National Institute for Health and Care Excellence

Final

Adrenal insufficiency: identification and management

Evidence review H: When to suspect adrenal crisis

NICE guideline NG243

Evidence reviews underpinning recommendations 1.6.1 to 1.6.2 and recommendation for research 3 in the NICE guideline

August 2024

Final

This evidence review was developed by NICE

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1.1. Review question

When should adrenal crisis be suspected?

1.1.1. Introduction

Adrenal crisis is a potentially life-threatening emergency caused by a lack of cortisol. Patients who have any form of adrenal insufficiency are at risk of adrenal crisis because they are unable to mount the usual response which is a rise in cortisol to physiological stress. Stressors may be related to intercurrent illness especially sepsis, surgery, injury, or significant emotional stress. Patients with, or at risk of adrenal crisis can present with a range of signs and symptoms that may develop into more severe symptoms indicative of adrenal crisis. There is evidence that cases are missed as reported in the National Patient Safety and Learning report which showed 4 deaths, 4 patients admitted to ICU and 320 incidents related to steroid hormone replacement.

This review was carried out to assess the range of symptoms and signs that may indicate an adrenal crisis to help health care professionals improve the diagnosis of a life-threatening adrenal crisis.

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: Adults and children with or without a diagnosis of adrenal insufficiency Exclusion: None identified.
Target condition	Adrenal insufficiency (adrenal crisis)
Index tests/exposures/ risk factors	• Low blood pressure (hypotension including postural hypotension) • Hyperpigmentation • Hyponatraemia • Hyperkalaemia • Hypoglycaemia is (rarely observed in adults but relatively frequent in children) • Circulatory shock or collapse • Failure to respond to initial treatments. • Any of the above, alone or in combination
Reference standard	• Clinical diagnosis of adrenal crisis by a specialist based on biochemical tests and patient history.
Statistical measures	Association data Adjusted hazard ratios, odds ratios or risk ratios Discrimination data

	• for example, C statistic, area under ROC curve Calibration data • for example, calibration slope Diagnostic accuracy data • Sensitivity (prioritised) • specificity If no sensitivity or specificity, we will report LR- and LR+ if raw data unavailable and unable to calculate from 2 x 2 table.
Study design	Prospective cohort studies looking at the association between individual or combinations of signs and symptoms (multivariable models/algorithms) and a confirmed diagnosis of adrenal crisis. Multivariable analysis should ideally include the following symptoms in combination with the red flags listed above: • Lethargy • Pallor • Clamminess • Confusion • Feeling cold • Confusion or altered mental states • Weakness and convulsions If no or insufficient prospective cohort studies are identified, cross-sectional studies (single- gate) diagnostic accuracy studies may be considered. Studies will only be included if key confounders have been accounted for in a multivariate analysis. Key confounders will vary based on each risk factor but should at least include age and sex. Published NMAs and IPDs will be considered for inclusion.

1.1.3. Methods and process

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

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

1.1.4. Diagnostic evidence

1.1.4.1. Included studies.

A search for prospective cohort studies, cross-sectional studies and (single gate) diagnostic accuracy studies was conducted. However, no relevant papers were identified. One retrospective study was included in the review; Katabami 2020[1] this is summarised in Table 2 below. Evidence from this study is summarised in the clinical evidence summary below in Table 7 and references. Despite being a retrospective cohort study and not fulfilling the protocol criteria, this study was included for consideration and discussion due to the sparsity of evidence available. It was the only study identified that reported diagnostic accuracy data and association data to answer the review question. Several prognostic studies were assessed for inclusion, but these did not report any useable outcome data.

No relevant studies investigating the following risk factors/exposures were identified: hyperpigmentation, hypoglycaemia, circulatory shock or collapse and failure to respond to initial treatments.

Katabami 2020[1] retrospectively analysed 92 inpatients from referral centres in Japan who were diagnosed with adrenal insufficiency (AI). The population included a mix of primary and secondary adrenal insufficiency and a mix of patients with pre-existing adrenal insufficiency or newly diagnosed adrenal insufficiency. Patients were excluded if they had an unverified diagnosis of AI or adrenal crisis (AC), oral steroids were used for AC treatment or there was insufficient data before and/or after parenteral steroid management.

The predictive value of the following risk factors; hypotension, hyponatraemia, and hyperkalaemia in relation to developing adrenal crisis were assessed through multivariate analysis. Further diagnostic accuracy analyses were carried out on hyponatraemia and C-reactive protein levels at specific cut-offs in order to determine the diagnostic accuracy in predicting adrenal crisis. The reference standard used for these analyses was the diagnosis of adrenal crisis as confirmed if there was documentation of a worsening of the patient's general condition with signs and symptoms of glucocorticoid and/or mineralocorticoid deficiency and at least one of the following conditions: hypotension (systolic BP<100 mmHg); nausea or vomiting; severe fatigue; or documented hyponatraemia, hyperkalaemia, anaemia, or hypoglycaemia. In addition, only patients whose symptoms were rapidly reversed by intravenous glucocorticoid administration were diagnosed as having an adrenal crisis and included in the analysis.

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 the person for this life-threatening 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, association data 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 J.

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/risk factor	Reference standard	Comments
Katabami2020[1]	92 inpatients (148 events) who were diagnosed with AI between November 2009 and June 2018. Total number of patients	Adrenal crisis	Hyponatraemia Hyperkalaemia Hypotension C reactive protein	Diagnosis of AC was confirmed if there was documentation of a worsening of the patient's general condition with signs and symptoms of glucocorticoid and/or mineralocorticoid deficiency and at	Analysis adjusted for: serum sodium, potassium, C-reactive creatine, and systolic BP. Odds ratio reported for association data.

Study	Population	Target condition	Index test/risk factor	Reference standard	Comments
	(events) with AC: 54 (90) Age (years) at onset of the AC event: 62.8±1.7 Ratio male: female: 26:28 AI status at the time of the AC, number of patients (events): Undiagnosed= 24 (24) Diagnosed= 30 (66) AI subtype, number of patients (events): Primary AI= 16 (26) Secondary AI= 38 (64)			least one of the following conditions: hypotension. (systolic BP<100 mmHg); nausea or vomiting; severe fatigue; or documented hyponatraemia, hyperkalaemia, anaemia, or hypoglycaemia.	Sensitivity and specificity and AUC reported for diagnostic accuracy data

See Appendix D for full evidence tables.

1.1.6. Summary of the association/prognostic evidence

Table 3: Clinical evidence summary: Systolic blood pressure as a predictor of adrenal crisis

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Systolic blood pressure (mmHg) for predicting **adrenal crisis** (adjusted OR for the diagnosis of adrenal crisis) (Inpatients at five referral centres in Japan who were diagnosed with AI between November 2009 and June 2018. 54 patients and 90 events of AC)	54 (1) **Follow up unclear. Assessed in the acute phase and chronic phase after admission.** Katabami 2020	VERY LOW[a,b] Due to risk of bias and imprecision	Adjusted OR: 0.99 (0.95 to 1.03)

[a] Downgraded by 2 increments as the majority of evidence was at very high risk of bias. Risk of bias was identified for study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting domains.
[b] Downgraded by 2 increments for very serious imprecision. Downgraded by 1 increment for serious imprecision as the confidence interval crossed the null line (1.0).

Table 4: Clinical evidence summary: Serum sodium level as a predictor of adrenal crisis

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Serum sodium level for predicting adrenal crisis (adjusted OR for the diagnosis of adrenal crisis) (Inpatients at five referral centres in Japan who were diagnosed with AI between November 2009 and June 2018. 54 patients and 90 events of AC)	54 (1) **Follow up unclear. Assessed in the acute phase and chronic phase after admission.** Katabami 2020	LOW[a] Due to risk of bias and imprecision	Adjusted OR: 0.39 (0.20 to 0.76)

[a] Downgraded by 2 increments as the majority of evidence was at high risk of bias. Risk of bias was identified for study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting domains.

Table 5: Clinical evidence summary: Serum potassium as a predictor of adrenal crisis

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Serum potassium level for predicting adrenal crisis (adjusted OR for the diagnosis of adrenal crisis) (Inpatients at five referral centres in Japan who were diagnosed with AI between November 2009 and June 2018. 54 patients and 90 events of AC)	54 (1) **Follow up unclear. Assessed in the acute phase and chronic phase after admission.** Katabami 2020	VERY LOW[a,b] Due to risk of bias, and imprecision	Adjusted OR: 0.19 (0.02 to 1.65)

[a] Downgraded by 2 increments as the majority of evidence was at high risk of bias. Risk of bias was identified for study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting domains.
[b] Downgraded by 2 increments for very serious imprecision. Downgraded by 1 increment for serious imprecision as the confidence interval crossed the null line (1.0).

Table 6: Clinical evidence summary: C-reactive protein level as a predictor of adrenal crisis

Risk factor and outcome (population)	Number of participants (studies) Follow up	Quality of the evidence (GRADE)	Effect (95% CI)
Higher C-reactive protein level (mg/dL) for predicting adrenal crisis (adjusted OR for the diagnosis of adrenal crisis) (Inpatients at five referral centres in Japan who were diagnosed with AI between November 2009 and June 2018. 54 patients and 90 events of AC)	54 (1) **Follow up unclear. Assessed in the acute phase and chronic phase after admission.** Katabami 2020	LOW[a] Due to risk of bias and imprecision	Adjusted OR: 2.76 (1.41 to 5.40)

[a] Downgraded by 2 increments as the majority of evidence was at high risk of bias. Risk of bias was identified for study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting domains.

1.1.7. Summary of the diagnostic evidence

Table 7: Clinical evidence summary: diagnostic predictive accuracy of hyponatraemia for the detection of adrenal crisis

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Hyponatraemia (serum sodium level <137 mEq/L) to predict adrenal crisis in people with adrenal insufficiency							
1 retrospective cohort studies	Unclear 54 pts and 90 events	Very serious[a]	Not serious	Not serious	Inestimable[b]	Sensitivity= 71.1%	VERY LOW
		Very serious[a]	Not serious	Not serious	Inestimable[b]	Specificity= 95.6%	VERY LOW
		Very serious[a]	Not serious	Not serious	serious[c]	AUC = 0.88 (0.83 – 0.93)	VERY LOW

[a] Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments as the majority of studies were rated at very high risk of bias.

[b] No measures of variance were provided and calculations were not possible from the primary data provided.

[c] The evidence was downgraded by 1 increment as the confidence interval crossed the decision thresholds corresponding to 'very good test' (>0.81 to 0.92) and 'excellent test' (>0.92-100).

Table 8: Clinical evidence summary: diagnostic predictive accuracy of C-reactive protein for the detection of adrenal crisis

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
C-reactive protein level >1.30 mg/dL to predict adrenal crisis in people with adrenal insufficiency							
1 retrospective cohort studies	Unclear 54 pts and 90 events	Very serious[a]	Not serious	Not serious	Inestimable[b]	Sensitivity= 84.4%	VERY LOW
		Very serious[a]	Not serious	Not serious	Inestimable[b]	Specificity= 94.9%	VERY LOW
		Very serious[a]	Not serious	Not serious	serious[c]	AUC = 0.93 (0.89 – 0.97)	VERY LOW

[a] Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded by 2 increments as the majority of studies were rated at very high risk of bias.

[b] The evidence was downgraded by 2 increments as no measures of variance were provided and calculations were not possible from the primary data provided.

[c] The evidence was downgraded by 1 increment as the confidence interval crossed the decision thresholds corresponding to 'very good test' (>0.81 to 0.92) and 'excellent test' (>0.92-100).

Table 9: Clinical evidence summary: diagnostic predictive accuracy of hyponatraemia and/or C-reactive protein for the detection of adrenal crisis

Studies	N	Risk of bias	Inconsistency	Indirectness	Imprecision	Effect size (95%CI)	Quality
Hyponatraemia (serum sodium level < 137.Eq/L) and/or C-reactive protein level >1.30 mg/dL to predict adrenal crisis in people with adrenal insufficiency							
1 retrospective cohort studies	Unclear - 54 pts and 90 events	Very serious[a]	Not serious	Not serious	Inestimable[b]	Sensitivity= 97.8%	VERY LOW
		Very serious[a]	Not serious	Not serious	Inestimable[b]	Specificity= 94.4%	VERY LOW
		Very serious[a]	Not serious	Not serious	not serious	AUC = 0.96 (0.93-0.99)	LOW

[a] Risk of bias was assessed using the QUADAS-2 checklist. The evidence was downgraded 2 increments if the majority of studies were rated at very high risk of bias.

[b] No measures of variance were provided and calculations were not possible from the primary data provided.

See appendix F for full GRADE tables.

1.1.8. Economic evidence

1.1.8.1. Included studies.

No health economic studies were included.

1.1.8.2. 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.

1.1.9. Economic model

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

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

There was limited evidence for this review question, so the committee used their clinical knowledge and experience to make the recommendations.

1.2.1. The outcomes that matter most

Diagnostic accuracy

The committee considered the diagnostic measures of sensitivity and specificity of the risk factors for detecting adrenal crisis along with ROC data which was reported in one study. Clinical decision thresholds were set by the committee as sensitivity/specificity=0.9 and 0.8 above which a test would be recommended and 0.1 and 0.5 below which a test is of no clinical use. For the ROC data, the thresholds were set at >0.50 to 0.60 indicating a very poor test, >0.61 to 0.70 a poor test, >0.71 to 0.80 a moderate test, >0.81 to 0.92 a very good test and >0.92 to 1.00 an excellent test.

The committee were interested in establishing whether any of the risk factors or red flags were more indicative than others in detecting adrenal crisis. Therefore, sensitivity was considered the most important measure, as adrenal crisis is a life-threatening medical emergency so the consequences of missing a patient with this condition would have very serious implications.

Association data

The committee also considered assessment of the risk factors in relation to the presence or absence of adrenal crisis for decision making.

One study reported the diagnostic association data of potential risk factors and reported these as adjusted odds ratios. The presence of a positive or negative association was determined by the point estimate in conjunction with the confidence interval not crossing the line of null effect.

1.2.2. The quality of the evidence

Evidence for this review was very limited and no prospective cohort studies, cross-sectional studies or (single gate) diagnostic accuracy studies were identified. One retrospective cohort study with multivariate analysis was included as the committee agreed to include this study

type due to the lack of available evidence. This study analysed the data of 92 in-hospital patients who were diagnosed with adrenal insufficiency and looked at the predictive value of systolic blood pressure, serum sodium levels and serum potassium levels in relation to developing adrenal crisis. This data was assessed through multivariate logistic regression analysis and expressed findings as adjusted odds ratios.

Diagnostic accuracy analyses were carried out for hyponatraemia and C-reactive protein levels at specific cut-off points in order to determine the diagnostic accuracy in predicting adrenal crisis. Results were presented as sensitivity, specificity, and ROC data.

All evidence was rated very low quality due to risk of bias and imprecision around the effect estimate. The risk of bias was rated very high due to concerns with patient selection, interpretation of the index test and the timing between recording of the risk factor and the diagnosis and concerns arising from patient flow due to no details on any missing data. Two outcomes reporting association data were downgraded for imprecision due to the confidence interval crossing the null line. Additionally, all diagnostic accuracy outcomes were downgraded for imprecision as no measures of variance were reported by the study and calculations were not possible from the primary data provided. Two outcomes reporting AUC data were also downgraded once for imprecision as the confidence interval crossed the decision thresholds corresponding to ‘very good test’ (>0.81 to 0.92) and ‘excellent test’ (>0.92-100).

No relevant clinical studies investigating the association of hyperpigmentation, hypoglycaemia, circulatory shock or collapse and failure to respond to initial treatments with the diagnosis of adrenal crisis were identified.

1.2.3. Benefits and harms

Evidence for the risk factors associated with adrenal crisis was very limited and of poor quality so the committee decided to use their expertise and knowledge of established literature to inform the recommendations and supplement the available evidence.

Evidence was available from one retrospective cohort study which suggested that lower sodium levels were associated with an increased risk of developing adrenal crisis. Diagnostic accuracy analysis showed that hyponatremia with a cut off of <137 mEq/L had a sensitivity of 71.1% and specificity of 95.6% for predicting adrenal crisis. It also reported an AUC of 0.88 which reached the threshold of >0.81 to 0.92 and indicates a very good test. While the sensitivity outcome did not reach the clinical decision threshold set by the guideline committee, they agreed that hyponatraemia (particularly below 135 mmol/L) may be indicative of adrenal insufficiency and hence an increase in the risk of adrenal crisis. They reasoned that this in part is due to the increased release of antidiuretic hormone (ADH), which results in water retention and a reduction in the plasma sodium concentration.

This study also suggested that increased C-reactive protein levels were associated with an increased risk of adrenal crisis, particularly when taken into consideration alongside the presence of hyponatremia (serum sodium <137mEq/L). However, C-reactive protein levels were not included as a risk factor in the original review protocol. The committee acknowledged the high AUC rating of these additional outcomes and explained that it could be due to associated infections such as sepsis, however, they decided that it was not a useful indicator for adrenal crisis and did not take these outcomes into account in their decision making.

Evidence from the included study showed that systolic BP and serum potassium level were not related to adrenal crisis events. However, these outcomes were downgraded twice for risk of bias and imprecision as the confidence intervals were judged to be consistent with multiple, conflicting interpretations, therefore, they were not taken into account in their decision making. The committee also argued that these findings do not correlate with their clinical experience and concluded that these risk factors can be indicative of adrenal crisis.

They suggested that these risk factors may present later than hyponatremia, however they should still be considered.

Ultimately, all risk factors listed in the review protocol including low blood pressure, hyperpigmentation, hyponatraemia, hyperkalaemia, circulatory shock or collapse and failure to respond to initial treatments were included as a consider recommendation, because the committee agreed by consensus that they are known to be associated with adrenal crisis. The committee also highlighted that hypoglycaemia should be considered in children. The committee reasoned that despite the limited evidence showing which symptoms and signs are most useful in suspecting and diagnosing adrenal crisis, it is crucial to raise awareness of the most common risk factors so that timely assessment and treatment can be delivered.

The committee explained that these diagnoses would generally be picked up in secondary care, as people presenting with these risk factors would be critically unwell. However, primary care clinicians should also be aware of these presenting features and if adrenal crisis is suspected and the patient is unwell then they should be referred to Accident and Emergency for immediate assessment.

The committee also decided by consensus to include a consider recommendation for a broader list of milder signs and symptoms that could indicate adrenal crisis in patients who are already diagnosed with, or at high risk of adrenal insufficiency. These factors were not included in the protocol as they are very general symptoms and the committee acknowledged it was unlikely that any relevant evidence would be identified for such non-specific symptoms. However, the committee wanted to highlight the following signs/symptoms including lethargy, pallor, clamminess, feeling cold or feverish, confusion or altered mental states, weakness and convulsions which may be too generalised to be suspicious of adrenal crisis in a general population, but would raise suspicion and more important to detect in people already diagnosed so that further relevant assessment and treatment can be delivered as quickly as possible (see recommendations on emergency management).

The committee acknowledged that the evidence base in this area is particularly limited. This may be due to the fact that symptoms are too general and there isn't much awareness of their link to adrenal insufficiency or their importance in adrenal crisis. However, they agreed that these signs and symptoms have been well-established in the literature for many years, which may explain why newer studies have not been undertaken. The committee also noted that a lack of an established gold standard assessment for adrenal crisis is another reason why diagnostic studies in this area are limited. The included study suggested that a rapid reversal of symptoms when intravenous glucocorticoids were administered was useful in clinically diagnosing patients with adrenal crisis. The committee agreed this may be a relevant indicator in confirming the diagnosis of adrenal crisis, but only once initial treatment has been initiated.

Despite the lack of evidence in this area, the committee noted that raising awareness of the most common risk factors and signs and symptoms, delayed and missed diagnosis of adrenal crisis could be reduced which could save lives.

The committee acknowledged, that glucocorticoids are prescribed widely across the NHS and the impact of this in patients is poorly understood by those professionals prescribing them. They believed that if those at risk of adrenal crisis could be more easily identified, education and support could be targeted more effectively. This will save the NHS money as it is highly likely the population at risk will be smaller if more clearly defined. Therefore, the committee decided to make a research recommendation, specifically looking at which patients taking long term steroids are at an increased risk of adrenal crisis and adverse hospital outcomes (see Appendix K).

1.2.4. Cost effectiveness and resource use

No economic evaluations were identified for this review question. The committee made recommendations reflective of current practice and therefore these recommendations are not expected to result in a significant resource impact.

1.2.5. Recommendations supported by this evidence review.

This evidence review supports recommendations 1.6.1 – 1.6.2 and the recommendation for research on which patients taking long-term steroids are at increased risk of adrenal crisis and adverse hospital outcomes.

References

1. Katabami T, Tsukiyama H, Tanabe M, Matsuba R, Murakami M, Nishine A et al. Development of a simple prediction model for adrenal crisis diagnosis. Scientific Reports. 2020; 10(1):13546

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

Appendices

Appendix A Review protocols

A.1 Review protocol for when to suspect adrenal crisis

ID	Field	Content
1.	Review title	When to suspect adrenal crisis
2.	Review question	4.3 When should adrenal crisis be suspected?
3.	Objective	To identify people who may be experiencing an adrenal crisis based on symptoms that are strongly associated with it.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review.

		Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Adrenal insufficiency
6.	Population	Inclusion: Adults and children with or without a diagnosis of adrenal insufficiency Exclusion: None identified
7.	Exposure	• Low blood pressure (hypotension including postural hypotension) • Hyperpigmentation • Hyponatraemia • Hyperkalaemia • Hypoglycaemia is (rarely observed in adults but relatively frequent in children) • Circulatory shock or collapse • Failure to respond to initial treatments. • Any of the above, alone or in combination
8.	Comparator/Reference standard/Confounding factors	**Reference standard for signs and symptoms review:** • Clinical diagnosis of adrenal crisis by a specialist based on biochemical tests and patient history
9.	Types of study to be included	Prospective cohort studies looking at the association between individual or combinations of signs and symptoms (multivariable models/algorithms) and a confirmed diagnosis of adrenal crisis. Multivariable analysis should ideally include the following symptoms in combination with the red flags listed above: • Lethargy • Pallor • Clamminess

		• Confusion • Feeling cold • Confusion or altered mental states. • Weakness and convulsions If no or insufficient prospective cohort studies are identified, cross-sectional studies (single- gate) diagnostic accuracy studies may be considered. Studies will only be included if key confounders have been accounted for in a multivariate analysis. Key confounders will vary based on each risk factor but should at least include age and sex. Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Retrospective cohort studies case-control (two-gate) diagnostic studies Before and after 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	The evidence from this review will be used to underpin recommendations on how to recognise someone with in an adrenal crisis. They are likely to be most useful for non-specialists. Most of the symptoms can be 'non-specific' (e.g., fatigue) but there are some symptoms that could be considered 'red flags' especially if presenting with other symptoms. Therefore, the committee wanted to look for studies that investigate combinations of signs/symptoms which include some red flags and at least some of the less specific signs/symptoms. Once these patients are identified, they will go on to have immediate lifesaving treatment which mainly consists of hydrocortisone and fluids.
12.	Primary outcomes (critical outcomes)	Association data Adjusted hazard ratios, odds ratios, or risk ratios <u>Discrimination data</u> • for example, C statistic, area under ROC curve <u>Calibration data</u> • for example, calibration slope

		Diagnostic accuracy data • Sensitivity (prioritised) • specificity If no sensitivity or specificity, we will report LR- and LR+ if raw data unavailable and unable to calculate from 2 x 2 table
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) • Cross sectional study: JBI checklist for cross sectional study • Nonrandomised study, including cohort studies: Cochrane ROBINS-I • Diagnostic association: QUADAS • Clinical prediction study (risk prediction modelling) for a prognosis or diagnosis: PROBAST
15.	Strategy for data synthesis	Diagnostic meta-analysis using Cochrane Review Manager (RevMan5) will be conducted where appropriate. For example, if more than one study reports the same combination of population, sign/symptom and outcomes. Where association data allows, pairwise meta-analysis will be performed using Cochrane Review manager (RevMan5) software. A fixed-effect meta-analysis, with hazard ratios, odds ratios, or risk ratios (as appropriate), and 95% confidence intervals will be calculated for each outcome. 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. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software. 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: People with AI diagnosis People on corticosteroids

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	From NICE: Sharon Swain [Guideline lead] Saoussen Ftouh [Senior 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	

A.2 Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2007, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[2] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable).

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

Appendix B Literature search strategies

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

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

B.1 Clinical search literature search strategy

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

Table 10: Database parameters, filters and limits applied.

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 September 2023	Observational studies Systematic review studies Prognostic studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 26 September 2023	Observational studies Systematic review studies Prognostic 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.	exp Hypotension/
36.	("low blood pressure" or hypotension or "hypotensive crisis").ti,ab,kf.
37.	Hyperpigmentation/
38.	(hyperpigmentation or pigmentation).ti,ab,kf.
39.	Hyponatremia/
40.	(hyponatraemia or hyponatremia).ti,ab,kf.
41.	(low adj3 (sodium or salt)).ti,ab,kf.
42.	Hypoglycemia/
43.	(hypoglycaemia or hypoglycemia).ti,ab,kf.
44.	(low adj3 ("blood glucose" or "blood sugar")).ti,ab,kf.
45.	Hyperkalemia/

46.	(hyperkalaemia or hyperkalemia).ti,ab,kf.
47.	(high adj3 potassium).ti,ab,kf.
48.	Shock/ or Shock, Cardiogenic/ or Shock, Hemorrhagic/ or Shock, Septic/ or Hypovolemia/
49.	((circulatory or hypovolemic or endocrinologic or distributive or obstructive or septic or cardiogenic or cardiovascular or vascular or haemorrhagic or hemorrhagic or vasodilatory) adj3 (shock or collapse or fail*)).ti,ab,kf.
50.	(fail* adj3 respon* adj3 (initial or treatment*)).ti,ab,kf.
51.	or/35-50
52.	34 and 51
53.	("adrenal crisis" or "acute adrenal" or "addisonian crisis").ti,ab,kf.
54.	53 not 32
55.	limit 54 to English language
56.	Epidemiologic studies/
57.	Observational study/
58.	exp Cohort studies/
59.	(cohort adj (study or studies or analys* or data)).ti,ab.
60.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
61.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
62.	Controlled Before-After Studies/
63.	Historically Controlled Study/
64.	Interrupted Time Series Analysis/
65.	(before adj2 after adj2 (study or studies or data)).ti,ab.
66.	exp case control study/
67.	case control*.ti,ab.
68.	Cross-sectional studies/
69.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
70.	or/56-69
71.	Meta-Analysis/
72.	Meta-Analysis as Topic/
73.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
74.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
75.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
76.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
77.	(search* adj4 literature).ab.
78.	(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.
79.	cochrane.jw.
80.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
81.	or/71-80
82.	exp Prognosis/
83.	Disease progression/
84.	(prognos* or predict*).ti,ab.
85.	(validat* or rule*).ti,ab.

86.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (model* or decision* or identif*)).ti,ab.
87.	(decision* and (model* or clinical*)).ti,ab.
88.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
89.	ROC curve/
90.	or/82-89
91.	52 and (70 or 81 or 90)
92.	55 or 91

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.	*hypotension/
35.	("low blood pressure" or hypotension or "hypotensive crisis").ti,ab,kf.
36.	*hyperpigmentation/
37.	(hyperpigmentation or pigmentation).ti,ab,kf.
38.	*hyponatremia/
39.	(hyponatraemia or hyponatremia).ti,ab,kf.
40.	(low adj3 (sodium or salt)).ti,ab,kf.
41.	*hypoglycemia/
42.	(hypoglycaemia or hypoglycemia).ti,ab,kf.
43.	(low adj3 ("blood glucose" or "blood sugar")).ti,ab,kf.
44.	*hyperkalemia/
45.	(hyperkalaemia or hyperkalemia).ti,ab,kf.
46.	(high adj3 potassium).ti,ab,kf.
47.	shock/ or cardiogenic shock/ or hemorrhagic shock/ or hypovolemic shock/ or septic shock/ or vasodilatory shock/
48.	((circulatory or hypovolemic or endocrinologic or distributive or obstructive or septic or cardiogenic or cardiovascular or vascular or haemorrhagic or hemorrhagic or vasodilatory) adj3 (shock or collapse or fail*)).ti,ab,kf.
49.	*treatment failure/
50.	(fail* adj3 respon* adj3 (initial or treatment*)).ti,ab,kf.
51.	or/34-50
52.	33 and 51
53.	("adrenal crisis" or "acute adrenal" or "addisonian crisis").ti,ab,kf.
54.	53 not 31
55.	limit 54 to English language
56.	Clinical study/
57.	Observational study/
58.	Family study/
59.	Longitudinal study/
60.	Retrospective study/
61.	Prospective study/
62.	Cohort analysis/
63.	Follow-up/
64.	cohort*.ti,ab.
65.	63 and 64
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.	(before adj2 after adj2 (study or studies or data)).ti,ab.
70.	exp case control study/
71.	case control*.ti,ab.
72.	cross-sectional study/

73.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
74.	or/56-62,65-73
75.	Systematic Review/
76.	Meta-Analysis/
77.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
78.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
79.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
80.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
81.	(search* adj4 literature).ab.
82.	(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.
83.	cochrane.jw.
84.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
85.	or/75-84
86.	prognosis/
87.	disease exacerbation/
88.	(prognos* or predict*).ti,ab.
89.	(validat* or rule*).ti,ab.
90.	((history or variable* or criteria or scor* or characteristic* or finding* or factor*) and (model* or decision* or identif*)).ti,ab.
91.	(decision* and (model* or clinical*)).ti,ab.
92.	(stratification or discrimination or discriminate or c statistic or "area under the curve" or AUC or calibration or indices or algorithm or multivariable).ti,ab.
93.	ROC curve/
94.	or/86-93
95.	52 and (74 or 85 or 94)
96.	55 or 95

Cochrane Library (Wiley) search terms

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

#11.	(CAH or "X-ALD"):ti,ab
#12.	((Waterhouse NEXT Friderichsen*) or "antiphospholipid syndrome"):ti,ab,kw
#13.	"Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy":ti,ab,kw
#14.	(or #1-#13)
#15.	MeSH descriptor: [Hypotension] explode all trees
#16.	("low blood pressure" or hypotension or "hypotensive crisis"):ti,ab,kw
#17.	MeSH descriptor: [Hyperpigmentation] this term only
#18.	(hyperpigmentation or pigmentation):ti,ab,kw
#19.	MeSH descriptor: [Hyponatremia] this term only
#20.	(hyponatraemia or hyponatremia):ti,ab,kw
#21.	(low near/3 (sodium or salt)):ti,ab,kw
#22.	MeSH descriptor: [Hypoglycemia] this term only
#23.	(hypoglycaemia or hypoglycemia):ti,ab,kw
#24.	(low near/3 ("blood glucose" or "blood sugar")):ti,ab,kw
#25.	MeSH descriptor: [Hyperkalemia] this term only
#26.	(hyperkalaemia or hyperkalemia):ti,ab,kw
#27.	(high near/3 potassium):ti,ab,kw
#28.	MeSH descriptor: [Shock] this term only
#29.	MeSH descriptor: [Shock, Cardiogenic] this term only
#30.	MeSH descriptor: [Shock, Hemorrhagic] this term only
#31.	MeSH descriptor: [Shock, Septic] this term only
#32.	MeSH descriptor: [Hypovolemia] this term only
#33.	((circulatory or hypovolemic or endocrinologic or distributive or obstructive or septic or cardiogenic or cardiovascular or vascular or haemorrhagic or hemorrhagic or vasodilatory) near/3 (shock or collapse or fail*)):ti,ab,kw
#34.	(fail* near/3 respon* near/3 (initial or treatment*)):ti,ab,kw
#35.	(or #15-#34)
#36.	#14 and #35
#37.	("adrenal crisis" or "acute adrenal" or "addisonian crisis"):ti,ab,kw
#38.	(or #36-#37)
#39.	conference:pt or (clinicaltrials or trialsearch):so
#40.	#38 not #39

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") AND ("low blood pressure" OR hypotension OR "hypotensive crisis" OR hyperpigmentation OR pigmentation OR hyponatraemia OR hyponatremia OR "low sodium" OR "low salt" OR hyperkalaemia OR hyperkalemia OR "high potassium" OR hypoglycaemia OR hypoglycemia OR "low blood glucose" OR "low blood sugar" OR "circulatory shock" OR "hypovolemic shock" OR "endocrinologic shock" OR "distributive shock" OR "obstructive shock" OR "septic shock" OR "cardiogenic shock" OR "cardiovascular shock" OR "vascular shock" OR "haemorrhagic shock" OR "hemorrhagic shock" OR "vasodilatory shock" OR "circulatory collapse" OR "cardiovascular collapse" OR "vascular collapse")) 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 ("low blood pressure" OR hypotension OR "hypotensive crisis" OR hyperpigmentation OR pigmentation OR hyponatraemia OR hyponatremia OR "low sodium" OR "low salt" OR hyperkalaemia OR hyperkalemia OR "high potassium" OR hypoglycaemia OR hypoglycemia OR "low blood glucose" OR "low blood sugar" OR "circulatory shock" OR "hypovolemic shock" OR "endocrinologic shock" OR "distributive shock" OR "obstructive shock" OR "septic shock" OR "cardiogenic shock" OR "cardiovascular shock" OR "vascular shock" OR "haemorrhagic shock" OR "hemorrhagic shock" OR "vasodilatory shock" OR "circulatory collapse" OR "cardiovascular collapse" OR "vascular collapse"))) OR (title:("adrenal crisis" OR "acute adrenal" OR "addisonian crisis") OR abstract:("adrenal crisis" OR "acute adrenal" OR "addisonian crisis"))

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 11: 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	

Database	Dates searched	Search filters and limits applied
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 26 September 2023	English language

Medline (Ovid) search terms

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

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

Embase (Ovid) search terms

1.	exp Adrenal cortex insufficiency/
2.	Congenital adrenal hyperplasia/
3.	(addison* disease or addisonian*).ti,ab,kf.
4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.
6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.

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

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Adrenal Insufficiency EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Adrenal Hyperplasia, Congenital EXPLODE ALL TREES
#3.	(addison* disease or addisonian)
#4.	(adrenal*) AND (insufficien* or inadequa* or deficien* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed)

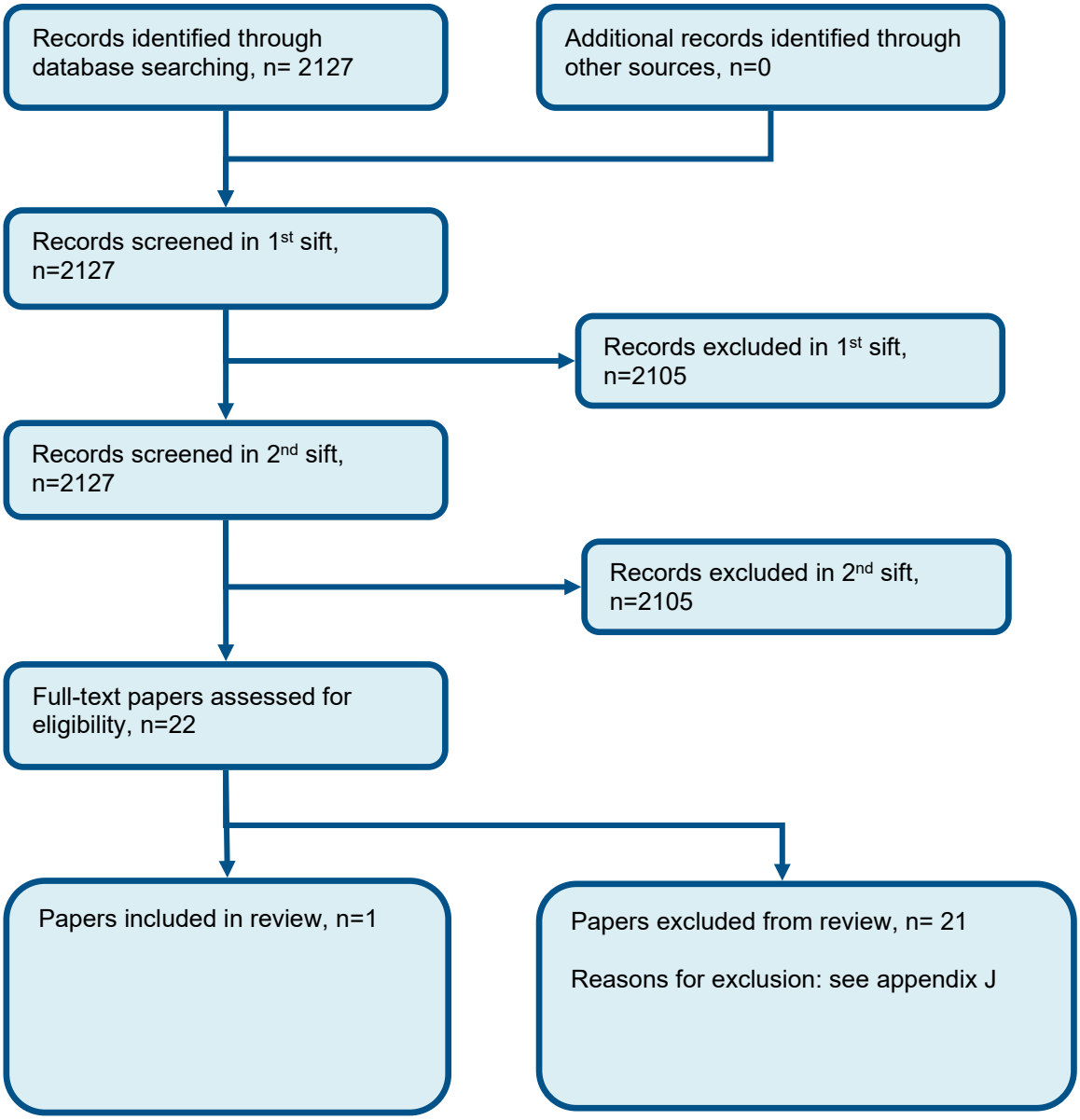
#5.	(cortisol or aldosterone or adrenocortical or adrenocorticotropi* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) AND (insufficien* or inadequac* or deficien* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or produc* or limited)
#6.	(hypoadrenalism or hypoadrenocorticism or adrenoleukodystrophy or adrenomyeloneuropathy or hypoaldosteronism)
#7.	((Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease))
#8.	(Allgrove or 3A or TripleA or AAA) AND (syndrome)
#9.	(X-ALD)
#10.	((Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome))
#11.	((Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy))
#12.	(adrenogenital or adreno genital) AND (syndrome)
#13.	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12

INAHTA search terms

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

Appendix C Diagnostic evidence study selection

Figure 1: Flow chart of clinical study selection for the review of when to suspect adrenal crisis



Appendix D Diagnostic evidence

Reference	**Katabami, 2020[1]**
Study type	Retrospective cohort study
Study methodology	Data source: Retrospective analysis of data from a multicentre collaborative study conducted at five referral centres in Japan. Data was extracted from the medical records of 92 inpatients (148 events) who were diagnosed with adrenal insufficiency between November 2009 and June 2018. Recruitment: not reported
Number of patients	n = 92
Patient characteristics	Age, mean (SD): 62.8 (1.7) Gender (male to female ratio): 26:28 Ethnicity: Not reported Setting: Inpatients at five referral centres Country: Japan Study type: retrospective study Inclusion criteria: Data was extracted from the medical records of 92 inpatients (148 events) who were diagnosed with adrenal insufficiency between November 2009 and June 2018. The diagnosis of AC was confirmed if there was documentation of a worsening of the patient's general condition with signs and symptoms of glucocorticoid and/or mineralocorticoid deficiency and at least one of the following conditions: hypotension (systolic BP<100 mmHg); nausea or vomiting; severe fatigue; or documented hyponatremia, hyperkalaemia, anaemia, or hypoglycaemia. In addition, to further ensure accurate AC diagnosis, patients whose symptoms were rapidly reversed by intravenous glucocorticoid administration were included. Exclusion criteria: Patients with an unverified diagnosis of AI or AC (10 patients, 10 events), oral steroid use for AC treatment (13 patients, 31 events) or insufficient data before and/or after parenteral steroid management (15 patients, 17 events) were excluded.

Reference	Katabami, 2020[1]
Target condition(s)	Adrenal crisis
Index test(s) and reference standard	Index tests and prognostic risk factors Data on all the predictors were collected both at AC onset (acute phase) and during the stable period during the administration of glucocorticoid replacement therapy (chronic phase). Patients were defined as being in the chronic phase if they received optimal glucocorticoid and/or mineralocorticoid replacement for at least three months within one year before and after the onset of AC. The presence of hyponatremia (< 136 mEq/L in four centres, <138 mEq/L in one centre) and CRP level elevations (>0.3 mg/dL in four centres,>0.14 mg/dL in one centre) were defined according to the reference range of each hospital. Hyperkalaemia was defined as a level>5.0 mEq/L, which has previously been reported to be useful in Addison's disease diagnosis. Hypoglycaemia was defined as a plasma glucose level<70 mg/dL2. The five factors (systolic BP and serum sodium, serum potassium, serum creatine, and CRP levels) showing significant differences between the two phases (chronic and acute) were included in the multivariate logistic regression models. Binary logistic regression analysis was performed to identify independent clinical parameters that were significantly related to the odds of having AC during the acute phase. In the binary multivariate regression analysis, serum sodium (odds ratio [OR], 0.385; 95% confidence interval [CI], 0.20–0.74; P=0.004) and CRP (OR 2.76, 95% CI 1.42–5.34, P=0.003) levels were associated with the presence of AC and further diagnostic analyses were carried out on these two factors. Reference standard The diagnosis of AC was confirmed if there was documentation of a worsening of the patient's general condition with signs and symptoms of glucocorticoid and/or mineralocorticoid deficiency and at least one of the following conditions: hypotension (systolic BP<100 mmHg); nausea or vomiting; severe fatigue; or documented hyponatremia, hyperkalaemia, anaemia, or hypoglycaemia. In addition, to further ensure accurate AC diagnosis, patients whose symptoms were rapidly reversed by intravenous glucocorticoid administration were included. Data from the same individuals in a stable period during glucocorticoid replacement therapy were used as a control. For all comparisons, AC, as defined above, was used as the comparator (true positive). Time between measurement of index test and reference standard: Predictors of AC were measured in the acute stage and the chronic stage. The interval between AC onset and blood sampling at the chronic phase was 175.9 ± 9.4 (range: 13–359) days.
Confounders	Factors showing significant differences between the acute and chronic phases were included in the multivariate logistic regression models. Binary logistic regression analysis was performed for the identification of clinical parameters in the acute phase that were independently significantly associated with AC presence using the values from the chronic phase as comparators.

Reference	Katabami, 2020[1]
Outcomes and effect sizes	Data is reported as OR (95% confidence intervals) in the paper, which is extracted below. Hypotension – time-point assessed at unclear (study reports at acute phase) N=unclear 90 events or 54 patients adjusted OR 0.39 (95% CI 0.20 to 0.76) Hyponatraemia – time-point assessed at unclear (study reports at acute phase) N=unclear 90 events or 54 patients adjusted OR 0.39 (95% CI 0.20 to 0.74) Hyperkalaemia – time-point assessed at unclear (study reports at acute phase) N= unclear 90 events or 54 patients adjusted OR 0.19 (95% CI 0.19 to 1.64)
Statistical measures	Index text Hyponatraemia - Serum sodium level. AUC at threshold < 137 mEq/L Sensitivity: 71.1 Specificity: 95.6 PPV: 94.2 NPV: 76.8 AUC: 0.88 (95% CI: 0.83-0.93) Index text C-reactive protein level- AUC at >1.30 mg/dL Sensitivity: 84.4 Specificity: 94.9 PPV: 94.9 NPV: 85.9 AUC: 0.93 (95% CI: 0.89-0.97) Index text Serum sodium level<137 mEq/L and/or C-reactive protein level>1.30 mg/dL Sensitivity: 97.8 Specificity: 94.4 PPV: 94.6 NPV: 97.7 AUC: 0.96 (95% CI: 0.93-0.99)
Source of funding	This work was partly supported by Research Committee on Disorders of Adrenal Hormones, a Grant-in-Aid from the Ministry of Health, Labour, and Welfare, Japan [Nanjiseisikkanseisakukenkyujigyo (20FC1020)]

Reference	**Katabami, 2020[1]**
Limitations	Risk of bias: Very serious due to concerns arising from patient selection (study excluded patients with unclear diagnosis), interpretation of the index test and reference standard (unclear when these were carried out) and concerns arising from the patient flow through the study (no information on participant numbers for each analysis) Indirectness: N/A
Comments	Paper only provides sensitivity and specificity data and not TP, FP, FN, or TN. These could not be calculated using the diagnostic calculation spreadsheet as the total number of participants was not reported. ORs were determined using multivariate binary logistic regression analysis and serum, sodium, potassium, C-reactive protein and creatine and systolic pressure were chosen as the explanatory variables. Significance indicated by P<0.05.

Appendix E Forest plots

E.1 Association data forest plots

Figure 2: Systolic BP (mmhg) in predicting adrenal crisis

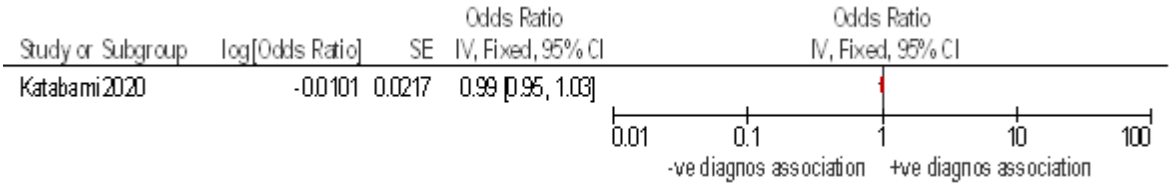


Figure 3: Serum sodium level (mEq/L) in predicting adrenal crisis

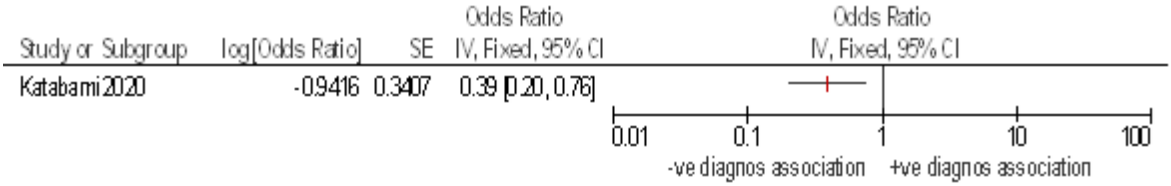


Figure 4: Serum potassium level (mEq/L) in predicting adrenal crisis

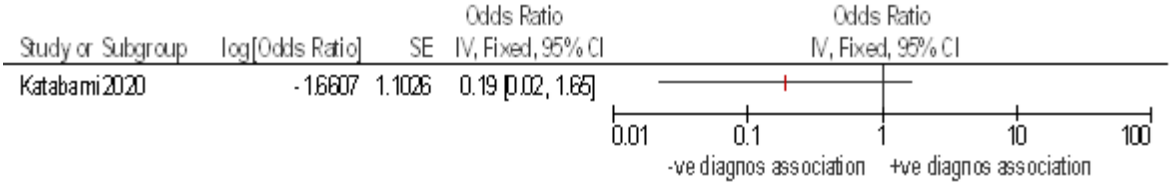
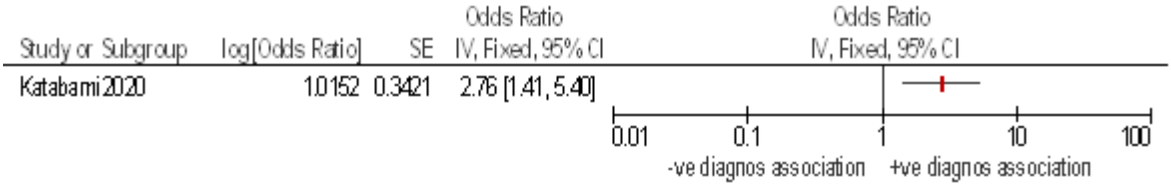


Figure 5: C-reactive protein level (mg/dL) in predicting adrenal crisis



Appendix F GRADE tables

F.1 Association/prognostic evidence

Table 12: Clinical evidence profile: Systolic blood pressure as a predictor of adrenal crisis

Quality assessment							Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OR (95% CI)**	
Systolic blood pressure as a predictor of adrenal crisis during hospital admission for adrenal insufficiency **MV analysis: serum, sodium, potassium, C-reactive protein and creatine and systolic pressure were chosen as the explanatory variables.**								
1	Retrospective cohort study	very serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	Adjusted OR 0.99 (0.95 to 1.03)	⊕OOO VERY LOW

[1]Risk of bias was assessed using the QUIPS checklist. Downgraded by 2 increments as the majority of the evidence was at very high risk of bias. Risk of bias was identified for study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting domains.
[2]Downgraded by 2 increments for very serious imprecision. Downgraded by 1 increment for serious imprecision as the confidence interval crossed the null line (1.0).

Table 13: Clinical evidence profile: Serum sodium level as a predictor of adrenal crisis

Quality assessment							Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OR (95% CI)**	
Serum sodium level as a predictor of adrenal crisis during hospital admission for adrenal insufficiency **MV analysis: serum, sodium, potassium, C-reactive protein and creatine and systolic pressure were chosen as the explanatory variables.**								
1	Retrospective cohort study	very serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	Adjusted OR 0.39 (0.20 to 0.76)	⊕⊕◯◯ LOW

[1]Risk of bias was assessed using the QUIPS checklist. Downgraded by 1 increment if the majority of the evidence was at high risk of bias and downgraded by 2 increments as the majority of the evidence was at very high risk of bias. Risk of bias was identified for study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting domains.

Table 14: Clinical evidence profile: Serum potassium level as a predictor of adrenal crisis

Quality assessment							Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OR (95% CI)**	
Serum potassium level as a predictor of adrenal crisis during hospital admission for adrenal insufficiency **MV analysis: serum, sodium, potassium, C-reactive protein and creatine and systolic pressure were chosen as the explanatory variables.**								
1	Retrospective cohort study	very serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious imprecision[2]	none	OR 0.19 (0.02 to 1.65)	⊕OOO VERY LOW

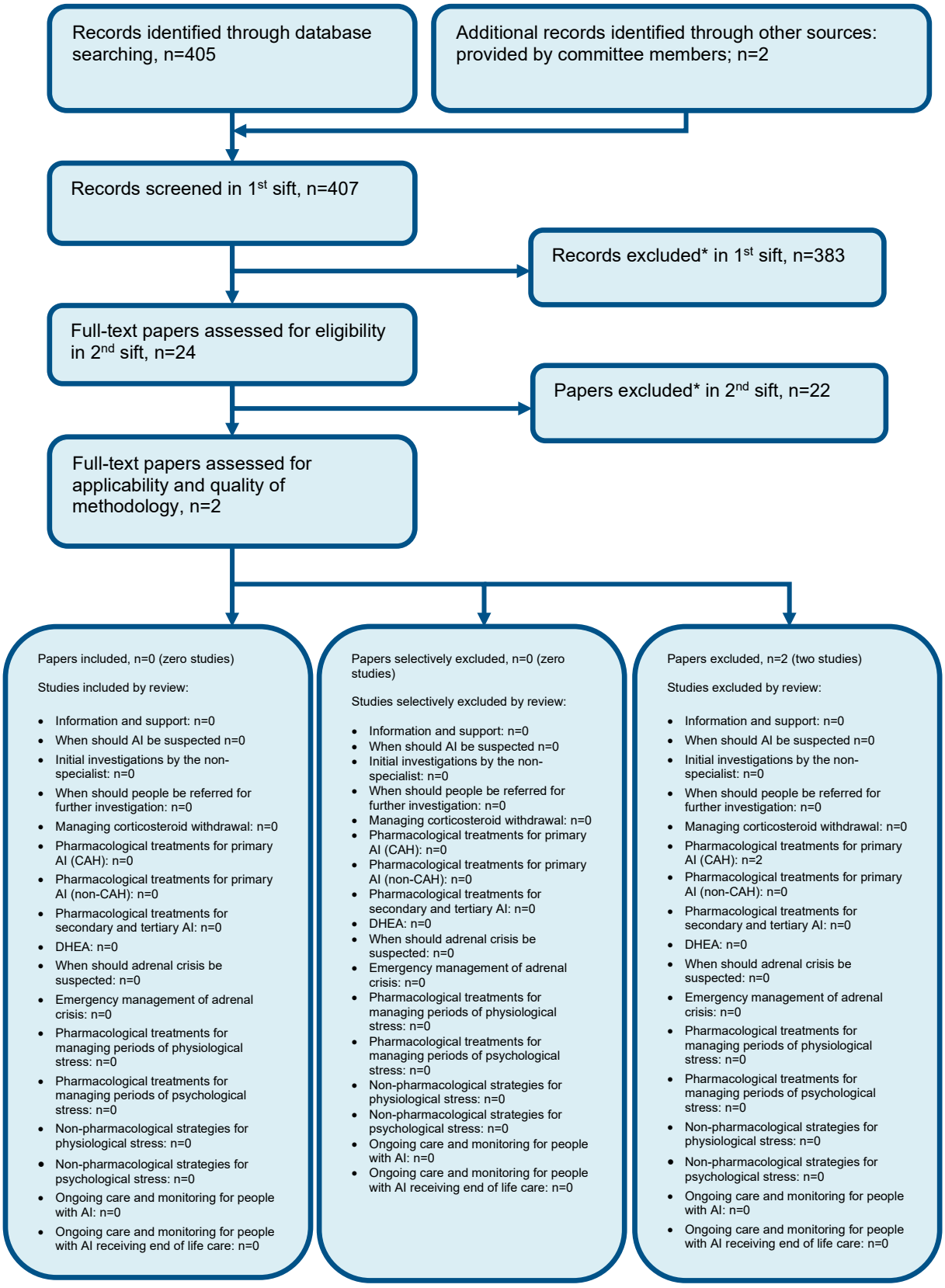
[1]Risk of bias was assessed using the QUIPS checklist. Downgraded by 2 increments as the majority of the evidence was at very high risk of bias. Risk of bias was identified for study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting domains.
[2]Downgraded by 2 increments for very serious imprecision. Downgraded by 1 increment for serious imprecision as the confidence interval crossed the null line (1.0).

Table 15: Clinical evidence profile: C-reactive protein level as a predictor of adrenal crisis

Quality assessment							Effect	Quality
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**OR (95% CI)**	
C-reactive protein level as a predictor of adrenal crisis during hospital admission for adrenal insufficiency **MV analysis: serum, sodium, potassium, C-reactive protein and creatine and systolic pressure were chosen as the explanatory variables.**								
1	Retrospective cohort study	very serious risk of bias[1]	no serious inconsistency	no serious indirectness	no serious imprecision[2]	none	OR 2.76 (1.41 to 5.40)	⊕⊕◯◯ LOW

[1]Risk of bias was assessed using the QUIPS checklist. Downgraded by 2 increments as the majority of the evidence was at very high risk of bias. Risk of bias was identified for study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding and statistical analysis and reporting domains.

Appendix G Economic evidence study selection



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

Appendix H Economic evidence tables

None.

Appendix I Health economic model

No original economic modelling was undertaken for this review question.

Appendix J Excluded studies

J.1 Clinical studies

Table 16: Studies excluded from the clinical review**Study**	**Reasons for exclusion.**
Abrigo, Enrica, Munarin, Jessica, Bondone, Claudia et al. (2023) Adrenal insufficiency management in the pediatric emergency setting and risk factors for adrenal crisis development. Italian journal of pediatrics 49(1): 63	- Data not reported in an extractable format or a format that can be analysed
Ali, S.R., Bryce, J., Krone, N.P. et al. (2022) Management of Acute Adrenal Insufficiency-Related Adverse Events in Children with Congenital Adrenal Hyperplasia: Results of an International Survey of Specialist Centres. Hormone Research in Paediatrics 95(4): 363-373	- Study design not relevant to this review protocol *Retrospective survey and no multivariate analysis. No protocol specified exposures reported.*
Eyal, Ori, Levin, Yair, Oren, Asaf et al. (2019) Adrenal crises in children with adrenal insufficiency: epidemiology and risk factors. European journal of pediatrics 178(5): 731-738	- Data not reported in an extractable format or a format that can be analysed *Only report prevelance data*
Gazal, Giath and Zafar, Muhammad S (2023) A new cause of the adrenal crisis in dental and medical patients: Opioid-induced adrenal insufficiency. Journal of Taibah University Medical Sciences 18(3): 427-428	- Not a peer-reviewed publication *Letter to the editor*
Hahner, Stefanie, Loeffler, Melanie, Bleicken, Benjamin et al. (2010) Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. European journal of endocrinology 162(3): 597-602	- Data not reported in an extractable format or a format that can be analysed
Hahner, Stefanie, Spinnler, Christina, Fassnacht, Martin et al. (2015) High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. The Journal of clinical endocrinology and metabolism 100(2): 407-16	- Data not reported in an extractable format or a format that can be analysed *Study only reports prevalence data.*
Ishii, Tomohiro, Adachi, Masanori, Takasawa, Kei et al. (2018) Incidence and Characteristics of Adrenal Crisis in Children Younger than 7 Years with 21-Hydroxylase Deficiency: A Nationwide Survey in Japan. Hormone research in paediatrics 89(3): 166-171	- Study design not relevant to this review protocol *Retrospective survey with no multivariate analysis*
Iwasaku, Masahiro, Shinzawa, Maki, Tanaka, Shiro et al. (2017) Clinical characteristics of adrenal crisis in adult population with and without predisposing chronic adrenal insufficiency: a retrospective cohort study. BMC endocrine disorders 17(1): 58	- Study design not relevant to this review protocol *retrospective cohort study with no MV analysis*
Khalaf, Mohd W, Khader, Ruba, Cobetto, Gregory et al. (2013) Risk of adrenal crisis in	- Systematic review used as source of primary studies

Table 16: Studies excluded from the clinical review**Study**	**Reasons for exclusion.**
dental patients: results of a systematic search of the literature. Journal of the American Dental Association (1939) 144(2): 152-60	*Only included case reports and case series*
Nabi, T., Rafiq, N., Ur Rahman, M.H. et al. (2021) Clinical characteristics, etiology, and outcome of patients with adrenal crisis: A single-center experience. Journal of Medical Sciences (Taiwan) 41(5): 228-235	- No useable outcome measures
Notter, Antje; Jenni, Stefan; Christ, Emanuel (2018) Evaluation of the frequency of adrenal crises and preventive measures in patients with primary and secondary adrenal insufficiency in Switzerland. Swiss medical weekly 148: w14586	- Data not reported in an extractable format or a format that can be analysed
Odenwald, Brigitte, Nennstiel-Ratzel, Uta, Dorr, Helmuth-Gunther et al. (2016) Children with classic congenital adrenal hyperplasia experience salt loss and hypoglycemia: evaluation of adrenal crises during the first 6 years of life. European journal of endocrinology 174(2): 177-86	- Study does not contain an intervention relevant to this review protocol *Does not report factors listed in protocol.*
Ono, Yosuke, Ono, Sachiko, Yasunaga, Hideo et al. (2017) Clinical features and practice patterns of treatment for adrenal crisis: a nationwide cross-sectional study in Japan. European journal of endocrinology 176(3): 329-337	- Data not reported in an extractable format or a format that can be analysed
Papierska, Lucyna and Rabijewski, Michal (2013) Delay in diagnosis of adrenal insufficiency is a frequent cause of adrenal crisis. International journal of endocrinology 2013: 482370	- Study design not relevant to this review protocol *Retrospective with no multivariate analysis*
Pellot, J., Pastrana, E., Saavedra, F. et al. (2014) Acute adrenal insufficiency in cervical spinal cord injury. Neurocritical Care 21(1suppl1): 55	- Conference abstract
Reisch, Nicole, Willige, Marina, Kohn, Denise et al. (2012) Frequency and causes of adrenal crises over lifetime in patients with 21-hydroxylase deficiency. European journal of endocrinology 167(1): 35-42	- Data not reported in an extractable format or a format that can be analysed *No relevant exposure data to extract as only reported in a graph with no values.*
Rushworth, R L and Torpy, D J (2015) Modern Hydrocortisone Replacement Regimens in Adrenal Insufficiency Patients and the Risk of Adrenal Crisis. Hormone and metabolic research = Hormon- und Stoffwechselforschung = Hormones et metabolisme 47(9): 637-42	- Study design not relevant to this review protocol *Retrospective with no multivariate analysis*
Rushworth, R Louise and Torpy, David J (2014) A descriptive study of adrenal crises in adults with adrenal insufficiency: increased risk with	- Study design not relevant to this review protocol

Table 16: Studies excluded from the clinical review **Study**	**Reasons for exclusion.**
age and in those with bacterial infections. BMC endocrine disorders 14: 79	*Retrospective design with no multivariate analysis and no exposures detailed in the protocol reported.*
Smans, Lisanne C C J, Van der Valk, Eline S, Hermus, Ad R M M et al. (2016) Incidence of adrenal crisis in patients with adrenal insufficiency. Clinical endocrinology 84(1): 17-22	- Study does not contain an intervention relevant to this review protocol *Does not report risk factors detailed in the protocol.*
White, Katherine G (2019) A retrospective analysis of adrenal crisis in steroid-dependent patients: causes, frequency and outcomes. BMC endocrine disorders 19(1): 129	- Study design not relevant to this review protocol *Retrospective survey with no multivariate analysis*
Worth, Chris, Vyas, Avni, Banerjee, Indraneel et al. (2021) Acute Illness and Death in Children With Adrenal Insufficiency. Frontiers in endocrinology 12: 757566	- Study design not relevant to this review protocol *retrospective survery with no MV analysis and no exposures reported from protocol.*

J.2 Health Economic studies

None.

Appendix K Recommendations for research

K.1.1 Recommendation for research

Which patients taking long-term steroids are at increased risk of adrenal crisis and adverse hospital outcomes?.

K.1.2 Why this is important

Use of exogenous glucocorticoids at supraphysiological doses causes hypothalamo-pituitary-adrenal (HPA) axis suppression. In this regard doses equivalent to prednisolone 3-5mg a day that are used for more than 4 weeks, or repeated cycles (such as dexamethasone used as an antiemetic in chemotherapy or prednisolone in COPD/asthma rescue packs), across all routes, that is oral, inhaled, intramuscular, intraarticular injection and topical are all potentially adrenally suppressive. This is summarised in SPS document (https://www.endocrinology.org/media/4091/spssfe_supporting_sec_-final_10032021-1.pdf). A review by Bornstein et al (JCEM 2015) describes how there is no dosing regimen or time of use for which HPA axis suppression can be safely excluded hence this leads to uncertainty for who is at risk of adrenal crisis.

K.1.3 Rationale for the recommendation for research

Importance to 'patients' or the population	There are over 900 000 prescriptions for glucocorticoids across all routes of administration in the NHS a year. In addition, IM injections are given by physiotherapists for example in the community and this prescribing is not recorded anywhere. Steroids are also widely prescribed in the private sector and whilst this does not directly come under NHS prescribing, impact of these drugs is picked up in NHS acute care and OP services. We know that exogenous GC causes HPA axis suppression, however we do not know exactly who is at risk. Hence a lot of time is spent educating patients thought to be at risk with Sick-day rules providing emergency supply of oral GC and even emergency hydrocortisone injection kits in case of vomiting. In addition, advice is for these patients need extra cover with glucocorticoids for invasive procedures including dental work) and surgery to avoid adrenal crisis. Six percent of all adrenal crisis occurred in health-care situations (White and Arlt 2010), all of which may be entirely preventable. This causes anxiety to patients and their carers and has a health economic impact on both mediation of person power to see these patients, offer advice and support.
Relevance to NICE guidance	The evidence for who is at risk of adrenal crisis was reviewed in section 4.3. There was only 1 relevant study identifying people at risk of adrenal crisis and this study excluded people on exogenous glucocorticoids so there is no data found to guide who is a risk of adrenal crisis for patients on exogenous steroids. Therefore, having good quality evidence to support recommendations would be extremely valuable to provide evidence for next version of this guideline.
Relevance to the NHS	Glucocorticoids are prescribed widely across the NHS. Impact of this in patients is poorly understood by those professionals prescribing them if we know who is at risk of AI and adrenal crisis we can then target education and support more effectively. This will save the NHS money as it is highly likely the population at risk will be smaller if more clearly defined.
National priorities	This links in to the National Patient Safety Alert as an identified patient safety concern https://www.england.nhs.uk/publication/national-patient-safety-alert-steroid-emergency-card-to-support-early-recognition-and-treatment-of-adrenal-crisis-in-adults/

Current evidence base	There is a paucity of data here on which to make recommendations. We need good quality studies with numbers sufficient to inform safe patient care.
Equality considerations	None known.

K.1.4 Modified PICO table

Population	Observational big-data analysis using existing primary care data resources identifying patients taking GCs.
Intervention	-
Comparator	Different indications for GC prescription, different routes of steroid administration, different doses
Outcome	Admission to hospital coded as adrenal crisis, death from NHS digital.
Study design	Observational
Timeframe	