National Institute for Health and Care Excellence

Final

Adrenal insufficiency: identification and management

Evidence review I: Emergency management of an adrenal crisis

NICE guideline NG243

Evidence reviews underpinning recommendations 1.3.7 to 1.3.11 and 1.7.1 to 1.7.10 in the NICE guideline

August 2024

Final

This evidence review was developed by NICE

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1.1. Review question

What is the clinical and cost effectiveness of pharmacological treatments for the emergency management of adrenal crisis?

1.1.1. Introduction

There is widespread agreement on the immediate treatment of adrenal crisis- parenteral hydrocortisone and fluid; however, treatment is often delayed in emergency departments or emergency services may be fearful to administer emergency lifesaving parenteral hydrocortisone as they are unfamiliar with the management of adrenal crisis. There are variations in practice between who should give the treatment, when, and where patients should be seen after emergency treatment.

Patients are often given emergency treatment kits to use themselves, however, there is variation on the contents of these kits, and the training given to them, family or carers.

This chapter sets out the emergency management of adrenal crisis, where patients should be seen, and the care expected following the immediate treatment.

1.1.2. Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

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

Interventions	**Drug management**
	Any preparation, any dose and any route of administration of the following:
	• **Glucocorticoids:**
	  ○ Hydrocortisone sodium phosphate
	  ○ Hydrocortisone sodium succinate
	  ○ Dexamethasone
	  ○ Prednisolone
	• **Saline any dose/concentration**
	Dextrose any dose/concentration glucose
	Timing
	• Early vs delayed (as defined by authors)
	• In ambulance vs at home

	• In ambulance (pre-hospital) vs in hospital **Settings** • Self-administered (including by parents and carers i.e. not in a healthcare setting) • Health care professional in pre-hospital setting for example in ambulance • Health care professional in hospital
Comparisons	**For glucocorticoids:** The following aspects compared to each other: • Different doses • Bolus vs continuous infusion • Preparations • Routes of administration **For saline, glucose/dextrose:** Comparisons of different fluid regimens including dose/ concentration, bolus vs continuous and route of administration. Exclusion: comparisons of saline to glucose/dextrose as these are given for different indications **For all interventions including timing and setting:** • compared to each other (i.e., different settings to each other and different timings to each other)
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Mortality • Health-related quality of life, for example EQ-5D, SF-36 • Complications of adrenal crisis • Acute adverse events of drugs • Admission to hospital and/or ITU • Hospital readmission • Length of hospital stay • Electrolyte abnormalities such as incidence of hyponatraemia • Adverse effects of hyponatraemia **Follow up:** Up to 4 weeks (all short-term outcomes within hours or days that should all be captured by 4 weeks) If studies report several timepoints – shorter ones are preferable
Study design	Systematic reviews of RCTs, RCTs Non-randomised studies if they have conducted a multivariate analysis adjusting for at least 3-4 of the following key confounders: age, sex, weight / BMI, smoking, time to treatment, doses (timing or actual dose), intravenous vs

	intramuscular (iv) vs intramuscular (im), comorbidities, e.g., heart disease, diabetes, kidney disease. Practice guidelines on emergency management of adrenal insufficiency

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. A summary of the criteria for assessing guidelines using the AGREE II tool is included in Appendix D and a more detailed description of its application is included in the methods document.

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

1.1.4. Effectiveness evidence

1.1.4.1. Included studies

A search was conducted for randomised controlled trials (RCTs) and observational studies comparing pharmacological treatments in the emergency management of adrenal crisis.

No relevant RCTs or observational studies were identified for inclusion in this review.

The committee agreed that emergency management of AI is one of their priority areas for this guideline and therefore, in the absence of any research evidence, wished to review existing guidance documents to inform their recommendations. For that reason, a further systematic review of the literature was carried out to identify adrenal insufficiency guidelines that include recommendations on the emergency management of adrenal crisis.

Six guidelines were identified and included in the review.

- Two guidelines were for adults with any type of AI (primary, secondary or tertiary) (Arlt 2016[3] and Simpson 2020[12])
- One for adults and children with any type of AI (Araujo-Castro 2020[2])
- Two were for adults and children with primary AI (Bornstein 2016[5]and Husebye 2014[6])
- One was for children only with any type of AI Mushtaq 2023(BSPED)[8]

All guidelines were assessed using the AGREE II tool and summaries of the relevant recommendations, methodology and scores are summarised Table 1.

1.1.4.2. Excluded studies

See the excluded studies list in Appendix J.

1.1.5. Summary of the evidence

Table 2 Summary guidelines included in the review and their AGREE II quality assessments

Study	Population	Recommendations	Quality assessment with AGREE II
Arlt 2016[3] UK	Adults only Primary, secondary and tertiary AI	• Hydrocortisone (immediate bolus injection of 100 mg hydrocortisone i.v. or i.m. followed by continuous intravenous infusion of 200	**Scope and Purpose 69%** The guideline clearly states that the aim is to take the non-specialist

Study	Population	Recommendations	Quality assessment with AGREE II
Society for Endocrinology Clinical Committee		mg hydrocortisone per 24 h (alternatively 50 mg hydrocortisone per i.v. or i.m. Injection every 6 h) • Rehydration with rapid intravenous infusion of 1000 mL of isotonic saline infusion within the first hour, followed by further intravenous rehydration as required (usually 4–6 L in 24 h; monitor for fluid overload in case of renal impairment and in elderly patients) • Contact an endocrinologist for urgent review of the patient, advice on further tapering of hydrocortisone, investigation of the underlying cause of disease including diagnosis of primary vs secondary adrenal insufficiency • Tapering of hydrocortisone can be started after clinical recovery guided by an endocrinologist. In patients with primary adrenal insufficiency, mineralocorticoid replacement needs to be initiated (starting dose 100 micrograms fludrocortisone once daily) as soon as the daily glucocorticoid dose is below 50 mg hydrocortisone/24 h	through the initial phase of assessment and management of adrenal crisis although the health questions covered were not specifically described. The authors do provide a clear description of the target population. **Stakeholder Involvement** **0%** The guideline does not report group membership or stakeholder involvement. It does not include target population representation and their views have not been sought. **Rigour of Development** **0%** This is a consensus guideline and does include any details about methodology. **Clarity of Presentation** **92%** Recommendations were clearly stated and unambiguous but lacked details on alternative management strategies. **Applicability** **4%** The guideline does not provide any information on how the recommendations may be implemented such as facilitators and barriers or potential resource implications.

Study	Population	Recommendations	Quality assessment with AGREE II
			Editorial Independence **0%** There is no statement of funding body or competing interests of the authors.
Araujo-Castro 2020[2] Spain Spanish Society of Endocrinology and Nutrition (SEEN guidelines)	Adults and children Primary, secondary and tertiary AI	➢ General life support measures, peripheral line catheterization, cardiac monitoring and, if possible, CVP monitoring **Intravenous corticosteroids** ➢ Hydrocortisone 100 mg as initial bolus followed by 200---300 mg/24 h as a continuous i.v. infusion in 5% glucose saline or bolus 50 mg i.v./6 h ➢ If hydrocortisone is not available, methylprednisolone (20 mg/12 h) or dexamethasone 4 mg/12 h i.v. may be used.a ➢ The i.m. route may be used in cases of vascular shock ➢ Children: hydrocortisone 50 mg/m2 initial bolus followed by 50---100 mg/m2 daily or every 6 h **Intravenous hydration** ➢ 2-3 l of saline solution (0.9%) in the first 24 h: if the patient is in shock: 1000 ml in 1 st h, then 500 ml in 2nd and then adjust rate as needed ➢ Children: bolus of isotonic saline solution (0.9%) at 20 ml/kg. Up to 50 ml/kg in 1 h may be repeated in the case of shock ➢ Also administer glucose saline (10%) in the event of hypoglycaemia ➢ Control of water balance, electrolytes (sodium, potassium, glomerular filtration) to avoid overload, rapid sodium correction[b] and subsequent hypopotassaemia.	**Scope and Purpose** **75 %** The guideline clearly states that it intended to provide practical recommendations for all healthcare professionals who may be involved in the diagnosis, treatment, and prevention of AC. It is also intended to provide patients and their families with action guidelines for AC management and prevention. However, the specific health questions covered were not clearly described. **Stakeholder Involvement** **36%** Does not report on stakeholder engagement or patient input. However, it does clearly state who the target population is. **Rigour of Development** **0%** This is a consensus-based guideline but there is no description of the methods used. **Clarity of Presentation** **92%** The recommendations are clear and unambiguous with different options for management clearly stated. However, there is no clear distinction

Study	Population	Recommendations	Quality assessment with AGREE II
			of what the key recommendations are.
		Treatment of the underlying disease ➢ Antibiotics, etc. **General support measures** ➢ Admission to intensive care ➢ Prophylactic dose heparin ➢ PPI (prevention of gastric stress ulcers)	**Applicability** **0%** The guideline does not provide any information on how the recommendations may be implemented such as facilitators and barriers or potential resource implications.
			Editorial Independence **0%** The authors state that the development group consists of the Adrenal Disorders Group of the Neuroendocrinology Area of the Spanish Society of Endocrinology and Nutrition (SEEN) was asked to draft the guideline at the proposal of the SEEN's board. However, no statement of competing interests of the authors is included.
Bornstein 2016[5] Multinational	Adults and children Primary AI	➢ We recommend that patients with suspected adrenal crisis should be treated with an immediate parenteral injection of 100 mg (50 mg/m2 for children) hydrocortisone, followed by appropriate fluid resuscitation and 200 mg (50–100 mg/m2 for children) of hydrocortisone/24 hours (via continuous iv therapy or 6 hourly injection); age- and body surface-appropriate dosing is required in children (see Table 3). (strong recommendation, moderate quality evidence)	**Scope and Purpose** **61%** The authors state that the guideline is on the diagnosis and management of AI. However, the specific health questions and specific populations covered were not clearly described.
			Stakeholder Involvement **17%** Group membership and stakeholder involvement only included endocrinologists.

Study	Population	Recommendations	Quality assessment with AGREE II
		Table 3 (note: only recommendations for adrenal crisis included here): • Rapid infusion of 1000 mL isotonic saline within the first hour or 5% glucose in isotonic saline, followed by continuous iv isotonic saline guided by individual patient needs. • Hydrocortisone 100 mg iv immediately followed by hydrocortisone 200 mg/d as a continuous infusion for 24 h, reduced to hydrocortisone 100 mg/d the following day. • Children, rapid bolus of normal saline (0.9%) 20 mL/kg. Can repeat up to a total of 60 mL/kg within 1 h for shock. • Children, hydrocortisone 50–100 mg/m2 bolus followed by hydrocortisone 50–100 mg/m2/d divided q 6 h • For hypoglycaemia: dextrose 0.5–1 g/kg of dextrose or 2–4 mL/kg of D25W (maximum single dose 25 g) infused slowly at rate of 2 to 3 mL/min. Alternatively, 5–10 mL/kg of D10W for children <12 y old. • Cardiac monitoring: Rapid tapering and switch to oral regimen depending on clinical state. *D10W, 10% dextrose solution; D25W, 25% dextrose solution* ➢ If hydrocortisone is unavailable, we suggest prednisolone as an alternative. Dexamethasone is the least preferred alternative and should only be given if no other glucocorticoid is available. (weak recommendation, low quality evidence) ➢ For the prevention of adrenal crisis, we suggest adjusting glucocorticoid dose according to severity of illness or magnitude of the stressor. (weak	There was no patient or lay member involvement. **Rigour of Development 11%** The guideline document reports that recommendations were based on evidence from systematic reviews and their strength was based on GRADE ratings. However, this is not published and there is no clear description of the review methods. We were unable to find any supplementary materials. Therefore, we were unable to verify this. The document does include a description of the consensus methods used. **Clarity of Presentation 86%** Recommendations were clear and unambiguous. Some management options were provided, and key recommendations were identifiable. **Applicability 0%** The guideline does not provide any information on how the recommendations may be implemented such as facilitators and barriers or potential resource implications. **Editorial Independence 92%**

Study	Population	Recommendations	Quality assessment with AGREE II
		recommendation, low quality evidence) ➢ We suggest patient education concerning glucocorticoid adjustments in stressful events and adrenal crisis prevention strategies including parenteral self- or lay-administration of emergency glucocorticoids. (Ungraded best practice statement) ➢ We recommend that all patients should be equipped with a steroid emergency card and medical alert identification to inform health personnel of the need for increased glucocorticoid doses to avert or treat adrenal crisis and the need of immediate parenteral steroid treatment in the event of an emergency. (Ungraded best practice statement) ➢ We recommend that every patient should be equipped with a glucocorticoid injection kit for emergency use and be educated on how to use it. (Ungraded best practice statement)	The guideline states the co-sponsoring associations: which are the European Society of Endocrinology and the American Association for Clinical Chemistry) but does not state if the views of the funding bodies have influenced the content of the guideline.
Mushtaq 2023[8] **British Society of Paediatric Endocrinology & Diabetes (BSPED)** **2022** UK	Children up to 15 years Primary, secondary and tertiary paediatric AI	**<u>Emergency management in the community</u>** **Intramuscular (IM) hydrocortisone or initial IV doses** ➢ Less than 1 year 25 mg ➢ 1 to 5 years 50 mg ➢ years and over 100 mg **<u>Emergency management in the hospital</u>** **Children (>28 days) *** **Hydrocortisone dose and frequency** <u>Severe illness</u> ➢ Age based doses given IM or IV (25mg < 1year, 50mg 1	**Scope and Purpose 100%** The authors clearly state that the document aims to provide guidance for intercurrent illness, medical, dental and surgical procedures to allow timely and appropriate recognition. and treatment of AI and adrenal crisis for children and young people. In addition, they state the health questions and provide

Study	Population	Recommendations	Quality assessment with AGREE II
		to 5 years, 100mg for 6 years and over - subsequent doses as in 2) below or ➢ 2) 2mg/kg (max 100mg) IV bolus initially then bolus dose 6 hourly* (*can consider giving 4 hourly or as an infusion if needed) <u>Stable and improving</u> ➢ 1mg/kg (max 50mg) IV 6 hourly (can consider giving 4 hourly or as an infusion **Neonates (<28 days)** **Hydrocortisone dose and frequency** <u>Severe illness</u> ➢ 4mg/kg IV initially 6 hourly (*can consider giving 4 hourly or as an infusion if needed) <u>Stable and improving</u> ➢ 2mg/kg IV 6 hourly (can consider giving 4 hourly or an infusion) <u>Stable and tolerating drinks / diet</u> ➢ Oral sick-day steroids: 30mg/m2 /day in 4 equally divided doses Restart fludrocortisone if indicated **Fluid type and volume** <u>Blood Glucose < 3mmol/L</u> ➢ 2ml/kg of 10% dextrose as IV bolus Recheck blood glucose after 15 minutes and repeat bolus if necessary. <u>Shock or moderate to severe dehydration</u> ➢ Give 10ml/kg of 0.9% sodium chloride as a bolus and repeat if necessary ➢ Check electrolytes immediately at presentation to inform fluid usage <u>Maintenance fluids type and amount</u> ➢ 0.9% sodium chloride / 5% dextrose is usually an appropriate starting point:	a clear description of the target population. **Stakeholder Involvement** **100%** The guideline membership consisted of a multidisciplinary group including 12 paediatric endocrinologists, 1 paediatric endocrinology trainee, 2 paediatric endocrinology clinical nurse specialists and 1 paediatric pharmacist. Stakeholder involvement including the BPSED clinical and executive committees, the BSPED membership, Society for Endocrinology clinical committee and patient organisations including the CAH support group, Addison's Disease Self-Help Group and The Pituitary Foundation. **Rigour of Development** **40%** The guideline states that some literature searches were conducted but there is no information provided on the methods used or the search strategies. It does state that draft consensus recommendations were reviewed by different groups. **Clarity of Presentation** **100%**

Study	Population	Recommendations	Quality assessment with AGREE II
		100ml/kg/day for 1st 10kg, 50ml/kg/day for 2nd 10kg, 20mls/kg/day >20kg *It would seem prudent to use the neonatal dosing for infants who are significantly small for gestational age or failing to thrive and as such, whilst not neonates, are a neonatal size.	Recommendations were clear and unambiguous and use tables and diagrams to illustrate them. Different management options for specific groups are provided and key recommendations are identifiable.
			Applicability **25%** The guideline does not discuss facilitators and barriers to implementation or cost implications. However, it does provide useful implementation tools such as the paediatric version of the NHS emergency steroid card.
			Editorial Independence **67%** A funding statement states that the authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors. A statement on competing interests states that there were none declared. The guideline was commissioned by BSPED but there is no information on how it influenced the recommendations in the guideline.
Husebye 2014[6] European	Adults and children Primary AI	**Hydrocortisone** ➢ Adults (18 years or older): 100 mg bolus intravenously given immediately, followed	**Scope and Purpose** **39%** The document very briefly describes the aim as being the

Study	Population	Recommendations	Quality assessment with AGREE II
		by 200 mg/day continuous infusion, or frequent intravenous or intramuscular boluses of 50 mg every 6 h ➢ ≤1 years: 25 mg bolus, 25–30 mg/day, procedure as above ➢ 1–6 years: 50 mg bolus, 50–60 mg/day, procedure as above ➢ >6 years: 100 mg bolus, 100 mg/day, procedure as above **Intravenous substitution of fluids** ➢ Adults (18 years or older): 3–4 L of 0·9% saline or 5% dextrose in isotonic saline, with an initial infusion rate of approximately 1 L per h; frequent haemodynamic monitoring and measurement of serum electrolytes is required to avoid fluid overload. ➢ Children and adolescents (up to 18 years of age): 0·9% sodium chloride, 20 mL/kg bolus intravenously given over 30–60 min (which is repeated until circulation is restored); remaining deficit is replaced with maintenance fluid over 24–48 h (with 0·9% sodium chloride and 5% glucose) ➢ Hypoglycaemia can be treated with an intravenous bolus of 10% dextrose 2–5 mL/kg under blood glucose monitoring.	provision of a European Expert Consensus Statement on the diagnosis treatment and follow up of patients with primary AI. The health questions being addressed are not clearly stated. **Stakeholder Involvement** **14%** The committee only included clinical members didn't include any patient representatives. Some recommendations were based on recommendations from patient groups, but these were not the recommendations on emergency management. **Rigour of Development** **0%** Consensus statement by committee of European clinical experts. No details on methodology are provided. **Clarity of Presentation** **56%** Some recommendations are clearly stated, and tables are provided for clarity. However, other recommendations and key recommendations are not easily discernible within the document. **Applicability** **0%**

Study	Population	Recommendations	Quality assessment with AGREE II
			The guideline does not provide any information on how the recommendations may be implemented such as facilitators and barriers or potential resource implications.
			Editorial Independence 79% It is clearly stated that some authors are members of the Plenadren International Advisory Board. It also states that guideline was supported by the Journal of Internal Medicine and the FP7 project (Euradrenal; Grant No. 201167). However, it does not state if the views of the funding bodies have influenced the content of the guideline.
Simpson 2020[12] UK Royal College of Physicians	Adults only All AI	➢ 100 mg hydrocortisone by iv injection, followed by 200 mg hydrocortisone/24 h continuous iv infusion in glucose 5%/24 h, or 50 mg* 6 hourly im† ➢ Rapid rehydration with sodium chloride 0.9% providing no evidence of hyponatraemia: ○ Resuscitation with 500 ml fluid bolus of sodium chloride 0.9% over 15 minutes and then replacement of any electrolyte deficits ○ Rehydration (3–4 litres of sodium chloride 0.9% solution in 24 h); careful monitoring of	**Scope and Purpose 81%** The guideline states that the aim is to go through causes of adrenal insufficiency, groups at risk of an adrenal crisis, emergency management and management for surgical procedures. However, the target health questions are not always clearly defined.
			Stakeholder Involvement 19% There was some stakeholder involvement through RCP patient safety committee and Society for Endocrinology clinical committee.

Study	Population	Recommendations	Quality assessment with AGREE II
		electrolytes and fluid balance ○ Drinking ad libitum ➢ Cardiac monitoring (if necessary, transfer to the intensive care unit for monitoring) ➢ Refer to endocrinology for further advice on diagnosis, starting regular oral steroids or tapering steroids back to usual dose, and education regarding 'sick-day rules' prior to discharge. ** In severe obesity consider substituting 50 mg hydrocortisone with 100 mg hydrocortisone.* *† While it is recommended hydrocortisone 50 mg every 6 h is given im, hydrocortisone can be given iv if patients are anticoagulated or clinically indicated.*	Also seen by NHSE/I patient safety team. **Rigour of Development** **8%** Consensus guidelines but no detail of the methodology is included in the document. **Clarity of Presentation** **86%** Recommendations were generally clear and key recommendations were easily identifiable and different management options were available. **Applicability** **19%** While there was no discussion of barriers and facilitators to implementation or any cost impact analysis, the authors have developed a new NHS Steroid Emergency Card (implementation tool) that can be held by patients at risk of adrenal crisis and includes a management summary for the emergency treatment of adrenal crisis alongside a link to the Society for Endocrinology emergency management guidelines. **Editorial Independence** **0%** There is no statement of funding body or

Study	Population	Recommendations	Quality assessment with AGREE II
			competing interests of the authors.

1.1.6. Economic evidence

1.1.6.1. Included studies.

No health economic studies were included.

1.1.6.2. Excluded studies.

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

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

1.1.7. Economic model

This review question was prioritised for new cost-effectiveness analysis – specifically the provision of emergency management kits. However, due to a lack of clinical evidence original economic modelling was not possible. A simple costing analysis was therefore conducted to aid the committee's consideration of cost-effectiveness.

1.1.7.1. Background information

For people with AI experiencing an adrenal crisis, emergency hydrocortisone is a lifesaving medicine. People with adrenal insufficiency can be prescribed emergency management kits – providing people with an initial dose of emergency hydrocortisone that can be administered prior to hospital admission. Once people experiencing an adrenal crisis are admitted to hospital, subsequent hydrocortisone and fluids are provided.

In current practice, people experiencing an adrenal crisis can either be treated solely at hospital; receive an emergency injection from a paramedic prior to hospital admission; or for people who have been prescribed an emergency management kit – can receive an initial dose of hydrocortisone before they attend hospital. This dose of emergency hydrocortisone can be self-administered or provided by a trained individual known to the person such as a parent, carer, or spouse.

1.1.7.2. Intervention

This costing exercise sought to determine the costs of providing emergency management kits.

1.1.7.3. Population

The population of the costing analysis was people with primary and secondary adrenal insufficiency; in addition to a proportion of people with tertiary AI at high risk of adrenal crisis (for example, those people with tertiary AI who have experienced a previous adrenal crisis).

This population was identified and defined by the committee to reflect the population of people who need an emergency management kit. Table 2 provides details on the number of people included in the analysis.

Table 3: Number of people included in the analysis

Type of adrenal insufficiency	Number of people
Primary AI	8500[(a)]
Secondary AI	9900[(a)]
Tertiary AI	5000[(b)]
Total	***23400***

Sources:

(a) Prevalence in UK reported by Addisons Disease Self-Help Group[1]

(b) Committee estimate of proportion with tertiary AI who are given an emergency kit due to history of previous adrenal crisis.

1.1.7.4. Cost calculations

The total cost of an emergency management kit was estimated based on unit costs and committee opinion. The cost of an emergency management kit was estimated for one kit but the committee noted people would typically be prescribed 2 to 3 kits – typically 2 for adults and 3 for some children.

The total cost of an emergency management kit included the cost of:

- One dose of emergency hydrocortisone
- The consumables required to administer emergency hydrocortisone.
    - Two blue needles
    - Two 2ml syringes
- The staff time associated with training people how to administer emergency hydrocortisone.

The total cost of an emergency management kit is presented in Table 4.

Table 4: Cost of an emergency management kit

Resource	Unit cost	Proportion prescribed[(b)]
Drugs		
Hydrocortisone (as Hydrocortisone sodium phosphate) 100 mg per 1 ml solution for injection ampoules[(a)]	£2.12	50%
Hydrocortisone (as Hydrocortisone sodium succinate) 100 mg powder for solution for injection vials[(a)]	£0.92	25%
5ml Sterile Water for Injection in Plastic(c)	£0.21	25%
Hydrocortisone (as Hydrocortisone sodium succinate) 100 mg powder and solvent for solution for injection vials[(a)]	£1.16	25%
Consumables required to administer emergency hydrocortisone		
Two blue needles and two syringes[(d)]	£0.14	100%
Training		
Staff training costs[(e)]	£20.00	100%
Total cost	**£21.78**	

Sources:

(a) British National Formulary (BNF).[4]

(b) Proportion prescribed based on committee consensus.

(c) NHS supply chain catalogue 2021[11] NPC code FTR2480.

(d) NHS supply chain catalogue 2021[11] NPC code FTR2611.

(e) Cost of a hospital-based band 6 nurse including qualification costs (excluding individual and productivity costs) and assuming 20 minutes of training per person with AI. PSSRU 2022[7]

Training costs were estimated assuming 20 minutes of Band 6 nurse's time. The committee noted that training could be delivered by a Band 5 – Band 7 nurse. The 20-minute time estimate provided by the committee was assumed to be the duration of initial 1-1 initial training sessions. Additional costs would be associated with refresher training, the duration of which was also likely to be 20 minutes. The committee noted training could also be provided as group training, particularly for training parents, friends, and carers. This additional cost is not included here but would be less per person compared to the 1-1 training listed above.

Emergency management kits will need replenishing if the kits have been used. Drugs will need replacing depending on the shelf life of drugs.

Based on the population outlined in Table 2, the committee assumed that in current practice, 80 to 90% of that population would be receiving two emergency kits in current practice. If 100% received two kits, the additional cost of providing these kits would be up to £203,817. This is not considered a significant resource impact.

Due to uncertainty in the staff time required for training, a sensitivity analysis was conducted increasing staff time to 1 hour (£60) which the committee acknowledged was likely an overestimate. The cost of a single kit would therefore increase to £61.78. In this sensitivity analysis, a significant resource impact was observed when in current practice approximately 60% of people (or less) were prescribed emergency management kits which is below the committee's estimate of 80% - 90% of people from the reference case population.

1.1.8. Unit costs

The cost of emergency hydrocortisone used in a hospital setting is the same as the cost of emergency management kits (see Table 3). Multiple doses may be required, and fluids will also be administered. Costs incurred would include an accident and emergency visit (£242, NHS reference costs 2021/2022)[10] and possibly a hospital admission (non-elective inpatient short stay £801, NHS reference costs 2021/2022).[10]

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, complications of adrenal crisis such as hypoglycaemia and hypovolaemia, admission to hospital or ITU, length of hospital stay and electrolyte abnormalities such as hyponatraemia.

However, no research evidence that addressed this review question was identified and therefore no data was available to assess these outcomes. The committee agreed to review existing guidelines on emergency management of adrenal crisis to inform the recommendations.

1.2.2. The quality of the evidence

A systematic review of the literature was conducted to identify adrenal insufficiency guidelines that include recommendations on pharmacological treatments for the emergency management of adrenal crisis. Seven guidelines were identified and included in this review. Four guidelines covered all types of AI (primary, secondary, and tertiary). Two of those were specifically for adults although one does include a few recommendations for children, one was for children only and one was for adults and children. Two guidelines covered primary AI in both children and adults one of them was specific to primary AI due to 21-hydroxylase deficiency.

The guidelines were assessed by 2 reviewers using the AGREE II tool. This instrument is intended for assessing the quality of systematically developed clinical practice guidelines, including assessments of methodological rigour, transparency, and applicability. Where information was lacking, authors were contacted to provide further clarification.

The included guidance documents scored between 39% and 100% for scope and purpose. The overall aim, specific health questions and population covered by the guidelines were generally well described but details such as the potential health impact of the guidelines were sometimes lacking or limited.

The guidance documents scored between 0% and 100% for stakeholder involvement. Generally, they were assessed as having not been developed by a broadly representative group of relevant professionals and did not report that the views of intended users (practitioners, patients, and their families) were represented. Correspondence with authors revealed that some guidelines had sought the views of patient organisations. Only one of the guidelines British Society for Paediatric Endocrinology and Diabetes (BSPED) clearly stated that there was stakeholder involvement which included various professional and patient organisations.

Scores for rigour of development were low, ranging from 0% to 40%. Details on whether a systematic process had been used to search for and synthesise evidence, were not clearly described. The committee acknowledged that this is to be expected as research on adrenal crisis is difficult to conduct and very limited. Therefore, guideline authors may not see the need for conducting systematic searches of the evidence and may directly resort to expert opinion. However, this should not preclude authors from explaining the methods used to formulate the recommendations and how final decisions were arrived at (e.g., informal consensus or formal consensus techniques such as Delphi).

The included guidance documents scored between 56% and 100% for clarity of presentation. Recommendations were generally well presented and key recommendations were clearly identifiable. However, some guidelines were lacking in clarity regarding different management options and therefore scored lower in this domain.

Scores for applicability were very low and ranged between 0% and 25%. There was a lack of advice on how the recommendations could be put into practice, and potential resource implications and no monitoring or auditing criteria were suggested. It was also unclear whether the likely barriers and facilitators to implementation and strategies to improve uptake of the guidance were considered.

The included guidance documents scored between 0% and 92% for editorial independence. Declaration of any bias or competing interests from guidance development group members and statement on whether the views of the funding bodies had influenced the content of the guidelines were not always clearly reported. One guideline did not include any declarations and others did so with varying degrees of detail leading to a lack of transparency in editorial independence.

Once the assessment of the 6 domains (23 items) is completed, the AGREE II tool suggests two overall assessments. One is a rating of the overall quality of the guideline and the other asks whether the guideline would be recommended for use in practice. However, the review of external guidelines was not intended to recommend a particular guideline but to obtain an overview of the recommendations in national and international guidelines to inform the committee's recommendations or to cross-refer to specific recommendations if they would add efficiencies to the guideline development process and add value to NICE guidance. The committee also acknowledged that whilst rigour of development is considered a high priority in evaluating guidelines, they were aware of the difficulty in producing evidence-based guidelines for AI due to the limited research in this area. Their experience from conducting this systematic review had also proved that. They acknowledged that, knowing that there is limited evidence,

most guideline authors do not conduct any literature searches and make recommendations solely on consensus. This inevitably leads to all the guidelines scoring low for rigour of development as they lack any details for assessing the rigour of their systematic reviewing process. Therefore, the committee agreed that prioritising specific domains that would help their decision-making would be more informative than assessing the guidelines based on an overall score. The committee agreed, that in the absence of evidence, a high-quality guideline should include a wide range of experience and expert opinion that represents the views of the intended users including patient representatives. The guideline should include a clear description of the methods by which opinions were sought and incorporated and final recommendations were reached (e.g. informal consensus, Delphi)

In addition, for the committee to consider cross-referring to external guideline recommendations, they should be applicable to a UK setting. Therefore, the committee agreed that stakeholder involvement, particularly patient representation, and suitability to UK settings should be given strong consideration when assessing the quality of the guidelines as they will be more informative than an overall score.

Adults

Although the majority of the guidelines scored low for stakeholder involvement, the committee agreed that the recommendations were applicable to UK settings and were generally in agreement on how to manage adrenal crisis. They were also in line with the committee's expertise and current practice. Therefore, the committee made consensus recommendations based on their clinical expertise and patient member experience and further supported by the recommendations from the guidelines they reviewed.

Children under 16yrs

The BSPED guideline[8] scored 100% for stakeholder involvement as it was developed by a multidisciplinary group including paediatric endocrinologists, a paediatric endocrinology trainee, paediatric endocrinology clinical nurse specialists and a paediatric pharmacist. The BSPED guideline committee also sought feedback and input from a variety of stakeholders including clinical specialist society members and patient groups. In addition, the guideline was developed in the UK and was directly applicable to NHS settings. The committee agreed that although other guidelines did include some recommendations for children, the BSPED guideline, in addition to scoring highly in the priority domains, was also more comprehensive, clearly laid out and easy to follow. The committee decided that rather than duplicate the efforts, a cross referral to the BSPED recommendations would be the best option. Therefore, in order to increase their confidence in the BSPED recommendations, a second stage assessment of the guideline recommendations using the NICE process for assessing applicability and acceptability, was conducted. This includes additional considerations such as inequality and cost impact considerations (see Appendix E for full details).
In the second stage assessment, the paediatric specialists committee members reviewed the BSPED recommendations and agreed that they are up to date and in line with current clinical practice. The committee did not anticipate any constraints or barriers to implementation as the recommendations were in line with current clinical practice. They did not have any concerns about compatibilities with cultures and values. They noted that no health economic evidence or economic modelling was considered but were aware from their own literature review that no economic evaluations were identified. Therefore, unit costs were presented to the committee to aid consideration of cost-effectiveness.

Overall, the BSPED guideline was considered to be of high quality using the AGREE II tool, as well as acceptable and applicable to the NHS setting using the second stage assessment of recommendations. Therefore, the committee were confident in cross-referring to the BSPED website recommendations for emergency management of adrenal insufficiency in children and young people.

1.2.3. Benefits and harms

Adults

The committee agreed that the three essential aspects of treatment should be giving the hydrocortisone, administering fluids, and ensuring the rapid transport of the person to a hospital.

All five adult guidelines recommended immediate intravenous (iv) administration of 100 mg dose of hydrocortisone but only one guideline further specified that the intramuscular (im) route may be used in specific situations such as vascular shock. All guidelines were also in agreement that a further 200 mg dose of hydrocortisone should be administered over the following 24 hours either in continuous or frequent infusions. The committee agreed with these recommendations but acknowledged that the guidelines mostly covered treatment in hospital and hence only mention the iv route. Therefore, the committee wished to recommend both the iv and im route to account for instances where the patient would need to self-administer.

In considering the balance of benefits and harms of administering a high dose of hydrocortisone in an emergency, the committee highlighted that hydrocortisone is a lifesaving hormone replacement in such situations and it has no toxic dose. Therefore, they made an additional consensus recommendation that was not featured in other guidelines to emphasise that if adrenal crisis is suspected, hydrocortisone should be given without delay and by anyone including patients, families, and carers using an emergency kit without concern for overdosing. The committee noted that sometimes General Practitioners delay treatment whilst they liaise with a hospital. General Practitioners should either give the hydrocortisone, if available, or phone for an emergency ambulance.

The committee wished to emphasise the importance of swift transfer to hospital during an adrenal crisis. This wasn't covered in other guidelines and therefore they made an additional consensus recommendation for immediate transfer to hospital. The committee discussed transport to a hospital in an ambulance compared to being driven by a carer/relative/friend. It was agreed that while transport in a car may sometimes be quicker, it is still safer to call for an ambulance as this would mean that treatment can be started on the way to the hospital and care can still be given while the patient is waiting to be seen.

The committee emphasised the importance of giving parental fluids noting that deaths can occur even if hydrocortisone is given but when fluids are not. Guidelines suggested various protocols for sodium chloride infusion (e.g. 1L continuous vs 500 ml bolus in first 15 minutes). However, they all agreed that after an initial 1L infusion, sodium chloride should be continued for 24 hours or until the patient is stable. The committee agreed that the main aim should be to give the initial dose of fluids as soon as possible ideally within 30 minutes but acknowledged that how this is delivered (intravenous or bolus) depends on the hospital setting.

All guidelines included recommendations on monitoring. This most commonly included monitoring of cardiac and haemodynamic parameters. Some recommendations also included transfer to intensive care if necessary. The committee agreed and made a recommendation to highlight the importance of monitoring. They agreed that not everyone needed to be admitted to high-dependency care, but many may still have resuscitation requirements.

The guidelines did not feature recommendations on the use of oral glucocorticoids following iv or im administration and once the patient is stable. Therefore, the committee made a strong consensus recommendation to offer oral glucocorticoids at a higher dose than the usual until any underlying cause has resolved and the person is haemodynamically stable as this is important to ensure that the dose is adequate for recovery and for preventing a relapse back into a crisis.

Although only 2 guidelines explicitly recommend referral to a specialist, most other guidelines do mention the need for specialist advice in managing patients. The committee agreed that recommendations were needed on referral to a specialist endocrine team for ongoing clinical advice and support throughout admission and during the hospital stay and for identifying and treating any underlying cause of adrenal crisis. This would prevent deterioration of the person's condition, aid in recovery and help to prevent further crises.

Children under 16yrs

The committee agreed with the recommendations from the BSPED guideline[8]. They noted that infusions of hydrocortisone are not recommended in children due to difficulties with venous access and the cannula tissuing. The committee agreed with the BSPED recommendations for titrating dose according to age rather than weight as the former is more practical, especially in the pre-hospital setting. The BSPED guideline had achieved higher scores using the AGREE tool and second stage NICE assessment had found it to be applicable and acceptable to UK NHS setting. Therefore, the committee agreed that a cross-reference should be made to the BSPED website recommendations for emergency management of adrenal insufficiency in children and young people.

Emergency Kits

Only one guideline explicitly recommended the provision of emergency kits. However, the majority of the guidelines did discuss the importance of emergency kits and patient education within the guidance documents.

The committee discussed what would be included in an emergency kit and agreed this would comprise one dose of intramuscular hydrocortisone injection, either premixed or in powder form with water for injection, 2 blue needles and 2 2ml syringes. For babies under 1 year, a smaller needle and syringe may be provided within the emergency kit. Written instructions on how to prepare and administer the hydrocortisone injection will also be provided. The committee noted using a visual format such as diagrams or pictures was often helpful to people when in an emergency situation, or for people not able to read written instructions. Steroid emergency cards would also usually be included. They acknowledged training would also be provided to explain to the person and family members or carers what the kit contained and how to prepare and administer the injection.

The probability of experiencing an adrenal crisis in people with tertiary AI is very low. This is due to the fact that they will still have some residual function of the HPA axis. Therefore, the committee made a weaker recommendation to provide an emergency kit only to those who have a history of adrenal crisis. A weaker consider recommendation was also made for those under 16 years old who are being treated for tertiary adrenal suppression who may be at more risk of adrenal crisis due to their underlying pathology and relative physical immaturity.

The committee agreed that emergency kits should be provided during routine management so that people have them available during an emergency and are already trained in their use. Some committee members commented that provision of kits and what is included is currently variable and it is important that people know how and where they can obtain one. They wished to highlight this by including recommendations on the provision of emergency kits with recommendations on routine pharmacological management (see section 1.3 of the guideline).

1.2.4. Cost-effectiveness and resource use

No published cost-effectiveness evidence was found for this review question. Therefore, unit costs were presented to aid the committee's consideration of cost-effectiveness.

There are two aspects to this review question in terms of health economics. Firstly, assessing the cost-effectiveness of emergency management care for people who do not

have, or have not used an emergency kit prior to hospital admission. And secondly, assessing the cost-effectiveness of prescribing emergency management kits for people with adrenal insufficiency.

The recommendations the committee made concerning emergency hospital treatment for people experiencing an adrenal crisis are reflective of current practice and therefore not anticipated to result in a substantial resource impact.

However, the committee noted that current practice surrounding the prescription of emergency management kits is less certain. Therefore, to aid the consideration of cost-effectiveness, the total cost of prescribing an initial emergency management kit was estimated. The total cost of prescribing an initial emergency management kit consisted of the cost of, one emergency dose of intramuscular hydrocortisone, the consumables to inject intramuscular hydrocortisone and the staff costs associated with training, individuals with AI (and their family and friends) on how to administer emergency hydrocortisone. Fluids were not included in this cost as these are only given to people once they present in a hospital setting.

The cost of prescribing an initial emergency management kit (£21.78) is an estimate of the cost of prescribing an emergency management kit to someone who has not received an emergency management kit before (or requires all parts of the kit because, for example, they have lost their emergency management kit). There are several factors that would influence the long-term costs of prescribing emergency management kits. For example, if the kit has been used, it will need replacing or if not used for some time drugs, needles and syringes will need replacing to ensure they do not exceed their expiration date. The need to replace kits, or part of kits and ongoing training (for example refresher training) is not included in this unit costs.

A Call for Evidence was submitted for this review question in the hope to obtain data to conduct a more detailed costing analysis on the prescription of emergency management kits (versus standard hospital care alone and current practice). The Call for Evidence sought to obtain data on the proportion of people prescribed intramuscular hydrocortisone for use outside of a healthcare setting, the type of AI people are diagnosed with who are prescribed intramuscular hydrocortisone and the proportion of people who use their emergency intramuscular hydrocortisone. The Call for Evidence did provide some information on this; however, the committee deemed the data was not suitable to be used in a costing analysis due to concerns that the population sample was not representative of all people with adrenal insufficiency in the UK, in addition to other methodological concerns such as the survey design. Although the Call for Evidence did not provide the explicit evidence hoped for, it did highlight additional information on sub-optimal care in current practice which was discussed with the committee and incorporated into our recommendations, such as the importance of adequate training.

Of note, the largest cost component in the cost estimate for initially prescribing an emergency management kit was the staff time associated with training individuals on how to administer intramuscular hydrocortisone (£20 out of a total cost of £21.78). This cost assumed 20 minutes of band 6 hospital nurse time to train individuals and their family friends or careers. The committee did however acknowledge that it was challenging to estimate the true staff costs associated with initially prescribing emergency intramuscular hydrocortisone as clinical practice varies between different NHS trusts.

When discussing the cost-effectiveness and potential resource impact of emergency management kits, the committee used a reference case population that assumed all people with primary and secondary adrenal insufficiency were prescribed emergency management kits and a proportion of high-risk people with tertiary adrenal insufficiency were also prescribed emergency management kits. This reference case population is reflective of best practice. The committee acknowledged it would not be feasible or cost-effective to prescribe emergency management kits to all people with tertiary adrenal insufficiency. Firstly, because

a large proportion of people with tertiary adrenal insufficiency are not diagnosed with adrenal insufficiency. In addition to this, unless identified as a high-risk person with tertiary adrenal insufficiency, the probability of experiencing an adrenal crisis is very small and therefore the cost of providing emergency management kits to this group of people would largely outweigh the small potential benefits observed. The committee discussed that in people under 16 years old who are being treated for tertiary adrenal suppression but with no history of adrenal crisis, provision of a kit should also be considered as they may be at more risk of adrenal crisis due to their underlying pathology and relative physical immaturity compared to adults. It was noted that this is current practice.

From the reference case population, the committee estimated that 80% to 90% of people are currently prescribed emergency management kits. Therefore, at the current estimated cost of prescribing two emergency management kits (£43.65), our recommendations would not result in a significant resource impact if all people within the reference case population were prescribed one (23,400 people). However, as mentioned above, staff time costs are uncertain and longer-term costs haven't been included in this cost estimate. To account for the uncertainty regarding training costs, a sensitivity analysis was conducted increasing staff time to 1 hour – which the committee acknowledged was likely an overestimate. In this sensitivity analysis, a significant resource impact was observed when in current practice approximately 60% of people (or less) were prescribed emergency management kits which is below the committee's estimate of 80% - 90% of people from the reference case population. This sensitivity analysis therefore indicates, that even if the staffing costs for training were up to an hour, then this recommendation is unlikely to have a significant resource impact.

It is more challenging to evaluate cost-effectiveness of emergency management kits when assessing the longer-term costs and effectiveness of the intervention. However, the committee acknowledged that the cost of replacing intramuscular hydrocortisone and the consumables to administer hydrocortisone is relatively small (£1.63). Emergency hydrocortisone is a potentially life-saving medication. Early treatment can lessen the symptoms of an adrenal crisis, which may result in avoiding hospital admission or reducing the length of stay in those admitted. Either would improve people's quality of life and also reduce costs associated with hospitalisation.

The degree of nurse's time allocated to providing yearly refreshers or additional training to people prescribed emergency management kits (and their friends, family and carers) may influence the cost-effectiveness of the provision of emergency management kits. The Call for Evidence highlighted that a large proportion of people did not feel confident administering their emergency management kit in an emergency situation, therefore illustrating the importance of appropriate training. Providing emergency management kits will not be cost-effective if only a small proportion of people are using them in emergency situations. Conversely, spending too much money on training may result in emergency management kits not being cost-effective. The committee therefore concluded that appropriate training should be delivered in a cost-saving efficient manner. For example, providing information on where to access training videos and providing information sheets. The committee highlighted the importance of in-person training for those who required it but noted, that, when possible, this should be conducted in a group setting to minimise costs.

Information from the Call for Evidence noted that some people were only being prescribed emergency hydrocortisone and were unaware that additional consumables are required. Therefore, in some instances, people have been unable to administer their injectable hydrocortisone in an emergency. The committee have therefore provided a list of all the consumables that should be provided with injectable hydrocortisone.

The committee recommended 2 to 3 emergency management kits. It was noted that for most people two kits are sufficient but considered that for some people, for example children with separated parents, they may require one kit in each home and one at school. The committee highlighted the importance of checking expiration dates regularly in the recommendation for

the hydrocortisone, needles, and syringes. These can have expiration dates between 6 months and 5 years.

Overall, the committee concluded that providing emergency management kits to people with primary and secondary adrenal insufficiency, and those at high risk of adrenal crisis with tertiary AI (or people under 16 years old treated for tertiary adrenal suppression), would be cost-effective and not result in a significant resource impact.

1.2.5. Recommendations supported by this evidence review.

This evidence review supports recommendations 1.3.7 – 1.3.11 and 1.7.1 – 1.7.10.

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Appendices

Appendix A Review protocols

A.1 Review protocol for Emergency pharmacological management of adrenal crisis

Table 5: Clinical review protocol

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

		The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Adrenal insufficiency
6.	Population	Inclusion: People with adrenal insufficiency (primary, secondary or tertiary) who are diagnosed or suspected of having an adrenal crisis including the following stratified groups: • Adults (aged ≥16 years) • Children aged ≥5 up to 16 years • Infants aged 1-5 years (because of more frequent dosing) • Infants aged <1 year including neonates
7.	Intervention	**Drug management** Any preparation, any dose and any route of administration of the following: • **Glucocorticoids:** o Hydrocortisone sodium phosphate o Hydrocortisone sodium succinate o Dexamethasone o Prednisolone • **Saline any dose/concentration** **Dextrose any dose/concentration glucose** **Notes**: Dextrose and glucose interchangeable terms so don't compare to each other just doses comparison Weight-based regimens should also be included Exclusion:

		Hydrocortisone acetate Long-acting methylprednisolone Prednisone (not used in the UK) **Timing** • Early vs delayed (as defined by authors) • In ambulance vs at home • In ambulance (pre-hospital) vs in hospital **Settings** • Self-administered (including by parents and carers i.e., not in a healthcare setting) • Health care professional in pre-hospital setting for example in ambulance. • Health care professional in hospital
8.	Comparator	**For glucocorticoids:** The following aspects compared to each other: • Different doses • Bolus vs continuous infusion • Preparations • Routes of administration **For saline, glucose/dextrose:** Comparisons of different fluid regimens including dose/ concentration, bolus vs continuous and route of administration. Exclusion: comparisons of saline to glucose/dextrose as these are given for different indications **For all interventions including timing and setting:** • compared to each other (i.e., different settings to each other and different timings to each other)

9.	Types of study to be included	Systematic reviews of RCTs and RCTs will be considered for inclusion. Cross-over trials will also be considered for inclusion regardless of washout period as it is unsafe for patients to be completely free of background medication especially glucocorticoids. If insufficient RCT evidence is available, a search for non-randomised studies will be conducted. Studies will only be considered for inclusion if they have conducted a multivariate analysis adjusting for at least 3-4 of the following key confounders: - Age - Sex - Weight / BMI - Smoking - Time to treatment - Doses (timing or actual dose) - Iv vs im - comorbidities e.g heart disease, diabetes, kidney disease Published NMAs and IPDs will be considered for inclusion. Practice guidelines on emergency management of adrenal insufficiency
10.	Other exclusion criteria	Non-English language studies. Non comparative cohort studies Before and after studies Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
11.	Context	-
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical:

		• **Mortality** • **Health-related quality of life, for example EQ-5D, SF-36** • **Complications of adrenal crisis**- for example neurological complications, psychological, hypotension, hypoglycaemia, shock, acute kidney injury may be as part of shock and related to hypovolaemia • **Acute adverse events of drugs:** (up to 2 weeks- if none at this FU include shortest FU time reported in paper) – Mania – mood disturbance – blood glucose disturbance – sleep disruption/ insomnia • **Admission to hospital and/or ITU** • **Hospital readmission** • **Length of hospital stay** • **Electrolyte abnormalities such as incidence of hyponatraemia** • **Adverse effects of hyponatraemia** **Follow up:** Up to 4 weeks (all short-term outcomes within hours or days that should all be captured by 4 weeks) If studies report several timepoints – shorter ones are preferable.
13.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above.

		A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately. • a sample of the data extractions • correct methods are used to synthesise data. • a sample of the risk of bias assessments Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary. Study investigators may be contacted for missing data where time and resources allow.
14.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Nonrandomised study, including cohort studies: Cochrane ROBINS-I • Practice guidelines: AGREE II (https://www.agreetrust.org/agree-ii/)
15.	Strategy for data synthesis	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). Fixed-effects (Mantel-Haenszel) techniques will be used to calculate risk ratios for the binary outcomes where possible. Continuous outcomes will be analysed using an inverse variance method for pooling weighted mean differences. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. An I^2 value greater than 50% will be considered indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented pooled using random-effects. GRADEpro will be used to assess the quality of evidence for each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and

		imprecision) will be appraised for each outcome. Publication bias will be considered with the guideline committee, and if suspected will be tested for when there are more than 5 studies for that outcome. The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. WinBUGS will be used for network meta-analysis, if possible, given the data identified.	
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: • Different types of adrenal insufficiency (primary, secondary, or tertiary) • Newly diagnosed vs known diagnosis. • CAH vs non-CAH (particularly infants and children)	
17.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)
18.	Language	English	
19.	Country	England	
20.	Anticipated or actual start date	June 2022	
21.	Anticipated completion date	April 2024	

22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
23.	Named contact	5a. Named contact Guideline Development Team NGC 5b Named contact e-mail Hypoadrenalism@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
24.	Review team members	From NICE: Sharon Swain [Guideline lead] Saoussen Ftouh [Senior systematic reviewer] Meena Tafazzoli [Systematic reviewer] Alexandra Bannon [Health economist] Stephen Deed [Information specialist]		
25.	Funding sources/sponsor	Development of this systematic review is being funded by NICE.		

26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.	
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10237.	
28.	Other registration details	-	
29.	Reference/URL for published protocol	-	
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	Hypoadrenalism, adrenal insufficiency, congenital adrenal hyperplasia, glucocorticoids, pharmacological management, hydrocortisone, dexamethasone, prednisolone, glucose, dextrose, emergency management	
32.	Details of existing review of same topic by same authors	-	
33.	Current review status	☐	Ongoing
		☒	Completed but not published

		☐	Completed and published
		☐	Completed, published and being updated
		☐	Discontinued
34.	Additional information	-	
35.	Details of final publication	www.nice.org.uk	

A.2 Health economic review protocol

Table 6: 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).[9] **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.[9]

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 7: Database parameters, filters and limits applied.

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 September 2023	Randomised controlled trials. Systematic review studies Observational studies Guidelines Exclusions (animal studies, letters, comments, editorials, case studies/reports) English language
Embase (OVID)	1974 – 26 September 2023	Randomised controlled trials. Systematic review studies Observational studies Guidelines Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 9 of 12, 26 September 2023 Cochrane Central Register of Controlled Trials to Issue 9 of 12, 26 September 2023	Exclusions (clinical trials, conference abstracts)
Epistemonikos (The Epistemonikos Foundation)	Inception to 26 September 2023	Systematic review Exclusions (Cochrane reviews)

Medline (Ovid) search terms

1.	exp Adrenal Insufficiency/
2.	Adrenal Hyperplasia, Congenital/
3.	(addison* disease or addisonian*).ti,ab,kf.
4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.
6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	or/1-13
15.	letter/
16.	editorial/
17.	news/
18.	exp historical article/
19.	Anecdotes as Topic/
20.	comment/
21.	case reports/
22.	(letter or comment*).ti.
23.	or/15-22
24.	randomized controlled trial/ or random*.ti,ab.
25.	23 not 24
26.	animals/ not humans/
27.	exp Animals, Laboratory/
28.	exp Animal Experimentation/
29.	exp Models, Animal/
30.	exp Rodentia/
31.	(rat or rats or mouse or mice or rodent*).ti.
32.	or/25-31
33.	14 not 32
34.	limit 33 to English language
35.	Glucocorticoids/
36.	((glucocorticoid* or glucocorticosteroid* or steroid* or corticosteroid* or cortisone) adj3 (replace* or treat* or therap* or supplement* or regimen* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or intra muscular* or intramuscular* or exogenous* or subcutaneous*)).ti,ab,kf.
37.	Hydrocortisone/ or Dexamethasone/ or Prednisolone/

38.	(hydrocortisone* or prednisolone* or methylprednisolone* or dexamethasone*).ti,ab,kf.
39.	(Solu-Cortef or Hydventia or Plenadren or Neofordex or Glensoludex or Martapan or Deltacortril or Deltastab or Dilacort or Pevanti).ti,ab,kf.
40.	Mineralocorticoids/
41.	(mineralocorticoid* adj3 (replace* or treat* or therap* or supplement* or regimen* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or intra muscular* or intramuscular* or exogenous* or subcutaneous*)).ti,ab,kf.
42.	Fludrocortisone/
43.	fludrocortisone*.ti,ab,kf.
44.	Florinef.ti,ab,kf.
45.	Androgens/
46.	Hormone Replacement Therapy/
47.	((androgen* or hormon*) adj4 (replace* or treat* or therap* or supplement*)).ti,ab,kf.
48.	exp Dehydroepiandrosterone/
49.	(dehydroepiandrosterone or dehydro epiandrosterone or DHEA).ti,ab,kf.
50.	prosterone*.ti,ab,kf.
51.	Sodium Chloride/
52.	((sodium or saline or salt*) adj3 (replace* or treat* or therap* or solution* or supplement* or regimen* or intake* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or IV)).ti,ab,kf.
53.	Glucose/
54.	((glucose or dextrose) adj3 (replace* or treat* or therap* or solution* or supplement* or regimen* or intake* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or IV)).ti,ab,kf.
55.	HypoGel.ti,ab,kf.
56.	or/35-55
57.	34 and 56
58.	randomized controlled trial.pt.
59.	controlled clinical trial.pt.
60.	randomi#ed.ab.
61.	placebo.ab.
62.	randomly.ab.
63.	clinical trials as topic.sh.
64.	trial.ti.
65.	cross-over studies/
66.	(crossover or "cross over").ti,ab.
67.	or/58-66
68.	Meta-Analysis/
69.	Meta-Analysis as Topic/
70.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
71.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
72.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
73.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
74.	(search* adj4 literature).ab.
75.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
76.	cochrane.jw.

77.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
78.	or/68-77
79.	Epidemiologic studies/
80.	Observational study/
81.	exp Cohort studies/
82.	(cohort adj (study or studies or analys* or data)).ti,ab.
83.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
84.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
85.	Controlled Before-After Studies/
86.	Historically Controlled Study/
87.	Interrupted Time Series Analysis/
88.	(before adj2 after adj2 (study or studies or data)).ti,ab.
89.	exp case control study/
90.	case control*.ti,ab.
91.	Cross-sectional studies/
92.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
93.	or/79-92
94.	guidelines as topic/ or practice guidelines as topic/
95.	exp guideline/
96.	Health Planning Guidelines/
97.	(guideline or practice guideline).pt.
98.	guideline*.ti.
99.	or/94-98
100.	57 and (67 or 78 or 93 or 99)

Embase (Ovid) search terms

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

13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	or/1-13
15.	letter.pt. or letter/
16.	note.pt.
17.	editorial.pt.
18.	case report/ or case study/
19.	(letter or comment*).ti.
20.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
21.	or/15-20
22.	randomized controlled trial/ or random*.ti,ab.
23.	21 not 22
24.	animal/ not human/
25.	nonhuman/
26.	exp Animal Experiment/
27.	exp Experimental Animal/
28.	animal model/
29.	exp Rodent/
30.	(rat or rats or mouse or mice or rodent*).ti.
31.	or/23-30
32.	14 not 31
33.	limit 32 to English language
34.	glucocorticoid/
35.	((glucocorticoid* or glucocorticosteroid* or steroid* or corticosteroid* or cortisone) adj3 (replace* or treat* or therap* or supplement* or regimen* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous or intra*muscular or exogenous* or subcutaneous*)).ti,ab,kf.
36.	hydrocortisone/ or dexamethasone/ or prednisolone/
37.	(hydrocortisone* or prednisolone* or methylprednisolone* or dexamethasone*).ti,ab,kf.
38.	(Solu-Cortef or Hydventia or Plenadren or Neofordex or Glensoludex or Martapan or Deltacortril or Deltastab or Dilacort or Pevanti).ti,ab,kf.
39.	mineralocorticoid/
40.	(mineralocorticoid* adj3 (replace* or treat* or therap* or supplement* or regimen* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous or intra*muscular or exogenous* or subcutaneous*)).ti,ab,kf.
41.	fludrocortisone/
42.	fludrocortisone*.ti,ab,kf.
43.	Florinef.ti,ab,kf.
44.	androgen therapy/
45.	hormone substitution/
46.	((androgen* or hormon*) adj4 (replace* or treat* or therap* or supplement*)).ti,ab,kf.
47.	(dehydroepiandrosterone or dehydro epiandrosterone or DHEA).ti,ab,kf.
48.	prosterone*.ti,ab,kf.
49.	sodium chloride/
50.	((sodium or saline or salt*) adj3 (replace* or treat* or therap* or solution* or supplement* or regimen* or intake* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or IV)).ti,ab,kf.
51.	glucose/

52.	((glucose or dextrose) adj3 (replace* or treat* or therap* or solution* or supplement* or regimen* or intake* or dose* or dosage or oral or tablet* or infusion* or inject* or intravenous* or IV)).ti,ab,kf.
53.	HypoGel.ti,ab,kf.
54.	or/34-53
55.	33 and 54
56.	random*.ti,ab.
57.	factorial*.ti,ab.
58.	(crossover* or cross over*).ti,ab.
59.	((doubl* or singl*) adj blind*).ti,ab.
60.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
61.	crossover procedure/
62.	single blind procedure/
63.	randomized controlled trial/
64.	double blind procedure/
65.	or/56-64
66.	Systematic Review/
67.	Meta-Analysis/
68.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
69.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
70.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
71.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
72.	(search* adj4 literature).ab.
73.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
74.	cochrane.jw.
75.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
76.	or/66-75
77.	Clinical study/
78.	Observational study/
79.	Family study/
80.	Longitudinal study/
81.	Retrospective study/
82.	Prospective study/
83.	Cohort analysis/
84.	Follow-up/
85.	cohort*.ti,ab.
86.	84 and 85
87.	(cohort adj (study or studies or analys* or data)).ti,ab.
88.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
89.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
90.	(before adj2 after adj2 (study or studies or data)).ti,ab.
91.	exp case control study/
92.	case control*.ti,ab.
93.	cross-sectional study/

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

Cochrane Library (Wiley) search terms

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

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

Epistemonikos search terms

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

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

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 8: 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 –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 26 September 2023	English language

Medline (Ovid) search terms

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

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

Embase (Ovid) search terms

1.	exp Adrenal cortex insufficiency/
2.	Congenital adrenal hyperplasia/

3.	(addison* disease or addisonian*).ti,ab,kf.
4.	((adrenal* or adrenocort* or adreno cort*) adj3 (insufficien* or inadequa* or deficien* or suppress* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or problem* or crisis or crises or dysgenesis or destruction or destroy* or hyperplasia or hypoplasia or failure* or fails or failed or fatigue or inhibit* or damage* or disruption*)).ti,ab,kf.
5.	((cortisol or aldosterone or adrenocorticotrop* or adreno corticotrop* or ACTH or corticotropi* releas* or corticotrophi* releas* or corticoliberin or CRH) adj3 (insufficien* or inadequa* or deficien* or suppress* or reduc* or decreas* or descend* or diminish* or lack* or less or lessen* or low or lower* or limited)).ti,ab,kf.
6.	(hypoadrenal* or hypo adrenal* or hypoadrenocorticism or hypo adrenocorticism or adrenoleukodystrophy or adreno leukodystrophy or adrenomyeloneuropathy or adreno myeloneuropathy or hypoaldosteronism or hypo aldosteronism).ti,ab,kf.
7.	((adrenogenital or adreno genital) adj (syndrome or disorder*)).ti,ab,kf.
8.	((haemorrhag* or hemorrhag* or bleed*) adj3 adrenal*).ti,ab,kf.
9.	(Bronze Schilder* Disease or Melanodermic Leukodystrophy or Schilder-Addison* Complex or Siemerling-Creutzfeldt* Disease).ti,ab,kf.
10.	((Allgrove or 3A or TripleA or AAA) adj syndrome).ti,ab,kf.
11.	(CAH or X-ALD).ti,ab.
12.	(Waterhouse-Friderichsen* syndrome or antiphospholipid syndrome).ti,ab,kf.
13.	Autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy.ti,ab,kf.
14.	or/1-13
15.	letter.pt. or letter/
16.	note.pt.
17.	editorial.pt.
18.	case report/ or case study/
19.	(letter or comment*).ti.
20.	(conference abstract* or conference review or conference paper or conference proceeding).db,pt,su.
21.	or/15-20
22.	randomized controlled trial/ or random*.ti,ab.
23.	21 not 22
24.	animal/ not human/
25.	nonhuman/
26.	exp Animal Experiment/
27.	exp Experimental Animal/
28.	animal model/
29.	exp Rodent/
30.	(rat or rats or mouse or mice or rodent*).ti.
31.	or/23-30
32.	14 not 31
33.	limit 32 to English language
34.	health economics/
35.	exp economic evaluation/
36.	exp health care cost/
37.	exp fee/
38.	budget/
39.	funding/
40.	budget*.ti,ab.

41.	cost*.ti.
42.	(economic* or pharmaco?economic*).ti.
43.	(price* or pricing*).ti,ab.
44.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
45.	(financ* or fee or fees).ti,ab.
46.	(value adj2 (money or monetary)).ti,ab.
47.	or/34-46
48.	33 and 47
49.	limit 48 to yr="2014 -Current"

NHS EED and HTA (CRD) search terms

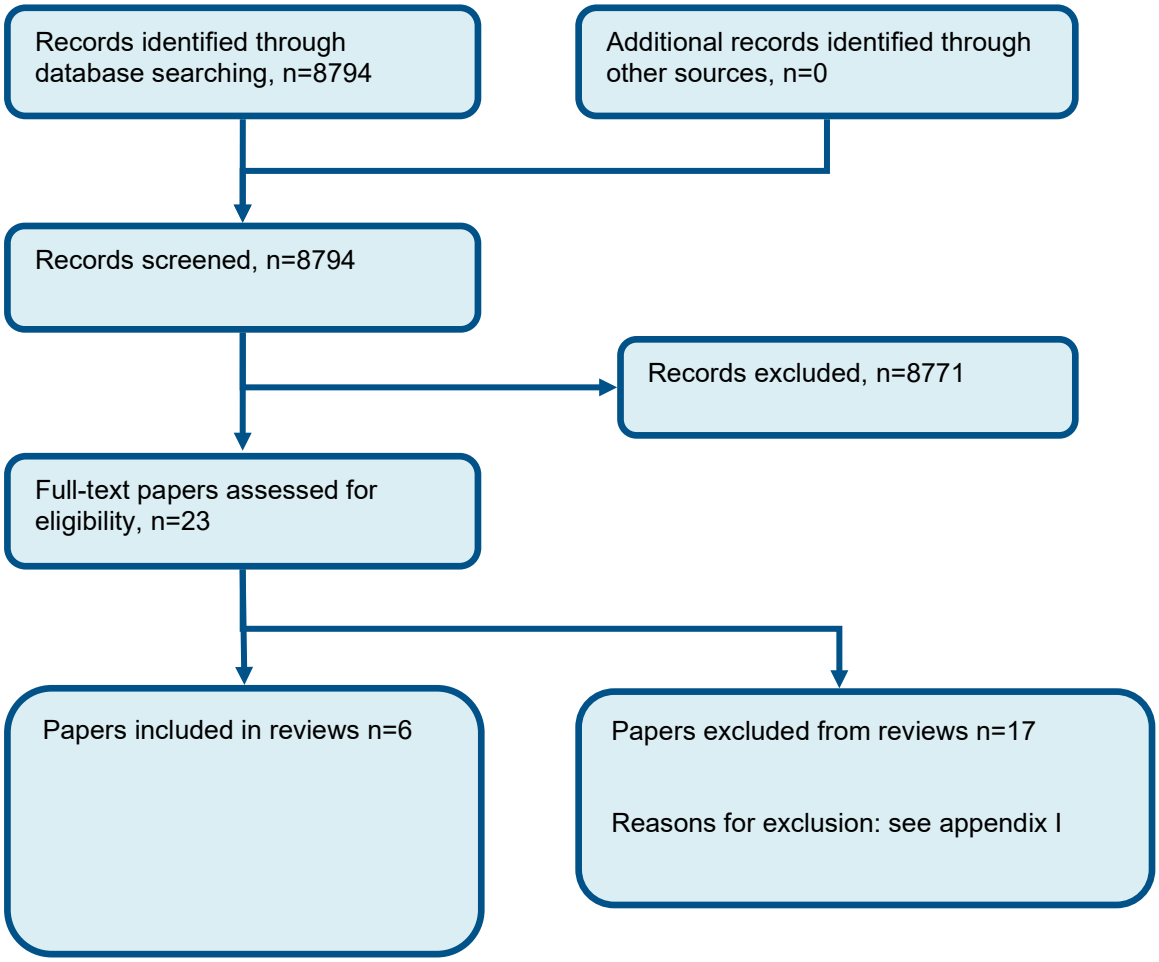
#1.	MeSH DESCRIPTOR Adrenal Insufficiency EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Adrenal Hyperplasia, Congenital EXPLODE ALL TREES
#3.	(addison* disease or addisonian)
#4.	(adrenal*) AND (insufficien* or inadequa* or deficien* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or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

INAHTA search terms

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

Appendix C Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of emergency management of adrenal crisis



Appendix D AGREE II reviewer scoring

	1. Scope and purpose				2. Stakeholder involvement				3. Rigour of development									4. Clarity of presentation				5. Applicability					6. Editorial independence		
Reviewer & guideline	Objectives	Question	Population	Totals and **scores %**	Group membership	Target population	Target users	Totals and **scores %**	Search methods	Evidence selection criteria	Evidence strengths and limitations	Formulation of recs	Considerations of benefits / harms	Link between recs & evidence	External review	Updating procedure	Totals and **scores %**	Specific & unambiguous recs	Management options	Identifiable key recs	Totals and **scores %**	Facilitators & barriers to application	Implementation advice/tools	Resource implications	Monitoring/auditing criteria	Totals and **scores %**	Funding body	Competing interests	Totals and **scores %**
R1 - Araujo Castro (SEEN)	7	3	7	17	2	1	7	10	1	1	1	1	1	1	1	1	8	6	6	7	19	1	1	1	1	4	1	1	2
R2 - Araujo Castro (SEEN)	6	4	6	16	1	1	7	9	1	1	1	1	1	1	1	1	8	6	7	7	20	1	1	1	1	4	1	1	2
Score % - Araujo Castro (SEEN)				**75**				**36**									**0**				**92**					**0**			**0**
R1 - Arlt 2016	7	6	4	17	1	1	1	3	1	1	1	1	1	1	1	1	8	6	6	7	19	1	3	1	1	6	1	1	2
R2 - Arlt 2016	6	2	6	14	1	1	1	3	1	1	1	1	1	1	1	1	8	6	7	7	20	1	1	1	1	4	1	1	2
Scores % - Arlt 2016				**69**				**0**									**0**				**92**					**4**			**0**
R1 - Bornstein 2016	7	3	4	14	5	1	1	7	1	1	2	3	3	1	2	1	14	5	5	7	17	1	1	1	1	4	6	7	13
R2 - Bornstein 2016	7	4	3	14	3	1	1	5	1	1	1	3	2	1	3	1	13	6	7	7	20	1	1	1	1	4	6	7	13
Scores % - Bornstein 2016				**61**				**17**									11				**86**					**0**			**92**
R1 - BSPED	7	7	7	21	7	7	7	21	1	1	3	1	5	5	7	1	24	7	7	7	21	1	7	1	1	10	6	7	13
R2 - BSPED	7	7	7	21	7	7	7	21	1	1	4	6	4	6	7	1	30	7	7	7	21	1	7	1	1	10	4	3	7
Scores % - BSPED				**100**				**100**									**40**				**100**					**25**			**67**
R1 - Husebye 2013	3	3	6	12	4	1	1	6	1	1	1	1	1	1	1	1	8	4	4	6	14	1	1	1	1	4	6	7	13
R2 - Husebye 2013	1	2	5	8	3	1	1	5	1	1	1	1	1	1	1	1	8	4	1	7	12	1	1	1	1	4	5	5	10
Scores % - Husebye 2013				**39**				**14**									**0**				**56**					**0**			**79**
R1 - Simpson 2020 (RCP)	7	4	7	18	5	1	2	8	1	1	1	1	1	1	5	1	12	5	5	7	17	1	7	1	1	10	1	1	2
R2 - Simpson 2020 (RCP)	7	4	6	17	3	1	1	5	1	1	1	1	1	1	5	1	12	6	7	7	20	1	4	1	1	7	1	1	2
Scores % - Simpson 2020 (RCP)				**81**				**19**									**8**				**86**					**19**			**0**

R1, Reviewer 1; R2, Reviewer 2

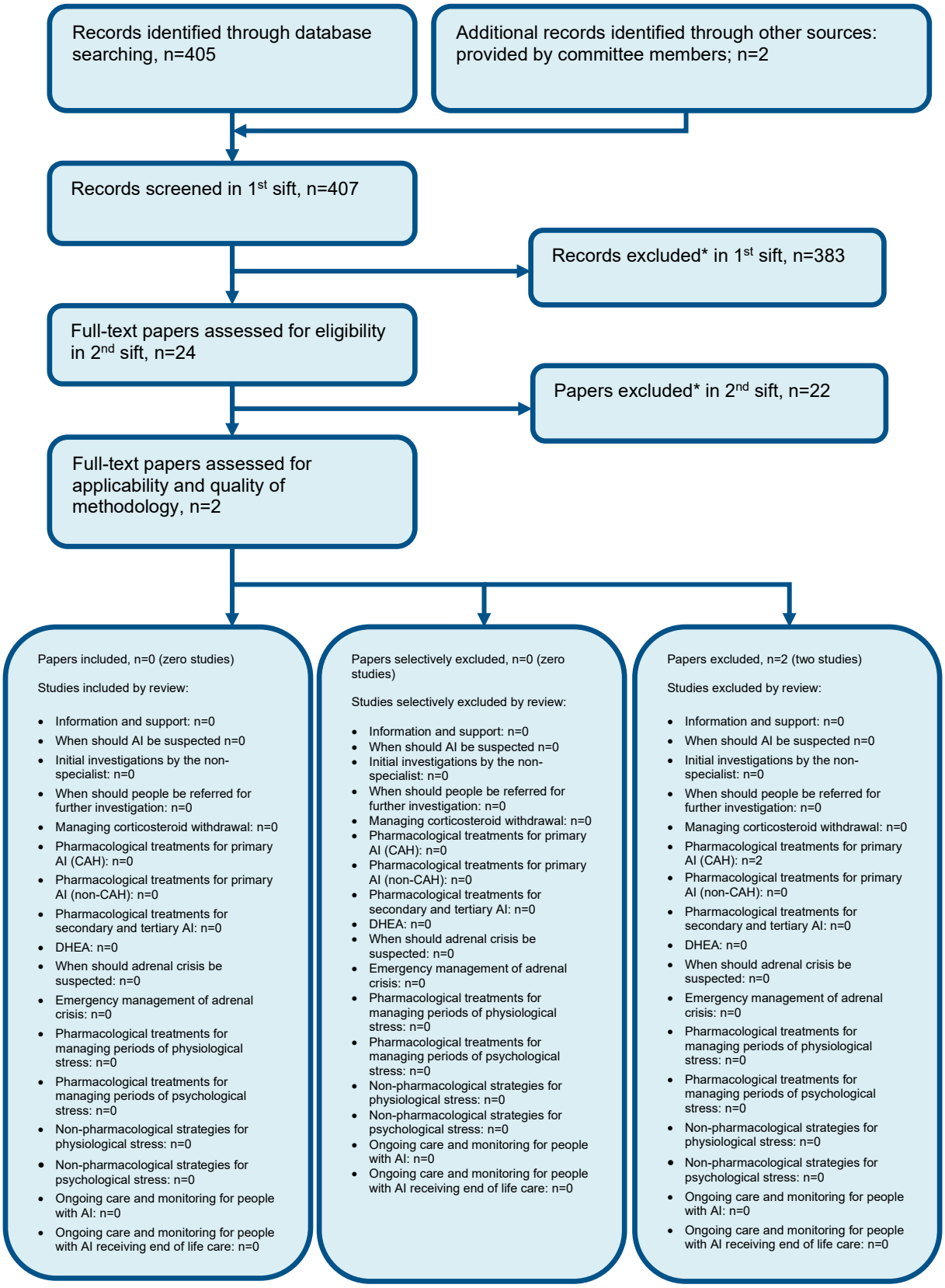
Appendix E BSPED - Discussion points for assessing recommendations on emergency management

	Details
Were the recommendations developed in accordance with the external organisation's development process (i.e., the process that has been assessed by either the NICE accreditation programme or AGREE II)?	The guideline document does not state if there was an established development process within BSPED that was followed. However, it does clearly report the methods used for this particular guideline. The document states that recommendations were developed by a multidisciplinary group called the Paediatric AI Group which was convened under the auspices of the BSPED with the aim to standardise the management of paediatric AI across the UK and Northern Ireland. It included 12 paediatric endocrinologists, 1 paediatric endocrinology trainee, 2 paediatric endocrinology clinical nurse specialists, 1 paediatric pharmacist. An initial literature search was performed and existing UK hospital guidelines for management of paediatric AI were reviewed. The recommendations were reviewed by the group prior to obtaining draft consensus. The final draft consensus was circulated to relevant stakeholders including the BSPED clinical and executive committees, the BSPED membership, Society for Endocrinology (SFE) clinical committee and patient organisations (CAH support group, Addison's Disease Self-Help Group and The Pituitary Foundation). The final guideline document is a consensus document of the BSPED Paediatric AI group which incorporates other stakeholders' views. In addition, the guideline was assessed by 2 reviewers from the NICE team using the AGREE II tool and scored higher than other guidelines in methodological rigour given the difficulties in this topic area and in applicability to UK settings. Therefore, the GC agreed to cross-refer to the recommendations.
Is the recommendation and the guideline development process low risk to NICE (this may be informed by other processes for example risk categories for QA or the multi criteria decision framework for updates)?	The recommendations are low risk to NICE. They are in line with current clinical practice and have been reviewed by the paediatric topic experts on the GC.
Is the recommendation and underpinning evidence current? Things to consider include:	Whether the recommendation is likely to change over time (for example, information and support recommendations are more likely to be static and the evidence may need to be less up to date, whereas a recent evidence base is likely to be more important for recommendations on diagnosis and management): • There is currently very little evidence in this area. The recommendations are mostly based on consensus but have been reviewed by the BSPED group and various stakeholders. New evidence may emerge in this area but there are currently no known large clinical trials that are due to publish soon.

	How recently were searches performed or updated for the underlying evidence base? • There is no information in the guideline about when the searches were conducted. The BSPED group was convened in 2021 so it is likely that the search is within the last 2-3 years. However, there doesn't seem to be any evidence identified from these searches and the recommendations are all based on consensus. Has there been a recent check that the recommendation is up to date? • The GC has reviewed all the relevant recommendations and agrees that they are up to date and in line with current clinical practice. How recent evidence searches or checks need to be may depend on, for example, how fast-moving or high-volume the evidence base is: • The paediatric AI population is quite small, and research is sparse and slow moving. The GC is not aware of any large clinical trials being conducted in this area that are publishing soon. Is the recommendation based on evidence that would be considered of appropriate quality within the area of the review question? • The recommendations are based on consensus. If based on evidence of inappropriate quality, or consensus: do topic experts agree with the recommendation? • Yes, the paediatric topic experts and wider GC members agree with the recommendations.
Was health economics (health economic studies, and/or an economic model) taken into account? If not, is the recommendation likely to be a low resource impact? [Ignore this question if health economics is not a relevant consideration for the recommendation, for example qualitative or signs and symptoms questions]	No health economic evidence or economic modelling was considered in the BSPED guideline. In addition, no economic evaluations were identified in the health economic literature review, therefore unit costs were presented to the committee to aid consideration of cost-effectiveness.
If health inequality issues relevant to the recommendation were identified by the EHIA for the NICE guideline, does the committee think the recommendation is likely to adversely impact on the identified health inequality issues? If yes, are additional	The external guideline recommendations were reviewed against the inequality issues identified by the GC and were not found to have any adverse impact.

recommendations required to address the unmet need or should the committee develop their own recommendations?	
Is the recommendation likely to be acceptable to the NHS and / or social care services? Things to consider include:	Population(s) in the evidence base for the source recommendation vs the target population of the NICE recommendation: • The population in the recommendations is the same target population as the NICE recommendations. Patient/service user views and preferences: • Guideline developers have sought the views of patient organisations on the recommendations. Constraints, organisational barriers, legislation, policy, or any other issues that could impede implementation: • There is no anticipated constraints or barriers as the recommendations are reflective of current clinical practice. Compatibility with cultures and values: • We do not anticipate there to be any issues of compatibilities with cultures and values

Appendix F Economic evidence study selection



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

Appendix G Economic evidence tables

None.

Appendix H Health economic model

No original economic modelling was undertaken for this guideline.

Appendix I Excluded studies

I.1 Clinical studies

Table 9: Studies excluded from the clinical review

Study	Reasons for exclusion
Arabi, Y. M., Aljumah, A., Dabbagh, O. et al. (2010) Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. CMAJ Canadian Medical Association Journal 182(18): 1971-7	- Study does not contain an intervention relevant to this review protocol
Burger-Stritt, Stephanie, Kardonski, Pavel, Pulzer, Alina et al. (2018) Management of adrenal emergencies in educated patients with adrenal insufficiency-A prospective study. Clinical endocrinology 89(1): 22-29	- Non-randomised - no multivariate analysis *Prospective, multicentre, questionnaire-based study*
Efird, M. M., Heerens, A. T., Gordon, P. V. et al. (2005) A randomized-controlled trial of prophylactic hydrocortisone supplementation for the prevention of hypotension in extremely low birth weight infants. Journal of Perinatology 25(2): 119-24	- Study does not contain an intervention relevant to this review protocol
Fadeev, V. V.; Gitel, E. P.; Mel'nichenko, G. A. (2001) The diurnal rhythm of adrenocorticotropic hormone secretion in the assessment of the adequacy of replacement therapy in primary chronic adrenal failure. Neuroscience and Behavioral Physiology 31(3): 237-242	- Population not relevant to this review protocol
Fernandez, J., Escorsell, A., Zabalza, M. et al. (2006) Adrenal insufficiency in patients with cirrhosis and septic shock: Effect of treatment with hydrocortisone on survival. Hepatology 44(5): 1288-95	- Study does not contain an intervention relevant to this review protocol
Hahner, S.; Burger-Stritt, S.; Allolio, B. (2013) Subcutaneous hydrocortisone administration for emergency use in adrenal insufficiency. European Journal of Endocrinology 169(2): 147-54	- Outcomes assessed not relevant to our review protocol *Very short term pharmacokinetic outcomes. The participants were in for 3 days in a row 1 day for im hydrocortisone, 1 for sc hydrocortisone and 1 for sodium chloride. The results were recorded within a few hours of administration.*
Hayek, A.; Crawford, J. D.; Bode, H. H. (1971) Single dose dexamethasone in treatment of congenital adrenocortical hyperplasia.	- Study does not contain an intervention relevant to this review protocol

Study	Reasons for exclusion
Metabolism: Clinical & Experimental 20(9): 897-901	
Hirvikoski, T., Nordenstrom, A., Wedell, A. et al. (2012) Prenatal dexamethasone treatment of children at risk for congenital adrenal hyperplasia: the Swedish experience and standpoint. Journal of Clinical Endocrinology & Metabolism 97(6): 1881-3	- Study design not relevant to this review protocol
Huh, Jw, Lim, Cm, Koh, Y et al. (2007) Effect of low doses of hydrocortisone in patient with septic shock and relative adrenal insufficiency: 3 days versus 7 days treatment. Critical care medicine 34suppl: a101	- Conference abstract
Vulto, A., van Faassen, M., Kerstens, M. N. et al. (2022) Susceptibility to Adrenal Crisis Is Associated With Differences in Cortisol Excretion in Patients With Secondary Adrenal Insufficiency. Frontiers in Endocrinology 13: 849188	- Outcomes assessed not relevant to our review protocol
Werumeus Buning, J., Kootstra-Ros, J. E., Brummelman, P. et al. (2016) Higher hydrocortisone dose increases bilirubin in hypopituitary patients- results from an RCT. European Journal of Clinical Investigation 46(5): 475-80	- Population not relevant to this review protocol
Winterer, J, Chrousos, Gp, Loriaux, Dl et al. (1985) Effect of hydrocortisone dose schedule on adrenal steroid secretion in congenital adrenal hyperplasia. Annals of the New York Academy of Sciences 458: 182-192	- Study does not contain an intervention relevant to this review protocol
Yang, C. H. (2006) Adrenal crisis in a patient with Escherichia coli bacteremia. Journal of Medical Sciences 26(5): 187-190	- Study design not relevant to this review protocol *Case report study*
Yong, S. L.; Coulthard, P.; Wrzosek, A. (2012) Supplemental perioperative steroids for surgical patients with adrenal insufficiency. Cochrane Database of Systematic Reviews 12: cd005367	- Population not relevant to this review protocol

I.2 Health Economic studies

None.