National Institute for Health and Care Excellence

Final

Adrenal insufficiency: identification and management

Evidence review K: Pharmacological management during psychological stress

NICE guideline NG243

Evidence reviews underpinning recommendations 1.5.1 to 1.5.3 in the NICE guideline

August 2024

Final

This evidence review was developed by NICE

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1.1. Review question

What is the clinical and cost effectiveness of pharmacological treatments for managing periods of psychological stress in people with adrenal insufficiency?

1.1.1 Introduction

Psychological stress may be a factor in precipitating or exacerbating adrenal crisis. A self-reported questionnaire-based study (White et al EJE) reported 1% of incidence of adrenal crisis being related to psychological stress. It is unclear how often this occurs as it is seen very rarely in clinical practice, and when it does is associated with severe sudden stress such as a bereavement. There is considerable variation in people's experience of psychological stress and its contributing factors. Although some stress is a normal part of life for most people, people with adrenal insufficiency may benefit from reducing their risk of severe psychological stress and adjusting their medicines when these happen, to maintain their health and well-being. It is important that patients do not take extra glucocorticoids when it is not needed as this is associated with symptoms and signs of glucocorticoid excess, that is Cushingoid features and risk of hypertension osteoporosis, Type 2 diabetes, and obesity.

This review examines the evidence for the need for pharmacological treatments, and optimum treatment regimens for managing periods of psychological stress in people with adrenal insufficiency.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

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

Intervention(s)	**Glucocorticoids:**
	• Hydrocortisone including:
	  ○ Oral (where possible, note oral granules, suspension, or crushed tablets)
	  ○ Modified release hydrocortisone
	  ○ Injected forms (sub cut and iv)
	• Prednisolone
	• Dexamethasone
	
	For management of hypoglycaemia – specific to children:
	• Dextrose - any dose/concentration

	• Glucose – oral or IV, any dose/concentration (usually 20% or hypogel in children) **Exclusions:** • Hydrocortisone acetate • Long-acting methylprednisolone • Prednisone (not used in the UK) **Notes:** • Dextrose and glucose interchangeable terms so don't compare to each other just doses comparison. • Weight-based regimens should also be included. • Be aware some are not licensed for children
Comparison(s)	**For glucocorticoids:** Glucocorticoids compared to each other including: • Different doses, • Different routes of administration, • Different preparations (e.g., modified release compared to standard, crushed tablets compared to whole tablets or oral suspensions) • Compared to not increasing the dose **For timing:** • Early vs delayed (as defined by authors) • In ambulance vs at home • In ambulance (pre-hospital) vs in hospital **For settings:** • Compared to each other (all interventions for any given setting)
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** • **Incidence of adrenal crisis** • **Acute adverse events of drugs:** (up to 2 weeks- if none at this follow-up include shortest follow-up time reported in paper) – Mania – mood disturbance – blood glucose disturbance. – sleep disruption/ insomnia. • **Long term cumulative adverse effects:** – impact on weight – impact on growth – Hypertension – Obesity/weight gain – Osteoporosis

	– Fracture – Heart disease/CVS – Cushingoid features: e.g., stretch marks. – Diabetes (newly diagnosed or exacerbated) – Impact on sleep (may be 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 – Stomach ulcers. • **Admission to hospital** • **Admission to ITU** • **Length of hospital stay.** • **Readmission to hospital** • **Psychological morbidities e.g., Incidence of stress or PTSD** • **Adverse effects of hypoglycaemia e.g., neurological damage, seizures,** • **Adverse effects of hyponatraemia e.g., neurological damage, seizures,** **Follow up** >12 months but will report other time points if 12 months not available
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 considered if they have conducted a multivariate analysis adjusting for at least 3-4 of the following key confounders: - Age - Sex - Weight / BMI - Smoking - Time to treatment - Doses - Iv vs Im - comorbidities e.g., heart or kidney disease Published NMAs and IPDs will be considered for inclusion.

1.1.3 Methods and process

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

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

1.1.4 Effectiveness evidence

1.1.4.1 Included studies.

A search was conducted for randomised controlled trials (RCTs) and observational studies comparing pharmacological interventions at times of psychological stress in people with adrenal insufficiency.

No relevant studies were identified for inclusion in this review.

Excluded studies.

For more details, see the excluded studies list in Appendix J.

1.1.5 Summary of studies included in the effectiveness evidence.

No relevant studies were identified for inclusion in this review.

1.1.6 Summary of the effectiveness evidence

No relevant studies were identified for inclusion in this review.

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 Appendix G.

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 consideration of cost effectiveness.

Table 2: Unit costs for pharmacological interventions for psychological stress in children

Resource[(a)]	Dose per day	Cost per day	Cost per month
Hydrocortisone	***8mg/m² - 15 mg/m²***		

Resource[a]	Dose per day	Cost per day	Cost per month
Neonate	2mg – 2.5mg		
Standard release	2mg – 2.5mg[b]	£0.29	£8.68
Alkindi	2mg – 2.5mg	£2.70 - £3.38	£82.13 - £102.66
Combination	n/a		
1 year	3.5mg – 4.5mg		
Standard release	3.5mg – 4.5mg[b]	£0.29	£8.68
Alkindi	3.5mg – 4.5mg	£4.73 - £6.08	£143.72 - £184.78
Combination	3.5mg – 4.5mg[c]	£2.04 - £3.39	£62.02 - £103.08
2 years	4.5mg – 5.5mg		
Standard release	4.5mg – 5.5mg[b]	£0.29	£8.68
Alkindi	n/a		
Combination	4.5mg – 5.5mg[d]	£3.39 - £4.74	£103.08 - £144.14
5 years	6mg – 7.5mg		
Standard release	6mg – 7.5mg[b]	£0.21	£6.51
Alkindi	n/a		
Combination	6mg – 7.5mg[e]	£5.41 - £4.75	£164.68 - £144.57
10 years	9mg – 11mg		
Standard release	9mg – 11mg[f]	£0.21 - £2.17	£6.51 - £66.10
Alkindi	n/a		
Combination	9mg – 11mg[g]	£3.51 - £3.52	£106.73 - £107.16
12 years	9.5mg – 12mg		
Standard release	9.5mg – 12mg[f]	£0.21 - £2.17	£6.51 - £66.10
Combination	9.5mg – 12mg[h]	£4.18 - £4.87	£127.26 - £148.22
14 years	12mg – 15mg		
Standard release	12mg – 15mg[i]	£0.21 - £2.97	£6.51 - £90.28
Combination	12mg[j]	£4.87	£148.22
16 years	13mg – 17mg		
Standard release	13mg – 17mg[i]	£0.21 - £2.97	£6.51 - £90.28
Combination	13mg – 17mg[k]	£3.54 - £3.57	£107.58 - £108.48

(a) Source of costs from The British National Formulary (BNF).[1] 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.

Resource[a]	Dose per day	Cost per day	Cost per month
Hydrocortisone	***8mg/m² - 15 mg/m²***		
Neonate	2mg – 2.5mg		
Standard release	2mg – 2.5mg[b]	£0.29	£8.68
Alkindi	2mg – 2.5mg	£2.70 - £3.38	£82.13 - £102.66
Combination	n/a		
1 year	3.5mg – 4.5mg		
Standard release	3.5mg – 4.5mg[b]	£0.29	£8.68
Alkindi	3.5mg – 4.5mg	£4.73 - £6.08	£143.72 - £184.78
Combination	3.5mg – 4.5mg[c]	£2.04 - £3.39	£62.02 - £103.08
2 years	4.5mg – 5.5mg		
Standard release	4.5mg – 5.5mg[b]	£0.29	£8.68
Alkindi	n/a		
Combination	4.5mg – 5.5mg[d]	£3.39 - £4.74	£103.08 - £144.14
5 years	6mg – 7.5mg		
Standard release	6mg – 7.5mg[b]	£0.21	£6.51
Alkindi	n/a		
Combination	6mg – 7.5mg[e]	£5.41 - £4.75	£164.68 - £144.57
10 years	9mg – 11mg		
Standard release	9mg – 11mg[f]	£0.21 - £2.17	£6.51 - £66.10
Alkindi	n/a		
Combination	9mg – 11mg[g]	£3.51 - £3.52	£106.73 - £107.16
12 years	9.5mg – 12mg		
Standard release	9.5mg – 12mg[f]	£0.21 - £2.17	£6.51 - £66.10
Combination	9.5mg – 12mg[h]	£4.18 - £4.87	£127.26 - £148.22
14 years	12mg – 15mg		
Standard release	12mg – 15mg[i]	£0.21 - £2.97	£6.51 - £90.28
Combination	12mg[j]	£4.87	£148.22
16 years	13mg – 17mg		
Standard release	13mg – 17mg[i]	£0.21 - £2.97	£6.51 - £90.28
Combination	13mg – 17mg[k]	£3.54 - £3.57	£107.58 - £108.48

(l) Source of costs from The British National Formulary (BNF);[1] date accessed: 05/11/2023. 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.

(m) 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.

(n) 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.

(o) 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.

(p) 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.

(q) 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.

(r) 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.

(s) 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.

(t) 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.
(u) Costed as one 5mg and two 2.5mg standard release tablets and 2mg Alkindi granules in capsules.
(v) 13mg costs as three 2.5mg and one 5mg standard release tablets and 0.5mg Alkindi granules in capsules;17mg costed as one 10mg and one 5mg standard release tablets and 2mg Alkindi granules in capsules.

Table 3: Unit costs for pharmacological interventions for psychological stress in adults

Resource[(a)]	Dose per day	Cost per day	Cost per month
Hydrocortisone	***15mg – 25mg[(b)]***		
Prescribed as one and a half 10mg tablets a day	15mg	£0.11	£3.25
Prescribed as two 10mg tablets a day	15mg – 20mg[(c)]	£0.14	£4.34
Prescribed as one 10mg tablet and one 15mg tablet a day	25mg	£1.19	£36.23
Prescribed as three 10mg tablets a day	15-mg – 25mg	£0.21	£6.51
Modified release hydrocortisone (Plenadren)	***15mg – 25mg***		
Prescribed as three 5mg tablets a day	15mg	£14.55	£442.56
Prescribed as four 5mg tablets a day	20mg	£19.40	£590.08
Prescribed as one 20mg tablet a day	20mg	£8.00	£243.33
Prescribed as one 5mg tablet and one 20mg tablet a day	25mg	£12.85	£390.85
Prednisolone	***3mg – 6mg***		
Prescribed as three 1mg tablets a day	3mg	£0.08	£2.51
Prescribed as one 1mg tablet and one 5mg tablet a day	6mg	£0.06	£1.86
Dexamethasone			
Dexamethasone	0.25mg – 0.5mg[(d)]	£0.05 - £0.10	£1.59 - £3.18

(a) Source of costs from The British National Formulary (BNF)[1]
(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.

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

No evidence on the clinical and cost effectiveness of pharmacological interventions for the management of psychological stress was identified. The recommendations were based on committee consensus.

1.1.10 The outcomes that matter most

The committee considered all outcomes listed in the protocol to be critical and of equal importance in decision-making. These outcomes included mortality, Health-related Quality of Life, incidence of adrenal crisis, acute and long term cumulative adverse events of drugs, admission to hospital or ITU and psychological morbidities such as incidence of stress or PTSD.

1.1.11 The quality of the evidence

No evidence meeting the review protocol criteria was identified.

1.1.12 Benefits and harms

The committee discussed that there is considerable variation in current clinical practice on whether to adjust glucocorticoid medication when a person is experiencing psychological stress. They noted this is partly due to the wide variation in situations or events that could cause psychological stress, ranging from a mental health crisis, or bereavement. The duration of psychological stress would also vary between a short-term or single event, and much longer periods lasting weeks or months. The committee agreed the variation in how people react to psychological stress makes it difficult to determine whether a person might be at risk of adrenal crisis due to psychological stress. The committee agreed that an occasional increase in glucocorticoid dose was unlikely to lead to side effects, but long-term increases were not advised due to the risk of glucocorticoid excess. An adjustment to the dose of glucocorticoid medication has the potential to reduce the risk of harm to a person experiencing an adrenal crisis due to psychological stress. Overall, the committee agreed that a short-term increase in glucocorticoid for 1-2 days using sick-day dosing rules should be considered for adults in times of acute or extraordinary psychological or emotional stress, and for people under 16 years 1-2 sick day doses may be considered. The recommendation for sick-day dosages was from the review of guidelines from other organisations on the pharmacological management of physiological stress. The quality of these guidelines was assessed using the AGREE II tool and NICE applicability and acceptability checklist. The committee made consensus recommendations, informed by these guidelines. The committee noted a person experiencing a severe mental health crisis may not be able to take an oral preparation and therefore recommended consideration of administering an intramuscular hydrocortisone instead.

1.1.13 Cost effectiveness and resource use

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

Because the committee noted that current practice was variable in terms of when, and for how long people should increase their oral steroid doses, the committee made recommendations to consider an increase in oral steroid doses for short periods of time (1 to 2 days) when experiencing psychological stress. The latter was defined as periods of sudden, intense psychological and emotional stress such as a bereavement. They also made a consider recommendation for intramuscular hydrocortisone if a person in unable to take oral glucocorticoid during a severe mental health crisis (for example a psychotic episode). This could be administered by a carer using the emergency management kit or by a health care professional. The duration of sick-day rules in people with severe mental health crisis would need to be until the crisis is resolved and would need to be reviewed by a specialist on a case by case.

These recommendations may potentially mitigate the risk of a person experiencing an adrenal crisis due to psychological stress. Of note, the committee were personally not aware of anyone who had experienced an adrenal crisis due to psychological stress alone. However, they acknowledged it was not possible to determine if people never experience an adrenal crisis due to psychological stress because in current practice people will likely increase their oral steroid doses. The committee did however note that in periods of psychological stress people with adrenal insufficiency may experience more pronounced symptoms of their adrenal insufficiency and therefore increasing the dose of an oral steroid will improve a person's overall quality of life.

An adrenal crisis can be a life-threatening event that significantly impacts a person's quality of life. There are also high costs associated with an adrenal crisis because hydrocortisone and fluids need to be administered intravenously and this typically requires a hospital admission. The committee discussed the impact of steroids on mood. It was noted that they can sometimes exacerbate a mental health crisis and this needs to be balanced with prescribing increased dosing of glucocorticoids. Sick-day dosing for both physiological and psychological stress is not established current practice and therefore the provision of glucocorticoids to enable sick-day dosing may be a change in practice for some. The recommendations made by the committee are likely to be cost-effective and given that these are consider recommendations, they are not expected to result in a significant resource impact. Of note, the committee highlighted that the recommendation for intramuscular hydrocortisone for those experiencing a severe mental health crisis and are unable to take oral glucocorticoids would apply to a very small proportion of people and therefore would not have a significant resource impact.

1.1.14 Recommendations supported by this evidence review.

This evidence review supports recommendations 1.5.1 – 1.5.3.

References

1. 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.

2. 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

Appendices

Appendix A Review protocols

A.1 Review protocol for 4.6: pharmacological management of periods of psychological stress

ID	Field	Content
1.	Review title	Pharmacological management of psychological stress
2.	Review question	4.6 What is the clinical and cost effectiveness of pharmacological treatments for managing periods of psychological stress in people with adrenal insufficiency?
3.	Objective	To determine the optimal pharmacological strategy for managing periods of psychological stress in people with adrenal insufficiency.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.

		The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Adrenal insufficiency
6.	Population	Inclusion: People with adrenal insufficiency (primary, secondary, or tertiary) who are diagnosed or suspected of having an adrenal crisis including the following groups: Strata: • Adults (aged ≥16 years). • Children aged ≥5up to 16 years. • Infants aged 1-5 years because of more frequent dosing. • Infants aged <1 year including neonates. Exclusion: None specified.

7.	Intervention	**Glucocorticoids:**
		Any preparation, any dose, and any route of administration of the following:
		• Hydrocortisone including:
		  ○ Oral (where possible, note oral granules, oral suspension, or crushed tablets)
		  ○ Modified release hydrocortisone (separate to normal release hydrocortisone)
		  ○ Injected forms (sub cut and iv)
		• Prednisolone
		• Dexamethasone
		For management of hypoglycaemia – specific to children
		• Dextrose any dose/concentration glucose oral or iv any dose/concentration usually 20% or hypogel in children

		Exclusion: Hydrocortisone acetate Long-acting methylprednisolone Prednisone (not used in the UK) **Notes**: Dextrose and glucose interchangeable terms so don't compare to each other just doses comparison. Weight-based regimens should also be included. Be aware some are not licensed for children. **Timing** • Early vs delayed (as defined by authors) • In ambulance vs at home • In ambulance (pre-hospital) vs in hospital **Settings** • Self-administered (including by parents and carers i.e., not in a healthcare setting) • Health care professional in pre-hospital setting for example in ambulance. • Health care professional in hospital
8.	Comparator	**For glucocorticoids:** • Different doses • Compared to each other • Compared to not increasing the dose • Routes of administration **For timing:** • Early vs delayed (as defined by authors)

		• In ambulance vs at home • In ambulance (pre-hospital) vs in hospital **For settings:** • Compared to each other (all interventions for any given setting)
9.	Types of study to be included	Systematic reviews of RCTs and RCTs will be considered for inclusion. Cross-over trials will also be considered for inclusion regardless of washout period as it is unsafe for patients to be completely free of background medication especially glucocorticoids. If insufficient RCT evidence is available, a search for non-randomised studies will be considered if they have conducted a multivariate analysis adjusting for at least 3-4 of the following key confounders: - Age - Sex - Weight / BMI - Smoking - Time to treatment - Doses - IV vs IM - comorbidities e.g., heart or kidney disease Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Non comparative cohort studies Before and after studies Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
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** • **Incidence of adrenal crisis** • **Acute adverse events of drugs:** (up to 2 weeks- if none at this FU include shortest FU time reported in paper) – Mania – mood disturbance – blood glucose disturbance – sleep disruption/ insomnia • **Long term cumulative adverse effects:** – impact on weight. – impact on growth. – Hypertension. – Obesity/weight gain. – Osteoporosis. – Fracture. – Heart disease/CVS. – Cushingoid features: e.g., stretch marks. – Diabetes (newly diagnosed or exacerbated). – Impact on sleep (may be 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. – Stomach ulcers. • **Admission to hospital** • **Admission to ITU** • **Length of hospital stay.** • **Readmission to hospital** • **Psychological morbidities e.g., Incidence of stress or PTSD** • **Adverse effects of hypoglycaemia e.g., neurological damage, seizures,** • **Adverse effects of hyponatraemia e.g., neurological damage, seizures,** **Follow-up.** >12 months but will report other time points if 12 months not 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 study, 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: • Different types of adrenal insufficiency (primary, secondary, or tertiary)

		• For settings- by intervention			
17.	Type and method of review	☒	Intervention		
		☐	Diagnostic		
		☐	Prognostic		
		☐	Qualitative		
		☐	Epidemiologic		
		☐	Service Delivery		
		☐	Other (please specify)		
18.	Language	English			
19.	Country	England			
20.	Anticipated or actual start date	June 2022			
21.	Anticipated completion date	April 2024			
22.	Stage of review at time of this submission	Review stage		Started	Completed
		Preliminary searches		☐	☐
		Piloting of the study selection process		☐	☐
		Formal screening of search results against eligibility criteria		☐	☐
		Data extraction		☐	☐
		Risk of bias (quality) assessment		☐	☐

		Data analysis	☐	☐
23.	Named contact	5a. Named contact Guideline Development Team NGC 5b Named contact e-mail Hypoadrenalism@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
24.	Review team members	From NICE: Sharon Swain [Guideline lead] Saoussen Ftouh [Senior systematic reviewer] Meena Tafazzoli [Systematic reviewer] Alexandra Bannon [Health economist] Stephen Deed [Information specialist]		
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, pharmacological management, hydrocortisone, dexamethasone, prednisolone, glucose, dextrose, psychological stress	
32.	Details of existing review of same topic by same authors	-	
33.	Current review status	☒	Ongoing
		☐	Completed but not published
		☐	Completed and published
		☐	Completed, published, and being updated
		☐	Discontinued
34.	Additional information	-	
35.	Details of final publication	www.nice.org.uk	

A.2 Health economic review protocol

Table 4: 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).[2] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies.

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

Appendix B Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual.[2]

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 5: Database parameters, filters, and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 September 2023	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 26 September 2023	Randomised controlled trials Systematic review studies Observational 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)
PsycINFO (OVID)	Inception to 26 September 2023	Human Exclusions (Medline records)

Database	Dates searched	Search filter used
		English Language

Medline (Ovid) search terms

1.	exp Adrenal Insufficiency/
2.	Adrenal Hyperplasia, Congenital/
3.	(addison* disease or addisonian*).ti,ab,kf.
4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.
6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	or/1-13
15.	letter/
16.	editorial/
17.	news/
18.	exp historical article/
19.	Anecdotes as Topic/
20.	comment/
21.	case reports/
22.	(letter or comment*).ti.
23.	or/15-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animals/ not humans/
27.	exp Animals, Laboratory/
28.	exp Animal Experimentation/
29.	exp Models, Animal/
30.	exp Rodentia/
31.	(rat or rats or mouse or mice or rodent*).ti.
32.	or/25-31
33.	14 not 32
34.	limit 33 to English language
35.	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.	Epidemiologic studies/
80.	Observational study/
81.	exp Cohort studies/
82.	(cohort adj (study or studies or analys* or data)).ti,ab.
83.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
84.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
85.	Controlled Before-After Studies/
86.	Historically Controlled Study/
87.	Interrupted Time Series Analysis/
88.	(before adj2 after adj2 (study or studies or data)).ti,ab.
89.	exp case control study/
90.	case control*.ti,ab.
91.	Cross-sectional studies/
92.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
93.	or/79-92
94.	guidelines as topic/ or practice guidelines as topic/
95.	exp guideline/
96.	Health Planning Guidelines/
97.	(guideline or practice guideline).pt.
98.	guideline*.ti.
99.	or/94-98
100.	57 and (67 or 78 or 93 or 99)

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.	Clinical study/
78.	Observational study/
79.	Family study/
80.	Longitudinal study/
81.	Retrospective study/
82.	Prospective study/
83.	Cohort analysis/
84.	Follow-up/
85.	cohort*.ti,ab.
86.	84 and 85
87.	(cohort adj (study or studies or analys* or data)).ti,ab.
88.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
89.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.

90.	(before adj2 after adj2 (study or studies or data)).ti,ab.
91.	exp case control study/
92.	case control*.ti,ab.
93.	cross-sectional study/
94.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
95.	or/77-83,86-94
96.	guidelines as topic/ or practice guidelines as topic/
97.	exp practice guideline/
98.	Health Planning Guidelines/
99.	guideline*.ti.
100.	or/96-99
101.	55 and (65 or 76 or 95 or 100)

Cochrane Library (Wiley) search terms

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

#24.	MeSH descriptor: [Mineralocorticoids] this term only
#25.	(mineralocorticoid* near/3 (replace* or treat* or therap* or supplement* or regimen* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or intra muscular* or intramuscular* or exogenous* or subcutaneous*)):ti,ab,kw
#26.	MeSH descriptor: [Fludrocortisone] this term only
#27.	fludrocortisone*:ti,ab,kw
#28.	Florinef:ti,ab,kw
#29.	MeSH descriptor: [Androgens] this term only
#30.	MeSH descriptor: [Hormone Replacement Therapy] this term only
#31.	((androgen* or hormon*) near/4 (replace* or treat* or therap* or supplement*)):ti,ab,kw
#32.	MeSH descriptor: [Dehydroepiandrosterone] explode all trees
#33.	(dehydroepiandrosterone or dehydro-epiandrosterone or DHEA):ti,ab,kw
#34.	prosterone*:ti,ab,kw
#35.	MeSH descriptor: [Sodium Chloride] this term only
#36.	((sodium or saline or salt*) near/3 (replace* or treat* or therap* or solution* or supplement* or regimen* or intake* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or IV)):ti,ab,kw
#37.	MeSH descriptor: [Glucose] this term only
#38.	((glucose or dextrose) near/3 (replace* or treat* or therap* or solution* or supplement* or regimen* or intake* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or IV)):ti,ab,kw
#39.	HypoGel:ti,ab,kw
#40.	(or #17-#39)
#41.	#16 and #40

Epistemonikos search terms

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

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

PsycINFO (OVID) search terms

1.	exp Adrenal Gland Disorders/
2.	(addison* disease or addisonian*).ti,ab,id.
3.	((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,id.
4.	((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,id.
5.	(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,id.
6.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,id.
7.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,id.
8.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,id.
9.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,id.
10.	(CAH or X-ALD).ti,ab.
11.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,id.
12.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,id.

13.	or/1-12
14.	Letter/
15.	Case report/
16.	exp Rodents/
17.	or/14-16
18.	13 not 17
19.	limit 18 to (human and English language)
20.	glucocorticoids/
21.	((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,id.
22.	hydrocortisone/
23.	dexamethasone/
24.	prednisolone/
25.	(hydrocortisone* or prednisolone* or methylprednisolone* or dexamethasone*).ti,ab,id.
26.	Florinef.ti,ab,id.
27.	or/20-26
28.	19 and 27

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 6: 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

Database	Dates searched	Search filters and limits applied
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 26 September 2023	English language

Medline (Ovid) search terms

1.	exp Adrenal Insufficiency/
2.	Adrenal Hyperplasia, Congenital/
3.	(addison* disease or addisonian*).ti,ab,kf.
4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.
6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	or/1-13
15.	letter/
16.	editorial/
17.	news/
18.	exp historical article/
19.	Anecdotes as Topic/
20.	comment/
21.	case reports/
22.	(letter or comment*).ti.

23.	or/15-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animals/ not humans/
27.	exp Animals, Laboratory/
28.	exp Animal Experimentation/
29.	exp Models, Animal/
30.	exp Rodentia/
31.	(rat or rats or mouse or mice or rodent*).ti.
32.	or/25-31
33.	14 not 32
34.	limit 33 to English language
35.	Economics/
36.	Value of life/
37.	exp "Costs and Cost Analysis"/
38.	exp Economics, Hospital/
39.	exp Economics, Medical/
40.	Economics, Nursing/
41.	Economics, Pharmaceutical/
42.	exp "Fees and Charges"/
43.	exp Budgets/
44.	budget*.ti,ab.
45.	cost*.ti.
46.	(economic* or pharmaco?economic*).ti.
47.	(price* or pricing*).ti,ab.
48.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
49.	(financ* or fee or fees).ti,ab.
50.	(value adj2 (money or monetary)).ti,ab.
51.	or/35-50
52.	34 and 51
53.	limit 52 to yr="2014 -Current"

Embase (Ovid) search terms

29.	exp Adrenal cortex insufficiency/
30.	Congenital adrenal hyperplasia/
31.	(addison* disease or addisonian*).ti,ab,kf.
32.	((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.
33.	((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.

34.	(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.
35.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
36.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
37.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
38.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
39.	(CAH or X-ALD).ti,ab.
40.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
41.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
42.	or/1-13
43.	letter.pt. or letter/
44.	note.pt.
45.	editorial.pt.
46.	case report/ or case study/
47.	(letter or comment*).ti.
48.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
49.	or/15-20
50.	randomized controlled trial/ or random*.ti,ab.
51.	21 not 22
52.	animal/ not human/
53.	nonhuman/
54.	exp Animal Experiment/
55.	exp Experimental Animal/
56.	animal model/
57.	exp Rodent/
58.	(rat or rats or mouse or mice or rodent*).ti.
59.	or/23-30
60.	14 not 31
61.	limit 32 to English language
62.	health economics/
63.	exp economic evaluation/
64.	exp health care cost/
65.	exp fee/
66.	budget/
67.	funding/
68.	budget*.ti,ab.
69.	cost*.ti.
70.	(economic* or pharmaco?economic*).ti.
71.	(price* or pricing*).ti,ab.
72.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
73.	(financ* or fee or fees).ti,ab.
74.	(value adj2 (money or monetary)).ti,ab.
75.	or/34-46
76.	33 and 47

77.	limit 48 to yr="2014 -Current"

NHS EED and HTA (CRD) search terms

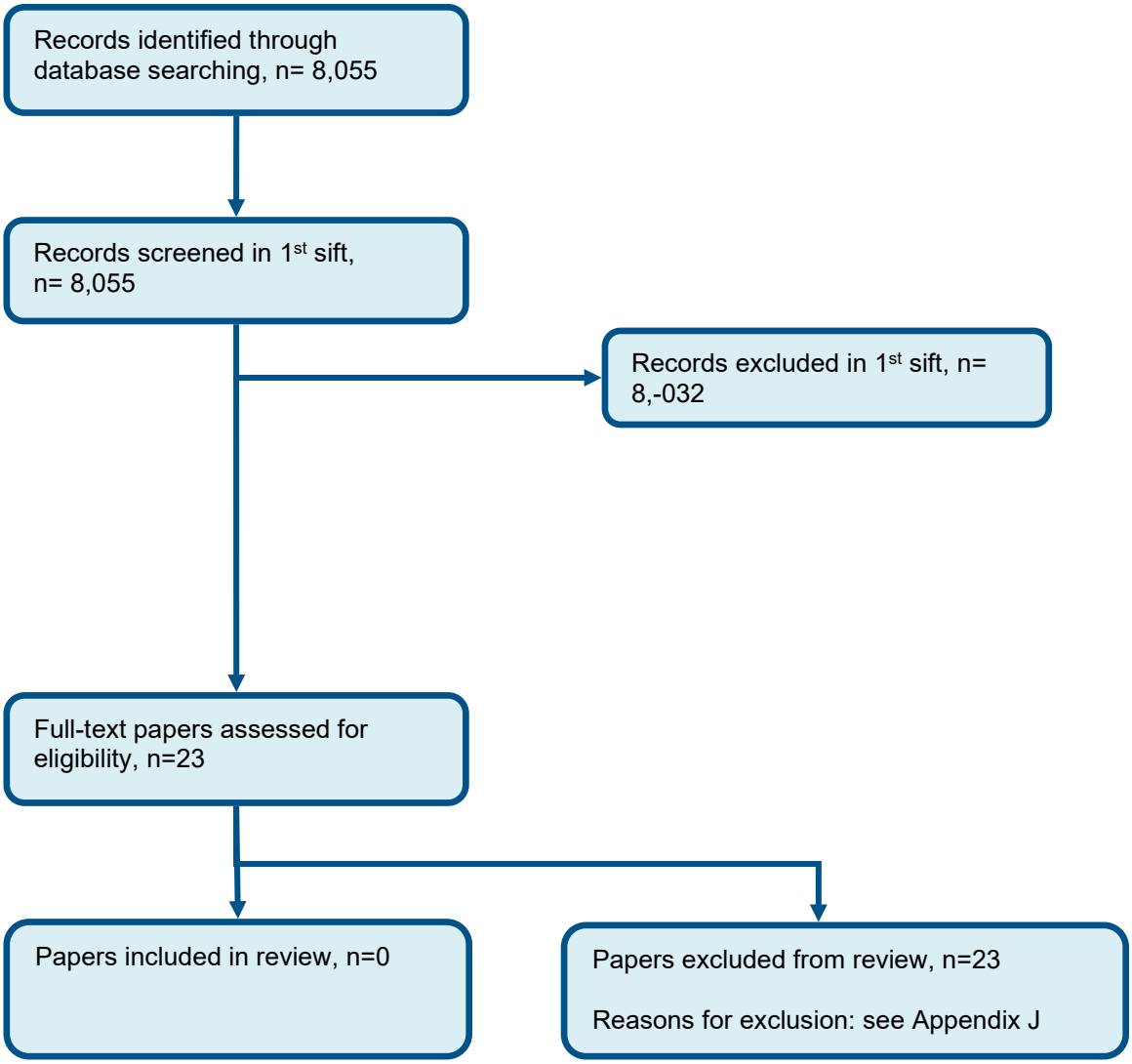
#1.	MeSH DESCRIPTOR Adrenal Insufficiency EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Adrenal Hyperplasia, Congenital EXPLODE ALL TREES
#3.	(addison* disease or addisonian)
#4.	(adrenal*) AND (insufficien* or inadequa* or deficien* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or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

INAHTA search terms

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

Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of Topic 4.6



Appendix D Effectiveness evidence

None.

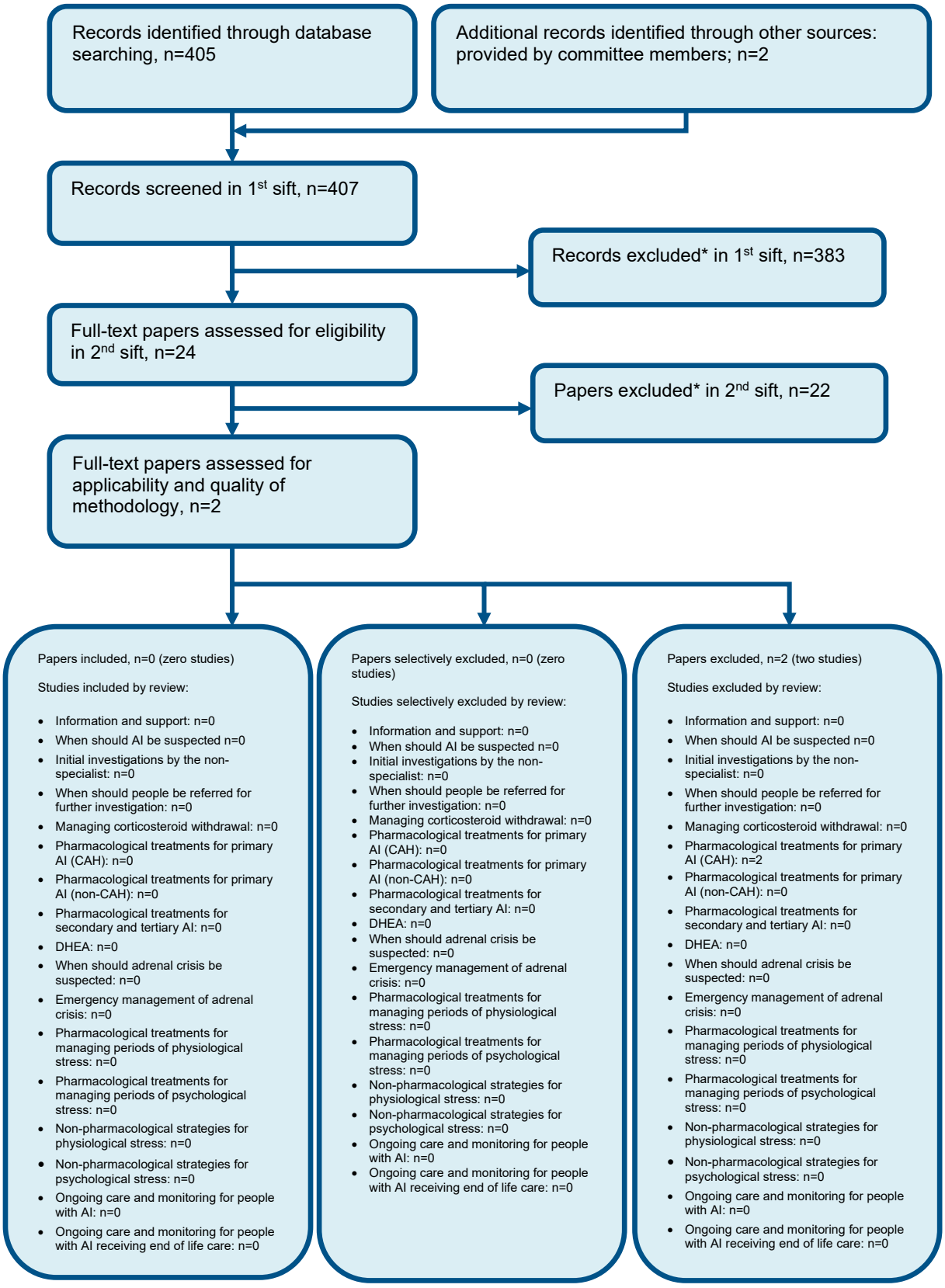
Appendix E Forest plots

None.

Appendix F GRADE tables

None.

Appendix G Economic evidence study selection



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

Appendix H Economic evidence tables

None.

Appendix I Health economic model

This area was not prioritised for health economic modelling.

Appendix J Excluded studies

J.1 Clinical studies

Table 7: Studies excluded from the clinical review

Study	Reasons for exclusion
Agha, A., Liew, A., Finucane, F. et al. (2004) Conventional glucocorticoid replacement overtreats adult hypopituitary patients with partial ACTH deficiency. Clinical Endocrinology 60(6): 688-93	- Outcomes do not meet review protocol - Study objective does not meet review protocol *Although this study evaluates the effects of glucocorticoid therapy for the management of adrenal insufficiency and includes QoL outcomes, it does not provide insight into the ability of GC therapy to benefit patients during periods of psychological distress.*
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)	- Systematic review used as source of primary studies. *All included studies have already been reviewed for relevance to review protocol.*
Al Nofal, A., Bancos, I., Benkhadra, K. et al. (2017) Glucocorticoid Replacement Regimens in Chronic Adrenal Insufficiency: A Systematic Review and Meta-Analysis. Endocrine Practice 23(1): 17-31	- Systematic review used as source of primary studies. *All included studies have already been reviewed for relevance to review protocol.*
Andela, Cornelie D, Staufenbiel, Sabine M, Joustra, Sjoerd D et al. (2016) Quality of life in patients with adrenal insufficiency correlates stronger with hydrocortisone dosage, than with long-term systemic cortisol levels. Psychoneuroendocrinology 72: 80-86	- Study objective does not meet review protocol. *Cross-sectional study investigates association between hair cortisol levels, HC intake and QoL. Does not provide insight into management of periods of psychological stress with HC.*
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. - Outcomes do not meet review protocol *No psychological outcomes evaluated.*

Study	Reasons for exclusion
Behan, L. A., Kelleher, G., Hannon, M. J. et al. (2014) Low-dose hydrocortisone replacement therapy is associated with improved bone remodelling balance in hypopituitary male patients. European Journal of Endocrinology 170(1): 141-50	- Outcomes do not meet review protocol.
Behan, L. A., Kelleherc, G., Hannon, M. J. et al. (2011) Low-dose hydrocortisone (HC) replacement therapy is associated with improved bone remodeling balance in hypopituitary subjects. Endocrine Reviews. Conference: 93rd Annual Meeting and Expo of the Endocrine Society, ENDO 32(3meetingabstracts)	- Outcomes do not meet review protocol.
Benson, S., Neumann, P., Unger, N. et al. (2012) Effects of standard glucocorticoid replacement therapies on subjective well-being: a randomized, double-blind, crossover study in patients with secondary adrenal insufficiency. European Journal of Endocrinology 167(5): 679-85	- Study objective does not meet review protocol. *Although this study evaluates the effects of glucocorticoid therapy for the management of adrenal insufficiency and includes QoL outcomes, it does not provide insight into the ability of GC therapy to benefit patients during periods of psychological distress.*
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 objective does not meet review protocol. *Although this study evaluates the effects of glucocorticoid therapy for the management of adrenal insufficiency and includes QoL outcomes, it does not provide insight into the ability of GC therapy to benefit patients during periods of psychological distress.*
Ekman, B., Bachrach-Lindstrom, M., Lindstrom, T. et al. (2012) 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 77(1): 18-25	- Study objective does not meet review protocol. *Although this study evaluates the effects of glucocorticoid therapy for the management of adrenal insufficiency and includes QoL outcomes, it does not provide insight into the ability of GC therapy to benefit patients during periods of psychological distress.*
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	- Study objective does not meet review protocol. *Although this study evaluates the effects of glucocorticoid therapy for the management of adrenal insufficiency and includes QoL outcomes, it does not provide insight into the ability of GC therapy to benefit patients during periods of psychological distress.*
Hahner, S.; Burger-Stritt, S.; Allolio, B. (2013) Subcutaneous hydrocortisone administration for	- Study objective does not meet review protocol.

Study	Reasons for exclusion
emergency use in adrenal insufficiency. European Journal of Endocrinology 169(2): 147-54	
Harbeck, Birgit, Danneberg, Sven, Rahvar, Amir-Hossein et al. (2016) Exploring the impact of short- and long-term hydrocortisone replacement on cognitive function, quality of life and catecholamine secretion: A pilot study. Applied Psychophysiology and Biofeedback 41(3): 341-347	- Study objective does not meet review protocol.
Isidori, A. M., Venneri, M. A., Graziadio, C. et al. (2018) 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 6(3): 173-185	- Study objective does not meet review protocol *Although this study evaluates the effects of glucocorticoid therapy for the management of adrenal insufficiency and includes QoL outcomes, it does not provide insight into the ability of GC therapy to benefit patients during periods of psychological distress.*
Johannsson, G., Nilsson, A. G., Bergthorsdottir, R. et al. (2012) 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 97(2): 473-81	- Outcomes do not meet review protocol.
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	- Outcomes do not meet review protocol. - Data not reported in an extractable format or a format that can be analysed.
Nilsson, A. G., Marelli, C., Fitts, D. et al. (2014) Prospective evaluation of long-term safety of dual-release hydrocortisone replacement administered once daily in patients with adrenal insufficiency. European Journal of Endocrinology 171(3): 369-77	- Study objective does not meet review protocol. *Although this study evaluates the effects of glucocorticoid therapy for the management of adrenal insufficiency and includes QoL outcomes, it does not provide insight into the ability of GC therapy to benefit patients during periods of psychological distress.*
Oksnes, M., Bjornsdottir, S., Isaksson, M. et al. (2014) Continuous subcutaneous hydrocortisone infusion versus oral hydrocortisone replacement for treatment of addison's disease: a randomized clinical trial. Journal of Clinical Endocrinology & Metabolism 99(5): 1665-74	- Outcomes do not meet review protocol.

Study	Reasons for exclusion
Riedel, M., Wiese, A., Schurmeyer, T. H. et al. (1993) Quality of life in patients with Addison's disease: effects of different cortisol replacement modes. Experimental & Clinical Endocrinology 101(2): 106-11	- Study objective does not meet review protocol. *Although this study evaluates the effects of glucocorticoid therapy for the management of adrenal insufficiency and includes QoL outcomes, it does not provide insight into the ability of GC therapy to benefit patients during periods of psychological distress.*
Schultebraucks, Katharina, Wingenfeld, Katja, Heimes, Jana et al. (2015) Cognitive function in patients with primary adrenal insufficiency (Addison's disease). Psychoneuroendocrinology 55: 1-7	- Study objective does not meet review protocol. *Although this study evaluates the effects of glucocorticoid therapy for the management of adrenal insufficiency and includes QoL outcomes, it does not provide insight into the ability of GC therapy to benefit patients during periods of psychological distress.*
Staufenbiel, S. M., Penninx, B. W., Spijker, A. T. et al. (2013) Hair cortisol, stress exposure, and mental health in humans: a systematic review. Psychoneuroendocrinology 38(8): 1220-35	- Study objective does not meet review protocol *Although this study evaluates the effects of glucocorticoid therapy for the management of adrenal insufficiency and includes QoL outcomes, it does not provide insight into the ability of GC therapy to benefit patients during periods of psychological distress.*
Vreeburg, Sophie A, Hoogendijk, Witte J. G, Pelt, Johannes van et al. (2009) Major depressive disorder and hypothalamic-pituitary-adrenal axis activity: Results from a large cohort study. Archives of General Psychiatry 66(6): 617-626	- Population not relevant to this review protocol. *Population does not focus on people with adrenal insufficiency or provide sub-group analysis for this group.*
Werumeus Buning, J., van Faassen, M., Brummelman, P. et al. (2016) Effects of Hydrocortisone on the Regulation of Blood Pressure: Results From a Randomized Controlled Trial. Journal of Clinical Endocrinology & Metabolism 101(10): 3691-3699	- Outcomes do not meet review protocol.

J.2 Health Economic studies

None.