National Institute for Health and Care Excellence

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Draft

Adrenal insufficiency: identification and management

Evidence review C: When to refer for specialist investigation when withdrawing corticosteroids

NICE guideline <number>

Evidence reviews underpinning recommendations 1.9.8 in the NICE guideline

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Draft for Consultation

This evidence review was developed by NICE

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1. When to refer for steroid withdrawal

1.1. Review question

When should a person who is having exogenous corticosteroids withdrawn be referred for investigation and management of adrenal insufficiency related to HPA-axis suppression?

1.1.1. Introduction

Exogenous glucocorticoids are used for their anti-inflammatory and immunosuppressive properties across many conditions ranging from asthma, inflammatory bowel disease, polymyalgia rheumatica and organ transplantation. Re-occurrence of symptoms during glucocorticoid withdrawal may reflect the return of the original disease for which the steroids were started or adrenal insufficiency, unmasked by the reducing steroid dose.

Mild symptoms during withdrawal of exogenous corticosteroids are an expected and common occurrence and generally do not indicate unmasked adrenal insufficiency. However, if there is underlying adrenal insufficiency, either owing to adrenal suppression or because of medication use or intrinsic pituitary/adrenal disease it is potentially life-threatening and needs to be taken seriously.

This evidence review seeks to address the approach required in managing patients being withdrawn from glucocorticoid therapy, and establishing when someone should be referred to a specialist for investigation of adrenal insufficiency, related to HPA-axis suppression.

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Population	Inclusion: People on long term glucocorticoids who are having them withdrawn. These include: • People on prednisolone doses > 3-5mg/day • People on dexamethasone doses > 0.3-0.5mg/day • People on glucocorticoids longer than 4 weeks Patient circumstances: • Those on lower doses and symptomatic • Those with co-morbidities • Those with clinical indications of AI • Individual risk factors • Speed of withdrawal e.g., rapid withdrawal vs slow tapering • Those who have had or are having steroids via multiple routes. Examples of populations: people with asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, polymyalgia, lupus or multiple sclerosis) Exclusion: None identified
Target condition	Adrenal Insufficiency
Index tests	Diagnostic accuracy based on cut-off: • Cortisol Tests –8- 9 am • Salivary cortisol • Salivary cortisone

	• Short Synacthen test • ACTH and cortisol Note assay specific cut-offs and which assays being used – exclude if they don't' state the assay.
Reference standards	• Short Synacthen Test (standard and low dose) Or • Insulin tolerance test (insulin hypoglycaemia test) Or • Clinical diagnosis by a specialist (a specialist will take into account the full clinical picture, including signs, symptoms, risk factors and test results)
Statistical measures	Diagnostic accuracy data • Sensitivity (prioritised) [fewer false negatives i.e. very few people with the condition will be missed] • Specificity
Study design	• Cross-sectional (single gate) studies • Systematic reviews of diagnostic accuracy studies • If no or insufficient diagnostic accuracy studies are identified, prospective cohort studies may be included

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. Diagnostic evidence

1.1.4.1. Included studies.

A search was conducted for cross-sectional (single-gate) studies to assess when a person who is having exogenous corticosteroids withdrawn should be referred to a specialist for investigation of adrenal insufficiency, based on HPA-axis suppression.

One diagnostic study was identified and included in the review;[3] it is summarised in Table 2 below. Evidence from this single UK-based study is summarised in the clinical evidence summary below in Table 3 and the reference is located in the listed References .

This study was conducted in the UK and included people who were attending the endocrine clinic for a short Synacthen test. This was to evaluate HPA recovery as they had previously been taking prolonged supraphysiological therapeutic doses of oral glucocorticoids.

It reported the diagnostic accuracy of early morning salivary cortisol, serum cortisol and salivary cortisone. The reference standard used in this study was the 0.25 mg short Synacthen test and if the 30-min serum cortisol was ≥450 nmol/L it was defined as an adequate response.

No relevant diagnostic test accuracy studies of the Short Synacthen test or ACTH and cortisol were identified.

The assessment of the evidence quality was conducted with emphasis on test sensitivity and specificity as this was identified by the committee as the primary measure in guiding decision-making. The committee also agreed that sensitivity is more important than

specificity, as avoiding false negatives would be the main aim in assessing for this condition. The committee set clinical decision thresholds as sensitivity/specificity 0.9 and 0.70 above which a test would be recommended and 0.6 and 0.5 below which a test is of no clinical use.

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

1.1.4.2. Excluded studies.

See the excluded studies list in Appendix I.

1.1.5. Summary of studies included in the diagnostic evidence.

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

Study	Population	Target condition	Index test	Reference standard	Comments
Kalaria 2020[3]	47 patients attending the endocrine clinic for a Short synacthen test (SST) to evaluate HPA recovery. All patients had previously been on prolonged supraphysiological therapeutic doses of oral glucocorticoids. **Age (years):** median (IQR): 60 (48.3–69.5) years **Ratio male: female:** 16:31 **Reason for referral:** To assess hypothalamic–pituitary–adrenal axis recovery in patients previously treated with prolonged supraphysiological therapeutic doses of oral glucocorticoids.	Adrenal Insufficiency	Basal serum cortisol, basal salivary cortisol and basal salivary cortisone. Baseline salivary sample was collected immediately before the baseline serum sample and then 0.25 mg of tetracosactide acetate (synacthen) was injected either intravenously or intramuscularly and a further blood sample collected 30 min later. Saliva was collected in SalivetteVR tubes. Blood was collected in S-MonovetteVR 4.7 mL Z-gel tubes. **Threshold cut-off value:** HPA suppression: Baseline serum cortisol: 170(nmol/L), baseline salivary cortisol: 1.92(nmol/L),	SSTs were performed between 09:00 and 10:30 after oral and inhaled glucocorticoid withdrawal for at least 24 h. Baseline salivary sample was collected immediately before the baseline serum sample and then 0.25 mg of tetracosactide acetate (synacthen) was injected either intravenously or intramuscularly and a further blood sample collected 30 min later. Blood was collected in S-MonovetteVR 4.7 mL Z-gel tubes. Threshold: A SST was labelled as ‘pass’ (adequate response) if the 30-min serum cortisol was >/=450 nmol/L.	Country: UK Study population = 47 (56 SSTs - seven patients underwent two SSTs each and one patient three SSTs)

Study	Population	Target condition	Index test	Reference standard	Comments
			baseline salivary cortisone: 9.42 (nmol/L). HPA recovery: Baseline serum cortisol: 365(nmol/L), baseline salivary cortisol: 25.4(nmol/L), baseline salivary cortisone: 37.2 (nmol/L)		

1 See Appendix D for full evidence tables.

1.1.6. Summary of the diagnostic evidence

Table 3: Clinical evidence summary: diagnostic test accuracy for morning serum cortisol for diagnosing AI in people being assessed for HPA recovery following supraphysiological therapeutic doses of oral glucocorticoids.

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Morning serum cortisol **(threshold 365 nmol/L)** to detect AI in people being assessed for HPA recovery following supraphysiological therapeutic doses of oral glucocorticoids (Kalaria 2020)							
1 cross-sectional study	47 (56 SSTs)	Serious[1]	Not serious	Not serious	Not Serious	Sensitivity=0.27 (0.08-0.55)	MODERATE
		Serious[1]	Not serious	Not serious	Not serious	Specificity=1.00(0.91-1.00)	MODERATE
Morning serum cortisol **(threshold 170 nmol/L)** to detect AI in people being assessed for HPA suppression following supraphysiological therapeutic doses of oral glucocorticoids (Kalaria 2020)							
1 cross-sectional study	47 (56 SSTs)	Serious[1]	Not serious	Not serious	Not Serious	Sensitivity=1.00 (0.78-1.00)	MODERATE
		Serious[1]	Not serious	Not serious	Serious[2]	Specificity=0.59 (0.42-0.74)	LOW

[1] Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment due to high risk of bias arising from unclear reporting on patient selection.

[2] Downgraded by 1 increment as the confidence interval crossed one decision threshold (thresholds set at 60% and 90% for sensitivity; 50% and 70% for specificity. Confidence interval crossed the decision threshold corresponding to 'high Specificity' (70%).

Table 4: Clinical evidence summary: diagnostic test accuracy for morning salivary cortisol for diagnosing AI in people being assessed for HPA recovery following supraphysiological therapeutic doses of oral glucocorticoids.

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Morning salivary cortisol **(threshold 25.4 nmol/L)** to detect AI in people being assessed for HPA recovery following supraphysiological therapeutic doses of oral glucocorticoids (Kalaria 2020)							
1 cross-sectional study	47 (56 SSTs)	Serious[1]	Not serious	Not serious	Not Serious	Sensitivity=0.00 (0.00-0.22)	MODERATE
		Serious[1]	Not serious	Not serious	Not serious	Specificity=1.00 (0.91-1.00)	MODERATE
Morning salivary cortisol **(threshold 1.92 nmol/L) to** detect AI in people being assessed for HPA suppression following supraphysiological therapeutic doses of oral glucocorticoids (Kalaria 2020)							

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
1 cross-sectional study	47 (56 SSTs)	Serious[1]	Not serious	Not serious	Not serious	Sensitivity=1.00 (0.78-1.00)	MODERATE
		Serious[1]	Not serious	Not serious	Serious[2]	Specificity=0.51 (0.35-0.67)	LOW

[1] Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment due to high risk of bias arising from unclear reporting on patient selection.

[2] Downgraded by 1 increment as the confidence interval crossed one decision threshold (thresholds set at 60% and 90% for sensitivity; 50% and 70% for specificity. Confidence interval crossed the decision threshold corresponding to 'low specificity' (50%).

Table 5: Clinical evidence summary: diagnostic test accuracy for salivary cortisone for diagnosing AI in people being assessed for HPA recovery following supraphysiological therapeutic doses of oral glucocorticoids.

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Salivary cortisone (threshold 37.2 nmol/L) to detect AI in people being assessed for HPA recovery following supraphysiological therapeutic doses of oral glucocorticoids (Kalaria 2020)							
1 cross-sectional study	47 (56 SSTs)	Serious[1]	Not serious	Not serious	Not Serious	Sensitivity=0.27 (0.08-0.55)	MODERATE
		Serious[1]	Not serious	Not serious	Not serious	Specificity=1.00 (0.91-1.00)	MODERATE
Salivary cortisone **(threshold 9.42 nmol/L)** to detect AI in people being assessed for HPA suppression following supraphysiological therapeutic doses of oral glucocorticoids (Kalaria 2020)							
1 cross-sectional study	47 (56 SSTs)	Serious[1]	Not serious	Not serious	Not serious	Sensitivity=1.00 (0.78-1.00)	MODERATE
		Serious[1]	Not serious	Not serious	Serious[2]	Specificity=0.54 (0.37-0.69)	LOW

[1] Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 1 increment due to high risk of bias arising from unclear reporting on patient selection.

[2] Downgraded by 1 increment as the confidence interval crossed one decision threshold (thresholds set at 60% and 90% for sensitivity; 50% and 70% for specificity. Confidence interval crossed the decision threshold corresponding to 'low specificity' (50%).

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 F.

1.1.8. Economic model

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

1.1.9. Unit costs

Relevant unit costs are provided below to aid the consideration of cost-effectiveness.

Table 6: Unit costs of tests and referral

Resource	Unit costs
Primary care	
Serum cortisol test (community / hospital outpatient) (a)	£5.88 - £6.25
Salivary cortisol test (b)	£28.17
Advice and guidance (c)	£12.08 - £24.17
Secondary care	
Referral to secondary care, adult / paediatric (d)	£293.42 / £417.78
Short synacthen test (e)	£398.36
Insulin tolerance test (f)	£469.60

Sources:

(a) Consisting of a blood test taken either in the community (ten minutes of a Band 3 health care assistant time £4.33 [calculated based on reported wage from PSSRU 2022[2] and proportional Salary oncosts, Overheads and Capital used by PSSRU for Community-based social care professionals, £26 per hour]) or in an outpatient hospital setting by a phlebotomist (£4.70 [Phlebotomy DAPS08, NHS reference costs 21/22[7]]). Blood test analysis: £1.55 (Clinical biochemistry DAPS04, NHS reference cost 21/22).[7]

(b) Salivary sample taken at home using Salivette, cost of Salivette (£184.95 for 500 units).[4]. Postage and packaging (£3.50) and laboratory analysis approximately (£14.30). Additional posting may be required when the local hospital needs to send to another laboratory (medical courier service £10). These estimates are based on committee opinion and communication with Debono et al.

(c) Cost based on 5 to 10 minutes of consultant endocrinology time required (based on committee opinion). Unit cost from PSSRU 2022[2]

(d) Weighted average (consultant led, non-consultant led and multi-professional) cost of first endocrinology face to face appointment. NHS reference costs 2021/2022).[7]

(e) Cost includes: day case £398.36 (KA08C Other Endocrine Disorders with CC Score 0-1, NHS reference costs 2021/2022) this is assumed to include cost of synacthen (synacthen 250µg ampoule: £38, BNF, November 2023).[1]

(f) Cost excluding VAT. Costed as part of NICE Medtech innovation briefing [MIB320] on 'Macimorelin for diagnosing growth hormone deficiency', published March 2023[6]

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

1.1.10.1. The outcomes that matter most

Diagnostic accuracy

The committee considered the diagnostic measures of sensitivity and specificity for the index tests; serum cortisol, salivary cortisol, and salivary cortisone for detecting adrenal insufficiency in people having long-term exogenous corticosteroids withdrawn. Clinical decision thresholds were set by the committee as sensitivity/specificity=0.9 and 0.7 above which a test would be recommended and 0.6 and 0.5 below which a test is of no clinical use.

The committee were interested in establishing in which circumstances should someone be referred to a specialist for investigation of adrenal insufficiency, (related to HPA-axis suppression and serum cortisol cut-offs) when they are having long-term glucocorticoid steroids withdrawn. Therefore, sensitivity was considered the most important measure, as it was important to avoid any false negative results that could result in a missed diagnosis of adrenal insufficiency and lead to potentially serious implications.

1.1.10.2. The quality of the evidence

One UK-based diagnostic study was included in this review. It reported the diagnostic accuracy of early morning serum cortisol, salivary cortisol and salivary cortisone in a specific adult population of people having long-term exogenous glucocorticoids withdrawn. The study specified that the withdrawal from the long-term therapeutic doses of oral corticosteroids involved tapering the steroid dose to 5 mg of prednisolone or equivalent and then switching to hydrocortisone. Assessment of the HPA axis was then performed with a short Synacthen test once the patient had been on the replacement dose for at least 4 weeks. The committee agreed that this study was relevant to the review question but in current practice, clinicians would not routinely recommend switching from prednisolone to hydrocortisone.

The reference standard used in this study was the 0.25 mg short Synacthen test and if the 30-min serum cortisol was ≥450 nmol/L it was defined as an adequate response.

This study provided sensitivity and specificity data for the three index tests at different cut points in order to maximise specificity when looking for HPA recovery and to maximise sensitivity when looking for HPA suppression.

The quality of the evidence was assessed by an adapted GRADE framework and rated moderate for the majority of outcomes. These were downgraded on the QUADAS-2 checklist for risk of bias due to unclear reporting of patient selection. Several outcomes were rated low quality and downgraded due to imprecision. This arose from the confidence interval crossing one of the decision thresholds (thresholds set at 60% and 90% for sensitivity; and 50% and 70% for specificity). Overall, the evidence available was very limited and based on one study with 47 participants.

1.1.10.3. Benefits and harms

The committee considered the diagnostic accuracy data available for serum and salivary cortisol and salivary cortisone, in diagnosing HPA suppression while withdrawing from corticosteroids. They concluded that there were no real differences in terms of the accuracy data for serum cortisol at 170 nmol/l, salivary cortisol at 1.92 nmo/l and cortisone at 9.42 nmol/l, with 100% sensitivity reported across the tests (specificity was: 59% for serum cortisol, 51% for salivary cortisol and 54% for salivary cortisone). These thresholds were set to avoid any false negative results and to not miss any potential diagnoses. Alternate thresholds were reported to identify HPA recovery, and these were set to maximise

specificity at 100% and limit false positive results. The corresponding sensitivity values for serum cortisol at 365 nmol/l were 26.7%, salivary cortisol at 25.4 nmol/l were 0% and salivary cortisone at 37.2 nmol/l were 26.7%.

As discussed in review D the committee decided to make a recommendation for serum cortisol over the other index tests due to its widespread availability, and cost-effectiveness. They agreed that while the evidence base for salivary cortisol and cortisone is growing, there are only 2 test centres in the UK able to interpret these tests. Therefore, due to resource implications and practical issues, the committee were not able to recommend these tests in the UK at present.

Ultimately, the committee agreed that a 9 am serum cortisol test should be considered for people who develop signs and symptoms of adrenal insufficiency while they are withdrawing from long-term glucocorticoids, providing they have attempted a slow taper and are down to physiological doses. The committee specified that a 9 am cortisol test should not be attempted prior to this as the patient would still be covered by their steroid doses.

If a patient is attempting a slow taper and becomes symptomatic, the committee recommended that corticosteroids be paused for a period, (12 hours from hydrocortisone, 24 hours from prednisolone and 72 hours from dexamethasone) so that a 9 am cortisol test can be carried out. Steroids can then be resumed at the physiological dose they were on previously. Signs and symptoms of when to suspect AI when tapering, are covered in review B.

The committee deliberated on which cut-off should a referral be made for further testing with a short Synacthen test. They discussed the cut-offs presented in the evidence, however, as this was so limited and the cut-offs reported were lower than expected, they decided to use their experience and consensus opinion to make a recommendation.

They took into account the specific population of people withdrawing from glucocorticoids but agreed that the cut points for 9 am cortisol tests should be the same as those used to screen for adrenal insufficiency in a general population, as recommended in review D (recommendation 1.2.6). The committee specified that if the 9 am cortisol test result comes back below 200 nmol/L then a referral to endocrinology or for a short Synacthen test should be arranged immediately. However, if test results are between 201 and 300 nmol/l the 9 am cortisol test could be repeated. If it remains in this grey zone after a second test, then a referral to endocrinology should be made. The committee agreed that if the test is above 300 nmol/L adrenal insufficiency is very unlikely, and that the tapering regime can continue.

Due to the limited evidence available and the uncertainty in the population size, the committee made a weaker ‘consider’ recommendation for when to refer for a 9 am cortisol test in people who become symptomatic while tapering from long term glucocorticoids.

1.1.10.4. Cost effectiveness and resource use

No health economic studies were identified for this review. Unit costs were presented and discussed with the committee to aid their consideration of cost-effectiveness.

Serum cortisol tests were estimated to be approximately £6 per test. The costs include the cost of a blood test taken either in the community at a GP practice by a health care assistant (ten minutes of a Band 3 health care assistant time £4.33) or in an outpatient hospital setting by a phlebotomist (£4.70) and the cost of laboratory analysis (£1.55 for clinical biochemistry).

Salivary cortisol testing includes the cost of the ‘Salivette’ to collect the saliva and then the laboratory and postage costs. The former was estimated to be £0.37 per unit, the latter £27.80. The committee noted that salivary cortisol testing is not widely used and there are only two testing centres in the UK with machines that enable the analysis of mass spectrometry assays. It was noted that there could be significant set-up costs if it were to be

recommended due to the current lack of infrastructure available for analysing these samples nationally. The committee noted that reliance on the available laboratories may result in delays in results of up to 5 weeks which would be impractical and possibly clinically inappropriate.

The unit cost of referral to secondary endocrinology care was presented, this was £293 for adults and £418 for paediatrics (a weighted average of consultant-led, non-consultant led and multi-professional cost of first endocrinology face-to-face appointments). The unit cost of a short synacthen test was presented as a day case cost (£398). The cost of synacthen would be included in the day case cost as it is not listed as a high-cost drug. This is a broad HRG unit cost which will cover many interventions so may not provide an exact estimate of the cost of this test. In addition, the committee noted that the unit cost of synacthen in hospitals currently is higher than that listed in the drug tariff / BNF (£45 versus £38). Insulin tolerance tests are likely to be bundled in the same day case cost as a short synacthen test, but the committee noted it is likely to be more expensive as it is a more resource-intensive test. The cost of an insulin tolerance test was calculated as part of the NICE Medtech innovation briefing [MIB320] on 'Macimorelin for diagnosing growth hormone deficiency' at £470.

The committee decided to set a cut-off for onwards referral at ≤200 nmol/l or for repeat testing if the value is between 201 – 300 nmol/l. This was based on the recommendations made for testing for adrenal insufficiency in a general population The committee deliberated that higher cut-offs would increase the risk of false positive results and lead to increased cost to the NHS associated with unnecessary referrals and short synacthen testing.

The committee agreed that in people who develop signs and symptoms of adrenal insufficiency after slow tapering of long-term glucocorticoids, an 8-9 am serum cortisol should be considered providing they are down to physiological doses. The committee recommended 9 am serum cortisol tests over the other index tests (for example salivary cortisol) as they are readily available, relatively inexpensive and would ultimately lead to cost savings if referrals for unnecessary short synacthen tests can be avoided. The timing of the test and the importance of tapering glucocorticoids to physiological doses were stressed to ensure the serum cortisol test measures accurate peak cortisol levels. Tests carried out later in the day (i.e., 10 am) or without tapering would not be of any clinical use and could lead to unnecessary referrals.

The exact size of the population at risk is difficult to accurately estimate. The committee noted that the number of people who are potentially at risk of HPA-axis suppression following long-term glucocorticoid use is uncertain due to a lack of suitable data. Furthermore, although there are one million glucocorticoid prescriptions per year in England, it is unclear the number of individuals receiving glucocorticoid prescriptions or what proportion are receiving them for over 4 weeks. Due to the uncertainty in the population size and to minimise the resource impact to the NHS, the committee were keen to restrict testing to those who develop signs and symptoms after attempting a slow taper, as opposed to all those withdrawing from long-term glucocorticoids and made a weaker 'consider' recommendation.

Of note a research recommendation looking at the diagnostic accuracy and cut-offs for referral (including cost-effectiveness) for salivary cortisol tests has been made as part of the review question looking at testing for adrenal insufficiency in a general population.

1.1.11. Recommendations supported by this evidence review.

This evidence review supports recommendation 1.9.8.

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Appendices

Appendix A Review protocols

A.1 Review protocol for when to refer for specialist investigation.

ID	Field	Content
1.	Review title	When to refer for specialist investigation
2.	Review question	When should a person who is having exogenous corticosteroids withdrawn be referred for investigation and management of adrenal insufficiency related to HPA-axis suppression?
3.	Objective	To determine when a person who is having exogenous corticosteroids withdrawn be referred to a specialist for investigation of AI related to HPA-axis suppression based on specific cut-offs for cortisol tests.
4.	Searches	The following databases (from inception) will be searched: • 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 on long term glucocorticoids who are having them withdrawn. These include: • People on prednisolone doses > 3-5mg/day • People on dexamethasone doses > 0.3-0.5mg/day • People on glucocorticoids longer than 4 weeks Patient circumstances: ○ Those on lower doses and symptomatic ○ Those with co-morbidities ○ Those with clinical indications of AI ○ Individual risk factors ○ Speed of withdrawal e.g. rapid withdrawal vs slow tapering ○ Those who have had or are having steroids via multiple routes. Examples of populations: people with asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, polymyalgia, lupus or multiple sclerosis) Exclusion: None identified.
7.	Test	Diagnostic accuracy based on cut-off: • Cortisol Tests –8- 9 am • Salivary cortisol • Salivary cortisone

		• Short Synacthen test • ACTH and cortisol Note assay specific cut-offs and which assays being used – exclude if they don't' state the assay.
8.	Reference standard	Short Synacthen Test (standard and low dose) Or Insulin tolerance test (insulin hypoglycaemia test) Or Clinical diagnosis by a specialist (a specialist will take into account the full clinical picture, including signs, symptoms, risk factors and test results)
9.	Types of study to be included	• Cross sectional (single gate) diagnostic studies • Systematic reviews of diagnostic accuracy studies • If no or insufficient diagnostic accuracy studies are identified, prospective cohort studies may be included
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)	Diagnostic accuracy data • Sensitivity (prioritised) *[fewer false negatives i.e., very few people with the condition will be missed]* • Specificity The GC has prioritised sensitivity and specificity as the most important outcomes for their interpretation of the evidence.

		The following thresholds will be used for imprecision for DTA measures and for deciding on the usefulness of the tests in detecting adrenal insufficiency: Sensitivity • Upper 0.9 • Lower 0.6 Specificity • Upper 0.7 • Lower 0.5 Likelihood ratios or other measures such as C statistic or area under ROC curve will only be reported if they are the only measures available, sensitivity and specificity are not reported and cannot be calculated from raw data. Should this be the case, cut-offs for summarising the performance of diagnostic tests or prediction models will be agreed with the guideline committee before the analysis of the evidence is conducted and the protocol will be updated accordingly.
13.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. 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 These may include: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Non-randomised study, including cohort studies: Cochrane ROBINS-I • Cross sectional study: JBI checklist for cross sectional study • Check list for diagnostic test accuracy studies: QUADAS-2	
15.	Strategy for data synthesis	Diagnostic meta-analysis using Cochrane Review Manager (RevMan5) will be conducted where appropriate. 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. Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. 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/	
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: None identified	
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			
21.	Anticipated completion date			
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	Sharon Swain [Guideline lead] Saoussen Ftouh [Senior systematic reviewer] [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		
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	

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A.2 Health economic review protocol

Table 7: 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).[5] **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.[5]

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 8: Database parameters, filters and limits applied.

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 September 2023	Systematic review studies Observational studies Diagnostic studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 26 September 2023	Systematic review studies Observational studies Diagnostic 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	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.	Hydrocortisone/
36.	((cortisol or cortisone) adj3 (assay* or test* or level* or measure* or serum or blood or plasma or saliva* or random or 8am or "8 am" or "8 a.m" or 9am or "9 am" or "9 a.m" or "8-9 am" or "8-9 a.m" or morning or awaken*)).ti,ab,kf.
37.	Electrolytes/
38.	electrolyte*.ti,ab,kf.
39.	Blood Glucose/
40.	((blood or serum or plasma) adj3 (sugar or glucose)).ti,ab,kf.
41.	(insulin adj4 test*).ti,ab,kf.
42.	(synacthen or tetracosactide).ti,ab,kf.
43.	exp Adrenocorticotropic Hormone/

44.	((adrenocorticotrop* or "adreno corticotrop*" or corticotrop* or ACTH or cosyntrop*) adj3 (assay* or test* or level* or measure* or stimulation)).ti,ab,kf.
45.	Dehydroepiandrosterone Sulfate/
46.	((DHEA* or "dehydroepiandrosterone sulfate" or "dehydroepiandrosterone sulphate" or "prasterone sulfate" or "prasterone sulphate") adj3 (assay* or test* or level* or measure*)).ti,ab,kf.
47.	or/35-46
48.	34 and 47
49.	exp "sensitivity and specificity"/
50.	(sensitivity or specificity).ti,ab.
51.	((pre test or pretest or post test) adj probability).ti,ab.
52.	(predictive value* or PPV or NPV).ti,ab.
53.	likelihood ratio*.ti,ab.
54.	likelihood function/
55.	((area under adj4 curve) or AUC).ti,ab.
56.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
57.	gold standard.ab.
58.	exp Diagnostic errors/
59.	(false positiv* or false negativ*).ti,ab.
60.	Diagnosis, Differential/
61.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
62.	or/49-61
63.	Epidemiologic studies/
64.	Observational study/
65.	exp Cohort studies/
66.	(cohort adj (study or studies or analys* or data)).ti,ab.
67.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
68.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
69.	Controlled Before-After Studies/
70.	Historically Controlled Study/
71.	Interrupted Time Series Analysis/
72.	(before adj2 after adj2 (study or studies or data)).ti,ab.
73.	exp case control study/
74.	case control*.ti,ab.
75.	Cross-sectional studies/
76.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
77.	or/63-76
78.	Meta-Analysis/
79.	Meta-Analysis as Topic/
80.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
81.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
82.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
83.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
84.	(search* adj4 literature).ab.

85.	(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.
86.	cochrane.jw.
87.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
88.	or/78-87
89.	48 and (62 or 77 or 88)

1 **Embase (Ovid) search terms**

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

32.	14 not 31
33.	limit 32 to English language
34.	hydrocortisone/
35.	((cortisol or cortisone) adj3 (assay* or test* or level* or measure* or serum or blood or plasma or saliva* or random or 8am or "8 am" or "8 a.m" or 9am or "9 am" or "9 a.m" or "8-9 am" or "8-9 a.m" or morning or awaken*)).ti,ab,kf.
36.	electrolyte/
37.	electrolyte*.ti,ab,kf.
38.	glucose blood level/
39.	((blood or serum or plasma) adj3 (sugar or glucose)).ti,ab,kf.
40.	(insulin adj4 test*).ti,ab,kf.
41.	tetracosactide/
42.	(synacthen or tetracosactide).ti,ab,kf.
43.	corticotropin/
44.	((adrenocorticotrop* or "adreno corticotrop*" or corticotrop* or ACTH or cosyntrop*) adj3 (assay* or test* or level* or measure* or stimulation)).ti,ab,kf.
45.	prasterone sulfate/
46.	((DHEA* or "dehydroepiandrosterone sulfate" or "dehydroepiandrosterone sulphate" or "prasterone sulfate" or "prasterone sulphate") adj3 (assay* or test* or level* or measure*)).ti,ab,kf.
47.	or/34-46
48.	33 and 47
49.	exp "sensitivity and specificity"/
50.	(sensitivity or specificity).ti,ab.
51.	((pre test or pretest or post test) adj probability).ti,ab.
52.	(predictive value* or PPV or NPV).ti,ab.
53.	likelihood ratio*.ti,ab.
54.	((area under adj4 curve) or AUC).ti,ab.
55.	(receive* operat* characteristic* or receive* operat* curve* or ROC curve*).ti,ab.
56.	diagnostic accuracy/
57.	diagnostic test accuracy study/
58.	gold standard.ab.
59.	exp diagnostic error/
60.	(false positiv* or false negativ*).ti,ab.
61.	differential diagnosis/
62.	(diagnos* adj3 (performance* or accurac* or utilit* or value* or efficien* or effectiveness or precision or validat* or validity or differential or error*)).ti,ab.
63.	or/49-62
64.	Clinical study/
65.	Observational study/
66.	Family study/
67.	Longitudinal study/
68.	Retrospective study/
69.	Prospective study/
70.	Cohort analysis/
71.	Follow-up/
72.	cohort*.ti,ab.
73.	71 and 72

74.	(cohort adj (study or studies or analys* or data)).ti,ab.
75.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
76.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
77.	(before adj2 after adj2 (study or studies or data)).ti,ab.
78.	exp case control study/
79.	case control*.ti,ab.
80.	cross-sectional study/
81.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
82.	or/64-70,73-81
83.	Systematic Review/
84.	Meta-Analysis/
85.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
86.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
87.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
88.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
89.	(search* adj4 literature).ab.
90.	(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.
91.	cochrane.jw.
92.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
93.	or/83-92
94.	48 and (63 or 82 or 93)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Adrenal Insufficiency] explode all trees
#2.	MeSH descriptor: [Adrenal Hyperplasia, Congenital] this term only
#3.	((addison* NEXT disease) or addisonian*):ti,ab,kw
#4.	((adrenal* or adrenocort* or adreno-cort*) near/3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)):ti,ab,kw
#5.	((cortisol or aldosterone or adrenocorticotrop* or adreno-corticotrop* or ACTH or (corticotropi* NEXT releas*) or (corticotrophi* NEXT releas*) or corticoliberin or CRH) near/3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)):ti,ab,kw
#6.	(hypoadrenal* or hypo-adrenal* or hypoadrenocorticism or "hypo adrenocorticism" or adrenoleukodystrophy or "adreno leukodystrophy" or adrenomyeloneuropathy or "adreno myeloneuropathy" or hypoaldosteronism or "hypo aldosteronism"):ti,ab,kw
#7.	((adrenogenital or "adreno genital") near/1 (syndrome or disorder*)):ti,ab,kw
#8.	((haemorrhag* or hemorrhag* or bleed*) near/3 adrenal*):ti,ab,kw
#9.	((Bronze NEXT Schilder*) or "Melanodermic Leukodystrophy" or (Schilder NEXT Addison*) or (Siemerling NEXT Creutzfeldt*)):ti,ab,kw
#10.	((Allgrove or 3A or TripleA or AAA) near/1 syndrome):ti,ab,kw
#11.	(CAH or "X-ALD"):ti,ab
#12.	((Waterhouse NEXT Friderichsen*) or "antiphospholipid syndrome"):ti,ab,kw
#13.	"Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy":ti,ab,kw

#14.	(#1-#13)
#15.	MeSH descriptor: [Hydrocortisone] this term only
#16.	((cortisol or cortisone) near/3 (assay* or test* or level* or measure* or serum or blood or plasma or saliva* or random or 8am or "8 am" or "8 a.m" or 9am or "9 am" or "9 a.m" or "8-9 am" or "8-9 a.m" or morning or awaken*)):ti,ab,kw
#17.	MeSH descriptor: [Electrolytes] this term only
#18.	electrolyte*:ti,ab,kw
#19.	MeSH descriptor: [Blood Glucose] this term only
#20.	((blood or serum or plasma) near/3 (sugar or glucose)):ti,ab,kw
#21.	(insulin near/4 test*):ti,ab,kw
#22.	(synacthen or tetracosactide):ti,ab,kw
#23.	MeSH descriptor: [Adrenocorticotropic Hormone] explode all trees
#24.	((adrenocorticotrop* or adreno-corticotrop* or corticotrop* or ACTH or cosyntrop*) near/3 (assay* or test* or level* or measure* or stimulation)):ti,ab,kw
#25.	MeSH descriptor: [Dehydroepiandrosterone Sulfate] this term only
#26.	((DHEA* or "dehydroepiandrosterone sulfate" or "dehydroepiandrosterone sulphate" or "prasterone sulfate" or "prasterone sulphate") near/3 (assay* or test* or level* or measure*)):ti,ab,kw
#27.	(or #15-#26)
#28.	#14 and #27
#29.	conference:pt or (clinicaltrials or trialsearch):so
#30.	#28 not #29

1 **Epistemonikos search terms**

1.	(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:("cortisol test" OR "serum cortisol" OR "salivary cortisol" OR "salivary cortisone" OR "random cortisol" OR "8am cortisol" OR "8 am cortisol" OR "8 a.m cortisol" OR "9am cortisol" OR "9 am cortisol" OR "9 a.m cortisol" OR "8-9 am cortisol" OR "8-9 a.m cortisol" OR "morning cortisol" OR "awakening cortisol" OR electrolyte* OR "blood sugar" OR "blood glucose" OR "insulin tolerance test" OR "insulin-induced hypoglycemia test" OR synacthen OR tetracosactide OR "adrenocorticotropic hormone test" OR "adrenocorticotropic hormone stimulation" OR "ACTH test" OR "ACTH stimulation" OR "cosyntropin test" OR "cosyntropin stimulation" OR DHEA* OR "dehydroepiandrosterone sulfate" OR "dehydroepiandrosterone sulphate" OR "prasterone sulfate" OR "prasterone sulphate") OR abstract:("cortisol test" OR "serum cortisol" OR "salivary cortisol" OR "salivary cortisone" OR "random cortisol" OR "8am cortisol" OR "8 am cortisol" OR "8 a.m cortisol" OR "9am cortisol" OR "9 am cortisol" OR "9 a.m cortisol" OR "8-9 am cortisol" OR "8-9 a.m cortisol" OR "morning cortisol" OR "awakening cortisol" OR electrolyte* OR "blood sugar" OR "blood glucose" OR "insulin tolerance test" OR "insulin-induced hypoglycemia test" OR synacthen OR tetracosactide OR "adrenocorticotropic hormone test" OR "adrenocorticotropic

	hormone stimulation" OR "ACTH test" OR "ACTH stimulation" OR "cosyntropin test" OR "cosyntropin stimulation" OR DHEA* OR "dehydroepiandrosterone sulfate" OR "dehydroepiandrosterone sulphate" OR "prasterone sulfate" OR "prasterone sulphate"))

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 2: 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"

1 **Embase (Ovid) search terms**

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

22.	randomized controlled trial/ or random*.ti,ab.
23.	21 not 22
24.	animal/ not human/
25.	nonhuman/
26.	exp Animal Experiment/
27.	exp Experimental Animal/
28.	animal model/
29.	exp Rodent/
30.	(rat or rats or mouse or mice or rodent*).ti.
31.	or/23-30
32.	14 not 31
33.	limit 32 to English language
34.	health economics/
35.	exp economic evaluation/
36.	exp health care cost/
37.	exp fee/
38.	budget/
39.	funding/
40.	budget*.ti,ab.
41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/34-46
48.	33 and 47
49.	limit 48 to yr="2014 -Current"

1 **NHS EED and HTA (CRD) search terms**

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

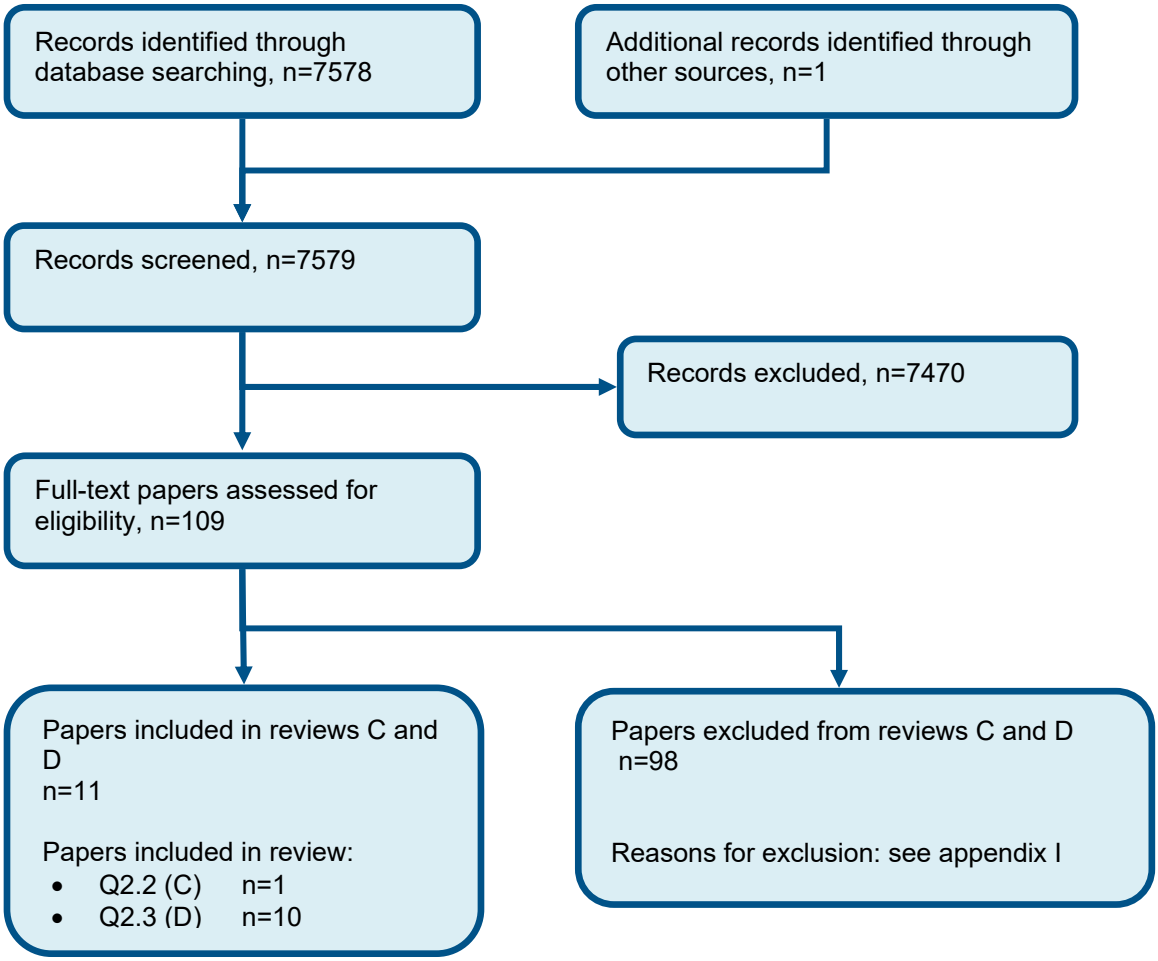
#12.	(adrenogenital or adreno genital) AND (syndrome)
#13.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12

INAHTA search terms

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

Appendix C Diagnostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of initial investigations by non-specialists



Appendix D Diagnostic evidence

Reference	Kalaria 2020[3]
Study type	Cross sectional diagnostic study
Study methodology	Data source: Outpatient assessments Recruitment: Between March 2016 and January 2019, consecutive patients attending the endocrine dynamic function clinic for a SST to evaluate HPA recovery were invited to participate
Number of patients	n = 47 (56 SSTs - seven patients underwent two SSTs each and one patient three SSTs)
Patient characteristics	Age, median (IQR): 60 (48.3–69.5) years Gender (male to female ratio): 16:31 Ethnicity: Not reported Setting: Single centre, department of endocrinology Country: UK Inclusion criteria: consecutive patients attending the endocrine dynamic function clinic for a SST to evaluate HPA recovery were invited to participate. All patients had previously been on prolonged supraphysiological therapeutic doses of oral glucocorticoids. Exclusion criteria: Those with periodontal disease were excluded. Reason for referral: To assess hypothalamic–pituitary–adrenal axis recovery in patients previously treated with prolonged supraphysiological therapeutic doses of oral glucocorticoids.
Target condition(s)	Adrenal insufficiency
Index test(s) and reference standard	**Index tests:** Basal serum cortisol, basal salivary cortisol and basal salivary cortisone SSTs were performed between 09:00 and 10:30 after oral and inhaled glucocorticoid withdrawal for at least 24 h. Baseline salivary sample was collected immediately before the baseline serum sample and then 0.25 mg of tetracosactide acetate (synacthen) was injected either intravenously or intramuscularly and a further blood sample collected 30 min later. Saliva was collected in

<table>
<tr><td>Reference</td><td colspan="4">Kalaria 2020[3]</td></tr>
<tr><td></td><td colspan="4">SalivetteVR tubes (plain cotton swab; Sarstedt, Germany) according to manufacturer’s instructions. Blood was collected in S-MonovetteVR 4.7 mL Z-gel tubes (Sarstedt, Aktiengesellschaft & Co, Germany).

<u>Threshold cut-off value</u>: HPA suppression: Baseline serum cortisol: 170(nmol/L), baseline salivary cortisol: 1.92(nmol/L), baseline salivary cortisone: 9.42 (nmol/L).
HPA recovery: Baseline serum cortisol: 365(nmol/L), baseline salivary cortisol: 25.4(nmol/L), baseline salivary cortisone: 37.2 (nmol/L)

<u>Assay:</u> Salivary samples were centrifuged at 1500 g for 5 min, the cotton was discarded and the extracted saliva frozen at 80C until analysed for cortisol and cortisone using liquid chromatography with tandem massspectrometry (LC-MS/MS) on a Shimadzu Prominence HPLC system coupled to an AB Sciex 3200 mass spectrometer based on previously described method. The LC-MS/ MS salivary cortisol and salivary cortisone assays both had a quantitation limit of 0.83 nmol/L. The intra-assay CVs were 4.9% at 9.5 nmol/L for both salivary cortisol and salivary cortisone and the inter-assay CVs were 10.8% at 9.7 nmol/L and 6.0% at 10 nmol/L, respectively.

<u>Reference standard</u> Short synacthen test
SSTs were performed between 09:00 and 10:30 after oral and inhaled glucocorticoid withdrawal for at least 24 h. Baseline salivary sample was collected immediately before the baseline serum sample and then 0.25 mg of tetracosactide acetate (synacthen) was injected either intravenously or intramuscularly and a further blood sample collected 30 min later.
Blood was collected in S-MonovetteVR 4.7 mL Z-gel tubes (Sarstedt, Aktiengesellschaft & Co, Germany).

<u>Threshold</u>: A SST was labelled as ‘pass’ (adequate response) if the 30-min serum cortisol was >/=450 nmol/L.

Assay: Blood was separated, and serum cortisol measured by a chemiluminescence microparticle immunoassay on an Abbott Architect i2000 (Abbott Laboratories, USA). The Abbott Architect cortisol assay has a quantitation limit of 22 nmol/L with an intra-assay and inter-assay coefficients of variation (CV) of 2.5% at 118 nmol/L and 3.5% at 110 nmol/L, respectively.

Time between measurement of index test and reference standard: reference standard approx 30 mins later</td></tr>
<tr><td>2×2 table (calculated from reported sensitivity, specificity and true positive and true negative rates)</td><td colspan="4">HPA suppression - baseline serum cortisol: 170(nmol/L)
<table><tr><td></td><td>Reference standard +</td><td>Reference standard −</td><td>Total</td></tr><tr><td>Index test +</td><td>15</td><td>17</td><td>32</td></tr><tr><td>Index test −</td><td>0</td><td>24</td><td>24</td></tr><tr><td>Total</td><td>15</td><td>41</td><td>56</td></tr></table></td></tr>
</table>

Reference	**Kalaria 2020**[3]			
(calculated from reported sensitivity, specificity and true positive and true negative rates)	HPA suppression - baseline salivary cortisol: 1.92(nmol/L)			
		Reference standard +	Reference standard −	Total
	Index test +	15	20	35
	Index test −	0	21	21
	Total	15	41	56
(calculated from reported sensitivity, specificity and true positive and true negative rates)	HPA suppression - baseline salivary cortisone: 9.42(nmol/L)			
		Reference standard +	Reference standard −	Total
	Index test +	15	19	34
	Index test −	0	22	22
	Total	15	41	56
(calculated from reported sensitivity, specificity and true positive and true negative rates)	HPA recovery - baseline serum cortisol: 365(nmol/L)			
		Reference standard +	Reference standard −	Total
	Index test +	4	0	4
	Index test −	11	41	52
	Total	15	41	56
(calculated from reported sensitivity, specificity and true positive and true negative rates)	HPA recovery - baseline salivary cortisol: 25.4(nmol/L)			
		Reference standard +	Reference standard −	Total
	Index test +	0	0	0
	Index test −	15	41	56
	Total	15	41	56
(calculated from reported sensitivity,	HPA recovery - baseline salivary cortisone: 37.2(nmol/L)			
		Reference standard +	Reference standard −	Total
	Index test +	4	0	4

Reference	**Kalaria 2020**[3]				
specificity and true positive and true negative rates)	Index test − Total	11 15	41 41	52 56	
Statistical measures	**<u>HPA suppression</u>** <u>Index text – HPA suppression - baseline serum cortisol: 170(nmol/L)</u> Sensitivity 100 Specificity 58.5 PPV 0.47h NPV 1 PLR 2.41 NLR 0 AUC 0.772 <u>Index text – HPA suppression - baseline salivary cortisol: 1.92(nmol/L)</u> Sensitivity 100 Specificity 51.2 PPV 0.43 NPV 1 PLR 2.0408 NLR 0 AUC 0.770 <u>Index text – HPA suppression - baseline salivary cortisone: 9.42(nmol/L)</u> Sensitivity 100 Specificity 53.7 PPV 0.44 NPV 1 PLR 2.1598 NLR 0 AUC 0.785 **HPA recovery**				

Reference	**Kalaria 2020**[3]
	Index text – HPA recovery - baseline serum cortisol: 365(nmol/L) Sensitivity 26.7 Specificity 100 PPV 1 NPV 0.79 PLR 0 NLR 0.73 AUC Index text – HPA recovery - baseline salivary cortisol: 25.4(nmol/L) Sensitivity 0 Specificity 100 PPV 0 NPV 0.73 PLR 0 NLR 1 AU Index text – HPA recovery - baseline salivary cortisone: 37.2(nmol/L) Sensitivity 26.7 Specificity 100 PPV 1 NPV 0.789 PLR 0 NLR 0.73 AUC
Source of funding	The author(s) received no financial support for the research, authorship, and/ or publication of this article.
Limitations	Risk of bias: serious (due to patient flow) Indirectness: none
Comments	Unclear if it was 47 patients or 56 SSTs included in analysis. The cut-offs derived in this study may not be applicable to the evaluation of HPA function in cohorts without HPA suppression or in females on oral oestrogen or premenopausal.

1

Appendix E Forest plots

E.1 Coupled sensitivity and specificity forest plots.

Figure 2: Sensitivity and specificity of serum cortisol for diagnosing AI in people being assessed for HPA recovery following supraphysiological therapeutic doses of oral glucocorticoids

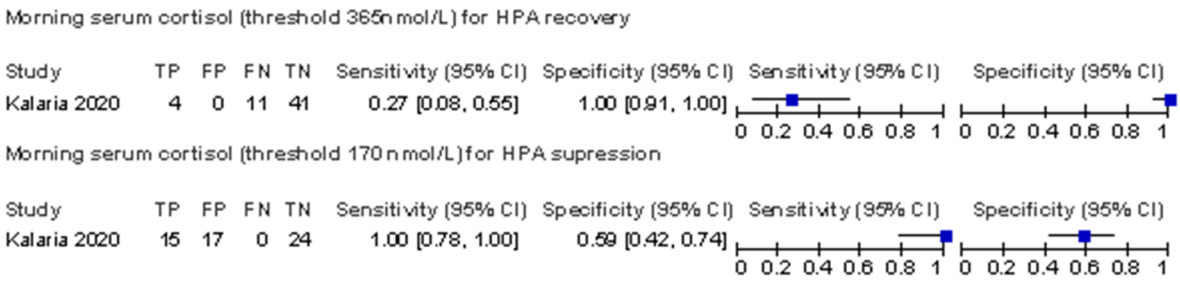


Figure 3: Sensitivity and specificity of salivary cortisol for diagnosing AI in people being assessed for HPA recovery following supraphysiological therapeutic doses of oral glucocorticoids

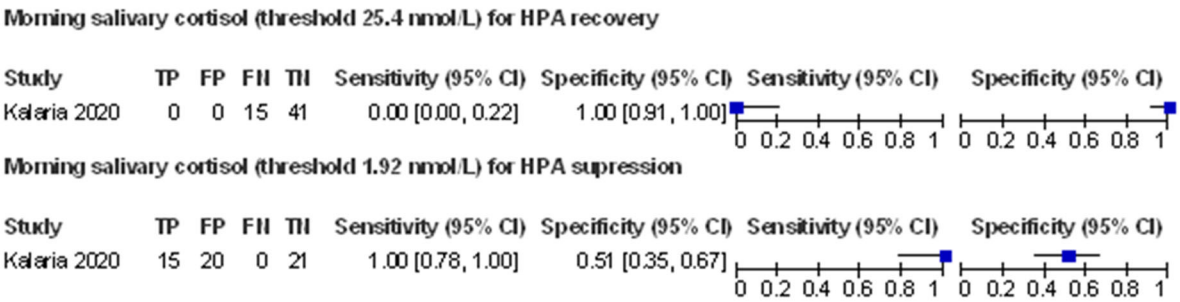
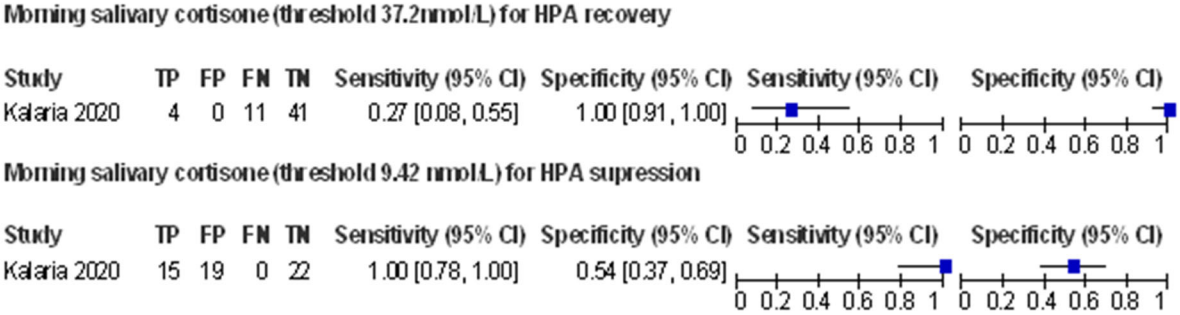
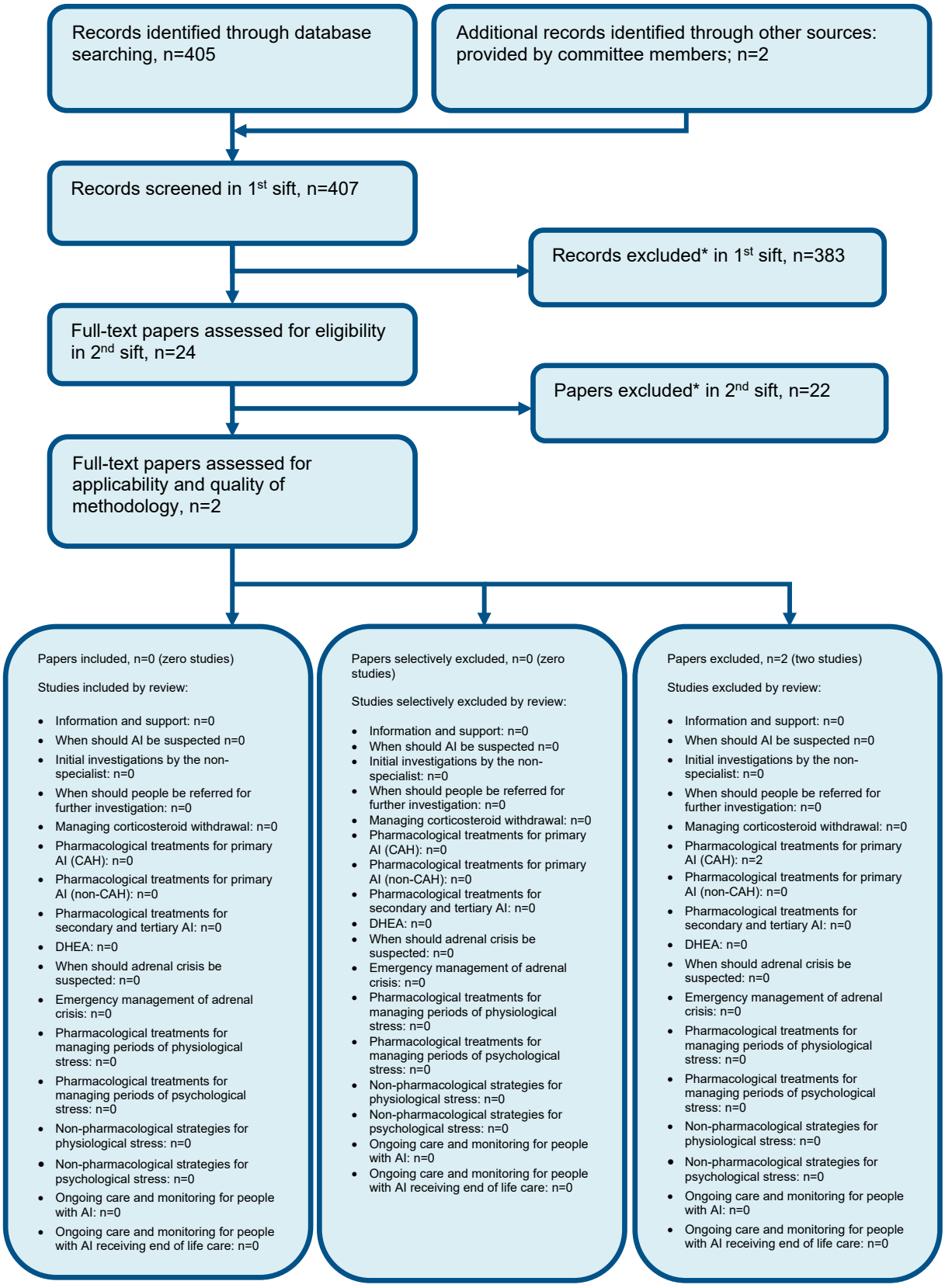


Figure 4: Sensitivity and specificity of salivary cortisone for diagnosing AI in people being assessed for HPA recovery following supraphysiological therapeutic doses of oral glucocorticoids



Appendix F Economic evidence study selection



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

Appendix G Economic evidence tables

None.

Appendix H Health economic model

No original economic modelling was undertaken for this review question.

1 Appendix I Excluded studies

2 I.1 Clinical studies

3 **Table 9: Studies excluded from the clinical review**

Study	Exclusion reason
Abdu, T A, Elhadd, T A, Neary, R et al. (1999) Comparison of the low dose short synacthen test (1 microg), the conventional dose short synacthen test (250 microg), and the insulin tolerance test for assessment of the hypothalamo-pituitary-adrenal axis in patients with pituitary disease. The Journal of clinical endocrinology and metabolism 84(3): 838-43	- Study does not contain any relevant index tests
Abdu, T.A.M. and Clayton, R.N. (2000) The low-dose synacthen test for the assessment of secondary adrenal insufficiency. Current Opinion in Endocrinology and Diabetes 7(3): 116-121	- Review article but not a systematic review
Abeed, N.N.A.N., Mohamad, W.M.I.W., Yahya, N. et al. (2022) ACCURACY OF RANDOM SERUM CORTISOL IN DIAGNOSING SECONDARY ADRENAL INSUFFICIENCY. Journal of the ASEAN Federation of Endocrine Societies 37(supplement2): 12	- Conference abstract
Abraham, Smita Baid, Abel, Brent S, Sinaii, Ninet et al. (2015) Primary vs secondary adrenal insufficiency: ACTH-stimulated aldosterone diagnostic cut-off values by tandem mass spectrometry. Clinical endocrinology 83(3): 308-14	- Study does not contain a relevant reference standard Plasma ACTH stimulation test - Population not relevant to this review protocol People with known AI
Agha, A., Tomlinson, J.W., Clark, P.M. et al. (2006) The long-term predictive accuracy of the short Synacthen (corticotropin) stimulation test for assessment of the hypothalamic-pituitary-adrenal axis. Journal of Clinical Endocrinology and Metabolism 91(1): 43-47	- Retrospective - Study does not contain diagnostic accuracy data
Albert, L., Profitos, J., Sanchez-Delgado, J. et al. (2019) Salivary cortisol determination in ACTH stimulation test to diagnose adrenal insufficiency in patients with liver cirrhosis. International Journal of Endocrinology 2019: 7251010	- Population not relevant to this review protocol Known AI and healthy controls
Ambrogio, Alberto G, Danesi, Leila, Baldini, Marina et al. (2018) Low-dose Synachten test with measurement of salivary cortisol in adult patients with beta-thalassemia major. Endocrine 60(2): 348-354	- Study does not report sensitvity or specificity Youden's index only
Ambrosi, B, Barbetta, L, Re, T et al. (1998) The one microgram adrenocorticotropin test in the assessment of hypothalamic-pituitary-adrenal function. European journal of endocrinology 139(6): 575-9	- Study does not contain any relevant index tests
Amin, H., Wynne-Edwards, K., Amin, P. et al. (2017) Is the Correlation between Salivary Cortisol and Serum Cortisol Reliable Enough to Enable Use of Salivary Cortisol Levels in	- Study does not contain diagnostic accuracy data correlation only

Study	Exclusion reason
Preterm Infants?. American Journal of Perinatology 34(13): 1302-1305	
Arregger, Alejandro L, Cardoso, Estela M L, Tumilasci, Omar et al. (2008) Diagnostic value of salivary cortisol in end stage renal disease. Steroids 73(1): 77-82	- Population not relevant to this review protocol critically ill - end stage renal disease
Arregger, Alejandro L, Cardoso, Estela M L, Zucchini, Alfredo et al. (2014) Adrenocortical function in hypotensive patients with end stage renal disease. Steroids 84: 57-63	- Population not relevant to this review protocol End stage renal disease
Atluri, Sridevi, Sarathi, Vijaya, Goel, Amit et al. (2022) Long-acting Porcine Sequence ACTH (Acton Prolongatum) Stimulation Test is a Reliable Alternative Test as Compared to the Gold Standard Insulin Tolerance Test for the Diagnosis of Adrenal Insufficiency. Indian journal of endocrinology and metabolism 26(1): 38-43	- Population not relevant to this review protocol Includes some with known AI - Study design not relevant to this review protocol Recruitment method not clear
Bancos, Irina, Erickson, Dana, Bryant, Sandra et al. (2015) PERFORMANCE OF FREE VERSUS TOTAL CORTISOL FOLLOWING COSYNTROPIN STIMULATION TESTING IN AN OUTPATIENT SETTING. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 21(12): 1353-63	- Study does not report sensitvity or specificity AUC only
Bangar, V. and Clayton, R.N. (1998) How reliable is the short synacthen test for the investigation of the hypothalamic-pituitary-adrenal axis?. European Journal of Endocrinology 139(6): 580-583	- Retrospective
Butt, Muhammad Imran, Alzuhayri, Nouf, Amer, Lama et al. (2020) Comparing the utility of 30- and 60-minute cortisol levels after the standard short synacthen test to determine adrenal insufficiency: A retrospective cross-sectional study. Medicine 99(43): e22621	- Retrospective
Ceccato, Filippo, Selmin, Elisa, Antonelli, Giorgia et al. (2021) Low-dose short synacthen test with salivary cortisol in patients with suspected central adrenal insufficiency. Endocrine connections 10(9): 1189-1199	- Retrospective
Cemeroglu, Ayse Pinar, Kleis, Lora, Postellon, Daniel C et al. (2011) Comparison of low-dose and high-dose cosyntropin stimulation testing in children. Pediatrics international : official journal of the Japan Pediatric Society 53(2): 175-80	- Study does not contain diagnostic accuracy data
Cetinkaya, Semra; Ozon, Alev; Yordam, Nursen (2007) Diagnostic value of salivary cortisol in children with abnormal adrenal cortex functions. Hormone research 67(6): 301-6	- Study does not contain any relevant index tests
Cheung, K.K.-T., So, W.-Y., Ma, R.C.-W. et al. (2015) Spot and morning cortisol in comparison to low dose short Synacthen test. Journal of the ASEAN Federation of Endocrine Societies 30(2): 147-154	- Data not reported in an extractable format or a format that can be analysed Text discussion confuses the interpretation of sensitivity and specificity for ruling in or out the condition; and threshold values for serum cortisol appear incorrect with low values linked

Study	Exclusion reason
	to maximum sensitivity and high values to maximum specificity.
Chitale, Aditi, Musonda, Patrick, McGregor, Alan M et al. (2013) Determining the utility of the 60 min cortisol measurement in the short synacthen test. Clinical endocrinology 79(1): 14-9	- Retrospective
Chng, E., Lam, S., Hawkins, R. et al. (2014) The use of short synacthen test in patients on exogenous steroids use in diagnosing adrenal insufficiency. Endocrine Reviews 35(suppl3)	- Conference abstract
Cho, Hwa Y, Kim, Jung H, Kim, Sang W et al. (2014) Different cut-off values of the insulin tolerance test, the high-dose short Synacthen test (250 mug) and the low-dose short Synacthen test (1 mug) in assessing central adrenal insufficiency. Clinical endocrinology 81(1): 77-84	- Study does not contain any relevant index tests
Colling, Caitlin, Nachtigall, Lisa, Biller, Beverly M K et al. (2022) The biochemical diagnosis of adrenal insufficiency with modern cortisol assays: Reappraisal in the setting of opioid exposure and hospitalization. Clinical endocrinology 96(1): 21-29	- Retrospective
Contreras, L.N., Arregger, A.L., Tumilasci, O. et al. (2006) Salivary steroids in response to ACTH: A less invasive approach to assess adrenal function in hypotensive patients with chronic renal failure. Endocrinologist 16(1): 30-35	- Study does not contain diagnostic accuracy data
Cornes, Michael P, Ashby, Helen L, Khalid, Yasmeen et al. (2015) Salivary cortisol and cortisone responses to tetracosactrin (synacthen). Annals of clinical biochemistry 52(pt5): 606-10	- Study does not contain diagnostic accuracy data correlation only
de Vries, Friso, Lobatto, Daniel J, Bakker, Leontine E H et al. (2020) Early postoperative HPA-axis testing after pituitary tumor surgery: reliability and safety of basal cortisol and CRH test. Endocrine 67(1): 161-171	- Retrospective
Dichtel, L.E., Schorr, M., De Assis, C.L. et al. (2017) Plasma free cortisol vs. Total cortisol in healthy individuals and in states of high and low cortisol binding globulin, including oral contraceptive use, cirrhosis and critical illness: implications for diagnosing adrenal insufficiency. Endocrine Reviews 38(3supplement1)	- Conference abstract
Dineen, Rosemary, Mohamed, Ahmed, Gunness, Anjuli et al. (2020) Outcomes of the short Synacthen test: what is the role of the 60 min sample in clinical practice?. Postgraduate medical journal 96(1132): 67-72	- Retrospective
Dluhy, R.G.; Himathongkam, T.; Greenfield, M. (1974) Rapid ACTH test with plasma aldosterone levels. Improved diagnostic discrimination. Annals of Internal Medicine 80(6): 693-696	- Study does not contain a relevant reference standard plasma ACTH test

Study	Exclusion reason
Dorin, Richard I; Qualls, Clifford R; Crapo, Lawrence M (2003) Diagnosis of adrenal insufficiency. Annals of internal medicine 139(3): 194-204	- Review article but not a systematic review
Fede, Giuseppe, Spadaro, Luisa, Privitera, Graziella et al. (2015) Hypothalamus-pituitary dysfunction is common in patients with stable cirrhosis and abnormal low dose synacthen test. Digestive and liver disease : official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver 47(12): 1047-51	- Population not relevant to this review protocol selected those with AI
Ferrante, Emanuele, Morelli, Valentina, Giavoli, Claudia et al. (2012) Is the 250 mug ACTH test a useful tool for the diagnosis of central hypoadrenalism in adult patients with pituitary disorders?. Hormones (Athens, Greece) 11(4): 428-35	- Study design not relevant to this review protocol Cohort study with 6 weeks between index and reference standard test
Fragoso Perozo, A F D, Fontes, R, Lopes, F P et al. (2023) Morning serum cortisol role in the adrenal insufficiency diagnosis with modern cortisol assays. Journal of endocrinological investigation	- Retrospective
Gasco, Valentina, Bima, Chiara, Geranzani, Alice et al. (2021) Morning Serum Cortisol Level Predicts Central Adrenal Insufficiency Diagnosed by Insulin Tolerance Test. Neuroendocrinology 111(12): 1238-1248	- Retrospective
Giordano, R, Picu, A, Bonelli, L et al. (2008) Hypothalamus-pituitary-adrenal axis evaluation in patients with hypothalamo-pituitary disorders: comparison of different provocative tests. Clinical endocrinology 68(6): 935-41	- Study does not contain any relevant index tests
Gleeson, H.K., Walker, B.R., Seckl, J.R. et al. (2003) Ten years on: Safety of short synacthen tests in assessing adrenocorticotropin deficiency in clinical practice. Journal of Clinical Endocrinology and Metabolism 88(5): 2106-2111	- Retrospective
Goggans, F C, Wilson, W R Jr, Gold, M S et al. (1984) Comparison of the dexamethasone suppression test and the cortisol suppression index. The American journal of psychiatry 141(5): 698-700	- Study does not contain any relevant index tests - Population not relevant to this review protocol
Gonc, E Nazli; Kandemir, Nurgun; Kinik, Sibel T (2003) Significance of low-dose and standard-dose ACTH tests compared to overnight metyrapone test in the diagnosis of adrenal insufficiency in childhood. Hormone research 60(4): 191-7	- Study does not contain a relevant reference standard metyrapone test
Gonc, E Nazli, Ozon, Z Alev, Alikasifoglu, Ayfer et al. (2011) Is basal serum 17-OH progesterone a reliable parameter to predict nonclassical congenital adrenal hyperplasia in premature adrenarche?. The Turkish journal of pediatrics 53(3): 274-80	- Retrospective

Study	Exclusion reason
Goto, Masahiro; Shibata, Nao; Hasegawa, Yukihiro (2016) Efficacy of single serum cortisol reading obtained between 9 AM and 10 AM as an index of adrenal function in children treated with glucocorticoids or synthetic adrenocorticotropic hormone. Clinical pediatric endocrinology : case reports and clinical investigations : official journal of the Japanese Society for Pediatric Endocrinology 25(3): 83-9	- Retrospective
Grassi, G, Morelli, V, Ceriotti, F et al. (2020) Minding the gap between cortisol levels measured with second-generation assays and current diagnostic thresholds for the diagnosis of adrenal insufficiency: a single-center experience. Hormones (Athens, Greece) 19(3): 425-431	- Study does not contain diagnostic accuracy data Correlation between different assays
Gruvstad, Eva, Hedner, Lars Pavo, Hoglund, Peter et al. (2014) Comparison of methods for evaluation of the suppressive effects of prednisolone on the HPA axis and bone turnover: changes in s-DHEAS are as sensitive as the ACTH test. International journal of clinical pharmacology and therapeutics 52(1): 15-26	- Study design not relevant to this review protocol - Population not relevant to this review protocol
Gundgurthi, Abhay, Garg, M K, Dutta, M K et al. (2013) Intramuscular ACTH stimulation test for assessment of adrenal function. The Journal of the Association of Physicians of India 61(5): 320-4	- Study does not contain diagnostic accuracy data insufficient information to calculate accuracy data
Hassan, Z., Nabi, S., Hussain, W. et al. (2021) Validation of Glucagon Stimulation Test in Establishing GH and ACTH Deficiency in Hypopituitarism. European Journal of Molecular and Clinical Medicine 8(4): 2005-2013	- Study design not relevant to this review protocol diagnostic accuracy for GH deficiency - Study does not contain any relevant index tests glucagon stimulation test
Javorsky, Bradley R, Raff, Hershel, Carroll, Ty B et al. (2021) New Cutoffs for the Biochemical Diagnosis of Adrenal Insufficiency after ACTH Stimulation using Specific Cortisol Assays. Journal of the Endocrine Society 5(4): bvab022	- Retrospective
Jayakumari, C., George, G.S., Nair, A. et al. (2017) ACTH stimulation test with long acting ACTH preparation for the diagnosis of adrenal insufficiency. Indian Journal of Endocrinology and Metabolism 21(8supplement1): 62	- Conference abstract
Kadiyala, R, Kamath, C, Baglioni, P et al. (2010) Can a random serum cortisol reduce the need for short synacthen tests in acute medical admissions?. Annals of clinical biochemistry 47(pt4): 378-80	- Retrospective
Kalaria, R.T., Agarwal, M., Kaur, S. et al. (2020) ANNALS EXPRESS: Hypothalamic-pituitary-adrenal (HPA) axis suppression a The value of salivary cortisol and cortisone in assessing HPA recovery. Annals of clinical biochemistry: 4563220961745	- Duplicate reference

Study	Exclusion reason
Kamrath, Clemens and Boehles, Hansjosef (2010) The low-dose ACTH test does not identify mild insufficiency of the hypothalamnic-pituitary-adrenal axis in children with inadequate stress response. Journal of pediatric endocrinology & metabolism : JPEM 23(11): 1097-104	- Retrospective
Karpman, Matthew S, Neculau, Madalina, Dias, Valerian C et al. (2013) Defining adrenal status with salivary cortisol by gold-standard insulin hypoglycemia. Clinical biochemistry 46(15): 1442-6	- Study does not contain any relevant index tests
Kazlauskaite, Rasa, Evans, Arthur T, Villabona, Carmen V et al. (2008) Corticotropin tests for hypothalamic-pituitary- adrenal insufficiency: a metaanalysis. The Journal of clinical endocrinology and metabolism 93(11): 4245-53	- Systematic review used as source of primary studies
Kline, G A; Buse, J; Krause, R D (2017) Clinical implications for biochemical diagnostic thresholds of adrenal sufficiency using a highly specific cortisol immunoassay. Clinical biochemistry 50(9): 475-480	- Study does not contain any relevant index tests Comparing different assays
Kumar, Rajeev; Carr, Peter; Wassif, Ws (2022) Diagnostic performance of morning serum cortisol as an alternative to short synacthen test for the assessment of adrenal reserve; a retrospective study. Postgraduate medical journal 98(1156): 113-118	- Retrospective
Langelaan, M.L.P., Kisters, J.M.H., Oosterwerff, M.M. et al. (2018) Salivary cortisol in the diagnosis of adrenal insufficiency: Cost efficient and patient friendly. Endocrine Connections 7(4): 560-566	- Retrospective
Laureti, S, Arvat, E, Candeloro, P et al. (2000) Low dose (1 microg) ACTH test in the evaluation of adrenal dysfunction in pre-clinical Addison's disease. Clinical endocrinology 53(1): 107-15	- Study does not contain any relevant index tests - Study design not relevant to this review protocol
Lee, May-Tze, Won, Justin Ging-Shing, Lee, Ting-I et al. (2002) The relationship between morning serum cortisol and the short ACTH test in the evaluation of adrenal insufficiency. Zhonghua yi xue za zhi = Chinese medical journal; Free China ed 65(12): 580-7	- Retrospective
Liu, Meng-Si, Lou, Yuan, Chen, Huan et al. (2022) Performance of DHEAS as a Screening Test for Autonomous Cortisol Secretion in Adrenal Incidentalomas: A Prospective Study. The Journal of clinical endocrinology and metabolism 107(5): e1789-e1796	- Study does not contain any relevant index tests DHEAS - Study does not contain a relevant reference standard Dexamethasone suppression test
Lomenick, Jefferson P and Smith, W Jackson (2007) Low-dose adrenocorticotropic hormone stimulation testing in term infants. Journal of pediatric endocrinology & metabolism : JPEM 20(7): 773-9	- Retrospective

Study	Exclusion reason
Mackenzie, S.D. and Gibb, F.W. (2016) Identification and validation of criteria for the use of random serum cortisol as a screening test for adrenal insufficiency. Endocrine Reviews 37(2supplement1)	- Conference abstract
Mackenzie, Scott D, Gifford, Robert M, Boyle, Luke D et al. (2019) Validated criteria for the interpretation of a single measurement of serum cortisol in the investigation of suspected adrenal insufficiency. Clinical endocrinology 91(5): 608-615	- Retrospective
Maguire, Ann M, Biesheuvel, Cornelis J, Ambler, Geoffrey R et al. (2008) Evaluation of adrenal function using the human corticotrophin-releasing hormone test, low dose Synacthen test and 9am cortisol level in children and adolescents with central adrenal insufficiency. Clinical endocrinology 68(5): 683-91	- Study does not contain a relevant reference standard plasma ACTH test
Manosroi, Worapaka, Atthakomol, Pichitchai, Buranapin, Supawan et al. (2020) 30-Minute Delta Cortisol Post-ACTH Stimulation Test and Proposed Cut-Off Levels for Adrenal Insufficiency Diagnosis. The journal of medical investigation : JMI 67(12): 95-101	- Retrospective - Study does not contain any relevant index tests
Manosroi, Worapaka, Phimphilai, Mattabhorn, Khorana, Jiraporn et al. (2019) Diagnostic performance of basal cortisol level at 0900-1300h in adrenal insufficiency. PloS one 14(11): e0225255	- Retrospective
Mansoor, S, Islam, N, Siddiqui, I et al. (2007) Sixty-minute post-Synacthen serum cortisol level: a reliable and cost-effective screening test for excluding adrenal insufficiency compared to the conventional short Synacthen test. Singapore medical journal 48(6): 519-23	- Study does not contain diagnostic accuracy data
Montes-Villarreal, Juan, Perez-Arredondo, Luis Alberto, Rodriguez-Gutierrez, Rene et al. (2020) SERUM MORNING CORTISOL AS A SCREENING TEST FOR ADRENAL INSUFFICIENCY. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 26(1): 30-35	- Retrospective
Munro, Vicki, Elnenaei, Manal, Doucette, Steve et al. (2018) The effect of time of day testing and utility of 30 and 60minute cortisol values in the 250mcg ACTH stimulation test. Clinical biochemistry 54: 37-41	- Retrospective - Study does not contain any relevant index tests
Nakhleh, Afif, Saiegh, Leonard, Shehadeh, Naim et al. (2022) Screening for non-classic congenital adrenal hyperplasia in women: New insights using different immunoassays. Frontiers in endocrinology 13: 1048663	- Study does not contain any relevant index tests 17-OHP - Study does not contain a relevant reference standard Diagnosis of non-classic congenital adrenal hyperplasia

Study	Exclusion reason
Ng, Sze May; Agwu, Juliana Chizo; Dwan, Kerry (2016) A systematic review and meta-analysis of Synacthen tests for assessing hypothalamic-pituitary-adrenal insufficiency in children. Archives of disease in childhood 101(9): 847-53	- Systematic review used as source of primary studies
O'Grady, Michael J, Hensey, Conor, Fallon, Miriam et al. (2013) Lack of sensitivity of the 1-mug low-dose ACTH stimulation test in a paediatric population with suboptimal cortisol responses to insulin-induced hypoglycaemia. Clinical endocrinology 78(1): 73-8	- Retrospective
Ortiz-Flores, Andres E, Santacruz, Elisa, Jimenez-Mendiguchia, Lucia et al. (2018) Role of sampling times and serum cortisol cut-off concentrations on the routine assessment of adrenal function using the standard cosyntropin test in an academic hospital from Spain: a retrospective chart review. BMJ open 8(5): e019273	- Retrospective
Ospina, Naykky Singh, Al Nofal, Alaa, Bancos, Irina et al. (2016) ACTH Stimulation Tests for the Diagnosis of Adrenal Insufficiency: Systematic Review and Meta-Analysis. The Journal of clinical endocrinology and metabolism 101(2): 427-34	- Study does not contain any relevant index tests ACTH stimulation test as the index test
Panamonta, O., Kirdpon, W., Sungsahachart, D. et al. (2003) Adrenocorticotropin stimulation test in congenital adrenal hyperplasia: Comparison between standard and low dose test. Journal of the Medical Association of Thailand 86(7): 634-640	- Population not relevant to this review protocol
Papierska, Lucyna, Rabijewski, Michal, Migda, Bartosz et al. (2022) Evaluation of plasma ACTH in the metyrapone test is insufficient for the diagnosis of secondary adrenal insufficiency. Frontiers in endocrinology 13: 1004129	- Study does not contain any relevant index tests
Patel, R S, Wallace, A M, Hinnie, J et al. (2001) Preliminary results of a pilot study investigating the potential of salivary cortisol measurements to detect occult adrenal suppression secondary to steroid nose drops. Clinical otolaryngology and allied sciences 26(3): 231-4	- Study does not contain diagnostic accuracy data
Patel, Rajan S, Shaw, Steve R, McIntyre, Halena E et al. (2004) Morning salivary cortisol versus short Synacthen test as a test of adrenal suppression. Annals of clinical biochemistry 41(pt5): 408-10	- Study does not contain diagnostic accuracy data
Perogamvros, Ilias, Owen, Laura J, Keevil, Brian G et al. (2010) Measurement of salivary cortisol with liquid chromatography-tandem mass spectrometry in patients undergoing dynamic endocrine testing. Clinical endocrinology 72(1): 17-21	- Population not relevant to this review protocol critically ill - end stage renal disease
Perton, F T, Mijnhout, G S, Kollen, B J et al. (2017) Validation of the 1 mug short synacthen test: an assessment of morning cortisol cut-off	- Retrospective

Study	Exclusion reason
values and other predictors. The Netherlands journal of medicine 75(1): 14-20	
Ramadoss, Vijay, Lazarus, Katharine, Prevost, Andrew Toby et al. (2021) Improving the Interpretation of Afternoon Cortisol Levels and SSTs to Prevent Misdiagnosis of Adrenal Insufficiency. Journal of the Endocrine Society 5(11): bvab147	- Retrospective
Rose, S R, Lustig, R H, Burstein, S et al. (1999) Diagnosis of ACTH deficiency. Comparison of overnight metyrapone test to either low-dose or high-dose ACTH test. Hormone research 52(2): 73-9	- Study does not contain a relevant reference standard Metyrapone test
Sbardella, E., Isidori, A.M., Woods, C.P. et al. (2017) Baseline morning cortisol level as a predictor of pituitary-adrenal reserve: a comparison across three assays. Clinical Endocrinology 86(2): 177-184	- Retrospective
Schindhelm, R K; van de Leur, J J C M; Rondeel, J M M (2010) Salivary cortisol as an alternative for serum cortisol in the low-dose adrenocorticotropic hormone stimulation test?. Journal of endocrinological investigation 33(2): 92-5	- Study does not contain any relevant index tests
Smolyar, D, Tirado-Bernardini, R, Landman, R et al. (2003) Comparison of 1-micro g and 250-micro g corticotropin stimulation tests for the evaluation of adrenal function in patients with acquired immunodeficiency syndrome. Metabolism: clinical and experimental 52(5): 647-51	- Study does not contain any relevant index tests
Steiner, H, Bahr, V, Exner, P et al. (1994) Pituitary function tests: comparison of ACTH and 11-deoxy-cortisol responses in the metyrapone test and with the insulin hypoglycemia test. Experimental and clinical endocrinology 102(1): 33-8	- Retrospective - Population not relevant to this review protocol
Struja, Tristan, Briner, Leonie, Meier, Aline et al. (2017) DIAGNOSTIC ACCURACY OF BASAL CORTISOL LEVEL TO PREDICT ADRENAL INSUFFICIENCY IN COSYNTROPIN TESTING: RESULTS FROM AN OBSERVATIONAL COHORT STUDY WITH 804 PATIENTS. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 23(8): 949-961	- Retrospective
Suliman, Abdulwahab M, Smith, Thomas P, Labib, Mourad et al. (2002) The low-dose ACTH test does not provide a useful assessment of the hypothalamic-pituitary-adrenal axis in secondary adrenal insufficiency. Clinical endocrinology 56(4): 533-9	- Study does not contain a relevant reference standard overnight metyrapone test
Thaler, L M and Blevins, L S Jr (1998) The low dose (1-microg) adrenocorticotropin stimulation test in the evaluation of patients with suspected	- Review article but not a systematic review

Study	Exclusion reason
central adrenal insufficiency. The Journal of clinical endocrinology and metabolism 83(8): 2726-9	
Tolkin, Lior; Vidberg, Michal; Munter, Gabriel (2022) Basal serum cortisol levels predict a normal response to the Synacthen stimulation test in hospitalised patients. Internal medicine journal 52(1): 105-109	- Retrospective
Ueland, Grethe A, Methlie, Paal, Oksnes, Marianne et al. (2018) The Short Cosyntropin Test Revisited: New Normal Reference Range Using LC-MS/MS. The Journal of clinical endocrinology and metabolism 103(4): 1696-1703	- Study does not contain any relevant index tests comparing different assays of the same test
Ulhaq, Imran, Ahmad, Tauseef, Khoja, Adeel et al. (2019) Morning cortisol as an alternative to Short Synecthan test for the diagnosis of primary adrenal insufficiency. Pakistan journal of medical sciences 35(5): 1413-1416	- Retrospective
Vaiani, Elisa, Lazzati, Juan Manuel, Ramirez, Pablo et al. (2019) The Low-Dose ACTH Test: Usefulness of Combined Analysis of Serum and Salivary Maximum Cortisol Response in Pediatrics. The Journal of clinical endocrinology and metabolism 104(10): 4323-4330	- Study does not contain any relevant index tests Does not report basal cortisol values.
Vaiani, Elisa, Maceiras, Mercedes, Chaler, Eduardo et al. (2014) Central adrenal insufficiency could not be confirmed by measurement of basal serum DHEAS levels in pubertal children. Hormone research in paediatrics 82(5): 332-7	- Study does not contain any relevant index tests
Weintrob, N, Sprecher, E, Josefsberg, Z et al. (1998) Standard and low-dose short adrenocorticotropin test compared with insulin-induced hypoglycemia for assessment of the hypothalamic-pituitary-adrenal axis in children with idiopathic multiple pituitary hormone deficiencies. The Journal of clinical endocrinology and metabolism 83(1): 88-92	- Study does not contain any relevant index tests
Yalovitsky, Guy, Shaki, David, Hershkovitz, Eli et al. (2023) Comparison of glucagon stimulation test and low dose ACTH test in assessing hypothalamic-pituitary-adrenal (HPA) axis in children. Clinical endocrinology 98(5): 678-681	- Retrospective - Study does not contain any relevant index tests
Younas, Alveena, Ali, Asif, Nawaz, Muhammad Asif et al. (2019) Comparative evaluation of 30 and 60 minutes cortisol levels during short synacthen test for diagnosis of adrenal insufficiency. JPMA. The Journal of the Pakistan Medical Association 69(11): 1628-1631	- Article could not be accessed
Zarkovic, M, Ciric, J, Stojanovic, M et al. (1999) Optimizing the diagnostic criteria for standard (250-microg) and low dose (1-microg) adrenocorticotropin tests in the assessment of adrenal function. The Journal of clinical endocrinology and metabolism 84(9): 3170-3	- Population not relevant to this review protocol Includes those with AI and controls in the accuracy analysis.

Study	Exclusion reason
Zha, Li, Li, Jieli, Krishnan, Subhashree Mallika et al. (2022) New Diagnostic Cutoffs for Adrenal Insufficiency After Cosyntropin Stimulation Using Abbott Architect Cortisol Immunoassay. Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists 28(7): 684-689	- Study does not contain any relevant index tests
Zollner, Ekkehard W, Lombard, Carl, Galal, Ushma et al. (2011) Hypothalamic-pituitary-adrenal axis suppression in asthmatic children on inhaled and nasal corticosteroids: is the early-morning serum adrenocorticotropic hormone (ACTH) a useful screening test?. Pediatric allergy and immunology : official publication of the European Society of Pediatric Allergy and Immunology 22(6): 614-20	- Study does not contain a relevant reference standard Post-metyrapone test
Zueger, Thomas, Jordi, Marlen, Laimer, Markus et al. (2014) Utility of 30 and 60 minute cortisol samples after high-dose synthetic ACTH-1-24 injection in the diagnosis of adrenal insufficiency. Swiss medical weekly 144: w13987	- Study does not contain diagnostic accuracy data

I.2 Health Economic studies

None.