 to 1.28)	49 per 1,000	43 fewer per 1,000 (49 fewer to 13 more)
Stress dosing (number of patients %) follow-up: 24 weeks (lower is better)	122 (1 RCT)	⊕◯◯◯ Very low[a,b,g]	RR 0.72 (0.50 to 1.03)	590 per 1,000	165 fewer per 1,000 (295 fewer to 18 more)
EQ-5D-5L index score follow-up: 24 weeks (higher is better)	105 (1 RCT)	⊕◯◯◯ Very low[a,b,c,h]	-	The mean EQ-5D-5L index score was 0.02	MD 0 (1.66 lower to 1.66 higher)
Global Fatigue Index - Change from baseline follow-up: 24 weeks (lower is better)	122 (1 RCT)	⊕⊕◯◯ Low[a,b,c,i]	-	The mean global Fatigue Index - Change from baseline was -0.26	MD 0.48 lower (3.88 lower to 2.92 higher)
SF36 general health perceptions change from baseline follow-up: 24 weeks (higher is better)	105 (1 RCT)	⊕◯◯◯ Very low[a,b,c,n]	-	The mean SF36 general health perceptions change from baseline was -1.88	MD 2.67 higher (0.07 higher to 5.27 higher)
SF36 - Mental health change from baseline follow-up: 24 weeks (higher is better)	105 (1 RCT)	⊕⊕◯◯ Low[a,c,k]	-	The mean SF36 - Mental health change from baseline was 0.35	MD 0.51 higher (2.39 lower to 3.41 higher)

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
SF36 - Physical functioning change from baseline follow-up: 24 weeks (higher is better)	105 (1 RCT)	⊕◯◯◯ Very low[a,b,c,k]	-	The mean SF36 - Physical functioning change from baseline was -0.52	MD 1.68 higher (0.4 lower to 3.76 higher)
SF36 - social functioning change from baseline follow-up: 24 weeks (higher is better)	105 (1 RCT)	⊕◯◯◯ Very low[a,b,c,k]	-	The mean SF36 - social functioning change from baseline was 0.87	MD 1.31 higher (1.8 lower to 4.42 higher)
SF36 - role emotional change from baseline follow-up: 24 weeks (higher is better)	105 (1 RCT)	⊕◯◯◯ Very low[a,b,c,l]	-	The mean SF36 - role emotional change from baseline was -0.34	MD 1.33 higher (2.34 lower to 5 higher)
SF36 - role physical change from baseline follow-up: 24 weeks (higher is better)	105 (1 RCT)	⊕◯◯◯ Very low[a,b,c,k]	-	The mean SF36 - role physical change from baseline was 0.5	MD 1.41 higher (1.48 lower to 4.3 higher)
SF36 - vitality change from baseline follow-up: 24 weeks (higher is better)	105 (1 RCT)	⊕◯◯◯ Very low[a,b,c,j]	-	The mean SF36 - vitality change from baseline was 0.92	MD 0.13 lower (3.17 lower to 2.91 higher)

Explanations

a. Downgraded by 1 increment as the majority of the evidence was at very high risk of bias (Risk of bias due to study attrition rate).

b. Downgraded by 1 increment due to intervention indirectness. Study authors explain that the control arm does not appropriately represent typical clinical practice: more aggressive dose up titration than usually performed.

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs as per MIDs below

d. Downgraded by 1 increment - MID = 0.39 (0.5 x control group SD for final value as no baseline values reported)

e. Downgraded by 1 increment - MID = 14.5 (0.5 x control group SD for final value as no baseline values reported)

f. Downgraded by 2 increment - MID = 0.8 to 1.25 (default MID for dichotomous outcomes)

g. Downgraded by 1 increment - MID = 0.8 to 1.25 (default MID for dichotomous outcomes)

h. Downgraded by 2 increments - MID = 0.03 (established value)

i. no imprecision - MID = 3.9 (0.5x median control group SDs baseline values not reported)

j. Downgraded by 2 increments - MID = 2 (established value)

k. Downgraded by 1 increment - MID = 3 (established value)

l. Downgraded by 1 increment - MID = 4 (established value)

m. SF36 bodily pain was not available for extraction. The paper states 'A technical issue with the scoring of the bodily pain domain meant that these data are not available'.

n. Downgraded by 1 increment - MID = 2 (established value)

Table 14: Hydrocortisone (TID, 15mg/day) compared to prednisolone (3mg/day) or dexamethasone (0.3mg/day) in people with congenital adrenal hyperplasia.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Impact
17OHP (17OHP) assessed with: nmol/L follow-up: 6 weeks (lower is better)	9 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	There were lower levels of 17 OHP reported in the DXA group compared to HC (P < 0.001) and compared to PD (P < 0.001).
Androstenedione (Androstenedione) assessed with: nmol/L follow-up: 6 weeks (lower is better)	9 (1 RCT)	⊕◯◯◯ Very low[a,b,c]	Androstenedione levels were significantly lower with DXA when compared to HC (P = 0.016) and PD (P = 0.002).

Explanations

a. Downgraded by 2 increments as the majority of the evidence was at very high risk of bias (Risk of bias due to unclear randomization procedure, unclear reporting of outcomes and study attrition rate).

b. Downgraded by one increment due to uncertainty around the effect estimate: small sample size so P values should be interpreted with caution.

c. Data taken directly from a published Cochrane review. Only P values and statistical significance reported.

Table 15: Hydrocortisone (15mg/day) with fludrocortisone (0.1mg/day) compared to hydrocortisone (25mg/day) with fludrocortisone (0.1mg/day) in children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Impact
Median 17OHP levels (17OHP) assessed with: nmol/L follow-up: 6 months (lower is better)	(1 RCT)	⊕◯◯◯ Very low[a,b]	In the prepubertal group (n=22), there was a statistically significant (p<0.05) difference in suppression of median 17OHP levels: 17OHP was lower among those treated with HC 25 mg/day (11.5 nmol/L, IQR 0.6 - 819.0) compared to HC 15 mg/day (113.7 nmol/L, IQR 0.5 - 1207). In the pubertal group (n=4), 17OHP levels were lower in those treated with HC 15 mg/day (91.7 nmol/L, IQR 6.8 - 453.0) compared to HC 25 mg/day (314.2 nmol/L, IQR 66.5 - 568.7).
Median androstenedione levels (Androstenedione) assessed with: nmol/L follow-up: 6 months (lower is better)	(1 RCT)	⊕◯◯◯ Very low[a,b]	In the prepubertal group, androstenedione was lower (p<0.05) among those treated with HC 25 mg/day (1.6 nmol/L, IQR 0.1 - 31.8) compared to HC 15 mg/day (3.4 nmol/L, IQR 0.5 - 40.2). In the pubertal group, 17OHP levels were lower in those treated with HC 15 mg/day (11 nmol/L, IQR 6.1 - 41.9) compared to HC 25 mg/day (22.3 nmol/L, IQR 10.5 - 46.5).

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Impact
Median testosterone levels (Testosterone) assessed with: nmol/L follow-up: 6 months (lower is better)	(1 RCT)	⊕◯◯◯ Very low[a,b]	No differences were noted in testosterone levels at 6 months. In the prepubertal group, median testosterone levels were 2.5 nmol/L (IQR 0.8 to 9.1) for those treated with HC 15 mg versus 2.3 nmol/L (IQR 1.2 to 11.3) for those treated with HC 25 mg. In the pubertal group, median testosterone levels were 4.7 nmol/L (IQR 3.9 to 6.9) for those treated with HC 15 mg versus 6.2 nmol/L (IQR 4.5 to 9.2) for those treated with HC 25 mg.

1

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Hydrocortisone (25mg/day) with fludrocortisone (0.1mg/day)	Risk difference with hydrocortisone (15mg/day) with fludrocortisone (0.1mg/day)
Final adult height follow-up: 6 months (higher is better)	52 (1 RCT)	⊕◯◯◯ Very low[a,c,d]	-	The mean final adult height was N/A	MD 0.34 higher (0.27 higher to 0.41 higher)

2 **Explanations**

3 a. Downgraded by 2 increments as the majority of the evidence was at very high risk of bias (Risk of bias due to issues surrounding randomisation method and selective outcome
4 reporting and incomplete outcome data).

5 b. Downgraded for imprecision due to small sample size and wide IQR

6 c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

7 d. Downgraded by 2 increments - MID = 0.04 (calculated from MD (SE) as no baseline values reported)

8 e. Data taken directly from a published Cochrane review and reported in median values and IQR so unable to perform additional analyses.

1
2

1.1.13. Economic evidence

1.1.13.1. Included studies.

No health economic studies were included.

1.1.13.2. Excluded studies.

Two economic studies relating to this review question were identified but excluded due to methodological limitations[1, 14] This study is listed in Appendix J, with reasons for exclusion given.

See also the health economic study selection flow chart in F.2.1.

1.1.14. Economic evidence

This area was not prioritised for new cost-effectiveness analysis.

1.1.15. Unit costs

Relevant unit costs are provided below to aid the consideration of cost-effectiveness. Costs for children with CAH are presented in **Table 16** and costs for adults are presented in **Table 17**. Combination hydrocortisone in children is a combination of standard release and Alkindi granules in capsules.

Table 16: Unit costs for children for the routine pharmacological management of CAH

Resource[(a)]	Dose per day	Cost per day	Cost per year
Hydrocortisone	***10mg/m² - 15 mg/m²***		
Neonate	2.5mg - 3.5mg		
Standard release	2.5mg - 3.5mg[(b)]	£0.29	£104.15
Alkindi	2.5mg - 3.5mg	£3.38 - £4.73	£1,231.88 - £1,724.63
Combination	n/a		
1 year	4.5mg - 7mg		
Standard release	4.5mg - 7mg[(b)]	£0.29	£104.15
Alkindi	n/a		
Combination	4.5mg - 7mg[(c)]	£3.39 - £4.08	£1,236.99 - £1,488.47
2 years	5.5mg - 8.5mg		
Standard release	5.5mg - 8.5mg[(b)]	£0.29	£104.15
Alkindi	n/a		
Combination	5.5mg - 8.5mg[(d)]	£4.74 - £2.83	£1,729.74 - £1,034.41
5 years	7.5mg - 11mg		
Standard release	7.5mg - 11mg[(b)]	£0.21	£78.11
Alkindi	n/a		
Combination	7.5mg - 11mg[(e)]	£4.75 - £2.94	£1,734.85 - £1,073.10
10 years	11mg – 16.5mg		
Standard release	11mg – 16.5mg[(b)]	£0.21	£78.11
Alkindi	n/a		

Resource[a]	Dose per day	Cost per day	Cost per year
Combination	11mg – 16.5mg[f]	£2.94 - £2.89	£1,073.10 - £1,055.34
12 years	12mg – 18mg		
Standard release	12mg – 18mg[b]	£0.21	£78.11
Combination	12mg – 18mg[g]	£4.87 - £2.23	£1,778.65 - £814.07
14 years	15mg – 22.5mg		
Standard release	15mg – 22.5mg[h]	£0.21 - £0.83	£78.11 - £303.56
Combination	n/a		
16 years	17mg – 25mg		
Standard release	17mg – 25mg[i]	£0.21 - £0.94	£78.11 - £342.25
Combination	17mg[j]	£3.57	£1,301.71
Modified-release hydrocortisone			
Modified release hydrocortisone (Efmody)	15mg – 25mg[k]	See Table 17	
Fludrocortisone			
Fludrocortisone	50mcg – 200mcg[l]	£0.10 - £0.42	£37.90 - £151.60
Sodium chloride			
Sodium chloride oral solution (5mmol/ml)	17mmol – 34mmol	£0.66-£1.33	£242.62 - £485.23

(a) Source of costs from The British National Formulary (BNF).[2]
(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) 4.5mg costed as one 2.5mg standard release tablet and 2mg Alkindi granules in capsules; 7mg costs as two 2.5mg standard release tablets and 2mg Alkindi granules in capsules.
(d) 5.5mg costed as one 2.5mg standard release tablet and 3mg Alkindi granules in capsules; 8.5mg costs as one 5mg + one 2.5mg standard release tablet and 1mg Alkindi granules in capsules.
(e) 7.5mg costed as two 2.5mg standard release tablets and 2.5mg Alkindi granules in capsules; 11mg costs as two 5mg standard release tablets and 1mg Alkindi granules in capsules.
(f) 11mg costs as two 5mg standard release tablets and 1mg Alkindi granules in capsules; 16.5mg costs as one 10mg + one 5mg standard release tablet and 1.5mg Alkindi granules in capsules.
(g) 12mg costed as one 5mg + two 2.5mg standard release tablets and 2mg Alkindi granules in capsules; 18mg costs as one 10mg + one 5mg + one 2.5mg standard release tablets and 0.5mg Alkindi granules in capsules.
(h) 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 + two 2.5 mg standard release tablets; 22.5mg costed as two 10mg+ 2.5mg standard release tablets.
(i) 25mg costs as two 10mg + one 5mg standard release tablet.
(j) Either one 10mg tablet used for each dose, assuming three doses daily, tablets can be split to make up doses or 17mg costed as one 10mg + one 5mg standard release tablet and 2mg Alkindi granules in capsules.
(k) Only prescribed to children ≥12 years old.
(l) Cost available in the BNF is for 100mcg per day. The cost for 50mcg a day assumes people take half a 100mcg tablet daily and there is no drug wastage.

Table 17: Unit costs for adults for the routine pharmacological management of CAH

Resource[a]	Dose per day	Cost per day	Cost per year
Hydrocortisone	***15mg – 25mg[b]***		
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
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

Resource[a]	Dose per day	Cost per day	Cost per year
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
Modified release hydrocortisone (Efmody)	***15mg – 25mg***		
Prescribed as three 5mg tablets a day	15mg	£8.10	£2,956.50
Prescribed as one 5mg tablet and one 10mg tablet a day	15mg	£8.20	£2,993.00
Prescribed as four 5mg tablets a day	20mg	£10.80	£3,942.00
Prescribed as two 10mg tablets a day	20mg	£11.00	£4,015.00
Prescribed as five 5mg tablets a day	25mg	£13.50	£4,927.50
Prescribed as three 5mg tablets and one 10mg tablets a day	25mg	£13.60	£4,964.00
Prescribed as one 5mg tablet and two 10mg tablets a day	25mg	£13.70	£5000.50
Prednisolone	***3mg – 6mg***		
Prescribed as three 1mg tablets a day	3mg	£0.08	£30.11
Prescribed as one 1mg tablet and one 5mg tablet a day	6mg	£0.06	£22.29
Dexamethasone			
Dexamethasone	0.25mg – 0.5mg[d]	£0.05 - £0.10	£19.10 - £39.19
Fludrocortisone			
Fludrocortisone	50mcg – 300mcg[e]	£0.10 - £0.62	£37.90 - £227.40

(a) Source of costs from The British National Formulary (BNF).[2]
(b) Standard release hydrocortisone is taken either 2 or 3 times a day.
(c) For a 15mg dose of hydrocortisone 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.
(e) Cost available in the BNF is for 100mcg per day. The cost for 50mcg a day assumes people take half a 100mcg 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

Due to the sparsity of available evidence the committee chose to investigate all outcomes at any follow up time point reported. Follow-up periods for these studies ranged between 4 weeks and 1 year.

The variability in the interventions, comparators and outcomes meant that a meta-analysis of the data was not possible.

1.2.1.1. All primary adrenal insufficiency

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.

Evidence was available for the following outcomes: Health-related quality of life (SF-36, AddiQOL), complications of adrenal insufficiency, adverse events, hospitalisation, cholesterol, blood pressure, weight, BMI, HbA1c, illness episodes, additional hydrocortisone doses, fatigue, and infections.

1.2.1.2. Primary adrenal insufficiency due to Congenital Adrenal hyperplasia (CAH)

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 of adrenal crisis, complications of adrenal crisis, androgen normalisation (specific to CAH) determined by biochemical parameters such as 17 OHP, androstenedione, testosterone and DHEAS, admission to hospital and/or ITU, readmission to hospital, length of stay at hospital or ITU, treatment-related adverse events, activities of daily living.

This review updated a published Cochrane review, Ng, 2020 [11]. Therefore, the majority of the outcomes included in this review are the same as those reported in the Cochrane review, but with several additions and exclusions that the committee agreed were necessary to be more in line with the review protocol and for their decision making.

Evidence was available for the following outcomes: Health related quality of life (EQ-5D-5L, SF-36), complications of adrenal insufficiency (growth related issues in children), fatigue, incidence of adrenal crisis and androgen normalisation. Androgen normalisation was determined by biochemical parameters such as 17 OHP, androstenedione, testosterone and was the most commonly reported outcome across the studies. Outcome data for growth related issues in children were not always directly reported by the papers. Therefore, bone age to chronological age ratio, height velocity and final adult height were used as surrogate markers.

1.2.2. The quality of the evidence

1.2.2.1. All primary adrenal insufficiency

Evidence was available from four cross over RCTs and one parallel RCT. The majority of trials used oral glucocorticoid replacement therapies at different daily doses administered in different daily schedules. One study (Oksnes 2014[13]) compared the effects of continuous subcutaneous hydrocortisone infusion with oral hydrocortisone replacement.

The majority of the evidence was assessed against GRADE as being of low to very low quality, mostly due to imprecision and risk of bias. A minority of outcomes were assessed as being of moderate quality.

Risk of bias was downgraded by 1 increment in three studies and 2 increments in 2 studies. This was due to unclear randomisation procedure or allocation concealment, bias in the measurement of the outcome, and study attrition rate or lack of information around missing outcome data.

One study (Isidori 2018[6]) was downgraded by 1 increment for population indirectness, as the population included people with both primary and secondary adrenal insufficiency (50% of

the population had secondary adrenal insufficiency). All outcomes reported by this study were downgraded accordingly.

The majority of outcomes were also downgraded by 1 or 2 increments for imprecision. This was due to uncertainty around the confidence interval which crossed one or both of the MIDs.

1.2.2.2. Primary adrenal insufficiency due to Congenital Adrenal hyperplasia (CAH)

Five randomised controlled trials were included in the review. Four were included in a published Cochrane review[11] and one was identified through a literature search[8]. One study (Winterer 1985[16]) was included in the Cochrane review as a narrative summary but excluded from this review as the data was not in an extractable format and could not be analysed.

The evidence varied from low to very low quality with the majority being of very low quality. Outcomes were commonly downgraded for risk of bias and imprecision due to uncertainty around the effect estimate.

Risk of bias was downgraded by 2 increments in the majority of studies, and this was most often due to; unclear randomisation procedure, study attrition rate, lack of information around missing outcome data and reporting bias (i.e. not all outcomes in the methods reported).

One study Merke 2021 was downgraded for intervention indirectness. The study authors explained that the control arm does not appropriately represent typical clinical practice and instead a more aggressive dose-up titration than is usually performed. All outcomes reported by this study were downgraded accordingly.

The majority of outcomes were also downgraded for imprecision. This was due to uncertainty around the confidence interval and it is crossing one or both of the MIDs.

3 studies (German 2008, Nebesio 2016 and Silva 1997) included in the Cochrane review reported data as median IQR or P values. These were not suitable for additional analyses through GRADE and therefore the results were taken directly from the Cochrane review and presented in the grade tables. Imprecision ratings for these outcomes were also taken from the Cochrane review and no additional analysis took place. These outcomes were included due to the lack of RCT evidence available.

Overall, the evidence for glucocorticoid replacement for primary adrenal insufficiency including CAH, did not provide adequate certainty for the basis of clinical recommendations. Therefore, the committee agreed to use their clinical expertise and experience to make recommendations.

1.2.3. Benefits and harms

Due to heterogeneity in the interventions, comparators, and outcomes across the included studies, it was not possible to generate meta-analyses. The committee therefore discussed the benefits and harms of each comparison individually.

Most of the studies were in adults and did not report data separately for the population strata that were prespecified in the protocol. Therefore, the committee were unable to assess the effectiveness of glucocorticoids in these specific strata but were able to glean some information that helped their discussion of the potential benefits and harms in different age groups.

1.2.3.1. All primary Adrenal Insufficiency

Twice daily (BID) doses (20 mg 12:00, 10mg 16:00) vs 4 daily doses 10mg 07:00, 10mg 12:00, 5 mg 16:00, 5mg 20:00)

One study (Ekman 2012[4]), compared a 2-dose regimen to a 4-dose regimen of 30mg total daily dose of Hydrocortisone. The committee noted that there were several clinically important harms of the 2-dose regimen for health-related quality of life on various subscales of the SF-36. These included: role function, bodily pain, general health, vitality, social function and mental health. However, one subscale, physical function, reported no clinically important difference. No clinically important differences in metabolic measures (bodyweight, BMI and blood pressure) from administering hydrocortisone 4 times per day compared to 2 times per day were reported.

Once-daily modified-release HC vs standard glucocorticoid

In discussing the evidence from one study (Isidori 2018[6]) comparing once-daily modified-release hydrocortisone 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. 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 compared to standard glucocorticoid therapy, the magnitude of benefit was not significant enough to change standard practice.

Once-daily dual-release hydrocortisone to hydrocortisone three times daily (TID)

Two studies (Johansson 2012[7] and Nilsson 2014[12]) compared once-daily dual-release hydrocortisone to hydrocortisone three times daily. The committee focused their discussion on the incidence of adverse events, serious adverse events and fatigue measured in the Johansson study and illness-related outcomes (additional HC dose per illness episode) measured in the Nilsson study. The committee noted that the incidence of these outcomes were all higher in the dual-release arm compared to hydrocortisone three times daily, indicating a clinical harm from the use of dual-release hydrocortisone. Clinical outcomes such as HbA1c and cholesterol showed no clinically important difference between the 2 interventions.

Continuous subcutaneous hydrocortisone via insulin pump vs hydrocortisone

Only one study (Oksnes 2014[13]) looked at continuous subcutaneous hydrocortisone via an insulin pump which was compared to oral hydrocortisone three times daily. This assessed HbA1c, BMI, weight, blood pressure, cholesterol, adverse events and serious adverse events at 12 weeks. All outcomes reported no clinically important difference except for a greater amount of adverse events the continuous subcutaneous hydrocortisone arm. The committee also noted that the inclusion criteria for this study excluded patients who were not comfortable with a subcutaneous pump, suggesting that the incidence of device-related adverse events might have been higher in a broader population. Overall, in light of the very low certainty of the evidence, the committee determined that there was not enough evidence to confirm a clinical harm/benefit from the use of a subcutaneous hydrocortisone pump compared to standard oral hydrocortisone.

Overall, the committee assessed that there was insufficient evidence of clinical benefit to support the use of modified-release, dual-release, or continuous subcutaneous formulations of hydrocortisone over the use of standard glucocorticoid replacement (oral BID or TID tablets).

1.2.3.2. Primary adrenal insufficiency due to Congenital Adrenal hyperplasia (CAH)

All trials employed an oral glucocorticoid replacement therapy but with different regimens and daily doses. Two trials compared different dose regimens of hydrocortisone (German 2008 [5], Silva 1997[15]), one trial compared hydrocortisone with fludrocortisone to prednisolone with fludrocortisone (Caldato 2004[3]) and one three-arm trial compared hydrocortisone to prednisolone and dexamethasone (Nebiso 2016[10]). One trial (Merke 2021[8]) compared modified-release hydrocortisone with standard-release glucocorticoid.

Prednisolone (1x daily) compared to hydrocortisone (3 x daily) in pubertal and prepubertal people with congenital adrenal hyperplasia

One study (Caldato 2004[3]) compared 1 single morning dose of prednisolone (plus 0.1 mg Fludrocortisone) to 3 x daily hydrocortisone (plus 0.1mg fludrocortisone) in both pubertal and pre-pubertal people with CAD. Three outcomes assessed Androgen normalisation by measuring 17OHP, androstenedione, and testosterone. These outcomes showed no clinically important differences between the two dosing strategies. Growth-related issues in children were assessed through several different outcomes including growth velocity, height (bone age), height (chronological age) and height in cm, and again showed no clinically important difference. An additional outcome related to growth-related issues was assessed through the bone age/chronological age ratio. This showed a clinically important benefit of once-daily prednisolone, indicating, that even on single morning dosages, prednisolone may control bone maturation more efficiently than three times daily hydrocortisone.

Hydrocortisone (high morning dose) compared to hydrocortisone (high evening dose) in children with congenital adrenal hyperplasia

One study (German 2008[5]) compared two dosing regimens of hydrocortisone and compared a high morning dose with a high evening dose. All patients also received a daily dose of fludrocortisone. This study assessed androgen normalisation by measuring 17OHP, testosterone, androstenedione and DHEAS. Data for these outcomes were reported as median and IQR in the Cochrane review so Revman and GRADE analysis and measurements of clinically important differences were not possible. However, the committee considered the overall direction of the data and analyses presented in the Cochrane review and agreed with the Cochrane review conclusion that there were no clinically important differences between any of the outcomes at the 4 week follow up.

Modified-release hydrocortisone compared to standard glucocorticoid in adults with congenital adrenal hyperplasia

One study (Merke 2021[8]) compared a modified-release Hydrocortisone that mimics physiologic cortisol secretion with a standard immediate-release glucocorticoid in adults with CAH. Several outcomes reported a benefit of the modified release hydrocortisone, however the majority showed no clinically important difference. The percentage of patients needing stress dosing by 24 weeks was less in the modified release group and represented a clinically important benefit. Additionally, measures of androgen normalisation were assessed through 17 OHP 7 am-3 pm profile at 24 weeks and showed a clinically important benefit of the modified release hydrocortisone (indicated by a lower rise in 17OPH). However, the 24-hour 17 OHP profile and percentage of patients with adrenal crises showed no clinically important difference between the groups. Additionally, the majority of patients self-reported outcomes such as measures of fatigue on the global fatigue index and health-related quality of life measures (reported on the EQ5D and SF-36), all showed no difference between the interventions. One subscale of the SF-36 (general health perceptions) did show a clinically important benefit of the modified-release hydrocortisone, however as this was the only subscale to indicate a difference between the two treatments the committee did not take this into account in their decision-making. The committee discussed the benefits of modified-release hydrocortisone but also acknowledged the increased costs associated with using the

form of hydrocortisone over the use of immediate-release hydrocortisone. They therefore agreed that modified-release Hydrocortisone should be considered in certain circumstances where patients are struggling to adhere to standard glucocorticoids.

Hydrocortisone (15mg/day) compared to prednisolone (3mg/day) or dexamethasone (0.3mg/day) in people with congenital adrenal hyperplasia.

One small 3-arm study of 9 children with CAH compared Hydrocortisone with Prednisolone and Dexamethasone and assessed androgen normalisation by measuring 17OHP, and androstenedione. However, outcomes were reported as P values in the Cochrane review so Revman and GRADE analysis and measurements of clinical importance were not possible. Despite this, the committee considered the overall direction of the data and analyses presented in the Cochrane review which concluded that treatment with Hydrocortisone (15mg/day) and Dexamethasone (0.3 mg/day) suppressed 17 OHP and androstenedione more than Prednisolone (3mg/day) treatment after six weeks of treatment. Despite these reported benefits the committee agreed that this evidence was too limited and of insufficient quality to take into account in their decision making.

Hydrocortisone (15mg/day) with fludrocortisone (0.1mg/day) compared to hydrocortisone (25mg/day) with fludrocortisone (0.1mg/day)

One study of 26 children with CAH compared a low dose of Hydrocortisone with fludrocortisone to a high dose of Hydrocortisone with fludrocortisone. The results were presented as median and IQR for majority of outcomes so Revman and GRADE analyses and measurements of clinical importance were not possible. The committee discussed the analyses presented in the Cochrane review which found that at six months 17 OHP and androstenedione levels were more suppressed in participants taking the 25 mg/m2/day Hydrocortisone compared to the 15 mg/m2/day. There were no differences noted in testosterone levels. Final adult height, measured as growth velocity was reported as mean values and their standard deviations so GRADE analyses were possible and showed a clinically important benefit (higher growth velocity) of the 15 mg/m2/day hydrocortisone compared to the higher daily dose. However, due to the very low-quality rating, the committee did not take this outcome into account in their decision making.

Other factors the committee took into account

One study (Ekman 2012[4]), compared a 2-dose regimen (20 mg 12:00, 10mg 16:00) to a 4-dose regimen (10mg 07:00, 10mg 12:00, 5 mg 16:00, 5mg 20:00) of 30mg total daily dose of Hydrocortisone. There were several clinically important harms of the 2-dose regimen for health-related quality of life on various subscales of the SF-36. These included: role function, bodily pain, general health, vitality, social function and mental health. The committee noted that participants also completed an overall experience questionnaire which was not extracted as a protocol outcome but could help to explain some of the differences in the SF36 scores. Reasons cited for preferring the 4-dose regimen to the 2-dose regimen included less fatigue, more alertness during the day and especially during the morning, fewer headaches and a feeling that the treatment effect was less varying during the day. This may be explained by the 4-dose regimen more closely following the physiological cortisol circadian rhythm.

1.2.4. Overall discussion

1.2.4.1. All primary adrenal insufficiency including adrenal insufficiency due to CAH.

Due to the limited and low-quality evidence available the committee agreed that there was insufficient evidence to form the basis of recommendations, so they used their clinical expertise and consensus opinion to formulate recommendations in this section. The committee wished to make strong recommendations despite the lack of convincing evidence as glucocorticoids are lifesaving drugs and the benefits of their use in adrenal insufficiency by far outweigh the risks which could include death.

The evidence for glucocorticoid replacement was insufficient but the committee concluded that overall and despite the disparities and the low certainty in the evidence, it mostly indicated that, total daily doses of immediate-release hydrocortisone between 15-25 mg in divided doses were safe to use in all people with AI including those with AI due to CAH. 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 but noted that the aim of dosing is to mimic the circadian rhythm with the largest dose given in the morning and the smallest dose in the evening. Dosing should be titrated to maximise well-being and minimise side effects. To avoid over or undertreatment side effects. Over-treatment side effects could include increased appetite, weight gain and changes in sleep patterns. Symptoms of under-treatment could include early-morning nausea, poor appetite, and weight loss.

Based on clinical experience, the committee acknowledged that adherence to glucocorticoid therapy is often an issue for people with adrenal insufficiency since standard care typically involves 2 (BID) or 3 (TID) daily oral doses of hydrocortisone tablets. They noted that multiple daily doses may not be appropriate for everyone, for example, younger people in particular, can often forget or choose to skip doses. For this reason, they recommended prednisolone for all people with AI provided they have stopped growing to avoid the growth hampering effects of prednisolone. In this situation, clinicians should discuss if the person would like to change to prednisolone 3mg-5mg daily in 1 or 2 doses.

The committee assessed that there was insufficient evidence of clinical benefit to support the use of modified-release hydrocortisone over the use of standard glucocorticoid replacement therapy (oral BID or TID tablets) for all patients. However, they agreed that modified-release hydrocortisone should be considered in certain circumstances. Specifically, in young people aged 12-15 years with primary adrenal insufficiency secondary to CAH and who are still growing and struggling to adhere to a standard hydrocortisone regimen or when standard regimens are not achieving adequate control. Alternatively, if they have stopped growing but immediate-release hydrocortisone or prednisolone is not suitable (such as in young people with diabetes or difficulties with medication adherence), then modified-release hydrocortisone may also be considered.

The committee acknowledged the limited evidence looking at dexamethasone compared to prednisolone and hydrocortisone. They concluded that dexamethasone should only be considered for people over 16 years old with primary adrenal insufficiency secondary to CAH if immediate-release hydrocortisone and prednisolone have not been successful in controlling androgens.. This is due to dexamethasone having the highest risk of side effects, including, weight gain, increased blood pressure, osteoporosis, stretch marks in adults and children especially teenagers. Therefore, dexamethasone should only be prescribed following specialist clinical advice and weighing up the balance of risks and benefits to the individual patients.

The committee recommended that in people with primary adrenal insufficiency due to CAH, an increase in the glucocorticoid dose may be required. They acknowledged that this is partly to control the underlying cause of AI rather than AI itself which is outside the scope of the guideline. Nevertheless, they agreed this was important to include as it is difficult to separate control of the disease from the control of its underlying cause since both require glucocorticoid replacement. Therefore, they recommended that specialist endocrinology advice should be sought.

Medications that induce the drug-metabolizing enzyme CYP3A4 (e.g., carbamazepine, mitotane, St John's wort, rifampicin and modafinil) also accelerate clearance and reduce the efficacy of glucocorticoids. Therefore, the committee recommended that people taking enzyme inducers should have an increased dose of glucocorticoids to account for the reduced efficacy of glucocorticoids in these situations and to avoid an adrenal crisis.

The committee did not recommend the use of a continuous subcutaneous hydrocortisone pump for routine daily management of glucocorticoid replacement for all people with AI. They noted that patients would require training before being able to use the device and that some patients may experience device-related adverse events. As a result, the committee concluded that the device was unlikely to be suitable for all patients with adrenal insufficiency.

There was no evidence for mineralocorticoids. The committee made a consensus recommendation to use fludrocortisone as first-line replacement of mineralocorticoids. However, if hyponatraemia persists or there is severe salt wasting which occurs most frequently in neonates, the committee recommended 0.9% sodium chloride solution given intravenously and according to endocrinology advice.

Children

The committee also recommended immediate-release hydrocortisone in children under 16. The dose should be titrated to maximise well-being and minimise side effects. Over-treatment side effects could include growth retardation, weight gain and changes in sleep patterns. Symptoms of under-treatment could include recurrent infections and fatigue.

1.2.5. Cost effectiveness and resource use

1.2.5.1. All primary adrenal Insufficiency

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.

Treatment for Addison's differs for adults and children due to the growth-hampering effects of some drugs used to treat Addison's in prepubescent children. Children with Addison's are not prescribed prednisolone or Plenadren (modified-release hydrocortisone). This was therefore taken into account when qualitatively assessing the cost effectiveness of treatments for the routine management of Addison's.

The committee assessed the clinical evidence and costs presented for standard-release hydrocortisone and modified-release hydrocortisone. Due to the modified-release preparation costing significantly more with equivalent efficacy, the committee made a do not routine offer recommendation for this formulation unless immediate-release hydrocortisone and prednisolone are not suitable. This would be in people who had completed growth and could include those with type 1 diabetes or those with difficulties with medicines adherence.

No clinical evidence was identified comparing prednisolone or dexamethasone to the other comparators listed in the review protocol. When the committee discussed the use of prednisolone and dexamethasone their discussion was specific to adults because prednisolone and dexamethasone are not routinely prescribed to prepubescent children. In current practice, dexamethasone is not routinely prescribed to adults with Addison's due to the high risk of side effects (such as sleep problems, mood changes, indigestion, weight gain and being more susceptible to picking up infections). A do not offer recommendation was made to reflect this. Approximately 20% of people with Addison's are prescribed prednisolone. The committee made a 'consider' recommendation for prednisolone in those who have stopped growing and with adherence difficulties with immediate-release hydrocortisone.

All adults and children with Addison's are also prescribed mineral corticosteroids (fludrocortisone and sodium chloride) – with fludrocortisone being the first-line treatment option. The recommendations reflect this current practice.

Overall, the recommendations made by the committee are reflective of current practice and therefore not anticipated to result in a significant resource impact.

1.2.5.1. Primary adrenal insufficiency due to Congenital Adrenal hyperplasia (CAH)

Two economic evaluations were identified for this review question but excluded due to applicability and methodological concerns. Therefore, unit costs were presented to aid the committee's consideration of cost-effectiveness. The same considerations for the provision of immediate-release hydrocortisone (the use of tablets and alkindi, alone or in combination) discussed above for people with non-CAH are applied here also.

The two cost-effectiveness analyses identified for this review were the All Wales Medicines Strategy Group (AWMSG) and Scottish Medicines Consortium (SMC) appraisals for Efmody (modified-release hydrocortisone). Reasons for exclusion are noted in section Table 25. However, of note, NHS Wales recommended Efmody as a second-line treatment option in adolescents not adequately controlled on maximum guideline doses of immediate-release hydrocortisone; and as a third-line treatment in adults not adequately controlled on maximum guideline doses of immediate-release hydrocortisone and/or prednisolone. The SMC did not recommend Efmody for use within NHS Scotland.

Treatment for CAH differs for adults and children due to the growth-hampering effects of some drugs used to treat CAH in pre-pubescent children. Children with CAH are not prescribed prednisolone, or Plenadren (modified-release hydrocortisone), and are only prescribed Efmody (modified-release hydrocortisone) over the age of 12. This was therefore taken into account when qualitatively assessing the cost-effectiveness of treatments for the routine management of CAH.

The committee assessed the clinical evidence and costs presented for immediate-release hydrocortisone and different modified-release hydrocortisones (Plenadren and Efmody).

Based on unit costs presented the committee concluded they were only able to make recommendations reflective of current practice for modified-release hydrocortisone due to this preparation costing significantly more with equivalent efficacy. It was therefore recommended that modified-release hydrocortisone be prescribed as a final line therapy option (as in line with the AWMSG recommendations) to people who either continue to be symptomatic whilst receiving standard-release hydrocortisone or to people with poor adherence to standard-release hydrocortisone.

Due to the significantly higher costs of modified-release hydrocortisone, it is important clinicians try to manage poor adherence to standard-release hydrocortisone, only prescribing modified-release hydrocortisone once other appropriate medications have been tried (for example, prednisolone in adults and children who have stopped growing). However, when poor adherence cannot be managed it is important modified-release hydrocortisone is prescribed. Modified-release hydrocortisone as a final-line therapy is likely a cost-effective treatment option, as, without glucocorticoids, people are at high risk of experiencing an adrenal crisis – a medical emergency which if not treated quickly enough can result in death. People who experience an adrenal crisis require emergency hydrocortisone and are likely to require hospital admission. The cost of a hospital admission will vary depending on the severity of the adrenal crisis, but overall will have high-cost implications for the NHS.

No clinical evidence was identified comparing prednisolone or dexamethasone to other comparators listed in the review protocol. When the committee discussed the use of prednisolone and dexamethasone their discussion was specific to adults because prednisolone and dexamethasone are not routinely prescribed to prepubescent children. In current practice, dexamethasone is occasionally prescribed to adults with CAH and approximately 20% of people with CAH are prescribed prednisolone. All adults and children with CAH are also prescribed mineral corticosteroids (fludrocortisone and sodium chloride) – with fludrocortisone being the first-line treatment option.

Of note, when the committee were comparing the costs of standard and modified-release hydrocortisone this was for adults and children ≥12 because the smallest dose of modified-release hydrocortisone (2.5mg) can only be prescribed to children over ≥12 based on body surface area dosing. Breaking modified-release hydrocortisone tablets into smaller doses deactivates their modified-release properties, so prescribing lower doses is not an option.

Overall, the recommendations made by the committee are reflective of current practice and therefore not anticipated to result in a significant resource impact.

1.3. Recommendations supported by this evidence review.

This evidence review supports recommendations 1.3.1 – 1.3.6.

References

1. All Wales Therapeutics & Toxicology Centre (AWTTC). AWMSG Secretariat Assessment Report. Hydrocortisone (Efmody) 5 mg, 10 mg and 20 mg modified-release hard capsules. Reference number: 3017. 2022. Available from: https://awttc.nhs.wales/files/appraisals-asar-far/appraisal-report-hydrocortisone-efmody-3017/

2. BMJ Group and the Royal Pharmaceutical Society of Great Britain. British National Formulary. 2023. Available from: https://bnf.nice.org.uk/ Last accessed: 05/11/2023.

3. Caldato MC, Fernandes VT, Kater CE. One-year clinical evaluation of single morning dose prednisolone therapy for 21-hydroxylase deficiency. Arquivos Brasileiros de Endocrinologia e Metabologia. 2004; 48(5):705-712

4. Ekman B, Bachrach-Lindstrom M, Lindstrom T, Wahlberg J, Blomgren J, Arnqvist HJ. A randomized, double-blind, crossover study comparing two- and four-dose hydrocortisone regimen with regard to quality of life, cortisol and ACTH profiles in patients with primary adrenal insufficiency. Clinical Endocrinology. 2012; 77(1):18-25

5. German A, Suraiya S, Tenenbaum-Rakover Y, Koren I, Pillar G, Hochberg Z. Control of childhood congenital adrenal hyperplasia and sleep activity and quality with morning or evening glucocorticoid therapy. Journal of Clinical Endocrinology and Metabolism. 2008; 93(12):4707-4710

6. Isidori AM, Venneri MA, Graziadio C, Simeoli C, Fiore D, Hasenmajer V et al. 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; 6(3):173-185

7. Johannsson G, Nilsson AG, Bergthorsdottir R, Burman P, Dahlqvist P, Ekman B et al. Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. Journal of Clinical Endocrinology and Metabolism. 2012; 97(2):473-481

8. Merke DP, Mallappa A, Arlt W, Brac de la Perriere A, Linden Hirschberg A, Juul A et al. Modified-release hydrocortisone in congenital adrenal hyperplasia. Journal of Clinical Endocrinology and Metabolism. 2021; 106(5):e2063-e2077

9. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. London. National Institute for Health and Care Excellence, 2014. Available from: https://www.nice.org.uk/process/pmg20/chapter/introduction

10. Nebesio TD, Renbarger JL, Nabhan ZM, Ross SE, Slaven JE, Li L et al. Differential effects of hydrocortisone, prednisone, and dexamethasone on hormonal and pharmacokinetic profiles: a pilot study in children with congenital adrenal hyperplasia. International Journal of Pediatric Endocrinology. 2016; 2016:17

11. Ng SM, Stepien KM, Krishan A. Glucocorticoid replacement regimens for treating congenital adrenal hyperplasia. Cochrane Database of Systematic Reviews 2020, Issue CD012517. DOI: 10.1002/14651858.CD012517.pub2.

12. Nilsson AG, Marelli C, Fitts D, Bergthorsdottir R, Burman P, Dahlqvist P et al. Prospective evaluation of long-term safety of dual-release hydrocortisone replacement administered once daily in patients with adrenal insufficiency. European Journal of Endocrinology. 2014; 171(3):369-377

13. Oksnes M, Bjornsdottir S, Isaksson M, Methlie P, Carlsen S, Nilsen RM et al. Continuous subcutaneous hydrocortisone infusion versus oral hydrocortisone replacement for treatment of addison's disease: a randomized clinical trial. Journal of Clinical Endocrinology and Metabolism. 2014; 99(5):1665-1674

14. Scottish Medicines Consortium. Hydrocortisone modified-release 5mg, 10mg and 20mg hard capsules (Efmody®). 2022. Available from: https://www.scottishmedicines.org.uk/medicines-advice/hydrocortisone-modified-release-hard-capsules-efmody-full-smc2414/

15. Silva IN, Kater CE, Cunha CF, Viana MB. Randomised controlled trial of growth effect of hydrocortisone in congenital adrenal hyperplasia. Archives of Disease in Childhood. 1997; 77(3):214-218

16. Winterer J, Chrousos GP, Loriaux DL, Cutler GB, Jr. Effect of hydrocortisone dose schedule on adrenal steroid secretion in congenital adrenal hyperplasia. Journal of Pediatrics. 1985; 106(1):137-142

Appendices

Appendix A Review protocols

A.1 Review protocol for routine pharmacological management of primary adrenal insufficiency

Table 18: Clinical review protocol

ID	Field	Content
1.	Review title	Routine pharmacological management of primary adrenal insufficiency
2.	Review question	What is the clinical and cost effectiveness of pharmacological treatments for the routine management of primary adrenal insufficiency?
3.	Objective	To determine the clinical effectiveness of pharmacological treatments for routine management of primary adrenal insufficiency (PAI).
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	Primary adrenal insufficiency

6.	Population	Inclusion: Babies, children, young people and adults with suspected and diagnosed primary adrenal insufficiency including those with Addison's disease and congenital adrenal hyperplasia (CAH) stratified as follows: • Adults (aged ≥16 years) – All adults with primary adrenal insufficiency including Addison's disease and CAH. • Children aged ≥1 up to 16 years with CAH. • Children aged ≥1 to <16 years with no CAH. • Infants aged <1 year with CAH (including neonates up to 28 days). • Infants aged <1 year with no CAH (including neonates up to 28 days). 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 or crushed tablets)
		  ○ Modified release hydrocortisone (separate to normal release hydrocortisone)
		  ○ Injected forms
		• Prednisolone
		• Dexamethasone
		
		Mineralocorticoid:
		Fludrocortisone
		
		Sodium chloride (specific to infants with CAH)
		
		Notes:
		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, regimens and preparations (e.g., modified release compared to standard) **For mineralocorticoid:** Comparisons of different mineralocorticoid doses and regimens (twice vs once a day) **For sodium chloride** Comparisons of different doses and regimens **For all:** Comparisons to standard care as defined by authors may also be included.
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 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 - Childhood onset vs adult onset for Autoimmune polyglandular syndrome type 1 (APS-1) as this may affect mortality in Addison's. Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Studies comparing glucocorticoids to mineralocorticoids or DHEAs to each other as each type of drug is given for different indications or symptoms and therefore a patient would not be prescribed one drug or the other. Non comparative cohort studies Before and after studies Comparisons of glucocorticoids or mineralocorticoids to placebo or no treatment 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** For all causes of PAI – growth related issues in children – Low blood sugar/ hypoglycaemia – Early satiety – Complications specifically related to mineralocorticoid deficiencies: ◊ Salt wasting / hyponatraemia ◊ Salt cravings

		◊ Dizziness ◊ Muscle cramps ◊ Low blood pressure ◊ Muscle weakness ◊ Nocturia Additional Complications of PAI for patients with CAH – delayed/ precocious puberty in children. – lack of periods /virilisation / fertility issues – Hirsutism • **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. • **Androgen normalisation** (specific to CAH) determined by biochemical parameters such as 17 OHP, androstenedione, testosterone and DHEAS) • **Admission to hospital and/or ITU** • **Readmission to hospital** • **Length of stay at hospital or ITU.** • **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) For QoL and activities of daily living we will also include longer term data where available.
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. • 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:

<table>
<tr><td></td><td></td><td colspan="3">Subgroups for children:
• Children 1-5
• Children >5-16

For CAH:
• Salt-wasting
• Classical
• Non-classical</td></tr>
<tr><td rowspan="7">17.</td><td rowspan="7">Type and method of review</td><td></td><td colspan="2">Intervention</td></tr>
<tr><td></td><td colspan="2">Diagnostic</td></tr>
<tr><td></td><td colspan="2">Prognostic</td></tr>
<tr><td></td><td colspan="2">Qualitative</td></tr>
<tr><td></td><td colspan="2">Epidemiologic</td></tr>
<tr><td></td><td colspan="2">Service Delivery</td></tr>
<tr><td></td><td colspan="2">Other (please specify)</td></tr>
<tr><td>18.</td><td>Language</td><td colspan="3">English</td></tr>
<tr><td>19.</td><td>Country</td><td colspan="3">England</td></tr>
<tr><td>20.</td><td>Anticipated or actual start date</td><td colspan="3">June 2022</td></tr>
<tr><td>21.</td><td>Anticipated completion date</td><td colspan="3">April 2024</td></tr>
<tr><td rowspan="5">22.</td><td rowspan="5">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td></td><td></td></tr>
<tr><td>Piloting of the study selection process</td><td></td><td></td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td></td><td></td></tr>
<tr><td>Data extraction</td><td></td><td></td></tr>
</table>

		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]		
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, congenital adrenal hyperplasia, glucocorticoids, mineralocorticoids, pharmacological management, DHEA, androgen replacement, hydrocortisone, dexamethasone, prednisolone	
32.	Details of existing review of same topic by same authors	None	
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	

1

A.2 Health economic review protocol

Table 19: 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).[9] **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.

1

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.[9]

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 20: 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)

1 **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)

1 **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

1 **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 21: 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

1 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"

1 **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"

1 **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

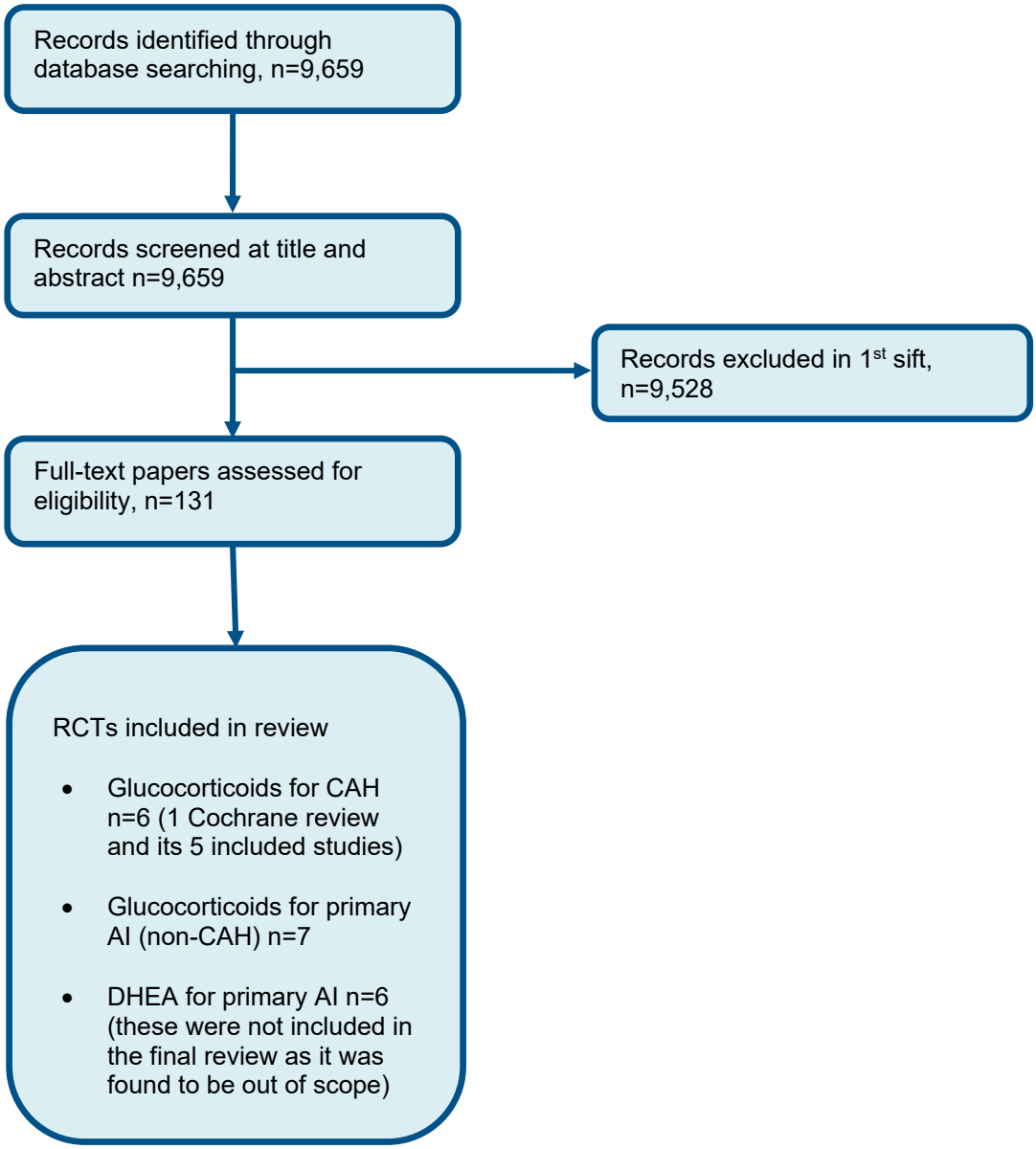
1 **INAHTA search terms**

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

2

Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of topic 4.1 [pharmacological management of adrenal insufficiency]



1 **Table 22: RCTs to be reviewed for topic 4.1 (Primary AI)**

Author	Title	Year	N-size	Type of AI	Patient subgroup	Intervention(s)
Caldato, M. C.	One-year clinical evaluation of single morning dose prednisolone therapy for 21-hydroxylase deficiency	2004	44	CAH	Children + Adults	Prednisolone
Christiansen, J. J.	Dehydroepiandrosterone supplementation in women with adrenal failure: impact on twenty-four hour GH secretion and IGF-related parameters	2004	10	Primary	Women	DHEA
Christiansen, J. J.	Very short term dehydroepiandrosterone treatment in female adrenal failure: impact on carbohydrate, lipid and protein metabolism	2005	9	Primary	Women	DHEA
Dhatariya, K.	Effect of dehydroepiandrosterone replacement on insulin sensitivity and lipids in hypoadrenal women	2005	28	Primary	Women	DHEA
Dhatariya, K. K.	Dehydroepiandrosterone replacement therapy in hypoadrenal women: protein anabolism and skeletal muscle function	2008	33	Primary	Women	DHEA
Ekman, B.	A randomized, double-blind, crossover study comparing two- and four-dose hydrocortisone regimen with regard to quality of life, cortisol and ACTH profiles in patients with primary adrenal insufficiency	2012	15	Primary	Adults	Hydrocortisone
German, A.	Control of childhood congenital adrenal hyperplasia and sleep activity and quality with morning or evening glucocorticoid therapy	2008	15	CAH	Children	Hydrocortisone
Gurnell, E. M.	Long-term DHEA replacement in primary adrenal insufficiency: a randomized, controlled trial	2008	106	Mixed	Adults	DHEA

Hunt, P. J.	Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial	2000	39	Primary	Adults	DHEA
Isidori, A. M.	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	2018	89	Mixed	Adults	Hydrocortisone (modified release)
Johannsson, G.	Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation	2012	64	Primary	Adults	Hydrocortisone (modified release)
Merke, D. P.	Modified-Release Hydrocortisone in Congenital Adrenal Hyperplasia	2021	122	CAH	Adults	Hydrocortisone (modified release)
Nebesio, T. D.	Differential effects of hydrocortisone, prednisone, and dexamethasone on hormonal and pharmacokinetic profiles: a pilot study in children with congenital adrenal hyperplasia	2016	9	CAH	Children	Hydrocortisone
Nilsson, A. G.	Prospective evaluation of long-term safety of dual-release hydrocortisone replacement administered once daily in patients with adrenal insufficiency	2014	64	Primary	Adults	Hydrocortisone (modified release)
Oksnes, M.	Continuous subcutaneous hydrocortisone infusion versus oral hydrocortisone replacement for treatment of addison's disease: a randomized clinical trial	2014	33	Primary	Adults	Hydrocortisone
Hunt, P. J.	Improvement in mood and fatigue after dehydroepiandrosterone replacement in Addison's disease in a randomized, double blind trial	2000	39	Primary	Adults	DHEA
Reidel, M.	Quality of life in patients with Addison's disease: effects of different cortisol replacement modes	1993	14	Mixed	Adults	Hydrocortisone

Silva, I. N.	Randomised controlled trial of growth effect of hydrocortisone in congenital adrenal hyperplasia	1997	26	CAH	Children	Hydrocortisone + Fludrocortisone
Winterer, J.	Effect of hydrocortisone dose schedule on adrenal steroid secretion in congenital adrenal hyperplasia	1985	8	CAH	Children	Hydrocortisone

1

Appendix D Effectiveness evidence

D.1 Non-congenital adrenal hyperplasia (non-CAH)

Ekman, 2012

Bibliographic Reference Ekman, B.; Bachrach-Lindstrom, M.; Lindstrom, T.; Wahlberg, J.; Blomgren, J.; Arnqvist, H. J.; A randomized, double-blind, crossover study comparing two- and four-dose hydrocortisone regimen with regard to quality of life, cortisol and ACTH profiles in patients with primary adrenal insufficiency; Clinical Endocrinology; 2012; vol. 77 (no. 1); 18-25

Study details

Secondary publication of another included study- see primary study for details	N/A
Other publications associated with this study included in review	NA
Trial name / registration number	EuduraCT number 2005-001768-30
Study type	Randomised controlled trial (RCT)
Study location	Linkoping University Hospital, Sweden
Study setting	Hospital
Sources of funding	Financial support was received from Medical Research Council of Southeast Sweden (04952), and the Linkoping University, Sweden.
Inclusion criteria	• Adults • Primary AI of autoimmune origin • Morning basal cortisol levels below 100 nmol/l or maximal plasma concentration of cortisol below 300 nmol/l after stimulation with synthetic ACTH

Exclusion criteria	• Diabetes mellitus
Recruitment / selection of participants	Not specified
Intervention(s)	Patients were randomised to receive 20-mg HC at 07:00h and 10 mg at 16:00h (two-dose regimen). After 4 weeks, they switched to the other treatment.
Population subgroups	Not specified
Comparator	Patients were randomised to receive 10 mg at 07:00 h, 10 mg at 12:00 h, 5 mg at 16:00 h and 5 mg at 22:00 h (four dose regimen). After 4 weeks, they switched to the other treatment.
Number of participants	15
Duration of follow-up	4 weeks
Indirectness	N/A

Study arms

Hydrocortisone [2 dose] (N = 15)

Hydrocortisone [4-dose] (N = 15)

Characteristics

Study-level characteristics

Characteristic	Study (N = 15)
% Female No of events	n = 6 ; % = 40

Characteristic	Study (N = 15)
Mean age (SD) Nominal	44.6
Mean age (SD) Range	21 to 74
Hydrocortisone at baseline # patients on HC at baseline (n) and daily dose (mean mg) Nominal	9
Hydrocortisone at baseline # patients on HC at baseline (n) and daily dose (mean mg) Mean (SD)	30
Cortisone acetate at baseline # patients on CA at baseline (n) and daily dose (mean mg) Nominal	6
Cortisone acetate at baseline # patients on CA at baseline (n) and daily dose (mean mg) Mean (SD)	43.75 (6.85)
Duration of adrenal insufficiency Mean (SD)	15 (15.5)
Concomitant thyroxine # patients on thyroxine at baseline (n) and daily dose (mean mg) Mean (SD)	81.25 (37.5)
Daily dose fludrocortisone (mg)	0.075 (0.03)

Characteristic	Study (N = 15)
Mean (SD)	

Outcomes

Study timepoints

4 week

Treatment effect at 4 weeks

Outcome	Hydrocortisone [2 dose], 4 week, N = 15	Hydrocortisone [4-dose], 4 week, N = 15
Bodyweight Mean (SD)	75.1 (14.2)	74.9 (14.2)
BMI Mean (SD)	24.2 (3.2)	24 (3.4)
SF-36 Physical Function Mean (SD)	91.3 (10.6)	92.3 (10.5)
SF-36 Role function Mean (SD)	76.7 (38.3)	91.7 (26.2)
SF-36 bodily pain Mean (SD)	77.1 (26.6)	85.6 (20.6)
SF-36 general health Mean (SD)	79.6 (15)	81.7 (14.5)

Outcome	Hydrocortisone [2 dose], 4 week, N = 15	Hydrocortisone [4-dose], 4 week, N = 15
SF-36 vitality Mean (SD)	71.2 (22.4)	77.3 (16.2)
SF-36 Social Function Mean (SD)	95 (9.2)	98.3 (4.4)
SF-36 Mental Health Mean (SD)	85.1 (18.4)	89.3 (12)
Systolic BP (mmHg) Supine Mean (SD)	125 (16)	124 (12)
Diastolic BP (mmHg) Supine Mean (SD)	77 (9)	79 (5)

1

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

3 **Bodyweight**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable *(Population and outcomes match review protocol)*

4

BMI

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable *(Population and outcomes match review protocol)*

Blood pressure

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable *(Population and outcomes match review protocol)*

SF-36

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable *(Population and outcomes match review protocol)*

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. 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.

1 **Study arms**

2 **MR-HC (N = 46)**

3 **Standard glucocorticoid (N = 43)**

4 **Characteristics**

5 **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

Characteristic	MR-HC (N = 46)	Standard glucocorticoid (N = 43)
Other autoimmune disorder No of events	n = 12 ; % = 26	n = 12 ; % = 28
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)

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

1

1 **Outcomes**

2 **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)
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)

Outcome	MR-HC vs Standard glucocorticoid, , N2 = 43, N1 = 35
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)

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

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

2 **BMI**

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

3 **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

4 **Bodyweight**

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

5 **FBG**

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

6

1 **Insulin**

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

2 **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

3 **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

4 **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

1 # Johannsson, 2012

Bibliographic Reference Johannsson, G.; Nilsson, A. G.; Bergthorsdottir, R.; Burman, P.; Dahlqvist, P.; Ekman, B.; Engstrom, B. E.; Olsson, T.; Ragnarsson, O.; Ryberg, M.; Wahlberg, J.; Biller, B. M.; Monson, J. P.; Stewart, P. M.; Lennernas, H.; Skrtic, S.; Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation; Journal of Clinical Endocrinology & Metabolism; 2012; vol. 97 (no. 2); 473-81

2 ## Study details

Other publications associated with this study included in review	
Trial name / registration number	EudraCT:2006-0007084-83
Study type	Randomised controlled trial (RCT)
Study location	Not specified
Study setting	Clinic
Study dates	The trial was conducted between August 21, 2007, and January 28, 2009
Sources of funding	DuoCort Pharma AB financially supported the trial
Inclusion criteria	Males and females aged at least 18 yr with primary AI diagnosed more than 6 months before study entry and with a total daily hydrocortisone dose of 20, 25, 30, or 40 mg were eligible for the study.
Exclusion criteria	• Clinical or laboratory signs of significant cerebral, cardiovascular, respiratory, hepatobiliary, or pancreatic disease, renal dysfunction, gastrointestinal emptying, or motility disturbances and underlying disease that could necessitate treatment with glucocorticoids. • Pregnant or lactating women were not eligible for the trial.

Recruitment / selection of participants	Not specified
Intervention(s)	The dual-release tablets (20 and 5 mg) were administered orally once daily in the fasting state in the morning (at 0800 h)
Population subgroups	Diabetes mellitus (n=11)
Comparator	The reference drug was a hydrocortisone 10-mg tablet administered three times daily (at 0800, 1200, and 1600 h)
Number of participants	64
Duration of follow-up	12 weeks
Additional comments	The study was designed as a two-period crossover study. For analyses of other PK endpoints, preference, QoL, and biochemical and safety variables, the differences between the period 1 and period 2 were calculated for each patient.

Study arms

- 3x daily hydrocortisone (N = 64)
- Dual-release hydrocortisone (N = 64)

Characteristics

- Study-level characteristics

Characteristic	**Study (N = 63)**
% Female No of events	n = 26 ; % = 41.3
Mean age (SD) Mean (SD)	47.3 (13.7)
Bodyweight Mean (SD)	79.6 (14.3)

Characteristic	Study (N = 63)
BMI Mean (SD)	26.2 (4)
Hypertension No of events	n = 11 ; % = 17.5
HBA1C Mean (SD)	4.9 (1.1)
Cholesterol Mean (SD)	5.3 (1.1)
Osteocalcin Mean (SD)	11.4 (5.6)
Regimen before trial: BID No of events	n = 33 ; % = 55
Regimen beforetrial: TID No of events	n = 27 ; % = 45
Systolic blood pressure (mmHg) Mean (SD)	123.6 (19.7)
Diastolic blood pressure (mmHg) Mean (SD)	75.8 (11.5)

1 **Outcomes**

2 **Outcomes during 12 wk crossover period: dual-release vs. 3x daily HC**

Outcome	3x daily hydrocortisone, , N = 59	Dual-release hydrocortisone, , N = 61
HBA1C (%) 3x daily: n=59 ; dual-release: n=61 Mean (SD)	5 (1.1)	4.9 (0.9)
Cholesterol (nmol/L) 3x daily: n=57 ; dual-release: n=57 Mean (SD)	5.3 (0.9)	5.2 (1)
Any adverse event n=64 (entire ITT population) No of events	n = 42 ; % = 65.6	n = 47 ; % = 73.4
AE: fatigue n=64 (entire ITT population) No of events	n = 3 ; % = 4.7	n = 8 ; % = 12.5
AE: Influenza n=64 (entire ITT population) No of events	n = 2 ; % = 3.1	n = 8 ; % = 12.5
Serious AE/ Hospitalisation n=64 (entire ITT population). All SAE were caused by infectious disorders and patients were hospitalised to prevent/treat acute AI No of events	n = 2 ; % = 3.1	n = 6 ; % = 9.3

3 N-sizes differ for each outcome and therefore are listed in each row. All 64 patients received at least one dose of study medication and are
4 included in the safety population. All 64 patients completed the study visits of the randomized crossover phase, but two patients reverted to

conventional treatment during the dual-release period. The ITT population includes 63 patients (excluding one patient with failed needle insertion); among these, 59 had complete dual-release and TID data for the analysis of the primary variable.

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

HbA1c

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Study authors do not state why outcome not reported for entire ITT population. Also, there is a risk of selective reporting of outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population matches review protocol)*

AEs

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Study authors do not state why outcome not reported for entire ITT population. Also, there is a risk of selective reporting of outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population matches review protocol)*

Psychosocial functioning

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population matches review protocol)*

1 **Cholesterol**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Study authors do not state why outcome not reported for entire ITT population. Also, there is a risk of selective reporting of outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population matches review protocol)*

2 **Fatigue**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Study authors do not state why outcome not reported for entire ITT population. Also, there is a risk of selective reporting of outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population matches review protocol)*

3 **Influenza**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Study authors do not state why outcome not reported for entire ITT population. Also, there is a risk of selective reporting of outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population matches review protocol)*

4

5 **Serious AE/Hospitalisation**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Study authors do not state why outcome not reported for entire ITT population. Also, there is a risk of selective reporting of outcomes)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population matches review protocol)*

1 Nilsson, 2014

Bibliographic Reference Nilsson, A. G.; Marelli, C.; Fitts, D.; Bergthorsdottir, R.; Burman, P.; Dahlqvist, P.; Ekman, B.; Engstrom, B. E.; Olsson, T.; Ragnarsson, O.; Ryberg, M.; Wahlberg, J.; Lennernas, H.; Skrtic, S.; Johannsson, G.; Prospective evaluation of long-term safety of dual-release hydrocortisone replacement administered once daily in patients with adrenal insufficiency; European Journal of Endocrinology; 2014; vol. 171 (no. 3); 369-77

2

3 Study details

Trial name / registration number	EudraCT number: 2006-007084-89
Study type	Randomised controlled trial (RCT)
Study location	Sweden
Study setting	Clinic
Study dates	Not specified
Sources of funding	ViroPharma SPRL, Maidenhead, UK
Inclusion criteria	• Adults • Primary AI • Stable treatment with total daily HC dose between 25-40 mg
Exclusion criteria	• Clinical or laboratory signs of significant cerebral cardiovascular, respiratory, hepato-biliary, or pancreatic diseases that could interfere with study assessments or completion. • clinically significant renal dysfunction with a serum creatinine level above 150 mmol/l; • any underlying disease possibly requiring treatment with glucocorticoids; and • administration of other investigational drugs within 8 weeks before screening

Recruitment / selection of participants	Not specified
Intervention(s)	The patients were instructed to take dual-release hydrocortisone orally once daily at 0800 hours. The dual-release tablet provides high levels of cortisol during the morning, followed by a gradual decrease throughout the day. All patients received thrice-daily hydrocortisone during a 1-month run-in period before randomisation. During periods of intercurrent illness, the total daily dose of hydrocortisone or DR-HC was doubled. The patients receiving DR-HC received a second DR-HC dose 8G2 h after the first dose.
Population subgroups	Not specified
Comparator	The patients were instructed to take hydrocortisone administered orally as 10 mg tablets. The total daily doses were divided into three individual doses administered at 0800, 1200, and 1600 h, with 50–60% of the total daily dose being given as the morning dose. All patients received thrice-daily hydrocortisone during a 1-month run-in period before randomisation. During periods of intercurrent illness, the total daily dose of hydrocortisone or DR-HC was doubled. The patients receiving conventional hydrocortisone therapy doubled the dose at each appointed administration time.
Number of participants	64
Duration of follow-up	3 months
Indirectness	N/A

1

1 **Study arms**

2 **Dual-release hydrocortisone (N = 64)**

3 **3x daily hydrocortisone (N = 64)**

4 **Characteristics**

5 **Study-level characteristics**

Characteristic	Study (N = 64)
% Female No of events	n = 27 ; % = 42.2
Mean age (SD) Mean (SD)	47.2 (13.6)
Bodyweight Mean (SD)	79.4 (14.3)
BMI Mean (SD)	26.2 (3.9)
Systolic BP (mmHg) Mean (SD)	123.5 (19.5)
Diastolic BP (mmHg) Mean (SD)	75.9 (11.4)
Mean daily dose: 20mg No of events	n = 8 ; % = 12.5

Characteristic	Study (N = 64)
Mean daily dose: 25 mg. No of events	n = 7; % = 10.9
Mean daily dose: 30 mg. No of events	n = 37; % = 57.8
Mean daily dose: 35 mg. No of events	n = 0; % = 0
Mean daily dose: 40 mg. No of events	n = 12; % = 18.8

Outcomes

Study timepoints

3 month

Illness episodes and days within 3 months.

Outcome	Dual-release hydrocortisone, 3-month, N = 64	3x daily hydrocortisone, 3-month, N = 64
Number of episodes per patient Mean/SD, Median/Range (not IQR) Mean (SD)	2.15 (1.87)	1.82 (1.67)
Number of episodes per patient Mean/SD, Median/Range (not IQR)	1.5 (1.9 to 9)	1 (1 to 8)

Outcome	Dual-release hydrocortisone, 3-month, N = 64	3x daily hydrocortisone, 3-month, N = 64
Median (IQR)		
Number of days per episode Mean/SD, Median/Range (not IQR) Mean (SD)	2.44 (1.6)	3.3 (4.46)
Number of days per episode Mean/SD, Median/Range (not IQR) Median (IQR)	2 (1 to 8)	2 (1 to 20)
Additional dose per episode (mg) Mean/SD, Median/Range (not IQR). Note that during periods of intercurrent illness, the total daily dose of hydrocortisone or DR-HC was doubled. Mean (SD)	22.84 (9.82)	17.65 (13.51)
Additional dose per episode (mg) Mean/SD, Median/Range (not IQR). Note that during periods of intercurrent illness, the total daily dose of hydrocortisone or DR-HC was doubled. Median (IQR)	20 (5 to 40)	10 (0 to 45)

1 **Total AEs**

Outcome	Dual-release hydrocortisone vs 3x daily hydrocortisone, 3 month, N2 = 64, N1 = 64
Total AEs Patients with >=1 event No of events	n = 53; % = 74.6
Serious AEs Patients with >=1 event No of events	n = 6; % = 8.5

Outcome	Dual-release hydrocortisone vs 3x daily hydrocortisone, 3 month, N2 = 64, N1 = 64
Discontinuation due to adverse events Patients with >=1 event No of events	n = 2; % = 2.8

- Data not proved at arm level in an extractable format.

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

Number of illness episodes per patient

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Open label trial design)*
Overall bias and Directness	Overall Directness	Directly applicable

Number of days per episode

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

Total AE

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

Serious AE

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

1 **Discontinuation due to AE**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Some concerns *(Risk that patients experiencing an AE differentially elected to discontinue the trial based on their awareness of assigned intervention)*
Overall bias and Directness	Overall Directness	Directly applicable

2 **Additional dose per episode**

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

3 # Oksnes, 2014

Bibliographic Reference Oksnes, M.; Bjornsdottir, S.; Isaksson, M.; Methlie, P.; Carlsen, S.; Nilsen, R. M.; Broman, J. E.; Triebner, K.; Kampe, O.; Hulting, A. L.; Bensing, S.; Husebye, E. S.; Lovas, K.; Continuous subcutaneous hydrocortisone infusion versus oral hydrocortisone replacement for treatment of addison's disease: a randomized clinical trial; Journal of Clinical Endocrinology & Metabolism; 2014; vol. 99 (no. 5); 1665-74

4

5 **Study details**

Secondary publication of another included study- see primary study for details	

Trial name / registration number	(EudraCT number 2009-010917-61).
Study type	Randomised controlled trial (RCT)
Study location	Norway and Sweden
Study setting	Hospital
Study dates	[Not specified]
Sources of funding	[Not specified]
Inclusion criteria	Verified autoimmune AD and aged 18–70 years
Exclusion criteria	Diabetes mellitus, cardiovascular or malignant disease, pregnancy, or pharmacological treatment with glucocorticoids or drugs that interfere with cortisol metabolism (antiepileptics, rifampicin, and St Johns wart)
Recruitment / selection of participants	Eligible patients were identified from a patient registry (Registry of Organ Specific Autoimmune Diseases) or from the hospital diagnosis registries and invited to participate.
Intervention(s)	During CSHI, the patients received hydrocortisone (Solu-Cortef Act-o-Vial; Pfizer Inc) administered by an insulin pump). The infusion gear was applied as with an insulin pump. The patients were instructed to clean the injection site with alcohol before needle insertion and replace the hydrocortisone solution and the infusion gear every 3 days. Initial doses were 10.5 mg/m2d with the following infusion rate distribution: hours 8:00 AM to 2:00 PM, 0.5 mg/ m2h; 2:00–8:00 PM, 0.2 mg/m2h; 8:00 PM to 2:00 AM, 0.05 mg/m2h; and 2:00–8:00 AM, 1.0 mg/m2h. The CSHI doses were adjusted according to salivary cortisol levels (h 6:00– 8:00 AM and 11:00–12:00 PM) and morning serum cortisol after 3–5 days. Authors aimed for a morning salivary cortisol in the middle to upper reference range, a normal morning serum cortisol, and an evening salivary cortisol in the lower reference range.
Population subgroups	None specified
Comparator	Oral treatment was weight adjusted and given three times daily as hydrocortisone 5-mg tablets as suggested. The oral doses were titrated according to a serum cortisol nomogram 4 hours after the morning dose at days 3–5. Smaller dose adjustments for both treatments were allowed based on best clinical judgment during dose titration, whereas all patients were treated with individually adjusted fixed daily doses of both treatments after randomisation.

Number of participants	33
Duration of follow-up	12 weeks
Indirectness	N/A
Additional comments	ITT

1 **Study arms**

2 **Continuous SC Hydrocortisone Infusion (N = 29)**

3 **Oral HC [Standard] (N = 31)**

4 **Characteristics**

5 **Study-level characteristics**

Characteristic	Study (N = 33)
% Female No of events	n = 25; % = 75.8
Mean age (SD) Mean (SD)	48 (12)
Addison's disease duration (years) Mean (SD)	12.4 (10.1)
Full time work No of events	n = 20; % = 60.6

Characteristic	Study (N = 33)
Exercise >3hrs /week No of events	n = 18; % = 55
Hydrocortisone at baseline All the Swedish patients received pretrial glucocorticoid replacement therapy with hydrocortisone. No of events	n = 15; % = 45
Cortisone acetate at baseline All the Norwegian patients received pretrial glucocorticoid replacement therapy with cortisone acetate. No of events	n = 18; % = 55
Hypothyroidism No of events	n = 14; % = 42
Hay fever No of events	n = 5; % = 15
Bronchial asthma No of events	n = 2; % = 6.1
Hypercholesterolemia No of events	n = 3; % = 9.1
Osteopenia No of events	n = 3; % = 9.1
Premature ovarian failure No of events	n = 2; % = 6.1

Characteristic	Study (N = 33)
Hypertension No of events	n = 2; % = 6.1
Received glucocorticoids 2x daily. No of events	n = 13; % = 39.4
Received glucocorticoids 3x daily. No of events	n = 14; % = 42.4
Received glucocorticoids 4-5x daily. No of events	n = 6; % = 18.2
Pretrial hydrocortisone equivalent dose of glucocorticoids (mg/kgd) HC-equivalent of glucocorticoid replacement therapy at baseline Mean (SD)	0.36 (0.13)

1

1 **Outcomes**

2 **Study timepoints**

3 **Baseline**

4 **12 weeks**

5 **Treatment effect at 12 weeks [baseline vs. 12 weeks]**

Outcome	Continuous SC Hydrocortisone Infusion, Baseline, N = 32	Continuous SC Hydrocortisone Infusion, 12-week, N = 32	Oral HC [Standard], Baseline, N = 33	Oral HC [Standard], 12-week, N = 33
HbA1c n= 14 for CHSI; n= 14 for Oral HC Mean (95% CI)	5.3 (5.1 to 5.4)	5.2 (5 to 5.3)	5.2 (5.1 to *empty data*)	5.1 (5 to 5.2)
Cholesterol n= 33 for CHSI; n= 32 for Oral HC Mean (95% CI)	5.3 (5 to 5.7)	5.5 (5.1 to 5.8)	5.1 (4.8 to 5.4)	5.3 (5 to 5.6)
BMI n= 32 for CHSI; n= 33 for Oral HC Mean (95% CI)	25.7 (24.3 to 27)	25.8 (24.5 to 27.2)	25.4 (24.2 to 26.7)	25.3 (24 to 26.6)
Bodyweight n= 32 for CHSI; n= 33 for Oral HC Mean (95% CI)	75.1 (70.1 to 80.1)	75.8 (70.8 to 80.7)	74.3 (69.8 to 78.8)	73.9 (69.3 to 78.5)
Systolic BP n= 32 for CHSI; n= 33 for Oral HC Mean (95% CI)	113.1 (109 to 117.2)	114.6 (110.8 to 118.4)	111.6 (107.6 to 115.6)	115.5 (112 to 119.1)

Outcome	Continuous SC Hydrocortisone Infusion, Baseline, N = 32	Continuous SC Hydrocortisone Infusion, 12-week, N = 32	Oral HC [Standard], Baseline, N = 33	Oral HC [Standard], 12-week, N = 33
Diastolic BP n= 32 for CHSI; n= 33 for Oral HC Mean (95% CI)	75.2 (72.7 to 77.6)	75.2 (73.1 to 77.2)	75.1 (72.9 to 77.3)	75.7 (73.6 to 77.8)
Total cholesterol n= 32 for CHSI; n= 33 for Oral HC Mean (95% CI)	5.3 (5 to 5.7)	5.3 (5.1 to 5.8)	5.1 (4.8 to 5.4)	5.3 (5 to 5.6)
Any adverse event N-size not specified. Nominal	0	24	0	22
Serious AE N-size not specified. Nominal	0	0	0	1
Treatment-related adverse events N-size not specified. Includes probably and possibly treatment related adverse events. Nominal	0	4	0	5

- Outcomes have different n-sizes and so n-sizes are listed below.

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

2 **HbA1c**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Concerns about missing patient data, as well as risk of bias from open-label trial design)*
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population meet review protocol)*

3 **Cholesterol**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Concerns about missing patient data, as well as risk of bias from open-label trial design)*
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population meet review protocol)*

4 **BMI**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Concerns about missing patient data, as well as risk of bias from open-label trial design)*
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population meet review protocol)*

5 **Bodyweight**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Concerns about missing patient data, as well as risk of bias from open-label trial design)*
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population meet review protocol)*

6

1 **Systolic BP**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Concerns about missing patient data, as well as risk of bias from open-label trial design)*
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population meet review protocol)*

2 **Diastolic BP**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Concerns about missing patient data, as well as risk of bias from open-label trial design)*
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population meet review protocol)*

3 **Total cholesterol**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Concerns about missing patient data, as well as risk of bias from open-label trial design)*
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population meet review protocol)*

4 **Any adverse event**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Concerns about missing patient data, as well as risk of bias from open-label trial design)*
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population meet review protocol)*

1 **Serious AE**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Concerns about missing patient data, as well as risk of bias from open-label trial design)*
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population meet review protocol)*

2 **Treatment-related AE**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Concerns about missing patient data, as well as risk of bias from open-label trial design)*
Overall bias and Directness	Overall Directness	Directly applicable *(Outcome and population meet review protocol)*

3 # D.2 Congenital Adrenal Hyperplasia

4 # Caldato, 2004

Bibliographic Reference	Caldato, M. C.; Fernandes, V. T.; Kater, C. E.; One-year clinical evaluation of single morning dose prednisolone therapy for 21-hydroxylase deficiency; Arquivos Brasileiros de Endocrinologia e Metabologia; 2004; vol. 48 (no. 5); 705-12

5 **Study details**

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR

Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Brazil
Study setting	Two Tertiary centres
Study dates	NR
Sources of funding	NR
Inclusion criteria	Patients previously diagnosed as having the salt-losing or simple-virilizing forms of 21OHD were included.
Exclusion criteria	NR
Recruitment / selection of participants	NR
Intervention(s)	Group 1 received PD phosphate (Prelone®, 3mg/ml oral solution, Asta Medica, Brazil), initially at Single Dose Prednisolone Therapy for 21OHD a dose of 2.4-3.75mg/m2 BSA once a day in the morning (7:00-8:00hs). The initial Hydrocortisone (HC) to Prednisolone (PD) bioequivalence dose ratio employed was 4:1. All patients also received fludrocortisone acetate tablets, 0.1 mg per day in the morning, as mineralocorticoid replacement.
Population subgroups	• Prepubertal • Pubertal
Comparator	Group 2 patients were maintained on oral Hydrocortisone acetate TID, 10- 15mg/m2 BSA (half of the dose administered at 7:00- 8:00hs, and 1/4 at 12:00-13:00hs and at 20:00- 21:00hs).
Number of participants	44
Duration of follow-up	1 year
Indirectness	NA

1

1 **Study arms**

2 **Prednisolone (N = 23)**

3 **(PD)**

4 **Hydrocortisone (N = 21)**

5 **(HC)**

6 **Characteristics**

7 **Arm-level characteristics**

Characteristic	Prednisolone (N = 23)	Hydrocortisone (N = 21)
Age (years) Median (range)	9.4(1.6 to 20)	8.3 (1.2 to 21)
Male Sample size	n = 7; % = 30.4	n = 3; % = 14.2
Female Sample size	n = 16; % = 69.5	n = 18; % = 85.7
Prepubertal Sample size	n = 10; % = 43.4	n = 11; % = 52.3
Pubertal Sample size	n = 8; % = 34.7	n = 5; % = 23.8
Post-pubertal	n = 5; % = 21.7	n = 5; % = 23.8

Characteristic	Prednisolone (N = 23)	Hydrocortisone (N = 21)
Sample size		

1 **Outcomes**

2 **Study timepoints**

3 **1 year**

4 **Clinical data**

Outcome	Prednisolone, 1 year, N = 16	Hydrocortisone, 1 year, N = 16
Growth velocity Mean (SD)	7.84 (2.11)	7.8 (3.38)
Height SDS (bone age) (Mean (SD) Mean (SD)	-0.17 (0.74)	-0.98 (1.12)
Height SDS (chronological age) (Mean (SD) Mean (SD)	0.57 (1.05)	0.43 (1.37)
Ratio BA/CA (Mean (SD) Mean (SD)	1.14 (0.16)	1.29 (0.33)
Height (cm) Mean (SD)	125.8 (27.7)	121 (26.2)

5 **Hormonal data (Prepubertal patients)**

Outcome	Prednisolone, 1 year, N = 10	Hydrocortisone, 1 year, N = 11
Testosterone Mean (SD)	67 (50)	102 (95)

Outcome	Prednisolone, 1 year, N = 10	Hydrocortisone, 1 year, N = 11
Androstenedione Mean (SD)	105 (66)	168 (91)
17OHP Mean (SD)	1267 (947)	2703 (2452)

Hormonal data (Pubertal patients)

Outcome	Prednisolone, 1 year, N = 13	Hydrocortisone, 1 year, N = 10
Testosterone Mean (SD)	97 (75)	139 (78)
Androstenedione Mean (SD)	147 (40)	200 (98)
17OHP Mean (SD)	2207 (1482)	2977 (2485)

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

Clinical data-Growth velocity-MeanSD-Prednisolone-Hydrocortisone-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to randomisation process, incomplete outcome data and selective reporting)*
Overall bias and Directness	Overall Directness	Directly applicable

1 **Hormonal data (Prepubertal patients)-Androstenedione-MeanSD-Prednisolone-Hydrocortisone-t1**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to randomisation process, incomplete outcome data and selective reporting)*
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Hormonal data (Prepubertal patients)-Testosterone-MeanSD-Prednisolone-Hydrocortisone-t1**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to randomisation process, incomplete outcome data and selective reporting)*
Overall bias and Directness	Overall Directness	Directly applicable

4

5 **Hormonal data (Prepubertal patients)-17OHP-MeanSD-Prednisolone-Hydrocortisone-t1**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to randomisation process, incomplete outcome data and selective reporting)*
Overall bias and Directness	Overall Directness	Directly applicable

6

7 **Hormonal data (Pubertal patients)-Testosterone-MeanSD-Prednisolone-Hydrocortisone-t1**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to randomisation process, incomplete outcome data and selective reporting)*
Overall bias and Directness	Overall Directness	Directly applicable

8

1 **Hormonal data (Pubertal patients)-Androstenedione-MeanSD-Prednisolone-Hydrocortisone-t1**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to randomisation process, incomplete outcome data and selective reporting)*
Overall bias and Directness	Overall Directness	Directly applicable

2

3 **Hormonal data (Pubertal patients)-17OHP-MeanSD-Prednisolone-Hydrocortisone-t1**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to randomisation process, incomplete outcome data and selective reporting)*
Overall bias and Directness	Overall Directness	Directly applicable

4

5 **Clinical data-Height-MeanSD-Prednisolone-Hydrocortisone-t1**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to randomisation process, incomplete outcome data and selective reporting)*
Overall bias and Directness	Overall Directness	Directly applicable

6

7 **Clinical data-RatioBA/CA-MeanSD-Prednisolone-Hydrocortisone-t1**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to randomisation process, incomplete outcome data and selective reporting)*
Overall bias and Directness	Overall Directness	Directly applicable

8

Clinical data-HeightSDS(chronologicalage)-MeanSD-Prednisolone-Hydrocortisone-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to randomisation process, incomplete outcome data and selective reporting)*
Overall bias and Directness	Overall Directness	Directly applicable

Clinical data-HeightSDS(bone age)-MeanSD-Prednisolone-Hydrocortisone-t1

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Due to randomisation process, incomplete outcome data and selective reporting)*
Overall bias and Directness	Overall Directness	Directly applicable

German, 2008

Bibliographic Reference	German, A.; Suraiya, S.; Tenenbaum-Rakover, Y.; Koren, I.; Pillar, G.; Hochberg, Z.; Control of childhood congenital adrenal hyperplasia and sleep activity and quality with morning or evening glucocorticoid therapy; Journal of Clinical Endocrinology & Metabolism; 2008; vol. 93 (no. 12); 4707-10

Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)

Study location	Israel
Study setting	NR
Study dates	NR
Sources of funding	NR
Inclusion criteria	Children with normal circadian rhythm and classical CAH due to 21-hydroxylase deficiency or 11-hydroxylase deficiency with reasonable disease control were enrolled in the study.
Exclusion criteria	Exclusion criteria included known sleep, behavioural, or movement disturbances.
Recruitment / selection of participants	A written, informed consent was signed by a parent
Intervention(s)	A high morning dose (50% of the daily HC was taken in the morning). Patients were randomised to receive 50% of the daily Hydrocortisone (HC) in the morning for 2 weeks; the other two doses included 25% of the daily dose each. The schedule was standardized to 0700 – 0800, 1300 –1400, and 2100 –2200 h according to patients' age. Patients received standard replacement therapy with an oral HC dose that was identical to each subject's pre study therapy, ranging from 13.5–15.3 mg/m2 given three times daily.
Comparator	Patients were randomised to receive 50% of the daily Hydrocortisone (HC) in the evening for 2 weeks; the other two doses included 25% of the daily dose each. A high-evening dose (50% was taken at bedtime). The schedule was standardized to 0700 – 0800, 1300 –1400, and 2100 –2200 h according to patients' age. Patients received standard replacement therapy with an oral HC dose that was identical to each subject's pre study therapy, ranging from 13.5–15.3 mg/m2 given three times daily.
Number of participants	15
Duration of follow-up	4 weeks
Indirectness	NA

1 **Study arms**

2 **Hydrocortisone high morning dose (N = 5)**

3 **Intervention**

4 **Hydrocortisone high evening dose (N = 6)**

5 **Intervention**

6 **Characteristics**

7 **Study-level characteristics**

Characteristic	**Study (N = 15)**
Age (Median (range)) Median (IQR)	10 (7.5 to 14.5)
Male Sample size	n = 9 ; % = 60
Female Sample size	n = 6 ; % = 40
Prepubertal patients Sample size	n = 9 ; % = 60
Pubertal patients Sample size	n = 6 ; % = 40
21-Hydroxylase deficiency	n = 14 ; % = 93.3

Characteristic	Study (N = 15)
Sample size	
11-Hydroxylase deficiency Sample size	n = 1 ; % = 6.6
Hydrocotisone dose (mg/m2) Median (IQR)	14 (13.5; 15.3)
Morning Sample size	n = 9 ; % = 60
Evening Sample size	n = 6 ; % = 40

1 **Outcomes**

2 **Study timepoints**

3 **4 week**

4 **Endocrine parameters**

Outcome	Hydrocortisone high morning dose, 4-week, N = 5	Hydrocortisone high evening dose, 4-week, N = 6
17OHP Median (IQR)	44 (16 to 116)	33 (15 to 76)
DHEA-S Median (IQR)	0.2 (0.2 to 0.6)	0.4 (0.2 to 0.7)
Androstenedione (nmol/litre)	1.8 (1 to 3)	1.9 (1.2 to 6.5)

Outcome	Hydrocortisone high morning dose, 4-week, N = 5	Hydrocortisone high evening dose, 4-week, N = 6
Median (IQR)		
Testosterone (nmol/litre) Median (IQR)	0.7 (0.3 to 2.3)	1.1 (0.6 to 2.7)

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

2 **Endocrine parameters-17OHP-Median IQR-Hydrocortisone high morning dose-Hydrocortisone high evening dose-t4**

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

3 **Endocrine parameters-DHEA-S-Median IQR-Hydrocortisone high morning dose-Hydrocortisone high evening dose-t4**

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

4 **Endocrine parameters-Androstenedione-Median IQR-Hydrocortisone high morning dose-Hydrocortisone high evening dose-t4**

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

5 **Endocrine parameters-Testosterone-Median IQR-Hydrocortisone high morning dose-Hydrocortisone high evening dose-t4**

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

6

1 Merke, 2021

Bibliographic Reference	Merke, D. P.; Mallappa, A.; Arlt, W.; Brac de la Perriere, A.; Linden Hirschberg, A.; Juul, A.; Newell-Price, J.; Perry, C. G.; Prete, A.; Rees, D. A.; Reisch, N.; Stikkelbroeck, N.; Touraine, P.; Maltby, K.; Treasure, F. P.; Porter, J.; Ross, R. J.; Modified-Release Hydrocortisone in Congenital Adrenal Hyperplasia; Journal of Clinical Endocrinology & Metabolism; 2021; vol. 106 (no. 5); e2063-e2077

2 Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	EudraCT registration Nos. 2015- 000711-40 and 2015-005448-32 (registered February 10, 2015) Clinicaltrials.gov registration Nos. NCT02716818 and NCT03062280 (registered March 22, 2016
Study type	Randomised controlled trial (RCT)
Study location	• Denmark • France • Germany • Netherlands • Sweden • UK • USA
Study setting	European and US health centers
Study dates	February 2016 to January 2018
Sources of funding	NR
Inclusion criteria	• Patients with classic 21-OHD-CAH diagnosed in childhood

	• Patients with adequate mineralocorticoid replacement with renin less than 2 times upper limit of normal • Patients on stable glucocorticoid therapy over the preceding 6 months
Exclusion criteria	Exclusion criteria included: • Use of medication interfering with glucocorticoid metabolism • Bilateral adrenalectomy • Night-shift work
Recruitment / selection of participants	NR
Intervention(s)	Patients were randomly assigned by an interactive web response system to receive MR-HC (Chronocort Diurnal Ltd UK) or to continue on standard therapy and after 6 months were offered MR-HC in the extension study. MR-HC was prescribed as 5-, 10-, or 20-mg capsules, and the initial dose was the hydrocortisone dose equivalent to their baseline therapy, with approximately one-third of the daily dose taken at 07:00h and two-thirds of the daily dose taken at 23:00h. At 4 and 12 weeks, dose titrations were made for both treatment groups, using identical rules, following centralised advice.
Population subgroups	
Comparator	Patients were randomly assigned by an interactive web response system to continue on standard therapy and after 6 months were offered MR-HC in the extension study. At 4 and 12 weeks, dose titrations were made for both treatment groups, using identical rules, following centralized advice.
Number of participants	122
Duration of follow-up	6 months
Indirectness	NA
Additional comments	

1

1 **Study arms**

2 **Modified-release Hydrocortisone group (N = 61)**

3 **Standard Glucocorticoid group (N = 61)**

4 **Characteristics**

5 **Arm-level characteristics**

Characteristic	Modified-release Hydrocortisone group (N = 61)	Standard Glucocorticoid group (N = 61)
Age (year) Range	19 to 61	19 to 68
Age (year) Median (IQR)	35 (*empty data* to *empty data*)	40 (*empty data* to *empty data*)
Female Sample size	n = 42; % = 68.9	n = 36; % = 59
Male Sample size	n = 19; % = 31.1	n = 25; % = 40.9
Salt wasting (n (%)) Sample size	n = 49; % = 80	n = 51; % = 84
Hydrocortisone Sample size	n = 36; % = 59	n = 39; % = 63.9
Prednisolone Sample size	n = 21; % = 34.4	n = 22; % = 36.1

Characteristic	Modified-release Hydrocortisone group (N = 61)	Standard Glucocorticoid group (N = 61)
Dexamethasone Sample size	n = 5; % = 8.2	n = 5; % = 8.2
Prednisone Sample size	n = 3; % = 4.9	n = 2; % = 3.3

1 **Outcomes**

2 **Study timepoints**

3 **24 week**

4 **Disease relevant clinical outcomes**

Outcome	Modified-release Hydrocortisone group, 24-week, N = 61	Standard Glucocorticoid group, 24-week, N = 61
Adrenal crisis No of events	n = 0; % = 0	n = 3; % = 5.8
Stress dosing No of events	n = 26; % = 49.1	n = 36; % = 69.2

5 **Quality of life assessments at 24 weeks**

Outcome	Modified-release Hydrocortisone group, 24-week, N = 53	Standard Glucocorticoid group, 24-week, N = 52
Global Fatigue Index absolute change in score from baseline Mean (SD)	-0.74 (11.1)	-0.26 (7.8)

Outcome	Modified-release Hydrocortisone group, 24-week, N = 53	Standard Glucocorticoid group, 24-week, N = 52
EQ-5D-5L index score Mean (SD)	0.02 (0.12)	0.02 (0.14)
T score: general health perceptions Mean (SD)	0.79 (7.54)	-1.88 (5.97)
T score: mental health Mean (SD)	0.86 (7.32)	0.35 (7.81)
T score: physical functioning Mean (SD)	1.16 (6.43)	-0.52 (4.27)
T score: social functioning Mean (SD)	2.18 (9.25)	0.87 (6.86)
T score: role emotional Mean (SD)	0.99 (9.95)	-0.34 (9.21)
T score: role physical Mean (SD)	1.91 (8.33)	0.5 (6.68)
T score: vitality Mean (SD)	0.79 (9.45)	0.92 (6.1)

- EQ-5D-5L index score - Polarity - Higher values are better.
- SF-36 absolute change from baseline - Polarity - Higher values are better.

Change from baseline in natural log

Outcome	Modified-release Hydrocortisone group, 24-week, N = 53	Standard Glucocorticoid group, 24-week, N = 52
17OHP SDS profile Mean (SD)	-0.4 (0.85)	-0.17 (0.78)
androstenedione 24-h AUC Mean (SD)	-37.7 (42.6)	-17.8 (29)

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

Primary Outcomes-Adrenal Crisis-No Of Events-Modified-release Hydrocortisone group-Standard Glucocorticoid group-t24

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

Disease relevant clinical outcomes-Stress Dosing-No Of Events-Modified-release Hydrocortisone group-Standard Glucocorticoid group-t24

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

Quality of life assessments at 24 weeks -Global Fatigue Index absolute change in score from baseline- Mean SD-Modified-release Hydrocortisone Group-Standard Glucocorticoid group-t24

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

Quality of life assessments at 24 weeks - EQ-5D-5L index score -MeanSD-Modified-release Hydrocortisone group-Standard Glucocorticoid group-t24

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

Quality of life assessments at 24 weeks -SF-36 absolute change from baseline -MeanSD-Modified-release Hydrocortisone group-Standard Glucocorticoid group-t24

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

Change from baseline in natural log-17OHPSDSprofile-MeanSD-Modified-release Hydrocortisone group-Standard Glucocorticoid group-t24

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

Change from baseline in natural log-and rostenedione 24-hAUC-MeanSD-Modified-release Hydrocortisone group-Standard Glucocorticoid group-t24

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

Nebesio, 2016

Bibliographic Reference	Nebesio, T. D.; Renbarger, J. L.; Nabhan, Z. M.; Ross, S. E.; Slaven, J. E.; Li, L.; Walvoord, E. C.; Eugster, E. A.; Differential effects of hydrocortisone, prednisone, and dexamethasone on hormonal and pharmacokinetic profiles: a pilot study in children with congenital adrenal hyperplasia; International Journal of Pediatric Endocrinology; 2016; vol. 2016; 17

1 Study details

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this study included in review	NR
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	USA
Study setting	Tertiary centre - Riley Hospital for Children
Study dates	NR
Sources of funding	Supported by an investigator-initiated research grant from Pfizer
Inclusion criteria	Prepubertal children between the ages of 4 and 12 years with classic CAH followed at Riley Hospital for Children were eligible
Exclusion criteria	Exclusion criteria included medical problems that affect growth, absorption, or clearance of glucocorticoids and medications known to affect the absorption or clearance of glucocorticoids.
Recruitment / selection of participants	NR
Intervention(s)	• Three sequential 6-week treatment courses arranged in random order during which they received the following medications: 1. Hydrocortisone (5 mg tablets; Pfizer, New York, NY) 15 mg/m2 /day divided three times a day administered at 08:00, 15:00, and 21:00 2. Prednisone (1 mg tablets; Roxane Laboratories Inc., Columbus, OH) 3 mg/m2 /day divided twice a day administered at 08:00 and 21:00 3. Dexamethasone (0.5 mg/5 mL elixir; Morton Grove Pharmaceuticals Inc., Morton Grove, IL) 0.3 mg/m2 /day administered daily at 21:00

	• All medications were taken orally. • Subjects remained on their usual dose of mineralocorticoid replacement throughout the study.
Population subgroups	
Comparator	Compared to each other
Number of participants	N=9
Duration of follow-up	18 weeks (6 weeks each treatment)
Indirectness	NR
Additional comments	

Study arms

Hydrocortisone (N = 9)

(5 mg tablets; Pfizer, New York, NY)

Prednisolone (N = 9)

(1 mg tablets; Roxane Laboratories Inc., Columbus, OH)

Dexamethasone (N = 9)

(0.5 mg/5 mL elixir; Morton Grove Pharmaceuticals Inc., Morton Grove, IL)

Characteristics

Study-level characteristics

Characteristic	Study (N = 9)
Age (years) Range	4.8 to 11.6 years
Age (years) Mean (SD)	8.1 (2.3)
Male Sample size	n = 4; % = 44.4
Female Sample size	n = 5; % = 55.5

1 **Outcomes**

2 **Study timepoints**

3 **18 week**

4 **Primary outcomes**

Outcome	Dexamethasone vs Hydrocortisone, 18 week, N2 = 9, N1 = 9	Dexamethasone vs Prednisolone, 18 week, N2 = 9, N1 = 9	Hydrocortisone vs Prednisolone, 18 week, N2 = 9, N1 = 9
ACTH Difference (95% CI)	−0.55 (−0.99, −0.12)	−0.90 (−1.33, −0.47)	−0.35 (−0.78, 0.09)
ACTH p value	0.016	Less than 0.001	0.110
Androstenedione Difference (95% CI)	−0.64 (−1.15, −0.14)	−0.90 (−1.40, −0.40)	−0.26 (−0.76, 0.25)
Androstenedione p value	0.016	0.002	0.293
17OHP Difference (95% CI)	−1.59 (−1.94, −1.23)	−2.44 (−2.80, −2.09)	−0.86 (−1.21, −0.50)
17OHP p value	Less than 0.001	Less than 0.001	Less than 0.001

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

2 **Primary outcomes-ACTH-Custom Value 0-Hydrocortisone-Prednisolone-Dexamethasone-t18**

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

3 **Primary outcomes-Androstenedione-Custom Value0-Hydrocortisone-Prednisolone-Dexamethasone-t18**

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

4 **Primary outcomes-17OHP-Custom Value 0-Hydrocortisone-Prednisolone-Dexamethasone-t18**

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

5 # Silva, 1997

Bibliographic Reference	Silva, I. N.; Kater, C. E.; Cunha, C. F.; Viana, M. B.; Randomised controlled trial of growth effect of hydrocortisone in congenital adrenal hyperplasia; Archives of Disease in Childhood; 1997; vol. 77 (no. 3); 214-8

6 **Study details**

Secondary publication of another included study- see primary study for details	NR
Other publications associated with this	NR

study included in review	
Trial name / registration number	NR
Study type	Randomised controlled trial (RCT)
Study location	Brazil
Study setting	Tertiary centre
Study dates	NR
Sources of funding	NR
Inclusion criteria	Children with the classic form of CAH due to 21-hydroxylase deficiency
Exclusion criteria	NR
Recruitment / selection of participants	NR
Intervention(s)	Children were randomised to receive either 15 mg/m2 daily of oral hydrocortisone with fludrocortisone 0.1 mg/day for six months and then had their dose schedule switched (crossover) for another six months
Population subgroups	• Prepubertal • Pubertal
Comparator	children were randomised to receive either 25 mg/m2 daily of oral hydrocortisone with fludrocortisone 0.1 mg/day for six months and then had their dose schedule switched (crossover) for another six months. Hydrocortisone 25mg dose was divided into three daily doses.
Number of participants	26
Duration of follow-up	1 year (6 months each phase)
Indirectness	NR

1 **Study arms**

2 **Hydrocortisone 15mg (N = 26)**

3 **Hydrocortisone 25mg (N = 26)**

4 **Characteristics**

5 **Study-level characteristics**

Characteristic	Study (N = 26)
Age (years) Median (range)	45.3 months (3.6 months to 15 years)
Male Sample size	n = 8; % = 30.7
Female Sample size	n = 18; % = 69.2

6 **Outcomes**

7 **Study timepoints**

8 **6 months**

9 **Prepubertal**

Outcome	Hydrocortisone 15mg, 6 months, N = 44	Hydrocortisone 25mg, 6 months, N = 44
17OHP (nmol/L) Median (range)	113.7 (0.5–1207.5)	11.5 (0.6–819.9)

Outcome	Hydrocortisone 15mg, 6 months, N = 44	Hydrocortisone 25mg, 6 months, N = 44
Androstenedione (nmol/litre) Median (range)	3.4 (0.5–40.2)	1.6 (0.1–31.8)
Testosterone (nmol/litre) Median (range)	2.5 (0.8–9.1)	2.3 (1.2–11.3)

1 **Pubertal**

Outcome	Hydrocortisone 15mg, 6 months, N = 8	Hydrocortisone 25mg, 6 months, N = 8
17OHP (nmol/litre) Median (range)	91.7 (6.8–453)	314.2 (66.5–568.7)
Androstenedione (nmol/litre) Median (range)	11 (6.1–41.9)	22.3 (10.5–47.5)
Testosterone (nmol/litre) Median (range)	4.7 (3.9–6.9)	6.2 (3.5–9.2)

2 **Growth hormone**

Outcome	Hydrocortisone 15mg, 6 months, N = 50	Hydrocortisone 25mg, 6 months, N = 51
Peak Mean (SE)	13.8 (1.8)	14.9 (1.5)
Increment Mean (SE)	9.6 (2)	6.9 (3)

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

2 **Prepubertal-17OHP-Custom Value 0-Hydrocortisone 15mg-Hydrocortisone 25mg-t1**

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

3 **Prepubertal-Androstenedione-Custom Value 0-Hydrocortisone 15mg-Hydrocortisone 25mg-t1**

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

4 **Prepubertal-Testosterone-Custom Value 0-Hydrocortisone 15mg-Hydrocortisone 25mg-t1**

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

5 **Pubertal-17OHP-Custom Value 0-Hydrocortisone 15mg-Hydrocortisone 25mg-t1**

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

6 **Pubertal-Androstenedione-Custom Value 0-Hydrocortisone 15mg-Hydrocortisone 25mg-t1**

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

1 **Pubertal-Testosterone-Custom Value 0-Hydrocortisone 15mg-Hydrocortisone 25mg-t1**

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

2 **Growth hormone-Peak-Mean SE-Hydrocortisone 15mg-Hydrocortisone 25mg-t1**

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

3 **Growth hormone-Increment-Mean SE-Hydrocortisone 15mg-Hydrocortisone 25mg-t1**

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

4

5

Appendix E Forest plots

E.1 All primary adrenal insufficiency

E.1.1 Continuous SC hydrocortisone 2 dose vs. standard hydrocortisone [Ekman 2012]

Figure 2: BMI (kg/m2) lower is better.

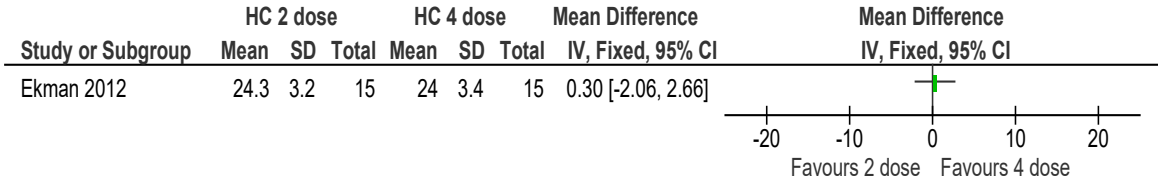


Figure 3: SF-36 Physical function (0-100) higher is better.

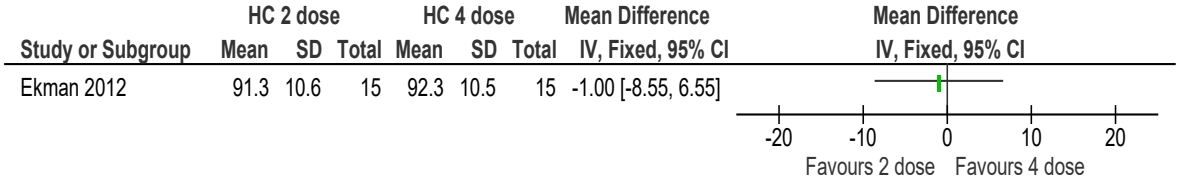


Figure 4: SF-36 Role function (0-100) higher is better.

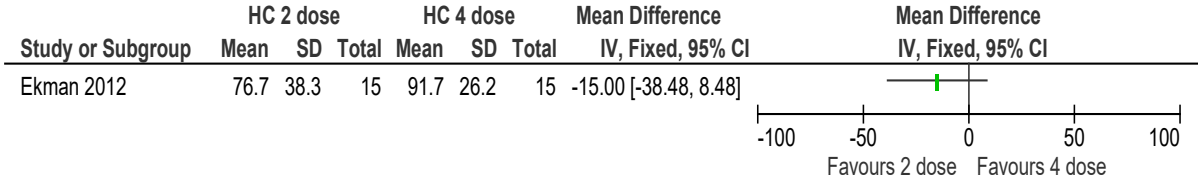
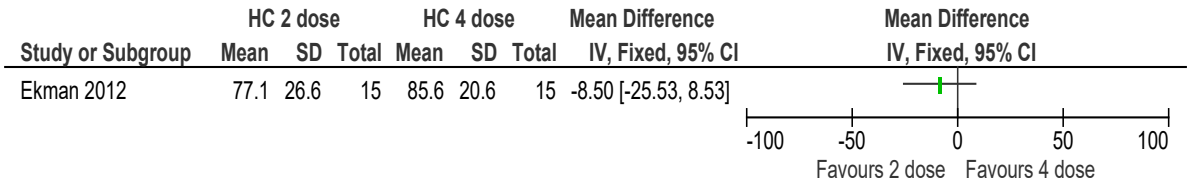


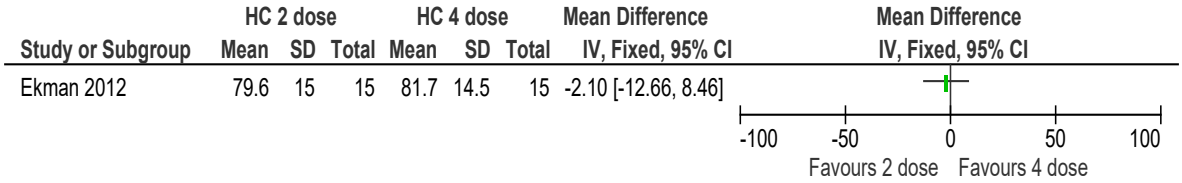
Figure 5: SF-36 Bodily pain (0-100) higher is better.



1

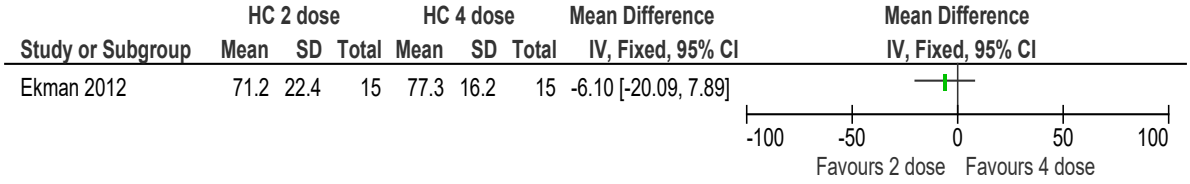
2

Figure 6: SF-36 General health (0-100) higher is better.



3

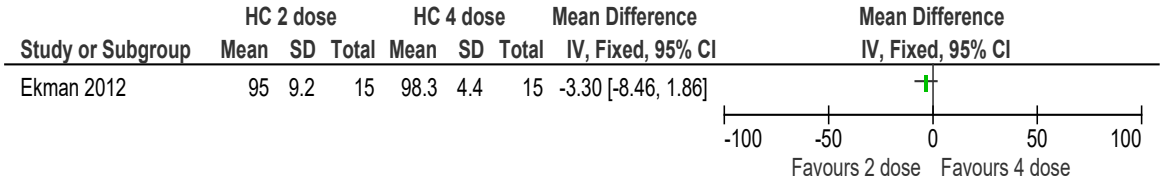
Figure 7: SF-36 Vitality (0-100) higher is better.



Source: <Insert Source text here>

4

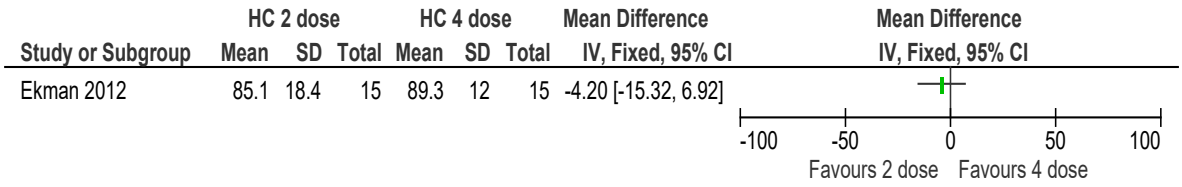
Figure 8: SF-36 Social function (0-100) higher is better.



Source: <Insert Source text here>

5

Figure 9: SF-36 Mental health (0-100) higher is better.

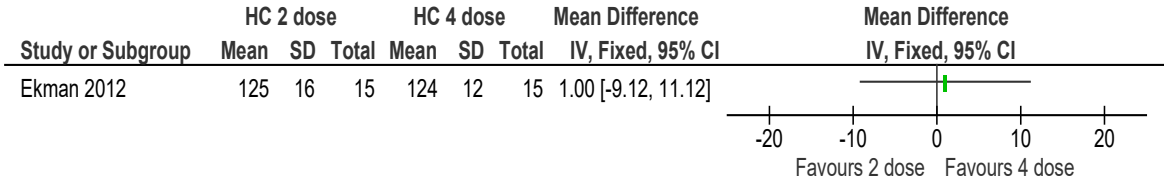


Source: <Insert Source text here>

1

2

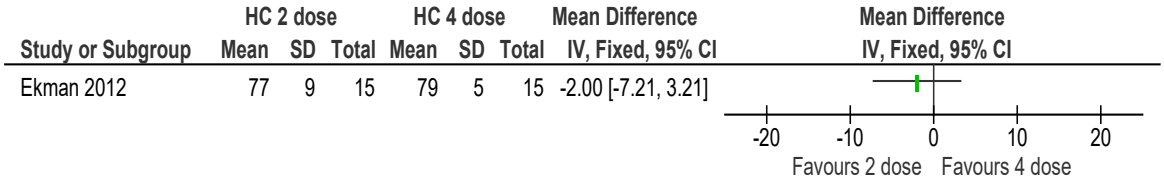
Figure 10: Systolic BP (mmHg) higher is better.



Source: <Insert Source text here>

3

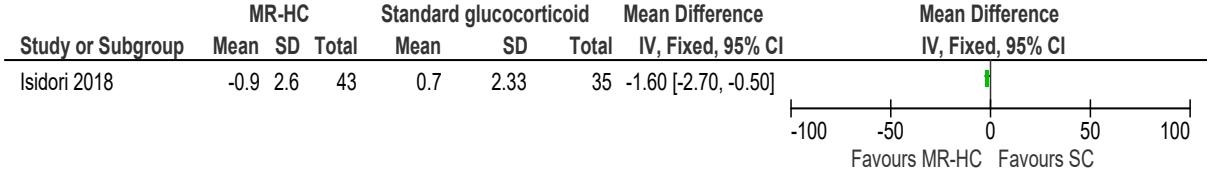
Figure 11: Diastolic BP (mmHg) lower is better



Source: <Insert Source text here>

4 ## E.1.2 Modified-Release HC vs Standard Glucocorticoid [Isidori 2018]

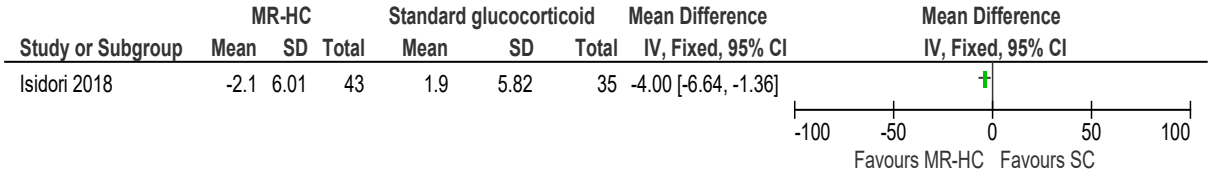
Figure 12: Change in BMI from baseline (kg/m2) lower is better



Source: <Insert Source text here>

5

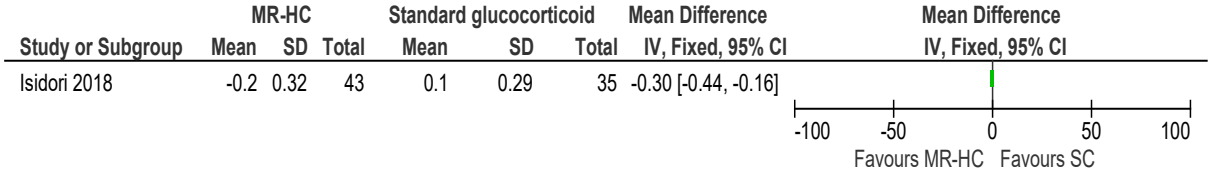
Figure 13: Change in bodyweight from baseline (kg) lower is better.



Source: <Insert Source text here>

1

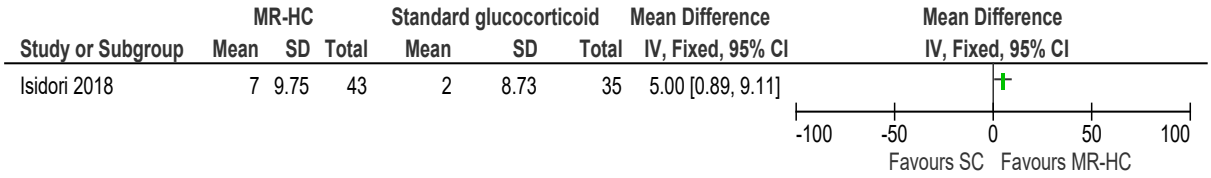
Figure 14: Change in HbA1c (%) from baseline lower is better.



Source: <Insert Source text here>

2

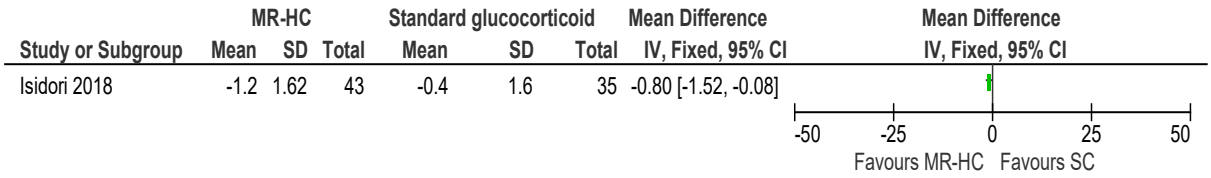
Figure 15: AddiQoL higher is better.



Source: <Insert Source text here>

3

Figure 16: Flu or flu-like events in 6 months



Source: <Insert Source text here>

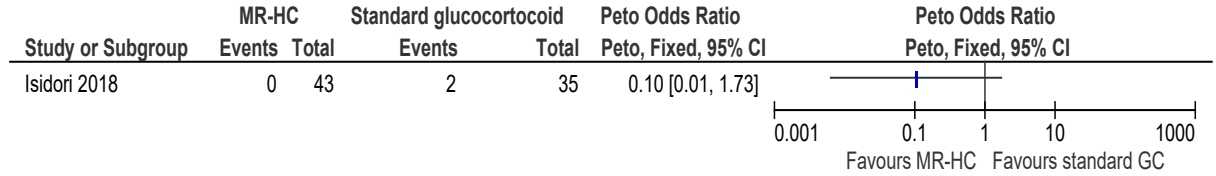
4

Figure 17: Change in total cholesterol (mg/dL) from baseline lower is better.

Source: <Insert Source text here>

1

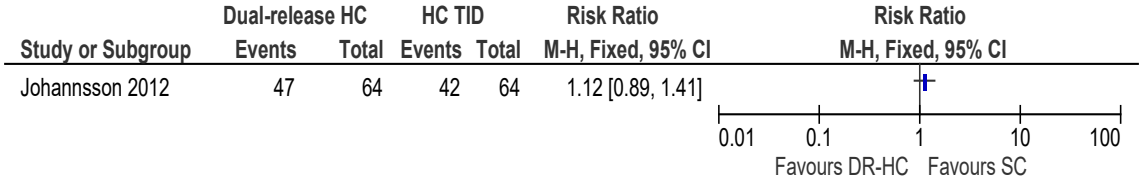
Figure 18: Serious adverse events lower is better



Source: <Insert Source text here>

2 **E.1.3 : Dual-Release HC vs Hydrocortisone TID [Johannsson 2012]**

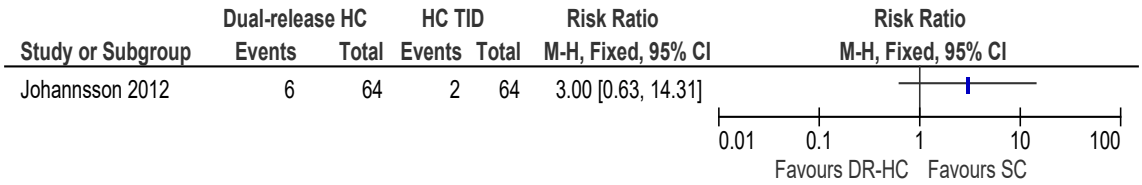
Figure 19: Adverse event (any) lower is better.



Source: <Insert Source text here>

3

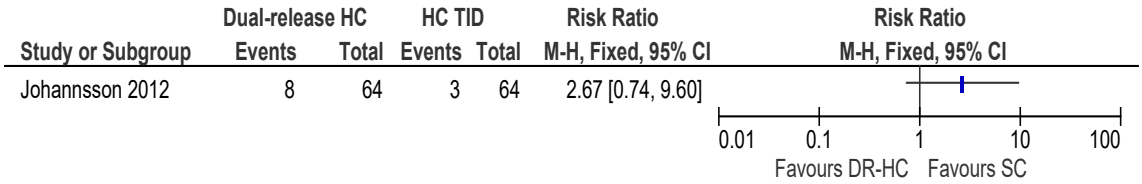
Figure 20: Serious AE/ Hospitalisation lower is better.



Source: <Insert Source text here>

4

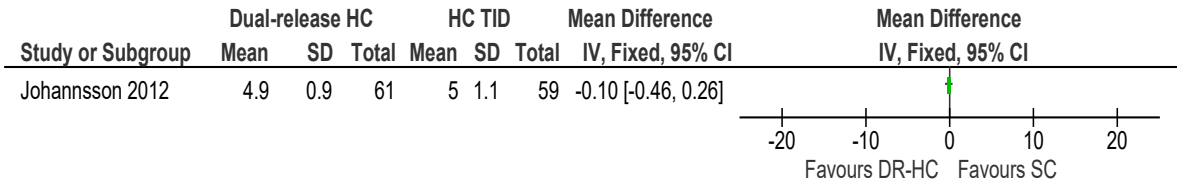
Figure 21: Adverse event (fatigue) lower is better.



Source: <Insert Source text here>

5

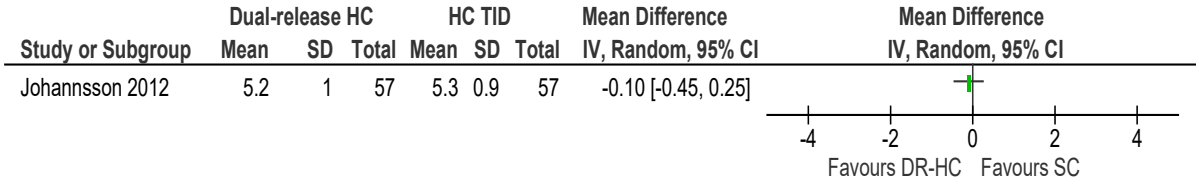
Figure 22: Change in HbA1c (%) from baseline lower is better.



Source: <Insert Source text here>

1

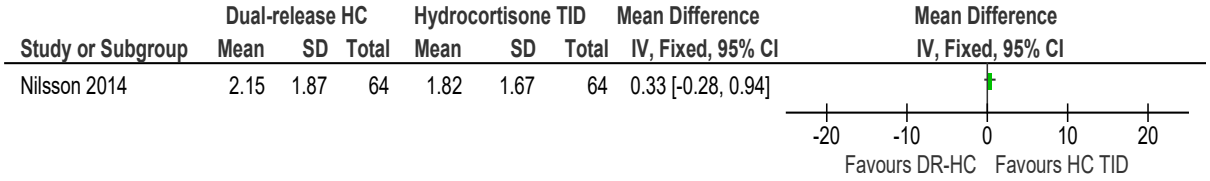
Figure 23: Change in total cholesterol (mg/dL) from baseline lower is better.



Source: <Insert Source text here>

2 **E.1.4 Dual-Release HC vs Hydrocortisone TID [Nilsson 2014]**

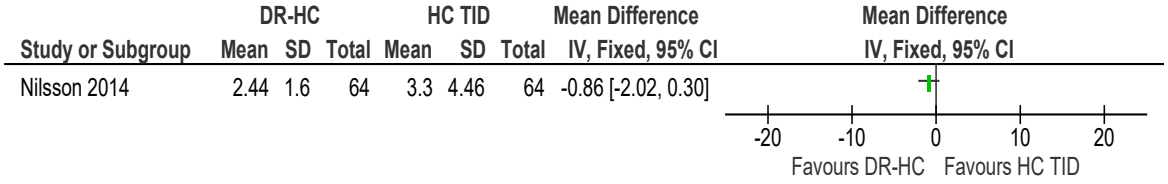
Figure 24: Illness episodes per patient within 3 months lower is better.



Source: <Insert Source text here>

3

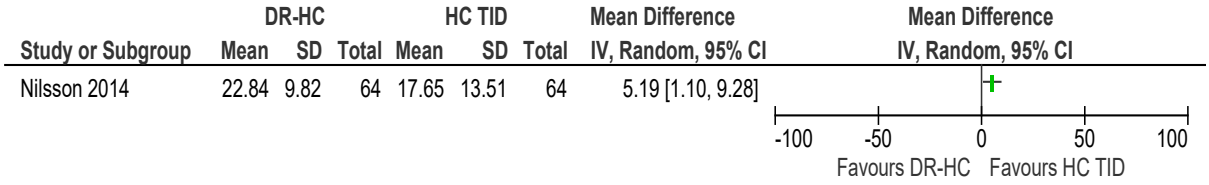
Figure 25: Number of days per illness episode lower is better.



Source: <Insert Source text here>

4

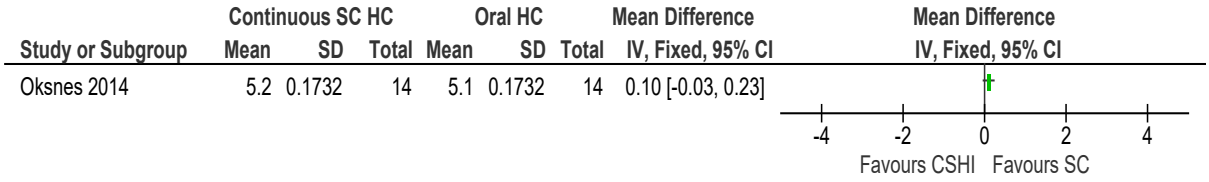
Figure 26: Additional HC dose per illness episode (mg) lower is better.



S

1 **E.1.5 Continuous SC HC vs Standard Hydrocortisone [Oksnes 2014]**

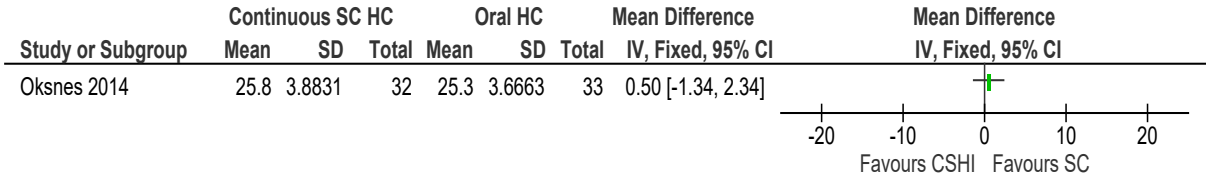
Figure 27: HbA1c (%) lower is better.



Source: <Insert Source text here>

2

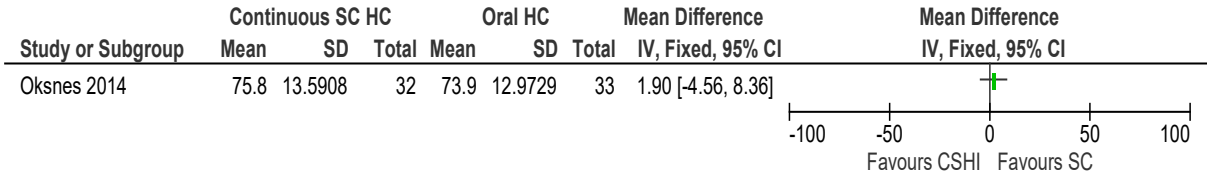
Figure 28: BMI (kg/m2) lower is better.



Source: <Insert Source text here>

3

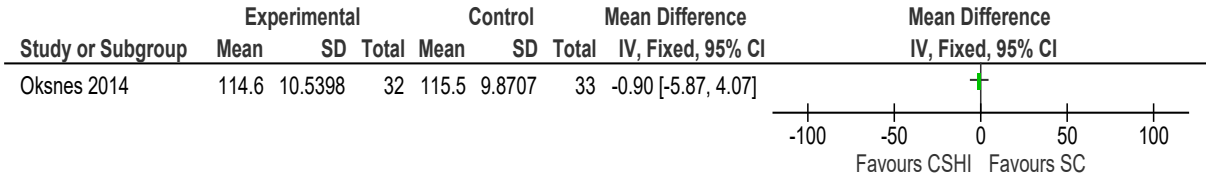
Figure 29: Weight (kg) lower is better.



Source: <Insert Source text here>

4

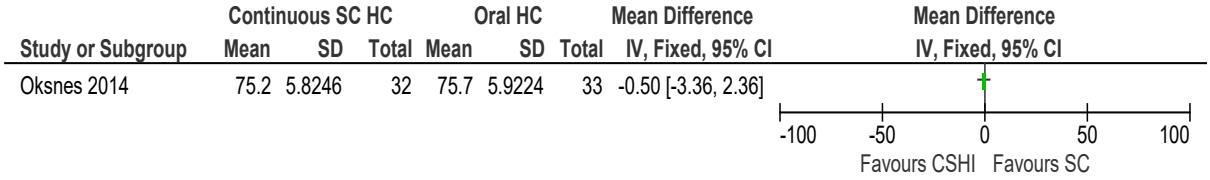
Figure 30: Systolic BP (mm/hg) lower is better.



Source: <Insert Source text here>

1

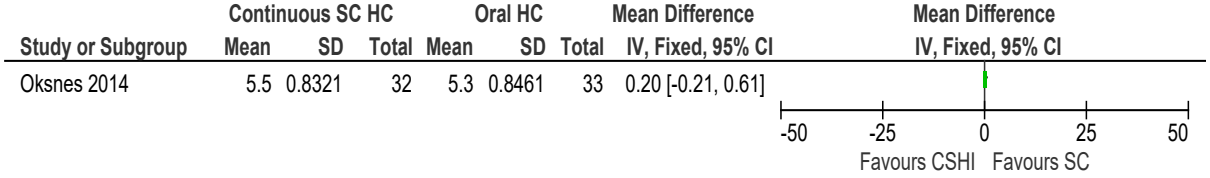
Figure 31: Diastolic BP (mm/hg) lower is better.



Source: <Insert Source text here>

2

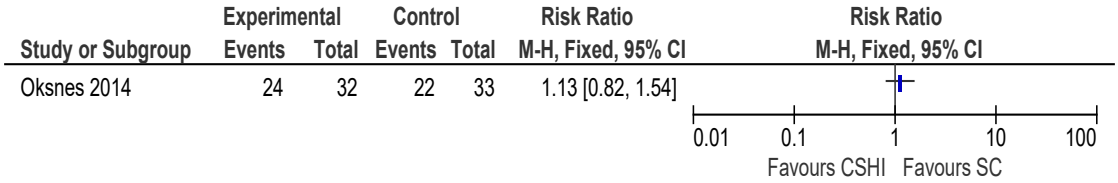
Figure 32: Total cholesterol (mg/dL) lower is better.



Source: <Insert Source text here>

3

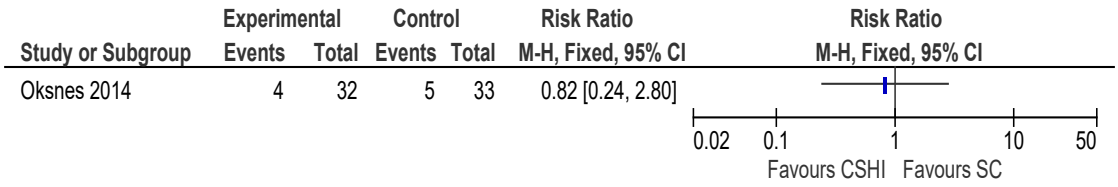
Figure 33: Any AE lower is better.



Source: <Insert Source text here>

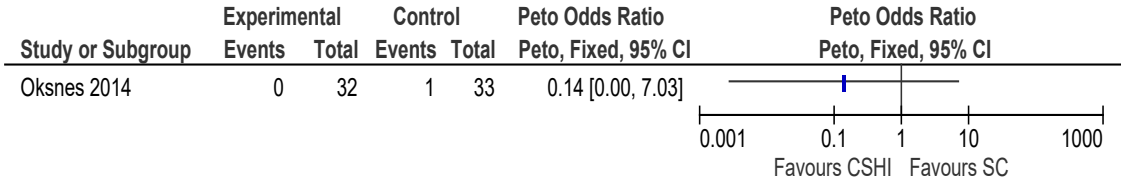
4

Figure 34: Treatment-related AE lower is better.



Source: <Insert Source text here>

Figure 35: Serious AE/Hospitalisation lower is better

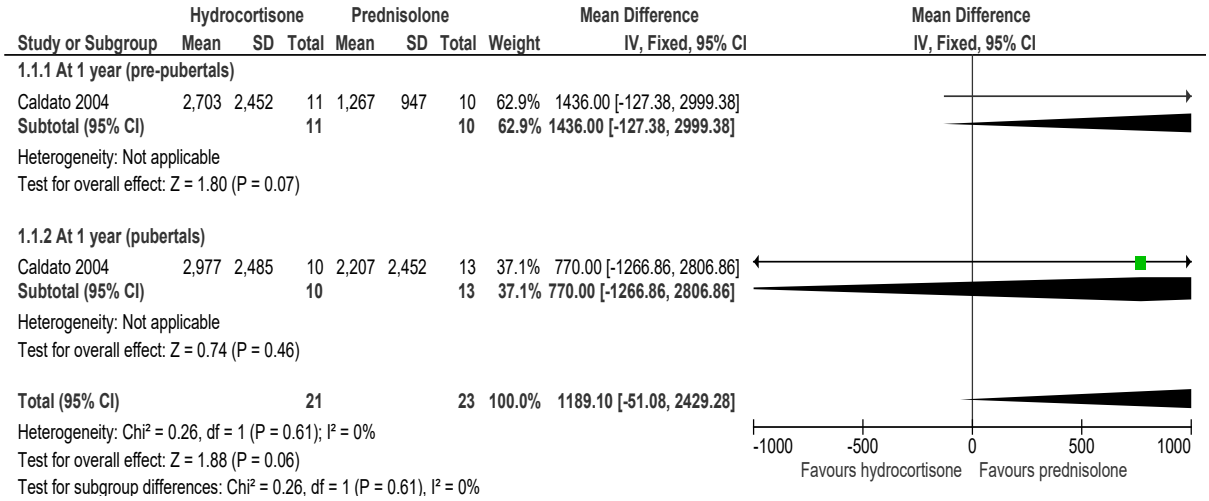


Source: <Insert Source text here>

E.2 Primary adrenal insufficiency due to CAH

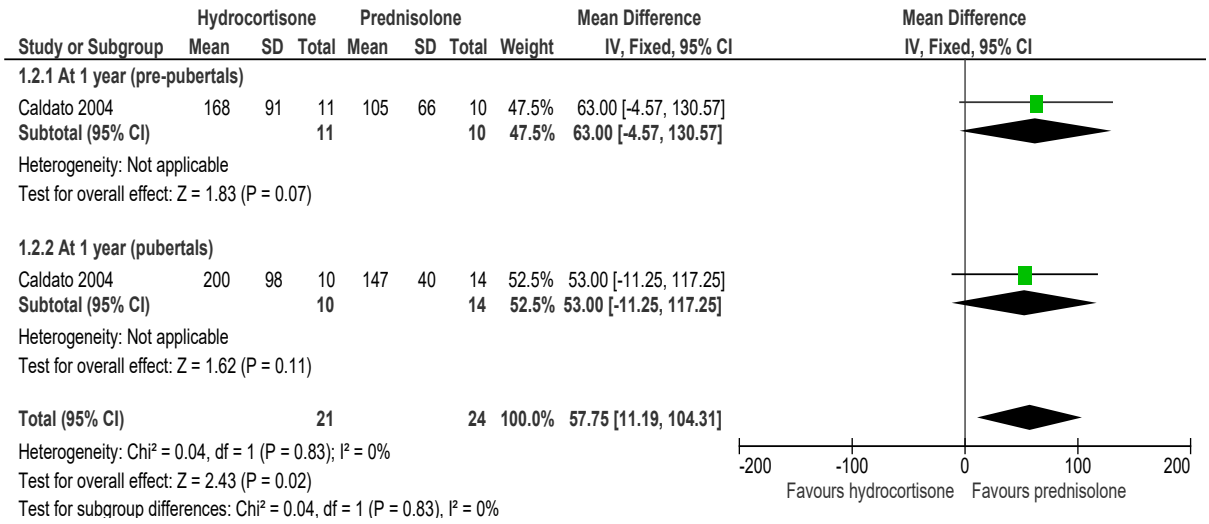
E.2.1 Prednisolone (1x daily) compared to hydrocortisone (3x daily) in pubertal and prepubertal people with congenital adrenal hyperplasia [Caldato 2004]

Figure 36: 17OHP lower is better



<Insert Note here>

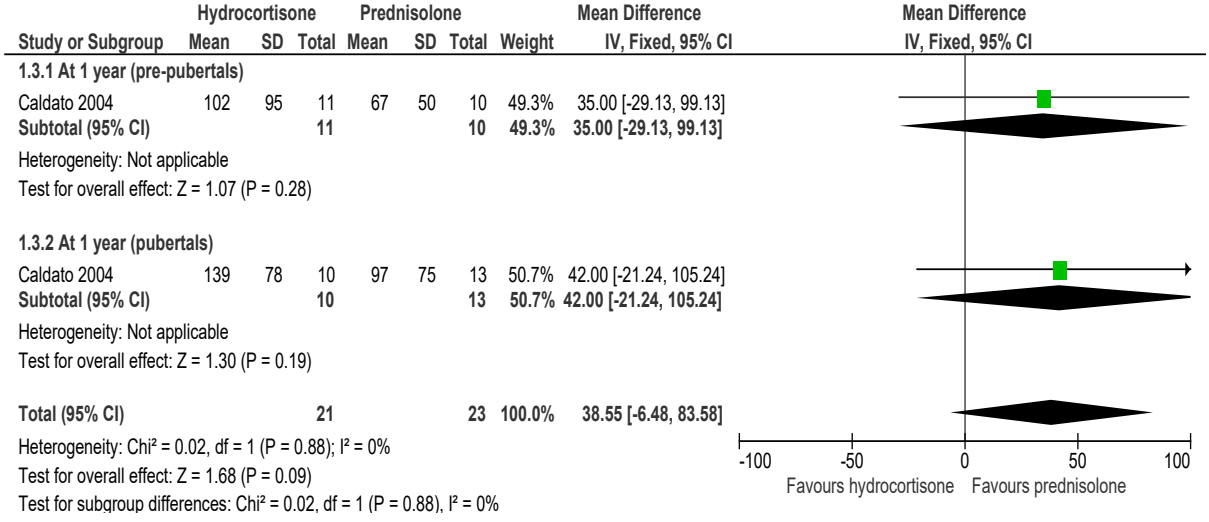
Figure 37: Androstenedione (ng/dL) lower is better



<Insert Note here>

1

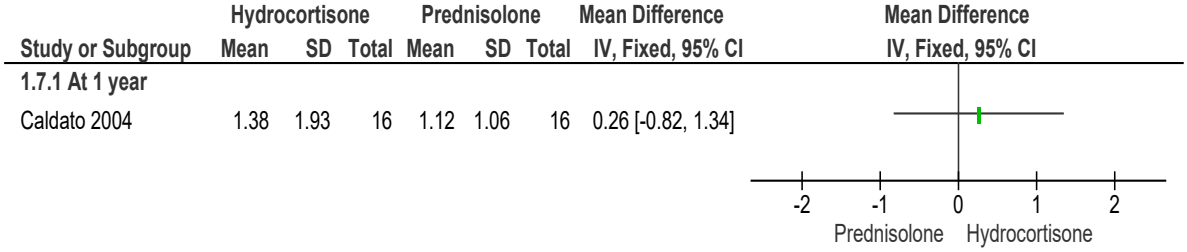
Figure 38: Testosterone (ng/dL) lower is better



<Insert Note here>

2

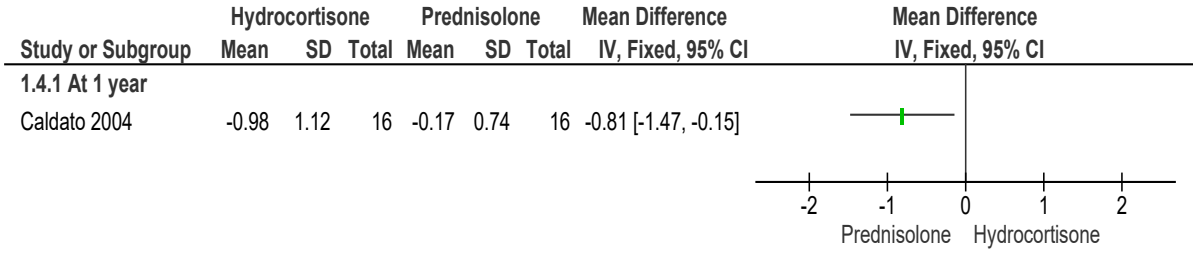
Figure 39: Growth velocity (cm/y) higher is better.



Source: <Insert Source text here>

1

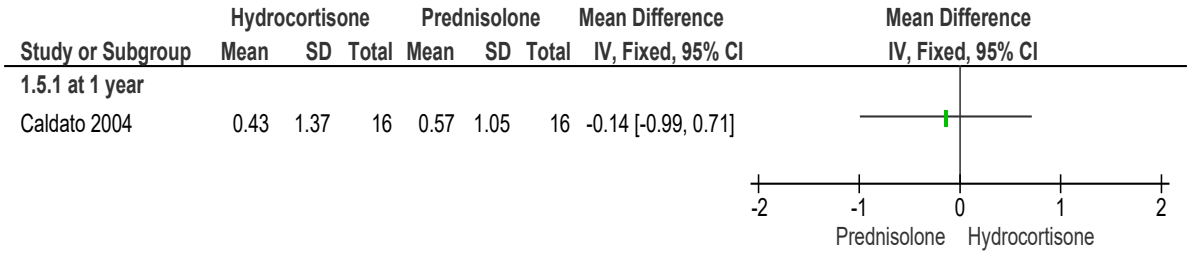
Figure 40: Height SDS (bone age) higher is better.



Source: <Insert Source text here>

2

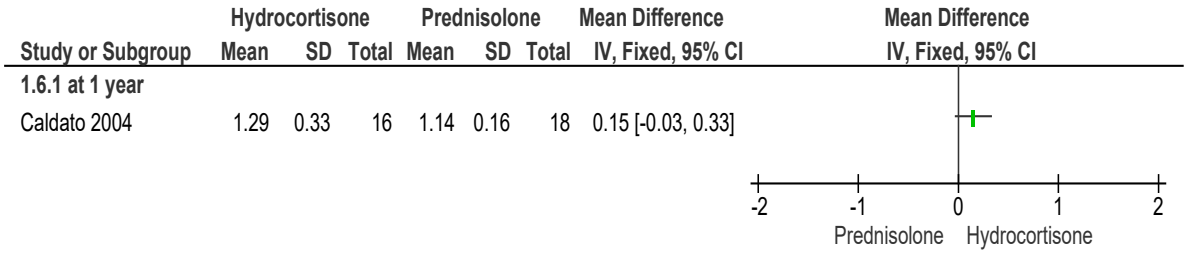
Figure 41: Height SDS (chronological age) higher is better.



Source: <Insert Source text here>

3

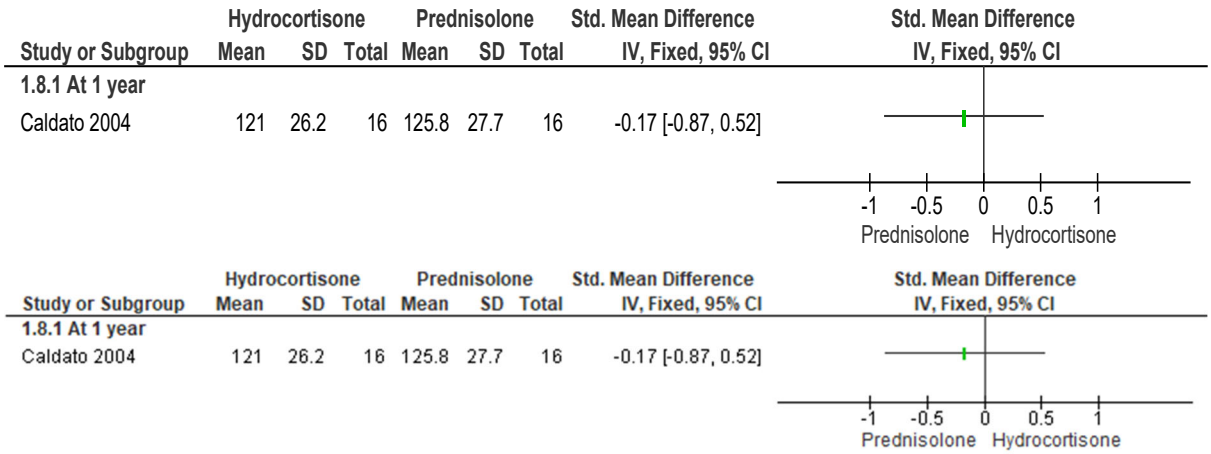
Figure 42: Ratio BA/CA lower is better.



Source: <Insert Source text here>

4

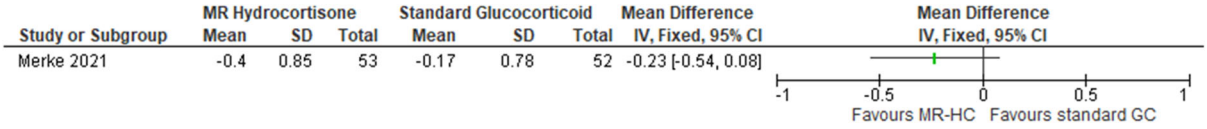
Figure 43: Height (cm) higher is better.



Source: <Insert Source text here>

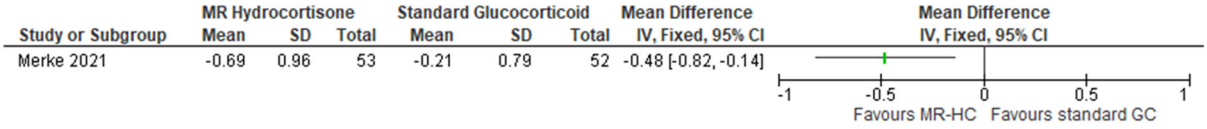
E.2.2 Modified-release hydrocortisone compared to standard glucocorticoid in adults with congenital adrenal hyperplasia.

Figure 44: Change from baseline natural log 17OHP SDS profile lower is better



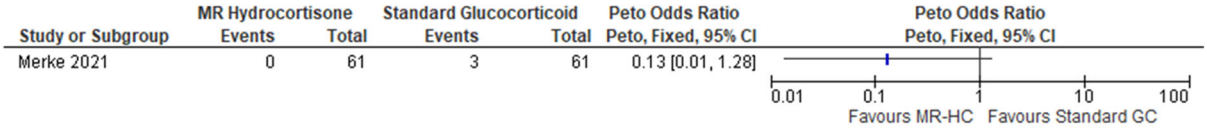
Source: <Insert Source text here>

Figure 45:Change from baseline 17OHP 7am-3pm profile at 24 weeks lower is better



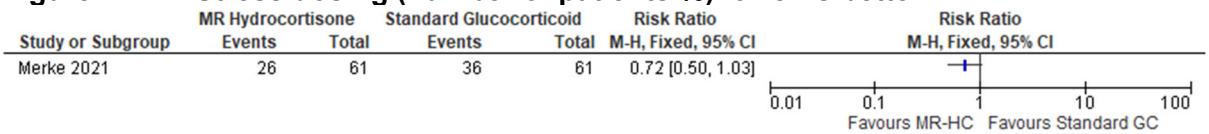
Source: <Insert Source text here>

Figure 46: Incidence of adrenal crisis (number of patients %) lower is better



Source: <Insert Source text here>

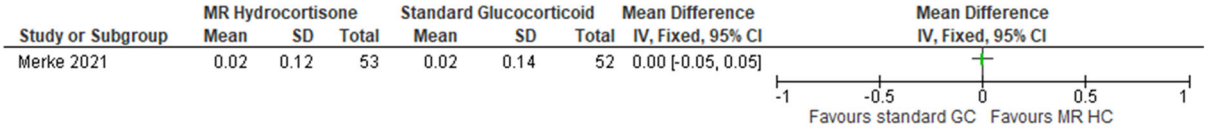
Figure 47: Stress dosing (number of patients %) lower is better



Source: <Insert Source text here>

1

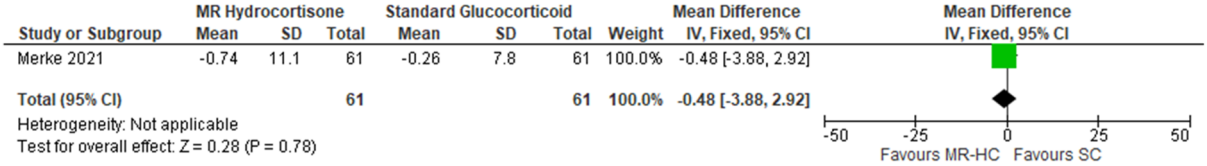
Figure 48: EQ-5D-5L (-0.11-1.00) higher is better



Source: <Insert Source text here>

2

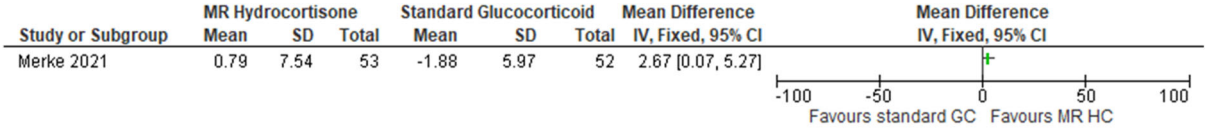
Figure 49: Global Fatigue Index - Change from baseline (1-50) lower is better



Source: <Insert Source text here>

3

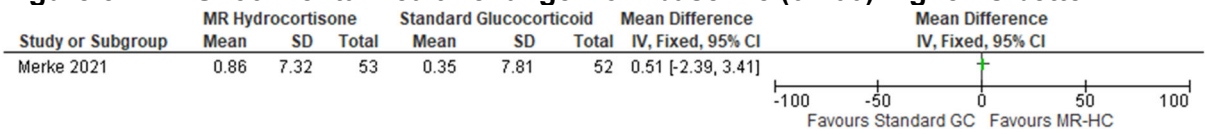
Figure 50: SF36 general health perceptions change from baseline (0-100) higher is better



Source: <Insert Source text here>

4

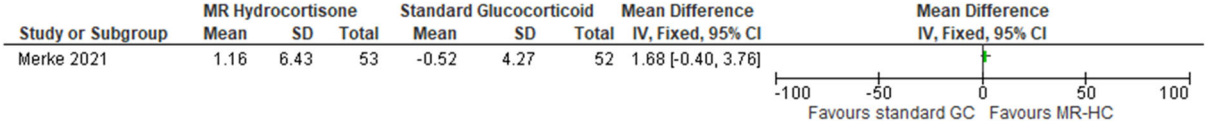
Figure 51: SF36 mental health change from baseline (0-100) higher is better



Source: <Insert Source text here>

5

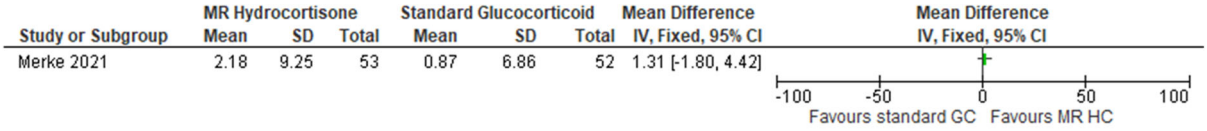
Figure 52: SF36 - Physical functioning change from baseline (0-100) higher is better



Source: <Insert Source text here>

1

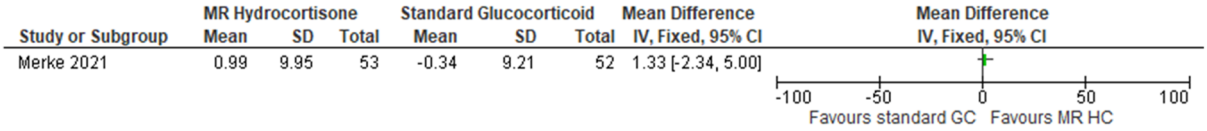
Figure 53: SF36 – Social functioning change from baseline (0-100) higher is better



Source: <Insert Source text here>

2

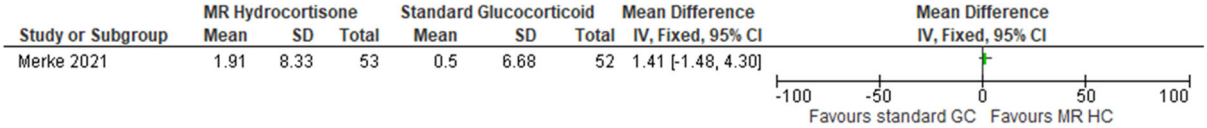
Figure 54: SF36 - Role emotional change from baseline (0-100) higher is better



Source: <Insert Source text here>

3

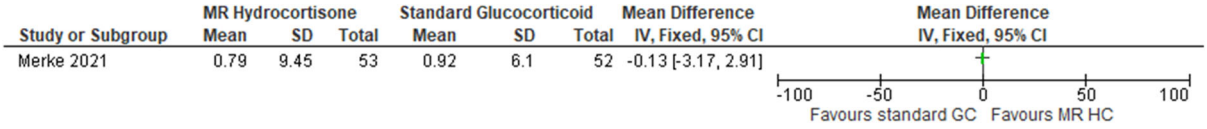
Figure 55: SF36 - Role physical change from baseline (0-100) higher is better



Source: <Insert Source text here>

4

Figure 56: SF36 – Vitality change from baseline (0-100) higher is better



Source: <Insert Source text here>

5

6

Appendix F GRADE and/or GRADE-CERQual tables

F.1 All primary adrenal insufficiency

F.1.1 Continuous SC hydrocortisone 2 dose vs. 4 dose standard hydrocortisone [Ekman 2014]

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Ekman/Primary] Hydrocortisone 2 dose	4 dose	Relative (95% CI)	Absolute (95% CI)		
Bodyweight (follow-up: 4 weeks) (lower is better)												
1	randomised trials	not serious	not serious	not serious	very serious[a]	none	15	15	-	MD **0.2 kg higher** (9.96 lower to 10.36 higher)	⊕⊕◯◯ Low	
BMI (follow-up: 4 weeks) (lower is better)												
1	randomised trials	not serious	not serious	not serious	very serious[b]	none	15	15	-	MD **0.3 kg higher** (2.06 lower to 2.66 higher)	⊕⊕◯◯ Low	
SF-36 Physical function (follow-up: 4 weeks) (higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[Ekman/Primary] Hydrocortisone 2 dose**	**4 dose**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[c]	not serious	not serious	very serious[d]	none	15	15	-	MD **1 out of 100 (SF-36 score). lower** (8.55 lower to 6.55 higher)	⨁◯◯◯ Very low	
SF-36 Role function (follow-up: 4 weeks) (higher is better)												
1	randomised trials	serious[c]	not serious	not serious	very serious[d]	none	15	15	-	MD **15 out of 100 (SF-36 score). lower** (38.48 lower to 8.48 higher)	⨁◯◯◯ Very low	
SF-36 Bodily pain (follow-up: 4 weeks) (higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[Ekman/Primary] Hydrocortisone 2 dose**	**4 dose**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[c]	not serious	not serious	very serious[d]	none	15	15	-	MD **8.5 out of 100 (SF-36 score). lower** (25.53 lower to 8.53 higher)	⨁◯◯◯ Very low	
SF-36 General health (follow-up: 4 weeks) (higher is better)												
1	randomised trials	serious[c]	not serious	not serious	very serious[e]	none	15	15	-	MD **2.1 out of 100 (SF-36 score). lower** (12.66 lower to 8.46 higher)	⨁◯◯◯ Very low	
SF-36 Vitality (follow-up: 4 weeks) (higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[Ekman/Primary] Hydrocortisone 2 dose**	**4 dose**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[c]	not serious	not serious	very serious[e]	none	15	15	-	MD **6.1 out of 100 (SF-36 score). lower** (20.09 lower to 7.89 higher)	⊕◯◯◯ Very low	
SF-36 Social function (follow-up: 4 weeks) (higher is better)												
1	randomised trials	serious[c]	not serious	not serious	serious[f]	none	15	15	-	MD **3.3 out of 100 (SF-36 score). lower** (8.46 lower to 1.86 higher)	⊕⊕◯◯ Low	
SF-36 Mental Health (follow-up: 4 weeks) (higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[Ekman/Primary] Hydrocortisone 2 dose**	**4 dose**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[c]	not serious	not serious	very serious[d]	none	15	15	-	MD **4.2 out of 100 (SF-36 score). lower** (15.32 lower to 6.92 higher)	⊕◯◯◯ Very low	
Systolic BP (follow-up: 4 weeks) (**lower is better)**												
1	randomised trials	not serious	not serious	not serious	very serious[g]	none	15	15	-	MD **1 mmHg higher** (9.12 lower to 11.12 higher)	⊕⊕◯◯ Low	
Diastolic BP (follow-up: 4 weeks) (**lower is better)**												
1	randomised trials	not serious	not serious	not serious	Very serious[h]	none	15	15	-	MD **2 mmHg lower** (7.21 lower to 3.21 higher)	⊕⊕◯◯ Low	

Explanations

a. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 7.1)

b. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 1.6)

c. Downgraded by 1 increment due to risk of measurement bias in patient-reported outcomes.

d. Downgraded by 2 increments for imprecision as confidence interval crossed both thresholds for established MID [3].

e. Downgraded by 2 increments for imprecision as confidence interval crossed both thresholds for established MID [2].

f. Downgraded by 1 increment for imprecision as confidence interval crossed the established MID [3]

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

h. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 2.5)

F.1.2 Modified-Release HC 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 (lower is better)												
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 (lower is better)												

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[d]	none	43	35	-	MD **4 kg lower** (6.64 lower to 1.36 lower)	⊕◯◯◯ Very low	CRITICAL
Change in HbA1c from baseline (lower is better)												
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
Change in AddiQoL from baseline (higher is better)												
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 (lower is better)												

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[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 (lower is better)												
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 (lower is better)												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[j,k]	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)

F.1.3 Dual-Release HC vs Hydrocortisone TID

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[Johannsson/Primary] Dual-release hydrocortisone**	**hydrocortisone TID**	**Relative (95% CI)**	**Absolute (95% CI)**		
Adverse event (any) (lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[Johannsson/Primary] Dual-release hydrocortisone**	**hydrocortisone TID**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[a]	not serious	not serious	serious[b]	none	47/64 (73.4%)	42/64 (65.6%)	**RR 1.12** (0.89 to 1.41)	**79 more per 1,000** (from 72 fewer to 269 more)	⨁⨁◯◯ Low	
Serious AE/Hospitalisation (lower is better)												
1	randomised trials	not serious	not serious	not serious	very serious[c]	none	6/64 (9.4%)	2/64 (3.1%)	**RR 3.00** (0.63 to 14.31)	**63 more per 1,000** (from 12 fewer to 416 more)	⨁⨁◯◯ Low	
AE: Fatigue (lower is better)												
1	randomised trials	serious[a]	not serious	not serious	very serious[c]	none	8/64 (12.5%)	3/64 (4.7%)	**RR 2.67** (0.74 to 9.60)	**78 more per 1,000** (from 12 fewer to 403 more)	⨁◯◯◯ Very low	
Change in HbA1c% from baseline (lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[Johannsson/Primary] Dual-release hydrocortisone**	**hydrocortisone TID**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	serious[d]	not serious	not serious[f]	not serious	none	61	59	-	MD **0.1 % lower** (0.46 lower to 0.26 higher)	⨁⨁⨁◯ Moderate	
Change in total cholesterol from baseline (lower is better)												
1	randomised trials	serious[d]	not serious	not serious	not serious[f]	none	57	57	-	MD **0.1 nmol/L lower** (0.45 lower to 0.25 higher)	⨁⨁⨁◯ Moderate	

Explanations

a. Downgraded by 1 increment as the majority of evidence was of high risk of bias due to bias arising from measurement of the outcome [risk of measurement bias in patient-reported outcome].
b. b. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 0.8)
c. c. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 0.8, 1.25)
d. d. Downgraded by 1 increment as the majority of evidence was of high risk of bias due to bias arising from incomplete outcome data: results are only reported for a subset of the ITT population, study authors do not make it clear why the outcome data is missing.
e. e. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 0.55)
f. f. No imprecision (+/- 0.45)

F.1.4 : Dual-Release HC vs Hydrocortisone TID

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[Nilsson/Primary] Dual-release hydrocortisone**	**hydrocortisone TID**	**Relative (95% CI)**	**Absolute (95% CI)**		
Illness episodes per patient within 3 months (lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	64	64	-	MD **0.33 episodes higher** (0.28 lower to 0.94 higher)	⊕◯◯◯ Very low	
Number of days per illness episode (lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	serious[c]	none	64	64	-	MD **0.86 days lower** (2.02 lower to 0.3 higher)	⊕◯◯◯ Very low	
Additional hydrocortisone dose per illness episode (mg) (lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	serious[d]	none	64	64	-	MD **5.19 mg higher** (1.1 higher to	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Nilsson/Primary] Dual-release hydrocortisone	hydrocortisone TID	Relative (95% CI)	Absolute (95% CI)		
										9.28 higher)		

Explanations

a. Downgraded by 2 increments as the majority of evidence was of very high risk of bias due to bias arising from the randomisation process and in measurement of the outcome [open-label study design, allocation not concealed from patients or outcome assessors].

b. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 0.935)

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

d. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 4.91)

F.1.5 GRADE Table: Continuous SC HC vs Standard Hydrocortisone

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	[Oksnes/Primary] Continuous SC hydrocortisone	Standard hydrocortisone	Relative (95% CI)	Absolute (95% CI)		
HbA1c (lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	14	14	-	MD **0.1 % higher** (0.03 lower to 0.23 higher)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[Oksnes/Primary] Continuous SC hydrocortisone**	**Standard hydrocortisone**	**Relative (95% CI)**	**Absolute (95% CI)**		
BMI (lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	serious[c]	none	32	33	-	MD **0.5 kg/m2 higher** (1.34 lower to 2.34 higher)	⊕◯◯◯ Very low	
Weight (lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	serious[d]	none	32	33	-	MD **1.9 kg higher** (4.56 lower to 8.36 higher)	⊕◯◯◯ Very low	
Systolic BP (lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	serious[e]	none	32	33	-	MD **0.9 mmHg lower** (5.87 lower to 4.07 higher)	⊕◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[Oksnes/Primary] Continuous SC hydrocortisone**	**Standard hydrocortisone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Diastolic BP (lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	serious[f]	none	32	33	-	MD **0.5 mmHg lower** (3.36 lower to 2.36 higher)	⨁◯◯◯ Very low	
Total cholesterol (lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[g]	none	32	33	-	MD **0.2 nmol/L higher** (0.21 lower to 0.61 higher)	⨁◯◯◯ Very low	
Any AE (lower is better)												
1	randomised trials	very serious[h]	not serious	not serious	serious[i]	none	24/32 (75.0%)	22/33 (66.7%)	**RR 1.13** (0.82 to 1.54)	**87 more per 1,000** (from 120 fewer to 360 more)	⨁◯◯◯ Very low	

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**[Oksnes/Primary] Continuous SC hydrocortisone**	**Standard hydrocortisone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Treatment-related AE (lower is better)												
1	randomised trials	very serious[h]	not serious	not serious	very serious[j]	none	4/32 (12.5%)	5/33 (15.2%)	**RR 0.82** (0.24 to 2.80)	**27 fewer per 1,000** (from 115 fewer to 273 more)	⨁◯◯◯ Very low	
Serious AE/Hospitalisation (lower is better)												
1	randomised trials	very serious[h]	not serious	not serious	very serious[j]	none	0/32 (0.0%)	1/33 (3.0%)	**OR 0.14** (0.00 to 7.03)	**26 fewer per 1,000** (from 30 fewer to 150 more)	⨁◯◯◯ Very low	

Explanations

a. Downgraded by 2 increments as the majority of evidence was of high risk of bias due to bias arising from missing outcome data [outcome not reported for entire ITT population] and open-label trial design.

b. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 0.085)

c. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 1.83)

d. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 6.485)

e. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 4.935)

f. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 2.96)

g. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 0.42)

h. Downgraded by 2 increments as the majority of evidence was of very high risk of bias due to risk of bias from measurement of the outcome [study authors do not state how adverse events are identified] and open-label trial design.

i. Downgraded by 1 increment as confidence interval crossed 1 MID (+/- 0.8, 1.25)

j. Downgraded by 2 increments as confidence interval crossed both MIDs (+/- 0.8, 1.25)

F.2 Primary adrenal insufficiency due to CAH

F.2.1 Prednisolone (1x daily) compared to hydrocortisone (3x daily) in pubertal and prepubertal people with congenital adrenal hyperplasia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	prednisolone (1x daily)	hydrocortisone (3x daily)	Relative (95% CI)	Absolute (95% CI)		
Mean level 17OHP (follow-up: 1 years; assessed with: nmol/L, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,c]	none	23	21	-	MD **1189.1 nmol/L higher** (51.08 lower to 2429.28 higher)	⨁◯◯◯ Very low[c]	CRITICAL
Mean level androstenedione (follow-up: 1 years; assessed with: nmol/L, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**prednisolone (1x daily)**	**hydrocortisone (3x daily)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	very serious[a]	not serious	not serious	serious[b,d]	none	23	21	-	MD **57.75 nmol/L lower** (11.19 lower to 104.31 lower)	⊕◯◯◯ Very low	CRITICAL
Mean level testosterone (follow-up: 1 years; assessed with: nmol/L, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,e]	none	23	21	-	MD **38.55 nmol/L higher** (6.48 lower to 83.58 higher)	⊕◯◯◯ Very low	CRITICAL
Mean growth velocity (follow-up: 1 years, higher is better)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,f]	none	23	21	-	MD **0.26 higher** (0.82 lower to 1.34 higher)	⊕◯◯◯ Very low	CRITICAL
Height (Standard deviation scores) (follow-up: 1 years; assessed with: Bone age, higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**prednisolone (1x daily)**	**hydrocortisone (3x daily)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	very serious[a]	not serious	not serious	serious[b,g]	none	16	16	-	MD **0.81 lower** (1.47 lower to 0.15 lower)	⊕◯◯◯ Very low	CRITICAL
Height (Standard deviation scores) (follow-up: 1 years; assessed with: chronological age, higher is better)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,h]	none	16	16	-	MD **0.14 lower** (0.99 lower to 0.71 higher)	⊕◯◯◯ Very low	CRITICAL
Ratio BA/CA - at 1 year (assessed with: bone age/chronological age ratio, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,i]	none	16	18	-	MD **0.15 lower** (0.03 lower to 0.33 higher)	⊕◯◯◯ Very low	CRITICAL
Height cm - At 1 year (follow-up: 1 years, higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**prednisolone (1x daily)**	**hydrocortisone (3x daily)**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,j]	none	16	16	-	SMD **0.17 lower** (0.87 lower to 0.52 higher)	⨁◯◯◯ Very low	CRITICAL

CI: confidence interval; MD: mean difference; SMD: standardised mean difference

Explanations

a. Downgraded by downgraded by 2 increments as the majority of the evidence was at very high risk of bias (Risk of bias due to performance/measurement bias: Reporting bias: not all outcome measures listed in the methods section were fully reported in results and Study attrition rate not reported).

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs as per the MIDs below

c. Downgraded by 1 interval - MID = 1236 (0.5 x control group SD for final value as vales taken from a published Cochrane review)

d. Downgraded by 1 interval - MID = 47.9 (0.5 x control group SD for final value as vales taken from a published Cochrane review)

e. Downgraded by 1 interval - MID = 44.6 (0.5 x control group SD for final value as vales taken from a published Cochrane review)

f. Downgraded by 2 intervals - MID = 0.53 (0.5 x control group SD for final value as vales taken from a published Cochrane review)

g. Downgraded by 1 interval - MID = 0.37 (0.5 x control group SD for final value as vales taken from a published Cochrane review)

h. Downgraded by 2 intervals - MID = 0.53 (0.5 x control group SD for final value as vales taken from a published Cochrane review)

i. Downgraded by 1 interval - MID = 0.08 (0.5 x control group SD for final value as vales taken from a published Cochrane review)

j. Downgraded by 2 intervals MID = 0.5 (SMD)

F.2.2 Hydrocortisone (TID, high morning dose) compared to hydrocortisone (TID, high evening dose) in children with congenital adrenal hyperplasia

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Median 17OHP (follow-up: 4 weeks; assessed with: nmol/L, lower is better)									
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	Results for 17 OHP are presented as medians(IQR); 44 (16 to 116) for the high morning dose (n=5)compared to 33 (15 to 76) for the high eveningdose (n=6).	⊕◯◯◯ Very low	
Median testosterone (follow-up: 4 weeks; assessed with: nmol/L, lower is better)									
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	Median testosterone was 0.70 nmol/L (IQR 0.30 - 2.30) for those in the high morning dose group (n=5) compared to 1.1 nmol/L (IQR 0.60 to 2.70) for those in the high evening dose group (n=6).	⊕◯◯◯ Very low	
Median androstenedione (follow-up: 4 weeks; assessed with: nmol/L, lower is better)									
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	Median androstenedione was 1.80 nmol/L (IQR 1.00 - 3.00) for those in the high morning dose group compared to 1.90 nmol/L (IQR 1.20 to 6.50) for those in the high evening dose group.	⊕◯◯◯ Very low	
Median DHEAS (follow-up: 4 weeks; assessed with: nmol/L, lower is better)									
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	Median DHEAS was 0.20 nmol/L (IQR 0.20 - 0.60) for those in the high morning dose group compared to 0.40 nmol/L (IQR 0.20 to 0.70) for those in the high evening dose group.	⊕◯◯◯ Very low	

CI: confidence interval

Explanations

a. Downgraded by 2 increments as the majority of the evidence was at very high risk of bias (Risk of bias due to bias due to missing outcome data for 4 patients and attrition rate not reported),

b. Downgraded due to uncertainty: small sample size and wide IQR (taken directly from published Cochrane review).

c. Data taken directly from a published Cochrane review. Reported as median values so unable to perform additional analyses.

F.2.3 Modified-release hydrocortisone compared to standard glucocorticoid in adults with congenital adrenal hyperplasia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	modified-release hydrocortisone	standard glucocorticoid	Relative (95% CI)	Absolute (95% CI)		
Change from baseline 17OHP 24-hour profile at 24 weeks (follow-up: 24 weeks) (lower is better)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c,d]	none	53	52	-	MD **0.23 lower** (0.54 lower to 0.08 higher)	⊕◯◯◯ Very low	CRITICAL
Change from baseline 17OHP 7am-3pm profile at 24 weeks (follow-up: 24 weeks) (lower is better)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c,d]	none	53	52	-	MD **0.48 lower** (0.82 lower to 0.14 lower)	⊕◯◯◯ Very low	CRITICAL
Change from baseline androstenedione 24h AUC (follow-up: 24 weeks) (lower is better)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c,e]	none	53	52	-	MD **19.9 lower** (33.82 lower to 5.98 lower)	⊕◯◯◯ Very low	CRITICAL
Incidence of adrenal crisis (number of patients %) (follow-up: 24 weeks) (lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	modified-release hydrocortisone	standard glucocorticoid	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	serious[b]	serious[c,f]	none	0/61 (0.0%)	3/61 (4.9%)	**OR 0.13** (0.01 to 1.28)	**43 fewer per 1,000** (from 49 fewer to 13 more)[g]	⊕◯◯◯ Very low	CRITICAL
Stress dosing (number of patients %) (follow-up: 24 weeks, lower is better)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[f]	none	26/61 (42.6%)	36/61 (59.0%)	**RR 0.72** (0.50 to 1.03)	**165 fewer per 1,000** (from 295 fewer to 18 more)	⊕◯◯◯ Very low	CRITICAL
EQ-5D-5L index score (follow-up: 24 weeks) (higher is better)												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c,h]	none	53	52	-	MD **0** (1.66 lower to 1.66 higher)	⊕◯◯◯ Very low	CRITICAL
Global Fatigue Index - Change from baseline (follow-up: 24 weeks) (lower is better)												
1	randomised trials	serious[a]	not serious	serious[b]	not serious[c,i]	none	61	61	-	MD **0.48 lower** (3.88 lower to 2.92 higher)	⊕⊕◯◯ Low	CRITICAL
SF36 general health perceptions change from baseline (follow-up: 24 weeks) (higher is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	modified-release hydrocortisone	standard glucocorticoid	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	serious[a]	not serious	serious[b]	serious[c,n]	none	53	52	-	MD **2.67 higher** (0.07 higher to 5.27 higher)	⊕◯◯◯ Very low	CRITICAL
SF36 - Mental health change from baseline (follow-up: 24 weeks) (higher is better)												
1	randomised trials	serious[a]	not serious	not serious	serious[c,k]	none	53	52	-	MD **0.51 higher** (2.39 lower to 3.41 higher)	⊕⊕◯◯ Low	CRITICAL
SF36 - Physical functioning change from baseline (follow-up: 24 weeks) (higher is better)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c,k]	none	53	52	-	MD **1.68 higher** (0.4 lower to 3.76 higher)	⊕◯◯◯ Very low	CRITICAL
SF36 - social functioning change from baseline (follow-up: 24 weeks) (higher is better)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c,k]	none	53	52	-	MD **1.31 higher** (1.8 lower to 4.42 higher)	⊕◯◯◯ Very low	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	modified-release hydrocortisone	standard glucocorticoid	Relative (95% CI)	Absolute (95% CI)		
SF36 - role emotional change from baseline (follow-up: 24 weeks) (higher is better)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c,l]	none	53	52	-	MD **1.33 higher** (2.34 lower to 5 higher)	⊕◯◯◯ Very low	CRITICAL
SF36 - role physical change from baseline (follow-up: 24 weeks) (higher is better)												
1	randomised trials	serious[a]	not serious	serious[b]	serious[c,k]	none	53	52	-	MD **1.41 higher** (1.48 lower to 4.3 higher)	⊕◯◯◯ Very low	CRITICAL
SF36 - vitality change from baseline (follow-up: 24 weeks) (higher is better)												
1	randomised trials	serious[a]	not serious	serious[b]	very serious[c,j]	none	53	52	-	MD **0.13 lower** (3.17 lower to 2.91 higher)	⊕◯◯◯ Very low	CRITICAL

Explanations

a. Downgraded by 1 increment as the majority of the evidence was at very high risk of bias (Risk of bias due to study attrition rate).

b. Downgraded by 1 increment due to intervention indirectness. Study authors explain that the control arm does not appropriately represent typical clinical practice: more aggressive dose up titration than usually performed.

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs as per MIDs below:

d. Downgraded by 1 increment - MID = 0.39 (0.5 x control group SD for final value as no baseline values reported)

e. Downgraded by 1 increment - MID = 14.5 (0.5 x control group SD for final value as no baseline values reported)

f. Downgraded by 2 increment - MID = 0.8 to 1.25 (default MID for dichotomous outcomes)

g. Downgraded by 1 increment - MID = 0.8 to 1.25 (default MID for dichotomous outcomes)

h. Downgraded by 2 increments - MID = 0.03 (established value)

i. no imprecision - MID = 3.9 (0.5x median control group SDs baseline values not reported)

j. Downgraded by 2 increments - MID = 2 (established value)

k. Downgraded by 1 increment - MID = 3 (established value)

l. Downgraded by 1 increment - MID = 4 (established value)

m. SF36 bodily pain was not available for extraction. The paper states 'A technical issue with the scoring of the bodily pain domain meant that these data are not available'.

n. Downgraded by 1 increment - MID = 2 (established value)

F.2.4 Hydrocortisone (TID, 15mg/day) compared to prednisolone (3mg/day) or dexamethasone (0.3mg/day) in people with congenital adrenal hyperplasia

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydrocortisone (TID, 15mg/day)	prednisolone (3mg/day) or dexamethasone (0.3mg/day)	Relative (95% CI)	Absolute (95% CI)		
17OHP (follow-up: 6 weeks; assessed with: nmol/L, lower is better)												
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	There were lower levels of 17 OHP reported in the DXA group compared to HC (P < 0.001) and compared to PD (P < 0.001).				⊕◯◯◯ Very low[c]	CRITICAL
Androstenedione (follow-up: 6 weeks; assessed with: nmol/L, lower is better)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydrocortisone (TID, 15mg/day)	prednisolone (3mg/day) or dexamethasone (0.3mg/day)	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	serious[b]	none	Androstenedione levels were significantly lower with DXA when compared to HC (P = 0.016) and PD (P = 0.002).				⊕◯◯◯ Very low[c]	CRITICAL

Explanations

a. Downgraded by 2 increments as the majority of the evidence was at very high risk of bias (Risk of bias due to unclear randomisation procedure, unclear reporting of outcomes and study attrition rate).

b. Downgraded by one increment due to uncertainty around the effect estimate: small sample size so P values should be interpreted with caution

c. Data taken directly from a published Cochrane review. Only P values and statistical significance reported.

F.2.5 Hydrocortisone (15mg/day) with fludrocortisone (0.1mg/day) compared to hydrocortisone (25mg/day) with fludrocortisone (0.1mg/day) in children with congenital adrenal hyperplasia due to 21-hydroxylase deficiency

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Median 17OHP levels (follow-up: 6 months; assessed with: nmol/L, lower is better)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	In the prepubertal group (n=22), there was a statistically significant (p<0.05) difference in suppression of median 17OHP levels: 17OHP was lower among those treated with HC 25 mg/day (11.5 nmol/L, IQR 0.6 - 819.0) compared to HC 15 mg/day (113.7 nmol/L, IQR 0.5 - 1207). In the pubertal group (n=4), 17OHP levels were lower in those treated with HC 15 mg/day (91.7 nmol/L, IQR 6.8 - 453.0) compared to HC 25 mg/day (314.2 nmol/L, IQR 66.5 - 568.7).	⨁◯◯◯ Very low	CRITICAL
Median androstenedione levels (follow-up: 6 months; assessed with: nmol/L, lower is better)									
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	In the prepubertal group, androstenedione was lower (p<0.05) among those treated with HC 25 mg/day (1.6 nmol/L, IQR 0.1 - 31.8) compared to HC 15 mg/day (3.4 nmol/L, IQR 0.5 - 40.2). In the pubertal group, 17OHP levels were lower in those treated with HC 15 mg/day (11 nmol/L, IQR 6.1 - 41.9) compared to HC 25 mg/day (22.3 nmol/L, IQR 10.5 - 46.5).	⨁◯◯◯ Very low	CRITICAL
Median testosterone levels (follow-up: 6 months; assessed with: nmol/L, lower is better)									

Certainty assessment							Impact	Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**			
1	randomised trials	very serious[a]	not serious	not serious	very serious[b]	none	No differences were noted in testosterone levels at 6 months. In the prepubertal group, median testosterone levels were 2.5 nmol/L (IQR 0.8 to 9.1) for those treated with HC 15 mg versus 2.3 nmol/L (IQR 1.2 to 11.3) for those treated with HC 25 mg. In the pubertal group, median testosterone levels were 4.7 nmol/L (IQR 3.9 to 6.9) for those treated with HC 15 mg versus 6.2 nmol/L (IQR 4.5 to 9.2) for those treated with HC 25 mg.	⨁◯◯◯ Very low	CRITICAL

1

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**hydrocortisone (15mg/day) with fludrocortisone (0.1mg/day)**	**hydrocortisone (25mg/day) with fludrocortisone (0.1mg/day)**	**Relative (95% CI)**	**Absolute (95% CI)**		
Final adult height (follow-up: 6 months, higher is better)												
1	randomised trials	very serious[a]	not serious	not serious	very serious[c,d]	none	26	26	-	MD **0.34 higher** (0.27 higher to 0.41 higher)	⨁◯◯◯ Very low	CRITICAL

2

Explanations

a. Downgraded by 2 increments as the majority of the evidence was at very high risk of bias (Risk of bias due to issues surrounding randomisation method and selective outcome reporting and incomplete outcome data).

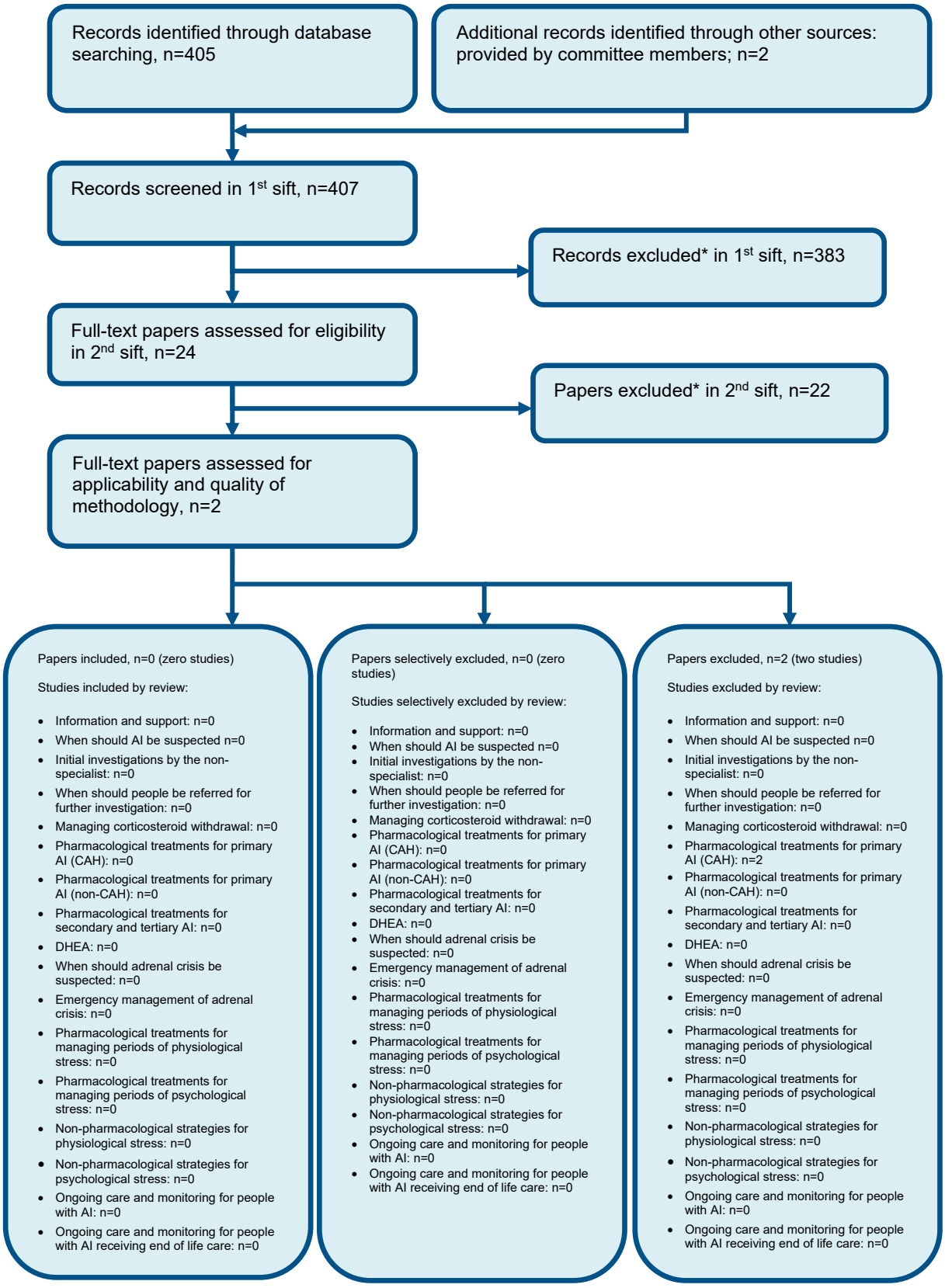
b. Downgraded for imprecision due to small sample size and wide IQR

c. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs.

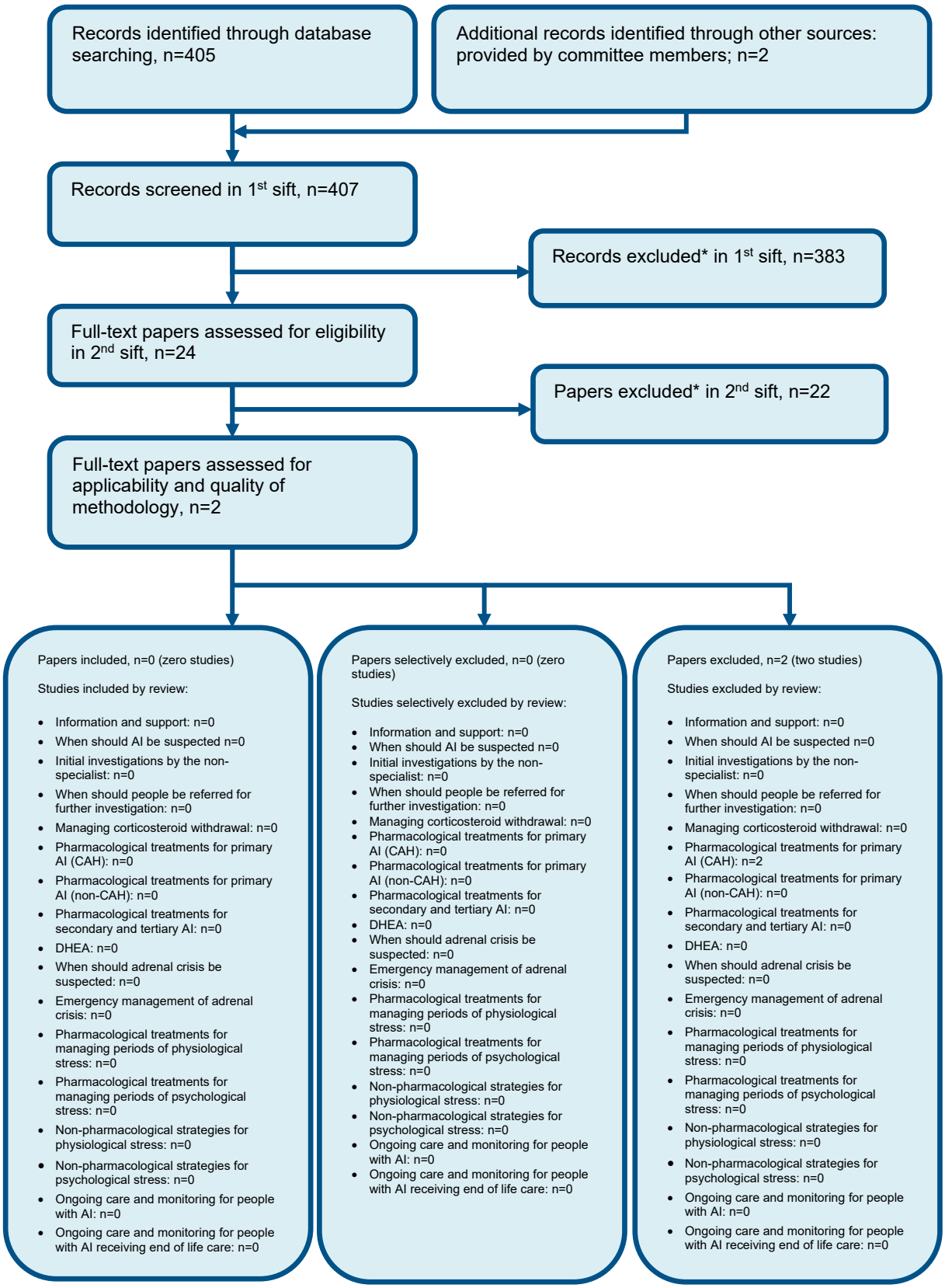
d. Downgraded by 2 increments - MID = 0.04 (calculated from MD (SE) as no baseline values reported)

e. Data taken directly from a published Cochrane review and reported in median values and IQR so unable to perform additional analyses.

Appendix G Economic evidence study selection



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



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

1

Appendix H Economic evidence tables

None.

Appendix I Health economic model

Note for the committee. To be updated once feasibility to be build a health economic model has been assessed.

Appendix J Excluded studies

J.1 Non Congenital Adrenal Hyperplasia

J.1.1 Clinical studies

Table 23: Studies excluded from the clinical review

Study	Reason for exclusion
Al Nofal, A., Bancos, I., Benkhadra, K. et al. (2015) The effect of various glucocorticoid replacement regimens on health outcomes in patients with adrenal insufficiency: A systematic review and meta-analysis. Endocrine Reviews. Conference: 97th Annual Meeting and Expo of the Endocrine Society, ENDO 36(supplement2)	- Conference abstract
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	- Duplicate reference
Bennett, G.; Cussen, L.; O'Reilly, M. W. (2022) The role for long-term use of dehydroepiandrosterone in adrenal insufficiency. Current Opinion in Endocrinology, Diabetes & Obesity 29(3): 284-293	- Review article but not a systematic review
Berardelli, R., Karamouzis, I., D'Angelo, V. et al. (2016) The acute effect of a mineralocorticoid receptor agonist on corticotrope secretion in Addison's disease. Journal of Endocrinological Investigation 39(5): 537-42	- Comparator in study does not match that specified in this review protocol
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	- Population not relevant to this review protocol
Bjornsdottir, S., Oksnes, M., Isaksson, M. et al. (2015) Circadian hormone profiles and insulin sensitivity in patients with Addison's disease: a comparison of continuous subcutaneous hydrocortisone infusion with conventional glucocorticoid replacement therapy. Clinical Endocrinology 83(1): 28-35	- Data not reported in an extractable format or a format that can be analysed

Study	Reason for exclusion
Bjornsdottir, S., Oksnes, M., Isaksson, M. et al. (2014) Circadian cortisol and growth hormone profiles in patients with addison's disease: A comparison of continuous subcutaneous hydrocortisone infusion with conventional glucocorticoid replacement therapy. Endocrine Reviews. Conference: 96th Annual Meeting and Expo of the Endocrine Society, ENDO 35(suppl3)	- Conference abstract
Bjornsdottir, S., Oksnes, M., Isaksson, M. et al. (2013) Insulin sensitivity in patients with addison's disease: A randomised cross-over trial comparing conventional glucocorticoid replacement therapy with continuous subcutaneous hydrocortisone infusion therapy. Endocrine Reviews. Conference: 95th Annual Meeting and Expo of the Endocrine Society, ENDO 34(3suppl1)	- Conference abstract
Burger-Stritt, Stephanie, Kardonski, Pavel, Pulzer, Alina et al. (2018) Management of adrenal emergencies in educated patients with adrenal insufficiency-A prospective study. Clinical endocrinology 89(1): 22-29	- Non-randomised - no multivariate analysis *Prospective, multicentre, questionnaire-based study*
Chen, H., Jin, Z., Sun, C. et al. (2021) Effects of dehydroepiandrosterone (DHEA) supplementation on cortisol, leptin, adiponectin, and liver enzyme levels: A systematic review and meta-analysis of randomised clinical trials. International Journal of Clinical Practice 75(11): e14698	- Population not relevant to this review protocol
Christiansen, J. J., Bruun, J. M., Christiansen, J. S. et al. (2011) Long-term DHEA substitution in female adrenocortical failure, body composition, muscle function, and bone metabolism: a randomized trial. European Journal of Endocrinology 165(2): 293-300	- Duplicate reference
Cohen, N., Gilbert, R., Wirth, A. et al. (1996) Atrial natriuretic peptide and plasma renin levels in assessment of mineralocorticoid replacement in Addison's disease. Journal of Clinical Endocrinology & Metabolism 81(4): 1411-5	- Study design not relevant to this review protocol
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	- Comparator in study does not match that specified in this review protocol

Study	Reason for exclusion
Gomes, L. G., Madureira, G., Mendonca, B. B. et al. (2013) Long-term low-dose dexamethasone treatment of non-classical congenital adrenal hyperplasia patients improves fertility without increasing metabolic or bone abnormalities. Endocrine Reviews. Conference: 95th Annual Meeting and Expo of the Endocrine Society, ENDO 34(3suppl1)	- Conference abstract
Kim, M. S.; Ryabets-Lienhard, A.; Geffner, M. E. (2012) Management of congenital adrenal hyperplasia in childhood. Current Opinion in Endocrinology, Diabetes & Obesity 19(6): 483-8	- Review article but not a systematic review
Ng, S. M. and Stepien, K. (2017) Glucocorticoid replacement regimens in the treatment of 21-hydroxylase deficiency congenital adrenal hyperplasia. Cochrane Database of Systematic Reviews 2017(1)	- Protocol only - for study or Systematic review
Oksnes, M., Bjornsdottir, S., Isaksson, M. et al. (2013) Continuous subcutaneous hydrocortisone infusion (CSHI) improves quality-of-life in Addison's disease (AD). Endocrine Reviews. Conference: 95th Annual Meeting and Expo of the Endocrine Society, ENDO 34(3suppl1)	- Conference abstract
Sarafoglou, K, Gonzalez-Bolanos, Mt, Zimmerman, CI et al. (2015) Comparison of cortisol exposures and pharmacodynamic adrenal steroid responses to hydrocortisone suspension VS. Commercial tablets. Journal of clinical pharmacology 55(4): 452-457	- Study design not relevant to this review protocol
Young, M. C. and Hughes, I. A. (1990) Dexamethasone treatment for congenital adrenal hyperplasia. Archives of Disease in Childhood 65(3): 312-314	- Comparator in study does not match that specified in this review protocol

1

2 ### J.1.2 Health Economic studies

3 None.

J.2 Congenital Adrenal Hyperplasia

J.2.1 Clinical studies

Table 24: Studies excluded from the clinical review

Study	Code [Reason]
Ajish, Tp, Praveen, Vp, Nisha, B et al. (2014) Comparison of different glucocorticoid regimens in the management of classical congenital adrenal hyperplasia due to 21-hydroxylase deficiency. Indian journal of endocrinology and metabolism 18(6): 815-820	- Comparator in study does not match that specified in this review protocol
Al Nofal, A., Bancos, I., Benkhadra, K. et al. (2015) The effect of various glucocorticoid replacement regimens on health outcomes in patients with adrenal insufficiency: A systematic review and meta-analysis. Endocrine Reviews. Conference: 97th Annual Meeting and Expo of the Endocrine Society, ENDO 36(supplement2)	- Conference abstract
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	- Duplicate reference
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
Bennett, G.; Cussen, L.; O'Reilly, M. W. (2022) The role for long-term use of dehydroepiandrosterone in adrenal insufficiency. Current Opinion in Endocrinology, Diabetes & Obesity 29(3): 284-293	- Review article but not a systematic review
Berardelli, R., Karamouzis, I., D'Angelo, V. et al. (2016) The acute effect of a mineralocorticoid receptor agonist on corticotrope secretion in Addison's disease. Journal of Endocrinological Investigation 39(5): 537-42	- Non-randomised - no multivariate analysis
Bjornsdottir, S., Oksnes, M., Isaksson, M. et al. (2014) Circadian cortisol and growth hormone profiles in patients with addison's disease: A comparison of continuous subcutaneous hydrocortisone infusion with conventional	- Conference abstract

Study	Code [Reason]
glucocorticoid replacement therapy. Endocrine Reviews. Conference: 96th Annual Meeting and Expo of the Endocrine Society, ENDO 35(suppl3)	
Bjornsdottir, S., Oksnes, M., Isaksson, M. et al. (2013) Insulin sensitivity in patients with Addison's disease: A randomised cross-over trial comparing conventional glucocorticoid replacement therapy with continuous subcutaneous hydrocortisone infusion therapy. Endocrine Reviews. Conference: 95th Annual Meeting and Expo of the Endocrine Society, ENDO 34(3suppl1)	- Conference abstract
Chen, H., Jin, Z., Sun, C. et al. (2021) Effects of dehydroepiandrosterone (DHEA) supplementation on cortisol, leptin, adiponectin, and liver enzyme levels: A systematic review and meta-analysis of randomised clinical trials. International Journal of Clinical Practice 75(11): e14698	- Population not relevant to this review protocol
Christiansen, J. J., Bruun, J. M., Christiansen, J. S. et al. (2011) Long-term DHEA substitution in female adrenocortical failure, body composition, muscle function, and bone metabolism: a randomized trial. European Journal of Endocrinology 165(2): 293-300	- Duplicate reference
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	- Duplicate reference
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	- Study design not relevant to this review protocol
Esposito, D.; Pasquali, D.; Johannsson, G. (2018) Primary Adrenal Insufficiency: Managing Mineralocorticoid Replacement Therapy. Journal of Clinical Endocrinology & Metabolism 103(2): 376-387	- Systematic review used as source of primary studies
Fernandez, J., Escorsell, A., Zabalza, M. et al. (2006) Adrenal insufficiency in patients with cirrhosis and septic shock: Effect of treatment	- Not a peer-reviewed publication

Study	Code [Reason]
with hydrocortisone on survival. Hepatology 44(5): 1288-95	
Gomes, L. G., Madureira, G., Mendonca, B. B. et al. (2013) Long-term low-dose dexamethasone treatment of non-classical congenital adrenal hyperplasia patients improves fertility without increasing metabolic or bone abnormalities. Endocrine Reviews. Conference: 95th Annual Meeting and Expo of the Endocrine Society, ENDO 34(3suppl1)	- Conference abstract
Kim, M. S.; Ryabets-Lienhard, A.; Geffner, M. E. (2012) Management of congenital adrenal hyperplasia in childhood. Current Opinion in Endocrinology, Diabetes & Obesity 19(6): 483-8	- Review article but not a systematic review
Ng, S. M. and Stepien, K. (2017) Glucocorticoid replacement regimens in the treatment of 21-hydroxylase deficiency congenital adrenal hyperplasia. Cochrane Database of Systematic Reviews 2017(1)	- Protocol only - for study or Systematic review
Oksnes, M., Bjornsdottir, S., Isaksson, M. et al. (2013) Continuous subcutaneous hydrocortisone infusion (CSHI) improves quality-of-life in Addison's disease (AD). Endocrine Reviews. Conference: 95th Annual Meeting and Expo of the Endocrine Society, ENDO 34(3suppl1)	- Conference abstract
Sarafoglou, K, Gonzalez-Bolanos, Mt, Zimmerman, CI et al. (2015) Comparison of cortisol exposures and pharmacodynamic adrenal steroid responses to hydrocortisone suspension VS. Commercial tablets. Journal of clinical pharmacology 55(4): 452-457	- Study design not relevant to this review protocol
Schroder, M. A. M., Van Herwaarden, A. E., Span, P. N. et al. (2022) Optimizing the Timing of Highest Hydrocortisone Dose in Children and Adolescents With 21-Hydroxylase Deficiency. Journal of Clinical Endocrinology and Metabolism 107(4): E1661-E1672	- Study design not relevant to this review protocol
Whittle, E. and Falhammar, H. (2019) Glucocorticoid Regimens in the Treatment of Congenital Adrenal Hyperplasia: A Systematic Review and Meta-Analysis. Journal of the Endocrine Society 3(6): 1227-1245	- Systematic review used as source of primary studies

Study	Code [Reason]
Young, M. C. and Hughes, I. A. (1990) Dexamethasone treatment for congenital adrenal hyperplasia. Archives of Disease in Childhood 65(3): 312-314	- Comparator in study does not match that specified in this review protocol

J.2.2 Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2007 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

Table 25: Studies excluded from the health economic review

Reference	Reason for exclusion
SMC 2022[14]	Excluded as rated very serious limitations due to the large number of assumptions made for the clinical inputs. Also rated very serious limitations due to limited description of the model structure and source / rationale for additional data inputs. In addition, this study was rated as partially applicable due to concerns of dexamethasone being a comparator and due to the fact QALYs were not derived using NICE's preferred method.
AWMSG 2022	Excluded as rated very serious limitations due to the results of analysis being redacted as these were commercial in confidence.