National Institute for Health and Care Excellence

Draft

Adrenal Insufficiency: identification and management

Evidence review N: Ongoing care and monitoring of people with Adrenal Insufficiency

NICE guideline <number>

Evidence reviews underpinning recommendations 1.8.1 – 1.8.16 in the NICE guideline

March 2024

Draft for Consultation

This evidence review was developed by NICE

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1. Ongoing care and monitoring

1.1. Review question

- What ongoing care and monitoring should be offered to people with adrenal insufficiency?
- What ongoing care and monitoring should be offered to people with adrenal insufficiency who are receiving end-of-life care?

1.1.1. Introduction

Ongoing care and monitoring

People with primary and secondary adrenal insufficiency need lifelong glucocorticoids, and for primary adrenal insufficiency mineralocorticoid replacement as well. People with tertiary adrenal insufficiency may be able to stop glucocorticoid replacement, but a proportion will need to continue lifelong. There are consequences of both over and under treatment with glucocorticoids and mineralocorticoids.

Signs and symptoms of glucocorticoid under-replacement include weight loss, early satiety, decreased appetite, nausea, fatigue that is significantly affecting the person's ability to carry out activities of daily living, worsening pigmentation (in primary adrenal insufficiency), muscle weakness. Additional signs and symptoms in children and young people include faltering growth and early puberty.

Signs and symptoms of glucocorticoid over-replacement (for people who are on a higher dose than standard replacement) include weight gain, increased appetite, disturbed sleep, skin thinning, new or worsening diabetes, new or worsening hypertension, cushingoid appearance, skin infections, acne, thrush, frequent or low-impact fractures, height loss, fragility fractures.

There is variation in practice, both in frequency of ongoing monitoring of people with adrenal insufficiency, and in what tests might be performed.

The purpose of this review is to determine the optimal frequency of monitoring and what needs to be monitored for consequences of over- or under-treatment with glucocorticoids to improve outcomes for people with adrenal insufficiency,

Ongoing care and monitoring for people receiving end-of-life care.

Glucocorticoids are essential for life in people with adrenal insufficiency. For people coming towards the end of their life comfort and symptom control become priorities rather than prolonging life. It can be difficult to take oral medication, or multiple doses towards end-of-life and so it may be necessary to adjust replacement regimen of glucocorticoids to once daily dosing, use of dispersible medications rather than tablets, or use of subcutaneous or intramuscular preparations. It also is not appropriate to be performing invasive monitoring and blood tests at end-of-life. Patients' wishes should be taken into account, and they may choose to stop all medication when they are actively dying.

The purpose of this review is to determine what ongoing care and monitoring should be offered to people who are receiving end-of-life care.

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) including the following stratified 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 · Adults or children receiving end-of-life care Exclusion: None identified
Intervention(s)	Any monitoring strategy for over/undertreatment with glucocorticoids. **Strategies may include monitoring for:** · Weight/obesity · Electrolyte abnormalities · Symptoms/signs for example, tiredness, abdominal or limb pain · Blood pressure · Osteoporosis/ bone health · Blood glucose · Lipids · Pigmentation (if under treating) · 24 hour cortisol profile · Cortisol day curve/day series · Activities of daily living **Frequency of monitoring as a general appointment** · 6 monthly · Yearly · Patient-initiated follow up (PIFU) · Other – as reported in the studies
Comparison(s)	**For monitoring over/undertreatment** · Monitoring for different indications compared to each other or to a suitable comparator such as no monitoring. **For frequency:** · Different frequencies compared to each other
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 example, in primary AI: - 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) · Incidence of adrenal crisis (as defined by authors) · Incidence Vascular events

	· Incidence of fractures · Incidence of diabetes · 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). Follow up: Longest follow up reported Where different follow up periods are reported in an individual study, we will choose the one most appropriate or most commonly reported to be able to conduct a meta-analysis.
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 age and sex. Published NMAs and IPDs will be considered for inclusion.

1.1.3. Methods and process

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 monitoring strategies for people with adrenal insufficiency and people with adrenal insufficiency who are receiving end-of-life care.

No relevant RCTs or observational studies were identified.

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

No relevant published evidence was identified.

1.1.6. Economic evidence

1.1.6.1. Included studies

No health economic studies were included.

1.1.6.2. 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.

1.1.7. Economic model

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

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

1.1.8.1. The outcomes that matter most

The committee considered all outcomes listed in the protocol to be critical and of equal importance in decision-making. These outcomes included mortality, health-related quality of life, complications of AI, incidence of vascular events or fractures or diabetes and measures of activities of daily living.

1.1.8.2. The quality of the evidence

No evidence was identified for ongoing care and monitoring of people with adrenal insufficiency including those who are receiving end-of-life care. Recommendations were made by consensus of the committee to reflect current practice.

1.1.8.3. Benefits and harms

The committee agreed that it was important to make recommendations despite the lack of evidence as adrenal insufficiency is a complex condition.

The committee didn't wish to specify the frequency of reviews as these would vary widely depending on patient needs as well as the type of adrenal insufficiency they have. For

example: newly diagnosed people with primary adrenal insufficiency may require more frequent monitoring until the health care professional is satisfied that the person understands the condition and how to manage it. The committee acknowledged this should be part of shared decision-making between clinical staff and the person. People who are symptomatic and have rapidly changing clinical needs will also need more frequent monitoring until their condition has stabilised. However, people with secondary or tertiary adrenal insufficiency who are confident with self-management or have stable clinical needs may need less frequent monitoring, as this group of people will still have some residual HPA axis function and therefore be at much lower risk of having an adrenal crisis.

Health care professionals would consider the most appropriate mode of follow-up and monitoring according to the person's needs. For example, some may need to be seen face-to-face and others may be followed up remotely through telephone consultations. A clear shared decision model such as Patient Initiated Follow Up (PIFU) should be discussed with the patient including the frequency and mode of follow up.

The committee agreed the appropriate specialist team providing ongoing care should be defined based on the needs of the individual.

Health care professionals should be aware of signs and symptoms of under-replacement of glucocorticoids which may include weight loss, nausea and fatigue. These can be quite broad and non-specific; therefore, it is important to investigate whether these can be attributed to under replacement of glucocorticoids or other reasons. For example, fatigue can occur just in the short term while patients are adjusting to steroids and should not be a reason to initiate a change in dosing. However, sudden onset fatigue or fatigue that is significantly affecting the person's ability to undertake activities of daily living should not be ignored.

Signs and symptoms indicating over-replacement of glucocorticoids particularly in patients on supraphysiological (higher than standard) doses may include unexplained weight gain, new or worsening diabetes or hypertension. Cushingoid appearance/ Cushing's syndrome is particularly indicative of over-replacement. This usually manifests as weight gain with increased fat on the chest and tummy, but thin arms and legs with muscle wasting and reduced muscle strength, a build-up of fat on the back of the neck and shoulders, and a red, puffy, rounded face, bruising and red stretch marks particularly found with the use of dexamethasone.

Treatment for people with primary adrenal insufficiency also includes mineralocorticoids which can also cause undesirable effects if over- or under-used and need to be carefully monitored. These include light headedness or salt craving (under replacement) and swollen ankles or high blood pressure (over replacement).

The committee noted that whilst measuring renin may be beneficial to some patients, this doesn't need to be routinely screened if there are no symptoms indicating any issues with fludrocortisone dosing. Renin levels have not been shown to correlate with symptoms.

Cortisol day series do not need to be performed routinely as the levels don't correlate to symptoms, especially fatigue. Some people may have very low afternoon cortisol levels but will be fine. Therefore, clinicians need to be careful of interpreting low levels in this context. In addition, most of the new assays don't correlate with the traditional thresholds that were based on the old literature. Consequently, cortisol day series values may be misleading.

An important aim of ongoing reviews is to make sure that people with adrenal insufficiency understand their condition, how to manage it and how to avoid having an adrenal crisis. Therefore, healthcare professionals should make sure that they discuss this with their patients and emphasise the importance of medication adherence and knowing what to do in emergency situations. The impact of the condition on a patient's psychological well-being

and activities of daily living should not be underestimated and should be discussed during each review.

Children

For children, the committee agreed appointments with the specialist team should be at least every six months, but similarly to adults, this would need to be adjusted according to patient needs. An annual face-to-face hospital appointment should be offered to measure height and weight of children to ensure the condition is being managed well. These measurements can be taken by any member of the multidisciplinary team including a specialist nurse. Progression to and through puberty for example, frequency and regularity of menstrual periods should be monitored as both over- and under-replacement of glucocorticoids can have an impact on puberty progression. The committee discussed more frequent monitoring may be needed during periods of rapid growth when dosages of medication may need to be changed when transitioning to adult services, if there are concerns with medicines adherence, or whether the child and their family or carers are able to safely manage the condition.

For people at the end of life, the committee agreed cross referring to the guidelines on end-of-life care for adults and end-of-life care for children and young people with life-limiting conditions was appropriate. Decisions on withdrawing active treatment should be made as part of shared decision-making and may not mean withdrawing steroids but may include changes to how medication is administered such as by injection rather than orally.

1.1.8.4. Cost effectiveness and resource use

No health economic evidence or clinical evidence was identified for this review question, therefore the committee made recommendations reflective of current practice. As the recommendations made are reflective of current practice no significant resource will be associated with this review question.

◊ 1.1.13 Recommendations supported by this evidence review

This evidence review supports recommendations1.8.1 – 1.8.16.

References

1. 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 ongoing care and monitoring of people with adrenal insufficiency including those receiving end-of-life care

ID	Field	Content
1.	Review title	Ongoing care and monitoring of people with AI
2.	Review question	5.1 What ongoing care and monitoring should be offered to people with adrenal insufficiency? 5.2. What ongoing care and monitoring should be offered to people with adrenal insufficiency who are receiving end-of-life care?
3.	Objective	To determine optimal frequency of monitoring and what needs to be monitored for consequences of over- or under-treatment with glucocorticoids to improve outcomes for 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	People with adrenal insufficiency (primary, secondary or tertiary) including the following stratified 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 • Adults or children receiving end-of-life care Exclusion: None identified
7.	Intervention /	**Any monitoring strategy for over/undertreatment with glucocorticoids.** Strategies may include monitoring for: • Weight/obesity • Electrolyte abnormalities • Symptoms/signs for example, tiredness, abdominal or limb pain • Blood pressure • Osteoporosis/ bone health • Blood glucose • Lipids

		• Pigmentation (if under treating) • 24 hour cortisol profile • Cortisol day curve/day series • Activities of daily living **Frequency of monitoring as a general appointment** • 6 monthly • Yearly • Patient-initiated follow up (PIFU) • Other – as reported in the studies
8.	Comparator	For monitoring over/undertreatment • Monitoring for different indications compared to each other or to a suitable comparator such as no monitoring. For frequency: • Different frequencies compared to each other
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 age and sex. Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non comparative cohort studies Before and after studies Non-English language studies. Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.

11.	Context	
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: **Mortality** **Health-related quality of life, for example EQ-5D, SF-36** **Complications of adrenal insufficiency** For example, in primary AI: – 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 **Incidence of adrenal crisis** (as defined by authors) **Incidence Vascular events** **Incidence of fractures** **Incidence of diabetes** **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). **Follow up:** Longest follow up reported Where different follow up periods are reported in an individual study, we will choose the one most appropriate or most commonly reported to be able to conduct a meta-analysis.
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 certainty 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 methods of monitoring for example different cortisol assays as some assays may be more sensitive than others Monitoring by different health care professionals

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] Alexandra Bannon [Health economist] Stephen Deed [Information specialist] Madelaine Zucker [Technical analyst]
25.	Funding sources/sponsor	Development of this systematic review is being funded by NICE.
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10237.
28.	Other registration details	

29.	Reference/URL for published protocol	-	
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	-	
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	

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A.2 Health economic review protocol

Table 2: 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).[1] **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.

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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.[1]

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 3: 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)

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.	("follow up" or followup or "ongoing care" or manage* or monitor* or review* or check-up* or checkup* or revisit* or retest* or surveillance).ti,ab,kf.
36.	((over or under or insufficient) adj3 (treatment or replacement or dose or dosing)).ti,ab,kf.
37.	Weight Gain/ or Weight Loss/
38.	(weight adj3 (loss or gain)).ti,ab,kf.
39.	Obesity/
40.	obesity.ti,ab,kf.

41.	Electrolytes/
42.	electrolyte*.ti,ab,kf.
43.	exp Abdominal Pain/
44.	((abdominal or abdomen or limb* or arm* or leg*) adj3 (pain* or discomfort)).ti,ab,kf.
45.	Blood Pressure/
46.	"blood pressure".ti,ab,kf.
47.	exp Hypotension/ or Hypertension/
48.	(hypertens* or hypotens*).ti,ab,kf.
49.	Osteoporosis/
50.	(osteoporosis or "bone health").ti,ab,kf.
51.	Bone Density/
52.	"bone mineral densit*".ti,ab,kf.
53.	Blood Glucose/
54.	((blood or serum or plasma) adj3 (sugar or glucose)).ti,ab,kf.
55.	Hypoglycemia/ or Hyperglycemia/
56.	(hypoglyc?emi* or hyperglyc?emi*).ti,ab,kf.
57.	exp Lipids/
58.	(lipid* or hyperlipidemia or dyslipidemia).ti,ab,kf.
59.	Pigmentation/ or Hyperpigmentation/
60.	(hyperpigmentation or pigmentation).ti,ab,kf.
61.	"Activities of Daily Living"/
62.	("activities of daily living" or "activities of daily life").ti,ab,kf.
63.	Lethargy/ or Fatigue/
64.	(fatigue or letharg* or tired* or "energy level*").ti,ab,kf.
65.	Nausea/
66.	nausea.ti,ab,kf.
67.	Appetite/
68.	(appetite adj3 loss).ti,ab,kf.
69.	Cushing Syndrome/
70.	(cushingoid or cushing).ti,ab,kf.
71.	"Sleep Initiation and Maintenance Disorders"/
72.	(insomnia or sleepless*).ti,ab,kf.
73.	Edema/
74.	(peripheral adj (edema or oedema)).ti,ab,kf.
75.	or/35-74
76.	34 and 75
77.	randomized controlled trial.pt.
78.	controlled clinical trial.pt.
79.	randomi#ed.ab.
80.	placebo.ab.
81.	randomly.ab.
82.	clinical trials as topic.sh.
83.	trial.ti.
84.	cross-over studies/
85.	(crossover or "cross over").ti,ab.
86.	or/77-85
87.	Meta-Analysis/

88.	Meta-Analysis as Topic/
89.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
90.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
91.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
92.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
93.	(search* adj4 literature).ab.
94.	(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.
95.	cochrane.jw.
96.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
97.	or/87-96
98.	Epidemiologic studies/
99.	Observational study/
100.	exp Cohort studies/
101.	(cohort adj (study or studies or analys* or data)).ti,ab.
102.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
103.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
104.	Controlled Before-After Studies/
105.	Historically Controlled Study/
106.	Interrupted Time Series Analysis/
107.	(before adj2 after adj2 (study or studies or data)).ti,ab.
108.	exp case control study/
109.	case control*.ti,ab.
110.	Cross-sectional studies/
111.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
112.	or/98-111
113.	76 and (86 or 97 or 112)

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.	("follow up" or followup or "ongoing care" or manage* or monitor* or review* or check-up* or checkup* or revisit* or retest* or surveillance).ti,ab,kf.
35.	((over or under or insufficient) adj3 (treatment or replacement or dose or dosing)).ti,ab,kf.
36.	body weight gain/ or exp body weight loss/
37.	(weight adj3 (loss or gain)).ti,ab,kf.
38.	obesity/
39.	obesity.ti,ab,kf.
40.	electrolyte/
41.	electrolyte*.ti,ab,kf.
42.	exp abdominal pain/
43.	exp limb pain/
44.	((abdominal or abdomen or limb* or arm* or leg*) adj3 (pain* or discomfort)).ti,ab,kf.
45.	blood pressure/
46.	"blood pressure".ti,ab,kf.
47.	hypotension/ or hypertension/
48.	(hypertens* or hypotens*).ti,ab,kf.
49.	exp osteoporosis/
50.	(osteoporosis or "bone health").ti,ab,kf.
51.	bone density/
52.	"bone mineral densit*".ti,ab,kf.

53.	glucose blood level/
54.	((blood or serum or plasma) adj3 (sugar or glucose)).ti,ab,kf.
55.	hypoglycemia/ or hyperglycemia/
56.	(hypoglyc?emi* or hyperglyc?emi*).ti,ab,kf.
57.	lipid/
58.	(lipid* or hyperlipidemia or dyslipidemia).ti,ab,kf.
59.	pigmentation/ or hyperpigmentation/
60.	(hyperpigmentation or pigmentation).ti,ab,kf.
61.	daily life activity/
62.	("activities of daily living" or "activities of daily life").ti,ab,kf.
63.	lethargy/ or fatigue/
64.	(fatigue or letharg* or tired* or "energy level*").ti,ab,kf.
65.	nausea/
66.	nausea.ti,ab,kf.
67.	appetite/ or decreased appetite/
68.	(appetite adj3 loss).ti,ab,kf.
69.	exp Cushing syndrome/
70.	(cushingoid or cushing).ti,ab,kf.
71.	insomnia/
72.	(insomnia or sleepless*).ti,ab,kf.
73.	peripheral edema/
74.	(peripheral adj (edema or oedema)).ti,ab,kf.
75.	or/34-74
76.	33 and 75
77.	random*.ti,ab.
78.	factorial*.ti,ab.
79.	(crossover* or cross over*).ti,ab.
80.	((doubl* or singl*) adj blind*).ti,ab.
81.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
82.	crossover procedure/
83.	single blind procedure/
84.	randomized controlled trial/
85.	double blind procedure/
86.	or/77-85
87.	Systematic Review/
88.	Meta-Analysis/
89.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
90.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
91.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
92.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
93.	(search* adj4 literature).ab.
94.	(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.
95.	cochrane.jw.
96.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
97.	or/87-96

98.	Clinical study/
99.	Observational study/
100.	Family study/
101.	Longitudinal study/
102.	Retrospective study/
103.	Prospective study/
104.	Cohort analysis/
105.	Follow-up/
106.	cohort*.ti,ab.
107.	105 and 106
108.	(cohort adj (study or studies or analys* or data)).ti,ab.
109.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
110.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
111.	(before adj2 after adj2 (study or studies or data)).ti,ab.
112.	exp case control study/
113.	case control*.ti,ab.
114.	cross-sectional study/
115.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
116.	or/98-104,107-115
117.	76 and 116
118.	76 and (86 or 97 or 117)

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.	("follow up" or followup or "ongoing care" or manage* or monitor* or review* or check-up* or checkup* or revisit* or retest* or surveillance):ti,ab,kw

#16.	((over or under or insufficient) near/3 (treatment or replacement or dose or dosing)):ti,ab,kw
#17.	MeSH descriptor: [Weight Gain] this term only
#18.	MeSH descriptor: [Weight Loss] this term only
#19.	(weight near/3 (loss or gain)):ti,ab,kw
#20.	MeSH descriptor: [Obesity] this term only
#21.	obesity:ti,ab,kw
#22.	MeSH descriptor: [Electrolytes] this term only
#23.	electrolyte*:ti,ab,kw
#24.	MeSH descriptor: [Abdominal Pain] explode all trees
#25.	((abdominal or abdomen or limb* or arm* or leg*) near/3 (pain* or discomfort)):ti,ab,kw
#26.	MeSH descriptor: [Blood Pressure] this term only
#27.	blood pressure:ti,ab,kw
#28.	MeSH descriptor: [Hypotension] explode all trees
#29.	MeSH descriptor: [Hypertension] this term only
#30.	(hypertens* or hypotens*):ti,ab,kw
#31.	MeSH descriptor: [Osteoporosis] this term only
#32.	(osteoporosis or "bone health"):ti,ab,kw
#33.	MeSH descriptor: [Bone Density] this term only
#34.	bone mineral density:ti,ab,kw
#35.	MeSH descriptor: [Blood Glucose] this term only
#36.	((blood or serum or plasma) near/3 (sugar or glucose)):ti,ab,kw
#37.	MeSH descriptor: [Hypoglycemia] this term only
#38.	MeSH descriptor: [Hyperglycemia] this term only
#39.	(hypoglyc?emi* or hyperglyc?emi*):ti,ab,kw
#40.	MeSH descriptor: [Lipids] explode all trees
#41.	(lipid* or hyperlipidemia or dyslipidemia):ti,ab,kw
#42.	MeSH descriptor: [Pigmentation] this term only
#43.	MeSH descriptor: [Hyperpigmentation] this term only
#44.	(hyperpigmentation or pigmentation):ti,ab,kw
#45.	MeSH descriptor: [Activities of Daily Living] this term only
#46.	("activities of daily living" or "activities of daily life"):ti,ab,kw
#47.	MeSH descriptor: [Lethargy] this term only
#48.	MeSH descriptor: [Fatigue] this term only
#49.	(fatigue or letharg* or tired* or energy-level*):ti,ab,kw
#50.	MeSH descriptor: [Nausea] this term only
#51.	nausea:ti,ab,kw
#52.	MeSH descriptor: [Appetite] this term only
#53.	(appetite near/3 loss):ti,ab,kw
#54.	MeSH descriptor: [Cushing Syndrome] this term only
#55.	(cushingoid or cushing):ti,ab,kw
#56.	MeSH descriptor: [Sleep Initiation and Maintenance Disorders] this term only
#57.	(insomnia or sleepless*):ti,ab,kw
#58.	MeSH descriptor: [Edema] this term only
#59.	("peripheral edema" or "peripheral oedema"):ti,ab,kw
#60.	(or #15-#59)
#61.	#14 and #60

#62.	conference:pt or (clinicaltrials or trialsearch):so
#63.	#61 not #62

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"))) 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:("follow up" OR followup OR "ongoing care" OR manage* OR monitor* OR review* OR "check-up" OR "check-ups" OR checkup* OR revisit* OR retest* OR surveillance OR "over treatment" OR "over replacement" OR "over dose" OR "over dosing" OR "under treatment" OR "under replacement" OR "under dose" OR "under dosing" OR "insufficient treatment" OR "insufficient replacement" OR "insufficient dose" OR "insufficient dosing" OR "weight gain" OR "weight loss" OR obesity OR electrolyte* OR "abdominal pain" OR "limb pain" OR "blood pressure" OR hypertens* OR hypotens* OR osteoporosis OR "bone health" OR "bone mineral density" OR blood glucose OR blood sugar OR hypoglycaemi* OR hyperglycaemi* OR hypoglycemi* OR hyperglycemi* OR lipid* OR hyperlipidemia OR dyslipidemia OR pigmentation OR hyperpigmentation OR "activities of daily living" OR "activities of daily life" OR fatigue OR letharg* OR tired* OR "energy level" OR "energy levels" OR nausea OR "appetite loss" OR "loss of appetite" OR cushingoid OR cushing OR insomnia OR sleepless* OR "peripheral edema" OR "peripheral oedema") OR abstract:("follow up" OR followup OR "ongoing care" OR manage* OR monitor* OR review* OR "check-up" OR "check-ups" OR checkup* OR revisit* OR retest* OR surveillance OR "over treatment" OR "over replacement" OR "over dose" OR "over dosing" OR "under treatment" OR "under replacement" OR "under dose" OR "under dosing" OR "insufficient treatment" OR "insufficient replacement" OR "insufficient dose" OR "insufficient dosing" OR "weight gain" OR "weight loss" OR obesity OR electrolyte* OR "abdominal pain" OR "limb pain" OR "blood pressure" OR hypertens* OR hypotens* OR osteoporosis OR "bone health" OR "bone mineral density" OR blood glucose OR blood sugar OR hypoglycaemi* OR hyperglycaemi* OR hypoglycemi* OR hyperglycemi* OR lipid* OR hyperlipidemia OR dyslipidemia OR pigmentation OR hyperpigmentation OR "activities of daily living" OR "activities of daily life" OR fatigue

	OR letharg* OR tired* OR "energy level" OR "energy levels" OR nausea OR "appetite loss" OR "loss of appetite" OR cushingoid OR cushing OR insomnia OR sleepless* OR "peripheral edema" OR "peripheral oedema"))

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 4: 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	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 26 September 2023	English language

Medline (Ovid) search terms

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

6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	or/1-13
15.	letter/
16.	editorial/
17.	news/
18.	exp historical article/
19.	Anecdotes as Topic/
20.	comment/
21.	case reports/
22.	(letter or comment*).ti.
23.	or/15-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animals/ not humans/
27.	exp Animals, Laboratory/
28.	exp Animal Experimentation/
29.	exp Models, Animal/
30.	exp Rodentia/
31.	(rat or rats or mouse or mice or rodent*).ti.
32.	or/25-31
33.	14 not 32
34.	limit 33 to English language
35.	Economics/
36.	Value of life/
37.	exp "Costs and Cost Analysis"/
38.	exp Economics, Hospital/
39.	exp Economics, Medical/
40.	Economics, Nursing/
41.	Economics, Pharmaceutical/
42.	exp "Fees and Charges"/
43.	exp Budgets/
44.	budget*.ti,ab.
45.	cost*.ti.

46.	(economic* or pharmaco?economic*).ti.
47.	(price* or pricing*).ti,ab.
48.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
49.	(financ* or fee or fees).ti,ab.
50.	(value adj2 (money or monetary)).ti,ab.
51.	or/35-50
52.	34 and 51
53.	limit 52 to yr="2014 -Current"

Embase (Ovid) search terms

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

28.	animal model/
29.	exp Rodent/
30.	(rat or rats or mouse or mice or rodent*).ti.
31.	or/23-30
32.	14 not 31
33.	limit 32 to English language
34.	health economics/
35.	exp economic evaluation/
36.	exp health care cost/
37.	exp fee/
38.	budget/
39.	funding/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/34-46
48.	33 and 47
49.	limit 48 to yr="2014 -Current"

NHS EED and HTA (CRD) search terms

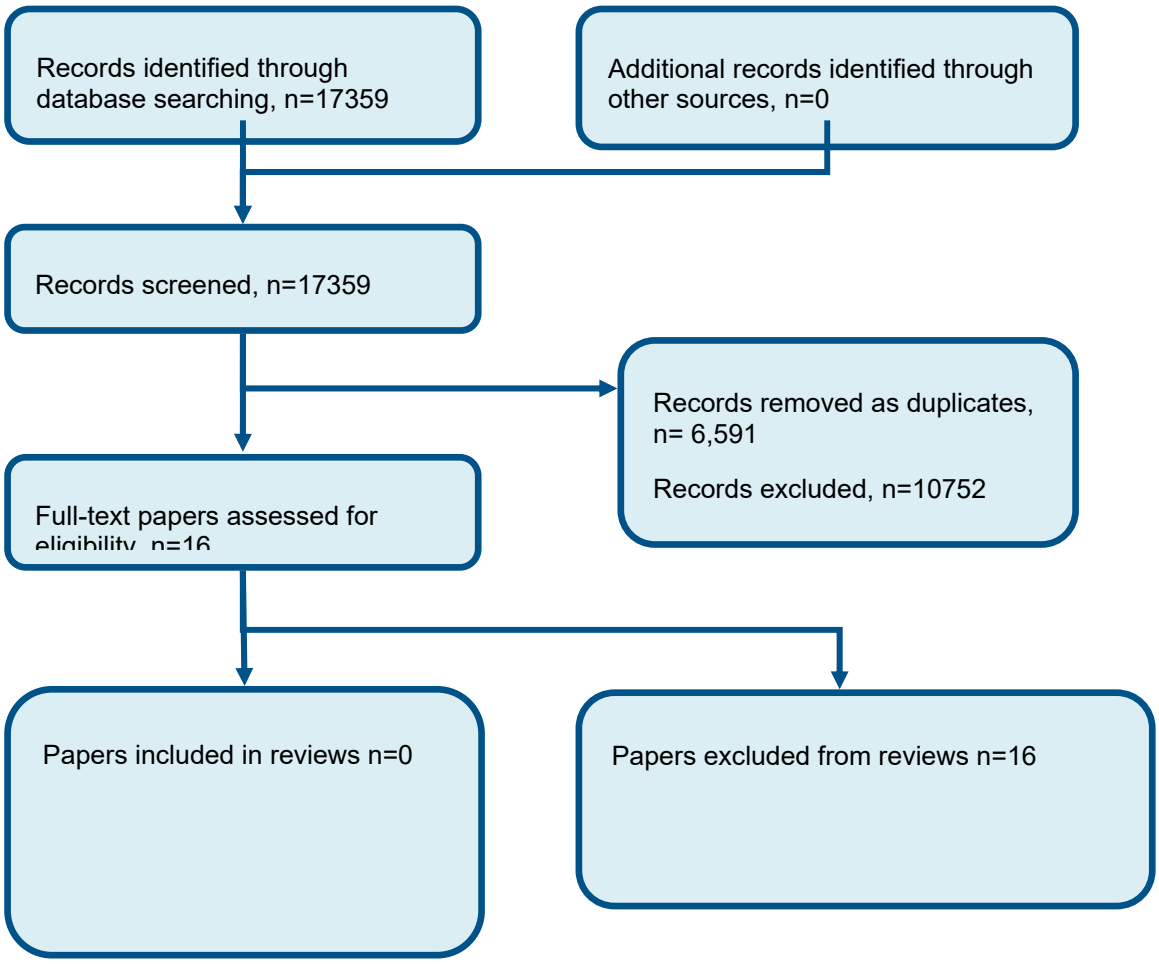
#1.	MeSH DESCRIPTOR Adrenal Insufficiency EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Adrenal Hyperplasia, Congenital EXPLODE ALL TREES
#3.	(addison* disease or addisonian)
#4.	(adrenal*) AND (insufficien* or inadequa* or deficien* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or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

INAHTA search terms

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

Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of ongoing care and monitoring of people with adrenal insufficiency including those receiving end-of-life care



Appendix D Effectiveness evidence

No evidence included.

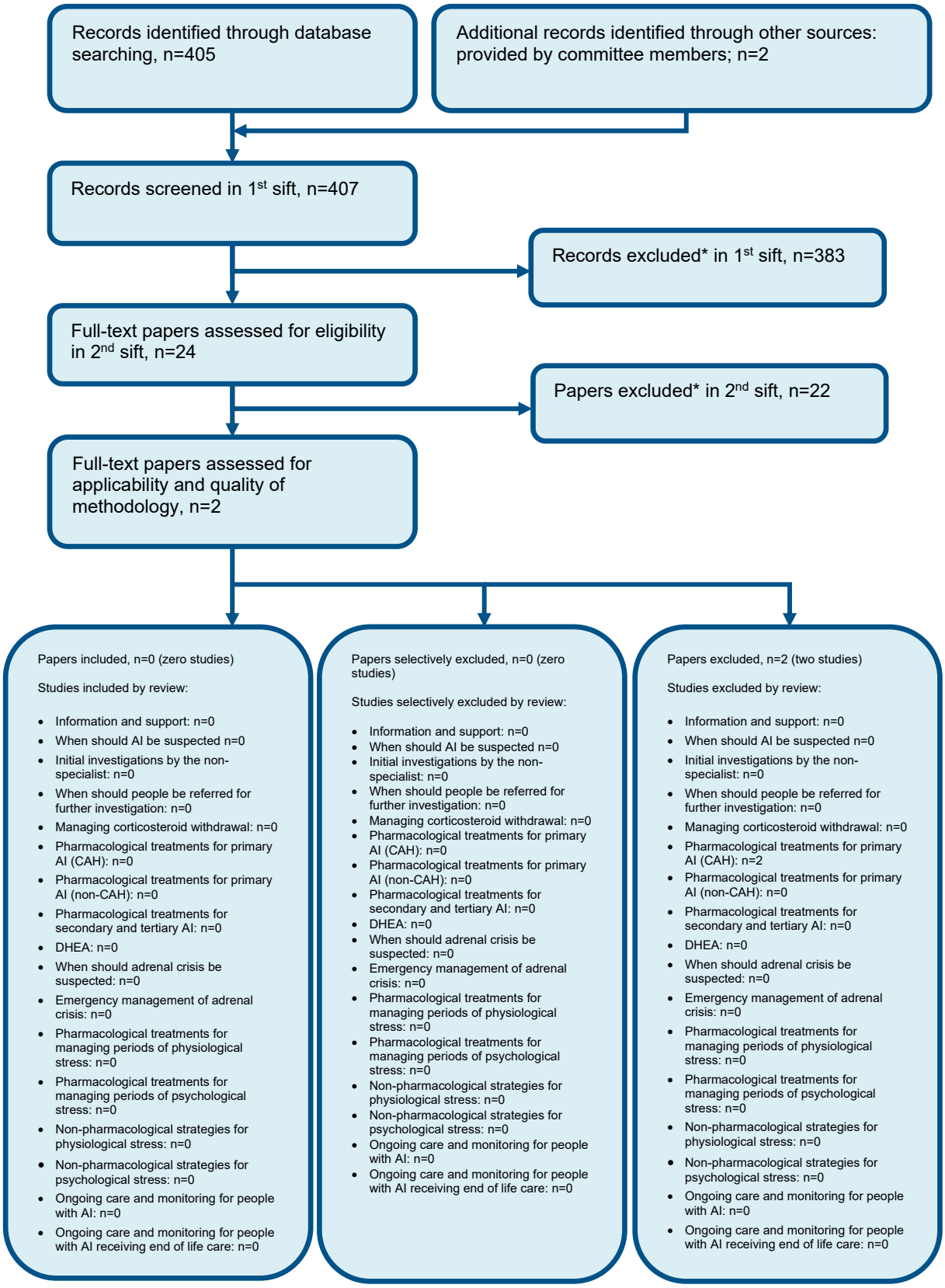
Appendix E Forest plots

None.

Appendix F GRADE and/or GRADE-CERQual 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

No original economic modelling was undertaken for this review question.

Appendix J Excluded studies

J.1 Clinical studies

Table 5: Studies excluded from the clinical review

Study	Code [Reason]
Appan, S; Hindmarsh, P C; Brook, C G (1989) Monitoring treatment in congenital adrenal hyperplasia. Archives of disease in childhood 64(9): 1235-9	- Study design not relevant to this review protocol *Non comparative cohort study*
Birkebaek, Niels H; Hougaard, David M; Cohen, Arieh S (2017) Monitoring steroid replacement therapy in children with congenital adrenal hyperplasia. Journal of pediatric endocrinology & metabolism : JPEM 30(1): 85-88	- Study does not address our clinical question *Comparison of 17-OHP by radio immunoassay in serum with analysis by liquid chromatography tandem mass spectrometry*
Dauber, Andrew; Kellogg, Mark; Majzoub, Joseph A (2010) Monitoring of therapy in congenital adrenal hyperplasia. Clinical chemistry 56(8): 1245-51	- Review article but not a systematic review
Deutschbein, T., Unger, N., Hauffa, B.P. et al. (2011) Monitoring medical treatment in adolescents and young adults with congenital adrenal hyperplasia: Utility of salivary 17alpha-hydroxyprogesterone day profiles. Experimental and Clinical Endocrinology and Diabetes 119(3): 131-138	- Study does not address our clinical question *Looking at diagnostic validity of 17OPH sampling*
Donatti, T.L., Koch, V.H.K., Takayama, L. et al. (2011) Effects of glucocorticoids on growth and bone mineralization. Jornal de Pediatria 87(1): 4-12	- Study not reported in English
Eugster, E A, Dimeglio, L A, Wright, J C et al. (2001) Height outcome in congenital adrenal hyperplasia caused by 21-hydroxylase deficiency: a meta-analysis. The Journal of pediatrics 138(1): 26-32	- Study does not address our clinical question *Retrospective chart review of final and target heights. Assessed impact of sex, time of diagnosis and compliance.*
Fleming, Louise; Van Riper, Marcia; Knafl, Kathleen (2017) Management of Childhood Congenital Adrenal Hyperplasia-An Integrative Review of the Literature. Journal of pediatric health care : official publication of National Association of Pediatric Nurse Associates & Practitioners 31(5): 560-577	- Study does not contain an intervention relevant to this review protocol
Gomes, Larissa G; Mendonca, Berenice B; Bachega, Tania A S S (2020) Long-term cardio-	- Study does not address our clinical question

Study	Code [Reason]
metabolic outcomes in patients with classical congenital adrenal hyperplasia: is the risk real?. Current opinion in endocrinology, diabetes, and obesity 27(3): 155-161	*Review of the frequency of metabolic syndrome components and other cardiovascular risk factors in CAH.*
Grossman, Ashley B (2010) Clinical Review#: The diagnosis and management of central hypoadrenalism. The Journal of clinical endocrinology and metabolism 95(11): 4855-63	- Systematic review used as source of primary studies *Addresses management and diagnosis but not monitoring.*
Hummel, Silvia R, Sadler, Susannah, Whitaker, Martin J et al. (2016) A model for measuring the health burden of classic congenital adrenal hyperplasia in adults. Clinical endocrinology 85(3): 361-98	- Study does not address our clinical question
Jodar, Esteban, Valdepenas, Maria Pilar Ruiz, Martinez, Guillermo et al. (2003) Long-term follow-up of bone mineral density in Addison's disease. Clinical endocrinology 58(5): 617-20	- Study does not address our clinical question *Looks at long-term follow up but no monitoring strategy*
Kim, Mimi S; Ryabets-Lienhard, Anna; Geffner, Mitchell E (2012) Management of congenital adrenal hyperplasia in childhood. Current opinion in endocrinology, diabetes, and obesity 19(6): 483-8	- Systematic review used as source of primary studies
Lim, Seung Gyun, Lee, Young Ah, Jang, Han Na et al. (2021) Long-Term Health Outcomes of Korean Adults With Classic Congenital Adrenal Hyperplasia Due to 21-Hydroxylase Deficiency. Frontiers in endocrinology 12: 761258	- Study does not address our clinical question *Looking at long term health outcomes. No monitoring strategy.*
Mah, Peak M, Jenkins, Richard C, Rostami-Hodjegan, Amin et al. (2004) Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency. Clinical endocrinology 61(3): 367-75	- Study does not address our clinical question *The objective of this study was to examine the variables determining hydrocortisone (HC) disposition in patients with adrenal insufficiency by comparing fixed vs 'body surface area-adjusted' dose in different states (fasted vs fed)*
Mallappa, A., Daley, L.-A., Van Ryzin, C. et al. (2013) Timing is everything: Hormonal evaluation of patients with congenital adrenal hyperplasia. Endocrine Reviews 34(3suppl1)	- Conference abstract
Wieacker, Isabelle, Peter, Michael, Borucki, Katrin et al. (2015) Therapy monitoring in congenital adrenal hyperplasia by dried blood samples. Journal of pediatric endocrinology & metabolism : JPEM 28(78): 867-71	- Study does not contain an intervention relevant to this review protocol

J.2 Health Economic studies

None.