

Adrenal insufficiency: identification and management

Evidence review L: Non-pharmacological strategies to prevent adrenal crisis during periods of intercurrent illness and periods of physiological stress

NICE guideline NG243

Evidence reviews underpinning recommendations 1.4.10 to 1.4.11 in the NICE guideline

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This evidence review was developed by NICE

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1. Non-pharmacological interventions for physiological stress

1.1. Review question:

What is the clinical and cost effectiveness of non-pharmacological strategies to prevent adrenal crisis during periods of intercurrent illness and periods of physiological stress?

1.1.1. Introduction

In times of physiological stress (increased physical need for cortisol/glucocorticoid replacement), individuals with adrenal insufficiency are unable to produce enough cortisol to meet these requirements. A failure to adjust glucocorticoid therapy in times of physiological stress may place individuals at risk of adrenal crisis or even death.

Patients, their family, or carers, may require the necessary information and training to develop the knowledge and skills to adjust their glucocorticoids in this way. Currently, there is variation in practice on the provision of information and in the level of content made available.

This review explores non-pharmacological strategies for managing periods of physiological stress in people with adrenal insufficiency.

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	<p>Inclusion:</p> <p>People with adrenal insufficiency (primary, secondary, or tertiary) who are diagnosed or presumed adrenal insufficiency including the following groups:</p> <p>Strata:</p> <ul style="list-style-type: none">• Adults (aged ≥ 16 years)• Children aged ≥ 5 up to 16 years.• Children aged < 5 <p>Exclusion:</p> <p>None specified.</p>
Intervention(s)	<ul style="list-style-type: none">• Patient support groups• Peer support groups• Clinical Nurse Specialist or pharmacist or other non-medical practitioners• Access to urgent advice• Structured counselling or counselling prior to a planned procedure• Flags on electronic records (e.g. schools, ambulance registrations)• Patient held alerts e.g. cards, bracelets, steroid card.
Comparison(s)	<ul style="list-style-type: none">• Compared to each other• no intervention• standard/usual care as defined by authors

Outcomes	<p>All outcomes are considered equally important for decision making and therefore have all been rated as critical:</p> <ul style="list-style-type: none"> • Mortality • Health-related quality of life, for example EQ-5D, SF-36 • Incidence of adrenal crisis • Admission to hospital • Admission to ITU • Length of hospital stay. • Readmission to hospital • Psychological morbidities e.g. Incidence of stress or PTSD <p>Follow up: Medium 6 months to a year If evidence only available for less than 6 months this will be included and downgraded for indirectness</p>
Study design	<p>Systematic reviews of RCTs and RCTs will be considered for inclusion. Cross-over trials will also be considered for inclusion regardless of washout period.</p> <p>If insufficient RCT evidence is available, a search for non-randomised studies will be considered if they have conducted a multivariate analysis adjusting for at least 3-4 of the following key confounders:</p> <ul style="list-style-type: none"> • Age • Sex • Weight / BMI • Smoking • Time to treatment • Doses (timing or actual dose) • Comorbidities e.g. heart disease, diabetes, kidney disease • Socioeconomic status • Educational attainment • Health literacy • Digital literacy <p>Published NMAs and IPDs will be considered for inclusion.</p>

1.1.3. Methods and process

This evidence review was developed using the methods and process described in [Developing NICE guidelines: the manual](#). Methods specific to this review question are described in the review protocol in Appendix A and the methods document.

Declarations of interest were recorded according to [NICE's conflicts of interest policy](#).

1.1.4. Effectiveness evidence

1.1.4.1. Included studies

A search was conducted for randomised controlled trials (RCTs) and observational studies comparing non-pharmacological interventions for the management of physiological stress in people with adrenal insufficiency.

No relevant RCTs or observational studies were identified.

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

1.1.4.2. Excluded studies

See the excluded studies list in Appendix J.

1.1.5. Summary of studies included in the effectiveness evidence

No relevant clinical studies were identified.

1.1.6. Summary of the effectiveness evidence

No relevant clinical studies were identified.

1.1.7. Economic evidence

1.1.7.1. Included studies

No health economic studies were included.

1.1.7.2. Excluded studies

No relevant health economic studies were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G.

1.1.8. Economic model

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

1.1.9. Unit costs

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

Table 2: Staff costs associated with non-pharmacological interventions.

Resource	Cost per hour
Nurse	
Band 5	£43.78
Band 6	£53.87
Band 7	£64.27
Pharmacist	
Band 6	£54.71
Band 7	£65.73
Psychologist	
Band 5	£52.72
Band 6	£63.74
Band 7	£73.03
Band 8a	£85.81

Resource	Cost per hour
Band 8b	£101.47
Psychiatrist	
Speciality register (48-hour week)	£68.89
Speciality register (56-hour week)	£58.96
Associate specialist	£144.22
Consultant	£152.65

Source: PSSRU 2020/21¹ including qualification costs (and excluding individual productivity costs)

Table 3: Other costs associated with non-pharmacological interventions

Resource	Unit costs
Steroid emergency card (100 cards)	£2.65

Source: Society for Endocrinology³ cost excludes VAT

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

1.2.1. The outcomes that matter most

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

1.2.2. The quality of the evidence

No clinical evidence was identified for this review.

1.2.3. Benefits and harms

In the absence of any identified evidence, the committee decided to make consensus recommendations to reflect best current clinical practice for non-pharmacological management of adrenal insufficiency. They wished to highlight emergency cards that should be given to people who are taking glucocorticoids or who have adrenal insufficiency and are at risk of serious complications.

The NHS Steroid Emergency Card is given to all adult patients at risk of adrenal crisis including people with primary adrenal insufficiency and people who may develop secondary adrenal insufficiency and become steroid dependent. Its purpose is to prompt all healthcare professionals to consider adrenal crises in people carrying the card, initiate appropriate management for surgery or invasive procedures and treat patients rapidly and appropriately when presenting as an emergency. It includes a summary of the management and emergency treatment of adrenal crisis and provides a link to the Society for Endocrinology emergency management guidelines. It is provided by health care professionals prescribing glucocorticoids or looking after patients with adrenal insufficiency.

The British Society of Paediatric Endocrinology and Diabetes (BSPED) has developed an emergency steroid card which summarises the emergency management and sick-day rules in children and young people. This card is given to children and young adults who have

adrenal insufficiency or who are at high risk of adrenal insufficiency due to exogenous steroids.

A Steroid treatment card (blue card) is also available and is provided to people who are at risk of tertiary adrenal insufficiency or can be ordered from NHS Forms at NHS Business Services Authority (NHS BSA). This generally affects people with non-endocrine conditions who are on exogenous steroids where dose and duration could lead to adrenal suppression. The card includes guidance on minimising the risks when taking steroids, such as not stopping glucocorticoids abruptly, or changes in dose if the person is experiencing any physiological stress, undergoing surgery or invasive procedures. It provides details of an individual's prescriber, drug, dosage, and duration of treatment for healthcare professionals treating the patient.

The committee emphasised the importance of providing information to people with or at high risk of adrenal insufficiency on how to manage their treatment at times of physiological stress such as intercurrent illness and on sick days. They also highlighted additional non-pharmacological methods that are available to alert health care professionals about a patient's condition, and which are easy to implement. These include medical alert jewellery such as bracelets, apps, and mobile phone medical IDs.

1.2.4. Cost-effectiveness and resource use

No economic evaluations were identified for this review; therefore, unit costs were presented to aid the committee's consideration of cost-effectiveness. Unit costs were obtained for a range of healthcare professionals who may deliver non-pharmacological interventions listed in the protocol. In addition, the cost of Steroid Emergency Cards was also presented.

In current best clinical practice, all people with a diagnosis of adrenal insufficiency are provided education about daily dosing, sick-day rules and crisis management. Adults with adrenal insufficiency are given steroid emergency cards which provide healthcare staff important information on when to prescribe emergency hydrocortisone and the person's personal information (such as NHS number and why they are prescribed steroids). Children with adrenal insufficiency are given a BSPED (British Society for Paediatric Endocrinology and Diabetes) adrenal insufficiency card which provides parents, carers, and healthcare staff a child's steroid care plan for sick-days and emergencies. People at risk of adrenal suppression because of corticosteroid use are also provided a blue steroid card which provides information and advice for healthcare professionals and people at risk of adrenal insufficiency.

Education on daily dosing, sick-day rules and crisis management is provided at the time of diagnosis and throughout a person's treatment. Education can be provided by various healthcare professionals as this information is continually relayed to a person with AI when they present in a healthcare setting. In current practice, the structure of endocrinology departments varies; making it challenging to estimate the cost of providing this education. However, because the provision of this education is best clinical practice and the cost of providing additional education when people are in a healthcare setting is minimal (a couple of minutes of extra staff time), this recommendation is not expected to result in a significant resource impact. In addition, this provision of information is highly likely to be cost-effective as without this information people are at increased risk of experiencing an adrenal crisis. An adrenal crisis not only negatively impacts a person's quality and life (and may result in death if not treated quickly enough), but also has large cost implications associated with it. Costs of an adrenal crisis will vary – and can range from a hospital admission in intensive care to a day case hospital admission.

Adult steroid emergency cards cost £2.65 (for 100 cards). The provision of BSPED adrenal insufficiency cards is current practice. The cost of providing BSPED adrenal insufficiency cards is likely already included in administrative budgets as these are downloaded from the

BSPED website and printed by endocrinology departments to be given to parents and carers. Blue steroid cards are provided by pharmacists when the person picks up their steroid prescription.

In best practice people are also provided information on the use of patient held alerts (such as medic alert bracelets) and directed to recognised patient support groups. Patient-held alerts are either free (for example, mobile phone medical ID) or the cost is borne by the person with adrenal insufficiency. Patient support groups are run by charities and therefore no cost is incurred to the NHS.

Overall, the recommendations made for non-pharmacological interventions for managing periods of physiological stress are largely reflective of clinical practice and will therefore not result in a significant resource impact.

1.2.5. Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.10 – 1.4.11.

References

1. Jones K, Burns A. Unit costs of health and social care 2021. Canterbury. Personal Social Services Research Unit University of Kent, 2021. Available from: <https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-of-health-and-social-care-2021/>
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>
3. Simpson H. New NHS Steroid Emergency Card: Available to order. Endocrinologist. 2020; (137)

Appendices

Appendix A Review protocols

A.1 Review protocol for non-pharmacological management of Adrenal Insufficiency during times of physiological stress

ID	Field	Content
1.	Review title	Non-pharmacological management of AI during times of physiological stress
2.	Review question	What is the clinical and cost effectiveness of non-pharmacological strategies to prevent adrenal crisis during periods of intercurrent illness and periods of physiological stress?
3.	Objective	To determine the most clinically effective non-pharmacological strategies to prevent adrenal crisis during intercurrent illness and physiological stress in people with adrenal insufficiency.
4.	Searches	<p>The following databases (from inception) will be searched:</p> <ul style="list-style-type: none"> • AMED • CINAHL • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistemonikos • MEDLINE • PsycINFO <p>Searches will be restricted by:</p> <ul style="list-style-type: none"> • English language studies

		<ul style="list-style-type: none"> • Human studies <p>The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant.</p> <p>The full search strategies will be published in the final review.</p> <p>Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).</p>
5.	Condition or domain being studied	Adrenal insufficiency
6.	Population	<p>Inclusion:</p> <p>People with adrenal insufficiency (primary, secondary or tertiary) who are diagnosed or presumed adrenal insufficiency including the following groups:</p> <p>Strata:</p> <ul style="list-style-type: none"> • Adults (aged ≥ 16 years) • Children aged ≥ 5 up to 16 years • Children aged < 5 <p>Exclusion:</p> <p>None specified</p>
7.	Intervention	<ul style="list-style-type: none"> • Patient support groups • Peer support groups • Clinical Nurse Specialist or pharmacist or other non-medical practitioners • Access to urgent advice • Structured counselling or counselling prior to a planned procedure • Flags on electronic records (e.g. schools, ambulance registrations) • Patient held alerts e.g. cards, bracelets, steroid card
8.	Comparator	<ul style="list-style-type: none"> • Compared to each other

		<ul style="list-style-type: none"> • no intervention • standard/usual care as defined by authors
9.	Types of study to be included	<p>Systematic reviews of RCTs and RCTs will be considered for inclusion.</p> <p>Cross-over trials will also be considered for inclusion regardless of washout period.</p> <p>If insufficient RCT evidence is available, a search for non-randomised studies will be considered if they have conducted a multivariate analysis adjusting for at least 3-4 of the following key confounders:</p> <ul style="list-style-type: none"> - Age - Sex - Weight / BMI - Smoking - Time to treatment - Doses (timing or actual dose) - comorbidities e.g heart disease, diabetes, kidney disease - socioeconomic status - educational attainment - health literacy - digital literacy <p>Published NMAs and IPDs will be considered for inclusion.</p>
10.	Other exclusion criteria	<p>Non comparative cohort studies</p> <p>Before and after studies</p> <p>Non-English language studies.</p> <p>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.</p>

11.	Context	
12.	Primary outcomes (critical outcomes)	<p>All outcomes are considered equally important for decision making and therefore have all been rated as critical:</p> <ul style="list-style-type: none"> Mortality Health-related quality of life, for example EQ-5D, SF-36 Incidence of adrenal crisis Admission to hospital Admission to ITU Length of hospital stay Readmission to hospital Psychological morbidities e.g Incidence of stress or PTSD <p>Follow up: Medium 6 months to a year If evidence only available for less than 6 months this will be included and downgraded for indirectness</p>
13.	Data extraction (selection and coding)	<p>All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated.</p> <p>10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.</p> <p>The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.</p> <p>A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).</p> <p>10% of all evidence reviews are quality assured by a senior research fellow. This includes checking:</p> <ul style="list-style-type: none"> • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data

		<ul style="list-style-type: none"> • a sample of the risk of bias assessments <p>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.</p> <p>Study investigators may be contacted for missing data where time and resources allow.</p>
14.	Risk of bias (quality) assessment	<p>Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual</p> <ul style="list-style-type: none"> • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non randomised study, including cohort studies: Cochrane ROBINS-I
15.	Strategy for data synthesis	<p>Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences.</p> <p>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.</p> <p>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.</p> <p>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/</p> <p>Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.</p> <p>WinBUGS will be used for network meta-analysis, if possible given the data identified.</p>
16.	Analysis of sub-groups	<p>Subgroups that will be investigated if heterogeneity is present:</p> <p>None identified</p>

17.	Type and method of review	<input checked="" type="checkbox"/>	Intervention	
		<input type="checkbox"/>	Diagnostic	
		<input type="checkbox"/>	Prognostic	
		<input type="checkbox"/>	Qualitative	
		<input type="checkbox"/>	Epidemiologic	
		<input type="checkbox"/>	Service Delivery	
		<input type="checkbox"/>	Other (please specify)	
18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date	June 2022		
21.	Anticipated completion date	April 2024		
22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	<input checked="" type="checkbox"/>	<input type="checkbox"/>
		Piloting of the study selection process	<input type="checkbox"/>	<input type="checkbox"/>
		Formal screening of search results against eligibility criteria	<input type="checkbox"/>	<input type="checkbox"/>
		Data extraction	<input type="checkbox"/>	<input type="checkbox"/>
		Risk of bias (quality) assessment	<input type="checkbox"/>	<input type="checkbox"/>
		Data analysis	<input type="checkbox"/>	<input type="checkbox"/>
23.	Named contact	5a. Named contact		

		<p>Guideline Development Team NGC</p> <p>5b Named contact e-mail</p> <p>Hypoadrenalism@nice.org.uk</p> <p>5e Organisational affiliation of the review</p> <p>National Institute for Health and Care Excellence (NICE)</p>
24.	Review team members	<p>From NICE:</p> <p>Sharon Swain [Guideline lead]</p> <p>Saoussen Ftouh [Senior systematic reviewer]</p> <p>Meena Tafazzoli [Technical Analyst]</p> <p>Lisa Miles [Technical Analyst]</p> <p>Alexandra Bannon [Health economist]</p> <p>Stephen Deed [Information specialist]</p>
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	<p>NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as:</p> <ul style="list-style-type: none"> • 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	<input type="checkbox"/> Ongoing
		<input type="checkbox"/> Completed but not published
		<input type="checkbox"/> Completed and published
		<input type="checkbox"/> Completed, published and being updated
		<input type="checkbox"/> Discontinued
34.	Additional information	-
35.	Details of final publication	www.nice.org.uk

A.2 Health economic review protocol

Table 4: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	<ul style="list-style-type: none"> • 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	<p>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.</p> <p>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</p> <p>Inclusion and exclusion criteria</p> <ul style="list-style-type: none"> • 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. <p>Where there is discretion</p> <p>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.</p> <p>The health economist will be guided by the following hierarchies. <i>Setting:</i></p>

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2007 or later but that depend on unit costs and resource data entirely or predominantly from before 2007 will be rated as 'Not applicable'.
- Studies published before 2007 be excluded before being assessed for applicability and methodological limitations.

Quality and relevance of effectiveness data used in the health economic analysis:

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B Literature search strategies

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

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

B.1 Clinical search literature search strategy

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

Table 5: Database parameters, filters and limits applied

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 6 January 2023	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 6 January 2023	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 1 of 12, 6 January 2023 Cochrane Central Register of Controlled Trials to Issue 1 of 12, 6 January 2023	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 6 January 2023	Systematic review Exclusions (Cochrane reviews)
Current Nursing and Allied Health Literature (CINAHL) (EBSCO)	Inception to 6 January 2023	Human Exclusions (Medline records)

Database	Dates searched	Search filter used
		English Language
PsycINFO (OVID)	1806 to 6 January 2023	Human Exclusions (letters, case reports, rodents) English Language
Allied and Complementary Medicine (AMED) (OVID)	1985 to 6 January 2023	

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 inadepua* 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 corticotropi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadepua* 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.	Self-Help Groups/
36.	((self help or selfhelp or support*) adj3 (group* or network*)).ti,ab,kf.
37.	(peer adj2 (network* or support*)).ti,ab,kf.
38.	Self-Management/
39.	(self adj2 (manag* or care)).ti,ab,kf.
40.	(stress* adj3 (manag* or reduc* or adjust* or control* or adapt*)).ti,ab,kf.
41.	exp Cognitive Behavioral Therapy/
42.	(cognit* adj3 (behaviour* or behavior* or therap*)).ti,ab,kf.
43.	exp Exercise/ or Meditation/ or Yoga/ or exp Mindfulness/
44.	(exercis* or meditat* or yoga or mindfulness or mind aware*).ti,ab,kf.
45.	Counseling/ or Directive Counseling/
46.	(counselling or counseling or psychotherap* or psychiatr* or psychologic* or "talking therap*" or "structur* therap*").ti,ab,kf.
47.	Emergency Medical Tags/
48.	((patient or alert* or steroid or emergency or medical) adj3 (tag* or card* or bracelet* or wristband* or necklace* or keyring or ID jewellery)).ti,ab,kf.
49.	Electronic Health Records/
50.	((electronic or patient* or school* or ambulance) adj4 (record* or registration* or alert*)).ti,ab,kf.
51.	Patient Education as Topic/ or Patient Education Handout/
52.	((patient* or inpatient* or outpatient*) adj3 (inform* or advice or advis* or need* or requirement* or support* or access* or service* or educat* or learn* or teach* or train* or network*)).ti,ab,kf.
53.	((("nurse specialist*" or pharmacist* or dentist* or "healthcare professional*" or "health care professional*" or "health professional*" or psychiatrist* or psychologist* or psychotherapist* or counselor* or counsellor*) adj3 (inform* or advice or advis* or need* or requirement* or support* or access* or educat* or learn* or teach* or train*)).ti,ab,kf.
54.	or/35-53
55.	34 and 54
56.	randomized controlled trial.pt.
57.	controlled clinical trial.pt.
58.	randomi#ed.ab.
59.	placebo.ab.
60.	randomly.ab.
61.	clinical trials as topic.sh.
62.	trial.ti.
63.	cross-over studies/
64.	(crossover or "cross over").ti,ab.
65.	or/56-64
66.	Meta-Analysis/
67.	Meta-Analysis as Topic/

68.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
69.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
70.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
71.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
72.	(search* adj4 literature).ab.
73.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
74.	cochrane.jw.
75.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
76.	or/66-75
77.	Epidemiologic studies/
78.	Observational study/
79.	exp Cohort studies/
80.	(cohort adj (study or studies or analys* or data)).ti,ab.
81.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
82.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
83.	Controlled Before-After Studies/
84.	Historically Controlled Study/
85.	Interrupted Time Series Analysis/
86.	(before adj2 after adj2 (study or studies or data)).ti,ab.
87.	exp case control study/
88.	case control*.ti,ab.
89.	Cross-sectional studies/
90.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
91.	or/77-90
92.	55 and (65 or 76 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 corticotropi* 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 hypoadosteronism 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.	self help/
35.	((self help or selfhelp or support*) adj3 (group* or network*)).ti,ab,kf.
36.	(peer adj2 (network* or support*)).ti,ab,kf.
37.	self care/
38.	(self adj2 (manag* or care)).ti,ab,kf.
39.	(stress* adj3 (manag* or reduc* or adjust* or control* or adapt*)).ti,ab,kf.
40.	exp cognitive behavioral therapy/
41.	(cognit* adj3 (behaviour* or behavior* or therap*)).ti,ab,kf.
42.	exp exercise/ or exp meditation/ or exp yoga/ or exp mindfulness/
43.	(exercis* or meditat* or yoga or mindfulness or mind aware*).ti,ab,kf.
44.	counseling/ or directive counseling/ or patient counseling/ or psychological counseling/
45.	(counselling or counseling or psychotherap* or psychiatr* or psycholog* or "talking therap*" or "structur* therap*").ti,ab,kf.
46.	emergency health service/
47.	((patient or alert* or steroid or emergency or medical) adj3 (tag* or card* or bracelet* or wristband* or necklace* or keyring or ID jewellery)).ti,ab,kf.
48.	electronic health record/
49.	((electronic or patient* or school* or ambulance) adj4 (record* or registration* or alert*)).ti,ab,kf.
50.	patient education/
51.	((patient* or inpatient* or outpatient*) adj3 (inform* or advice or advis* or need* or requirement* or support* or access* or service* or educat* or learn* or teach* or train* or network*)).ti,ab,kf.

52.	((("nurse specialist*" or pharmacist* or dentist* or "healthcare professional*" or "health care professional*" or "health professional*" or psychiatrist* or psychologist* or psychotherapist* or counselor* or counsellor*) adj3 (inform* or advice or advis* or need* or requirement* or support* or access* or educat* or learn* or teach* or train*)).ti,ab,kf.
53.	or/34-52
54.	33 and 53
55.	random*.ti,ab.
56.	factorial*.ti,ab.
57.	(crossover* or cross over*).ti,ab.
58.	((doubl* or singl*) adj blind*).ti,ab.
59.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
60.	crossover procedure/
61.	single blind procedure/
62.	randomized controlled trial/
63.	double blind procedure/
64.	or/55-63
65.	Systematic Review/
66.	Meta-Analysis/
67.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
68.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
69.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
70.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
71.	(search* adj4 literature).ab.
72.	(medline or pubmed or cochrane or embase or psychlit or psychlit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
73.	cochrane.jw.
74.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
75.	or/65-74
76.	Clinical study/
77.	Observational study/
78.	Family study/
79.	Longitudinal study/
80.	Retrospective study/
81.	Prospective study/
82.	Cohort analysis/
83.	Follow-up/
84.	cohort*.ti,ab.
85.	83 and 84
86.	(cohort adj (study or studies or analys* or data)).ti,ab.
87.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
88.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
89.	(before adj2 after adj2 (study or studies or data)).ti,ab.
90.	exp case control study/
91.	case control*.ti,ab.

92.	cross-sectional study/
93.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
94.	or/76-82,85-93
95.	54 and (64 or 75 or 94)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Adrenal Insufficiency] explode all trees
#2.	MeSH descriptor: [Adrenal Hyperplasia, Congenital] this term only
#3.	((addison* NEXT disease) or addisonian*):ti,ab,kw
#4.	((adrenal* or adrenocort* or adreno-cort*) near/3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)):ti,ab,kw
#5.	((cortisol or aldosterone or adrenocorticotrop* or adreno-corticotrop* or ACTH or (corticotropi* NEXT releas*) or (corticotrophi* NEXT releas*) or corticoliberin or CRH) near/3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)):ti,ab,kw
#6.	(hypoadrenal* or hypo-adrenal* or hypoadrenocorticism or "hypo adrenocorticism" or adrenoleukodystrophy or "adreno leukodystrophy" or adrenomyeloneuropathy or "adreno myeloneuropathy" or hypoaldosteronism or "hypo aldosteronism"):ti,ab,kw
#7.	((adrenogenital or "adreno genital") near/1 (syndrome or disorder*)):ti,ab,kw
#8.	((haemorrhag* or hemorrhag* or bleed*) near/3 adrenal*):ti,ab,kw
#9.	((Bronze NEXT Schilder*) or "Melanodermic Leukodystrophy" or (Schilder NEXT Addison*) or (Siemerling NEXT Creutzfeldt*)):ti,ab,kw
#10.	((Allgrove or 3A or TripleA or AAA) near/1 syndrome):ti,ab,kw
#11.	(CAH or "X-ALD"):ti,ab
#12.	((Waterhouse NEXT Friderichsen*) or "antiphospholipid syndrome"):ti,ab,kw
#13.	"Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy":ti,ab,kw
#14.	(or #1-#13)
#15.	conference:pt or (clinicaltrials or trialsearch):so
#16.	#14 not #15
#17.	MeSH descriptor: [Self-Help Groups] this term only
#18.	(("self help" or selfhelp or support*) near/3 (group* or network*)):ti,ab,kw
#19.	(peer near/2 (network* or support*)):ti,ab,kw
#20.	MeSH descriptor: [Self-Management] this term only
#21.	(self near/2 (manag* or care)):ti,ab,kw
#22.	(stress* near/3 (manag* or reduc* or near/ust* or control* or adapt*)):ti,ab,kw
#23.	MeSH descriptor: [Cognitive Behavioral Therapy] explode all trees
#24.	(cognit* near/3 (behaviour* or behavior* or therap*)):ti,ab,kw
#25.	MeSH descriptor: [Exercise] explode all trees
#26.	MeSH descriptor: [Meditation] this term only
#27.	MeSH descriptor: [Yoga] this term only
#28.	MeSH descriptor: [Mindfulness] explode all trees
#29.	(exercis* or meditat* or yoga or mindfulness or mind-awar*):ti,ab,kw
#30.	MeSH descriptor: [Counseling] this term only
#31.	MeSH descriptor: [Directive Counseling] this term only
#32.	(counselling or counseling or psychotherap* or psychiatr* or psycholog* or talking-therap* or structured-therap*):ti,ab,kw
#33.	MeSH descriptor: [Emergency Medical Tags] this term only

#34.	((patient or alert* or steroid or emergency or medical) near/3 (tag* or card* or bracelet* or wristband* or necklace* or keyring or "ID jewellery")):ti,ab,kw
#35.	MeSH descriptor: [Electronic Health Records] this term only
#36.	((electronic or patient* or school* or ambulance) near/4 (record* or registration* or alert*)):ti,ab,kw
#37.	MeSH descriptor: [Patient Education as Topic] this term only
#38.	MeSH descriptor: [Patient Education Handout] this term only
#39.	((patient* or inpatient* or outpatient*) near/3 (inform* or advice or advis* or need* or requirement* or support* or access* or service* or educat* or learn* or teach* or train* or network*)):ti,ab,kw
#40.	((nurse-specialist* or pharmacist* or dentist* or ("health care" or healthcare or health) NEXT professional*) or psychiatrist* or psychologist* or psychotherapist* or counselor* or counsellor*) near/3 (inform* or advice or advis* or need* or requirement* or support* or access* or educat* or learn* or teach* or train*)):ti,ab,kw
#41.	(or #17-#40)
#42.	#16 and #41

Epistemonikos search terms

1.	(title:(title:(("adrenal insufficiency" OR "adrenal inadequacy" OR "adrenal deficiency" OR "adrenal suppression" OR "adrenal hypofunction" OR "adrenal disorder" OR "adrenal underactivity" OR "adrenal dysfunction" OR "adrenal crisis" OR "adrenal crises" OR "adrenal hypoplasia" OR "adrenal congenital hyperplasia" OR "addison disease" OR "addisons disease" OR "addison's disease" OR addisonian* OR hypoadrenal* OR "hypo adrenalism" OR hypoadrenocorticism OR "hypo adrenocorticism" OR adrenoleukodystrophy OR "adreno leukodystrophy" OR adrenomyeloneuropathy OR "adreno myeloneuropathy" OR hypoaldosteronism OR "hypo aldosteronism") OR abstract:(("adrenal insufficiency" OR "adrenal inadequacy" OR "adrenal deficiency" OR "adrenal suppression" OR "adrenal hypofunction" OR "adrenal disorder" OR "adrenal underactivity" OR "adrenal dysfunction" OR "adrenal crisis" OR "adrenal crises" OR "adrenal hypoplasia" OR "adrenal congenital hyperplasia" OR "addison disease" OR "addisons disease" OR "addison's disease" OR addisonian* OR hypoadrenal* OR "hypo adrenalism" OR hypoadrenocorticism OR "hypo adrenocorticism" OR adrenoleukodystrophy OR "adreno leukodystrophy" OR adrenomyeloneuropathy OR "adreno myeloneuropathy" OR hypoaldosteronism OR "hypo aldosteronism")) OR abstract:(title:(("adrenal inadequacy" OR "adrenal deficiency" OR "adrenal suppression" OR "adrenal hypofunction" OR "adrenal disorder" OR "adrenal underactivity" OR "adrenal dysfunction" OR "adrenal crisis" OR "adrenal crises" OR "adrenal hypoplasia" OR "adrenal congenital hyperplasia" OR "addison disease" OR "addisons disease" OR "addison's disease" OR addisonian* OR hypoadrenal* OR "hypo adrenalism" OR hypoadrenocorticism OR "hypo adrenocorticism" OR adrenoleukodystrophy OR "adreno leukodystrophy" OR adrenomyeloneuropathy OR "adreno myeloneuropathy" OR hypoaldosteronism OR "hypo aldosteronism")))) AND (title:(("self help" OR selfhelp OR "self management" OR "self care" OR "stress managment" OR "cognitive behavioral therapy" OR "cognitive behavioural therapy" OR exercise OR meditation OR yoga OR mindfulness OR "mind awarenes" OR counselling OR counseling OR psychotherap* OR psychiat* OR psycholog* OR "talking therap*" OR "structured therapy" OR "emergency medical tag" OR "emergency medical tags" OR "patient alert" OR "steroid card" OR "steroid cards" OR "emergency card" OR "emergency cards" OR bracelet* OR wristband* OR necklace* OR keyring OR "ID jewellery" OR "electronic record" OR "electronic records" OR "electronic health record" OR "electronic health
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	records" OR "school record" OR "school records" OR "patient education" OR "patient support" OR "patient advice" OR "patient needs" OR "nurse specialist" OR pharmacist* OR dentist* OR "healthcare professional" OR "healthcare professionals" OR "health care professional" OR "health care professionals" OR "health professional" OR "health professionals" OR psychiatrist* OR psychologist* OR psychotherapist* OR counselor* OR counsellor*) OR abstract:("self help" OR selfhelp OR "self management" OR "self care" OR "stress managment" OR "cognitive behavioral therapy" OR "cognitive behavioural therapy" OR exercise OR meditation OR yoga OR mindfulness OR "mind awarenes" OR counselling OR counseling OR psychotherap* OR psychiatr* OR psychologic* OR "talking therap*" OR "structured therapy" OR "emergency medical tag" OR "emergency medical tags" OR "patient alert" OR "steroid card" OR "steroid cards" OR "emergency card" OR "emergency cards" OR bracelet* OR wristband* OR necklace* OR keyring OR "ID jewellery" OR "electronic record" OR "electronic records" OR "electronic health record" OR "electronic health records" OR "school record" OR "school records" OR "patient education" OR "patient support" OR "patient advice" OR "patient needs" OR "nurse specialist" OR pharmacist* OR dentist* OR "healthcare professional" OR "healthcare professionals" OR "health care professional" OR "health care professionals" OR "health professional" OR "health professionals" OR psychiatrist* OR psychologist* OR psychotherapist* OR counselor* OR counsellor*))
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CINAHL (EBSCO) search terms

S1.	(MH "Adrenal Insufficiency+")
S2.	(MH "Adrenal Hyperplasia, Congenital")
S3.	TI ((addison* disease or addisonian*)) OR AB ((addison* disease or addisonian*))
S4.	TI (((adrenal* or adrenocort* or adreno cort*) AND (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*))) OR AB (((adrenal* or adrenocort* or adreno cort*) AND (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*)))
S5.	TI (((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) AND (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))) OR AB (((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) AND (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)))
S6.	TI ((hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoadosteronism or hypo aldosteronism)) OR AB ((hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoadosteronism or hypo aldosteronism))
S7.	TI (((adrenogenital or adreno genital) AND (syndrome or disorder*))) OR AB (((adrenogenital or adreno genital) AND (syndrome or disorder*)))
S8.	TI (((haemorrhag* or hemorrhag* or bleed*) AND adrenal*)) OR AB (((haemorrhag* or hemorrhag* or bleed*) AND adrenal*))
S9.	TI ((Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease)) OR AB ((Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease))
S10.	TI (((Allgrove or 3A or TripleA or AAA) AND syndrome)) OR AB (((Allgrove or 3A or TripleA or AAA) AND syndrome))
S11.	TI ((CAH or X-ALD)) OR AB ((CAH or X-ALD))

S12.	TI ((Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome)) OR AB ((Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome))
S13.	TI Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy OR AB Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy
S14.	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13
S15.	MH Support Groups
S16.	TI (((self help or selfhelp or support*) n3 (group* or network*))) OR AB (((self help or selfhelp or support*) n3 (group* or network*)))
S17.	TI ((peer n2 (network* or support*))) OR AB ((peer n2 (network* or support*)))
S18.	MH Self-Management
S19.	MH Self Care
S20.	TI ((self n2 (manag* or care))) OR AB ((self n2 (manag* or care)))
S21.	TI ((stress* n3 (manag* or reduc* or adjust* or control* or adapt*))) OR AB ((stress* n3 (manag* or reduc* or adjust* or control* or adapt*)))
S22.	MH Cognitive Therapy
S23.	TI ((cognit* n3 (behaviour* or behavior* or therap*))) OR AB ((cognit* n3 (behaviour* or behavior* or therap*)))
S24.	(MH "Exercise")
S25.	MH Meditation
S26.	MH Yoga
S27.	MH Mindfulness
S28.	TI ((exercis* or meditat* or yoga or mindfulness or mind awar*)) OR AB ((exercis* or meditat* or yoga or mindfulness or mind awar*))
S29.	MH Counseling
S30.	TI ((counselling or counseling or psychotherap* or psychiatr* or psycholog* or "talking therap*" or "structur* therap*")) OR AB ((counselling or counseling or psychotherap* or psychiatr* or psycholog* or "talking therap*" or "structur* therap*"))
S31.	(MH "Emergency Medical Tags")
S32.	TI (((patient or alert* or steroid or emergency or medical) n3 (tag* or card* or bracelet* or wristband* or necklace* or keyring or ID jewellery))) OR AB (((patient or alert* or steroid or emergency or medical) n3 (tag* or card* or bracelet* or wristband* or necklace* or keyring or ID jewellery)))
S33.	MH Electronic Health Records
S34.	TI (((electronic or patient* or school* or ambulance) n4 (record* or registration* or alert*))) OR AB (((electronic or patient* or school* or ambulance) n4 (record* or registration* or alert*)))
S35.	MH Patient Education
S36.	TI (((patient* or inpatient* or outpatient*) n3 (inform* or advice or advis* or need* or requirement* or support* or access* or service* or educat* or learn* or teach* or train* or network*))) OR AB (((patient* or inpatient* or outpatient*) n3 (inform* or advice or advis* or need* or requirement* or support* or access* or service* or educat* or learn* or teach* or train* or network*)))
S37.	TI ((("nurse specialist*" or pharmacist* or dentist* or "healthcare professional*" or "health care professional*" or "health professional*" or psychiatrist* or psychologist* or psychotherapist* or counselor* or counsellor*) n3 (inform* or advice or advis* or need* or requirement* or support* or access* or educat* or learn* or teach* or train*))) OR AB ((("nurse specialist*" or pharmacist* or dentist* or "healthcare professional*" or "health care professional*" or "health professional*" or psychiatrist* or psychologist* or psychotherapist* or counselor* or counsellor*) n3 (inform* or advice or advis* or need* or requirement* or support* or access* or educat* or learn* or teach* or train*)))

S38.	S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37
S39.	S14 AND S38

PsycINFO (OVID) search terms

1.	exp Adrenal Gland Disorders/
2.	(addison* disease or addisonian*).ti,ab,id.
3.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*).ti,ab,id.
4.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotropi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,id.
5.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,id.
6.	((adrenogenital or adreno genital) adj (syndrome or disorder*).ti,ab,id.
7.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,id.
8.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,id.
9.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,id.
10.	(CAH or X-ALD).ti,ab.
11.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,id.
12.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,id.
13.	or/1-12
14.	Letter/
15.	Case report/
16.	exp Rodents/
17.	or/14-16
18.	13 not 17
19.	limit 18 to (human and English language)
20.	support groups/
21.	((("self help" or selfhelp or support*) adj3 (group* or network*).ti,ab,id.
22.	(peer adj2 (network* or support*).ti,ab,id.
23.	self-management/ or self-help techniques/
24.	(self adj2 (manag* or care)).ti,ab,id.
25.	(stress* adj3 (manag* or reduc* or adjust* or control* or adapt*).ti,ab,id.
26.	exp cognitive behavior therapy/
27.	(cognit* adj3 (behaviour* or behavior* or therap*).ti,ab,id.
28.	exp exercise/ or meditation/ or yoga/ or mindfulness/
29.	(exercis* or meditat* or yoga or mindfulness or "mind aware").ti,ab,id.
30.	exp counseling/
31.	(counselling or counseling or psychotherap* or psychiatr* or psycholog* or "talking therap*" or "structur* therap*").ti,ab,id.

32.	((patient or alert* or steroid or emergency or medical) adj3 (tag* or card* or bracelet* or wristband* or necklace* or keyring or "ID jewellery")).ti,ab,id.
33.	electronic health records/
34.	((electronic or patient* or school* or ambulance) adj4 (record* or registration* or alert*)).ti,ab,id.
35.	client education/
36.	((patient* or inpatient* or outpatient*) adj3 (inform* or advice or advis* or need* or requirement* or support* or access* or service* or educat* or learn* or teach* or train* or network*)).ti,ab,id.
37.	((("nurse specialist*" or pharmacist* or dentist* or "healthcare professional*" or "health care professional*" or "health professional*" or psychiatrist* or psychologist* or psychotherapist* or counselor* or counsellor*) adj3 (inform* or advice or advis* or need* or requirement* or support* or access* or educat* or learn* or teach* or train*)).ti,ab,id.
38.	or/20-37
39.	19 and 38

AMED (OVID) search terms

1.	Adrenal gland disease/
2.	(addison* disease or addisonian*).af.
3.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).af.
4.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotropi* 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)).af.
5.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).af.
6.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).af.
7.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).af.
8.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).af.
9.	((Allgrove or 3A or TripleA or AAA) adj syndrome).af.
10.	(CAH or X-ALD).af.
11.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).af.
12.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.af.
13.	or/1-12
14.	self help groups/
15.	((("self help" or selfhelp or support*) adj3 (group* or network*)).af.
16.	(peer adj2 (network* or support*)).af.
17.	self care/
18.	(self adj2 (manag* or care)).af.
19.	(stress* adj3 (manag* or reduc* or adjust* or control* or adapt*)).af.
20.	Cognitive therapy/

21.	(cognit* adj3 (behaviour* or behavior* or therap*)).af.
22.	exp exercise/ or meditation/ or yoga/
23.	(exercis* or meditat* or yoga or mindfulness or "mind aware").af.
24.	counseling/
25.	(counselling or counseling or psychotherap* or psychiatr* or psychologic* or "talking therap*" or "structur* therap*").af.
26.	((patient or alert* or steroid or emergency or medical) adj3 (tag* or card* or bracelet* or wristband* or necklace* or keyring or "ID jewellery")).af.
27.	medical records/
28.	((electronic or patient* or school* or ambulance) adj4 (record* or registration* or alert*)).af.
29.	exp patient education/
30.	((patient* or inpatient* or outpatient*) adj3 (inform* or advice or advis* or need* or requirement* or support* or access* or service* or educat* or learn* or teach* or train* or network*)).af.
31.	((("nurse specialist*" or pharmacist* or dentist* or "healthcare professional*" or "health care professional*" or "health professional*" or psychiatrist* or psychologist* or psychotherapist* or counselor* or counsellor*) adj3 (inform* or advice or advis* or need* or requirement* or support* or access* or educat* or learn* or teach* or train*)).af.
32.	or/14-31
33.	13 and 32

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Adrenal Insufficiency population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards.

Table 6: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	1 January 2014 – 26 September 2023	Health economics studies Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language

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

Medline (Ovid) search terms

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

40.	exp Adrenal cortex insufficiency/
41.	Congenital adrenal hyperplasia/

42.	(addison* disease or addisonian*).ti,ab,kf.
43.	((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.
44.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotropi* 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.
45.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoadosteronism or hypo aldosteronism).ti,ab,kf.
46.	((adrenogenital or adreno genital) adj (syndrome or disorder*).ti,ab,kf.
47.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
48.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
49.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
50.	(CAH or X-ALD).ti,ab.
51.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
52.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
53.	or/1-13
54.	letter.pt. or letter/
55.	note.pt.
56.	editorial.pt.
57.	case report/ or case study/
58.	(letter or comment*).ti.
59.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
60.	or/15-20
61.	randomized controlled trial/ or random*.ti,ab.
62.	21 not 22
63.	animal/ not human/
64.	nonhuman/
65.	exp Animal Experiment/
66.	exp Experimental Animal/
67.	animal model/
68.	exp Rodent/
69.	(rat or rats or mouse or mice or rodent*).ti.
70.	or/23-30
71.	14 not 31
72.	limit 32 to English language
73.	health economics/
74.	exp economic evaluation/
75.	exp health care cost/
76.	exp fee/
77.	budget/
78.	funding/
79.	budget*.ti,ab.

80.	cost*.ti.
81.	(economic* or pharmaco?economic*).ti.
82.	(price* or pricing*).ti,ab.
83.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
84.	(financ* or fee or fees).ti,ab.
85.	(value adj2 (money or monetary)).ti,ab.
86.	or/34-46
87.	33 and 47
88.	limit 48 to yr="2014 -Current"

NHS EED and HTA (CRD) search terms

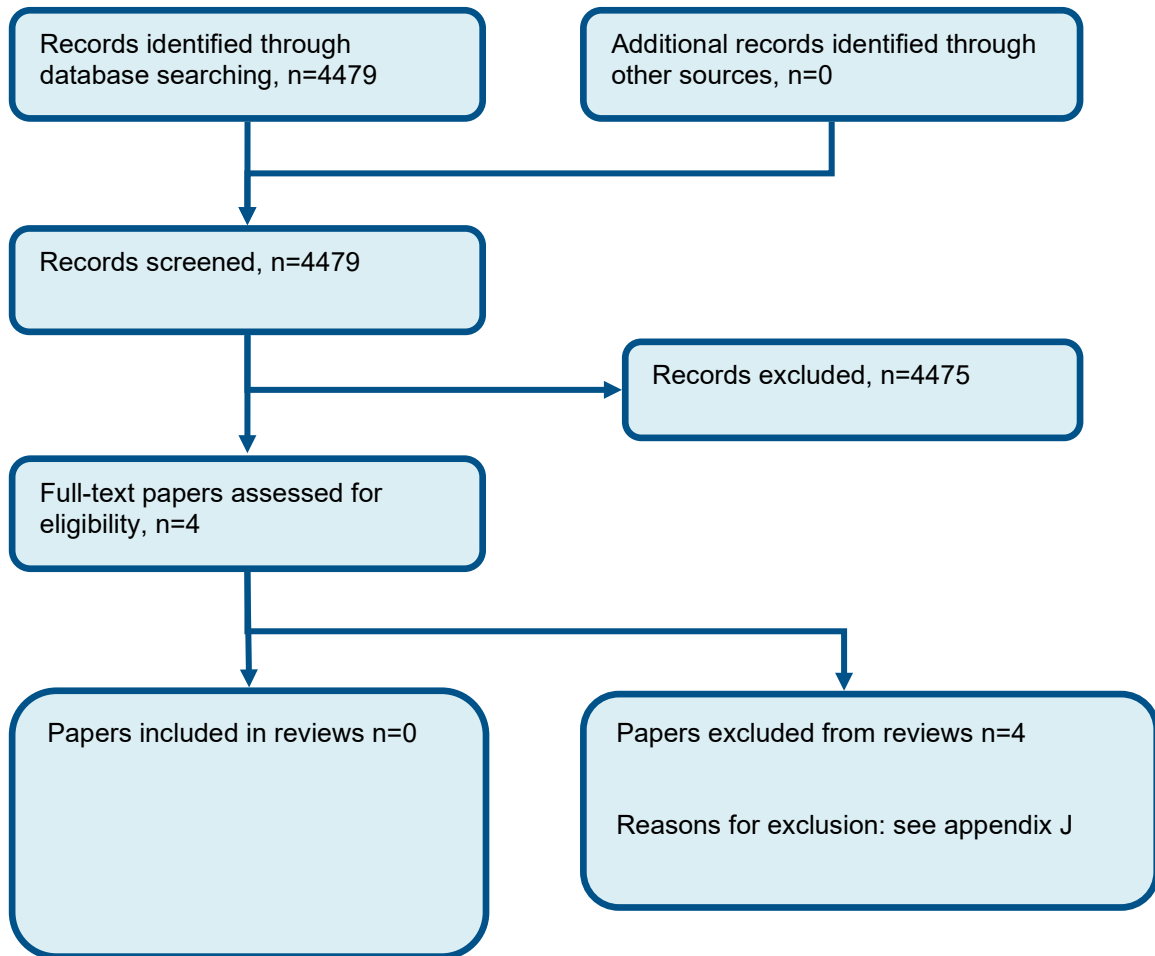
#1.	MeSH DESCRIPTOR Adrenal Insufficiency EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Adrenal Hyperplasia, Congenital EXPLODE ALL TREES
#3.	(addison* disease or addisonian)
#4.	(adrenal*) AND (insufficien* or inadequa* or deficien* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or 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 corticotropi* 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))
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Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of non-pharmacological management for physiological and psychological stress



Appendix D Effectiveness evidence

None.

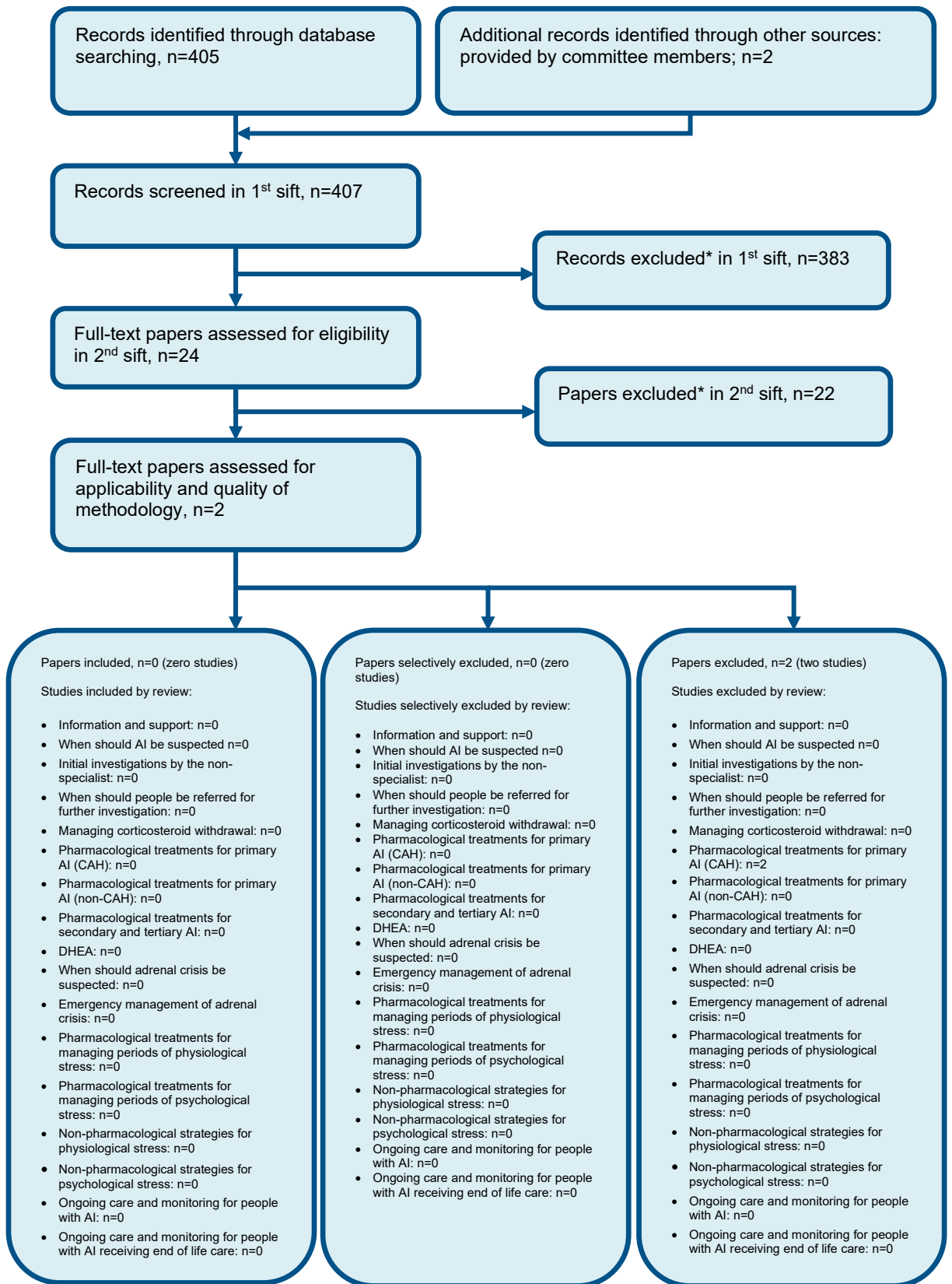
Appendix E Forest plots

None.

Appendix F GRADE and/or GRADE-CERQual tables

None.

Appendix G Economic evidence study selection



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

Appendix H Economic evidence tables

None.

Appendix I Health economic model

No original economic modelling was undertaken for this review question.

Appendix J Excluded studies

J.1 Clinical studies

Study	Reasons for exclusion
<p>Burger-Stritt, Stephanie, Eff, Annemarie, Quinkler, Marcus et al. (2020) Standardised patient education in adrenal insufficiency: a prospective multi-centre evaluation. European journal of endocrinology 183(2): 119-127</p>	<p>- Study does not address our clinical question</p>
<p>Halpin, K.L.; Paprocki, E.L.; McDonough, R.J. (2019) Utilizing health information technology to improve the recognition and management of life-threatening adrenal crisis in the pediatric emergency department: Medical alert identification in the 21st century. Journal of Pediatric Endocrinology and Metabolism 32(5): 513-518</p>	<p>- Study does not address our clinical question</p>
<p>Repping-Wuts, H.J.W.J., Stikkelbroeck, N.M.M.L., Noordzij, A. et al. (2013) A glucocorticoid education group meeting: An effective strategy for improving self-management to prevent adrenal crisis. European Journal of Endocrinology 169(1): 17-22</p>	<p>- Study design not relevant to this review protocol</p>
<p>Vidmar, Alaina P, Weber, Jonathan F, Monzavi, Roshanak et al. (2018) Improved medical-alert ID ownership and utilization in youth with congenital adrenal hyperplasia following a parent educational intervention. Journal of pediatric endocrinology & metabolism : JPEM 31(2): 213-219</p>	<p>- Study does not address our clinical question</p>

J.2 Health Economic studies

None.