National Institute for Health and Care Excellence

Final

Adrenal insufficiency: identification and management

Evidence review J: Pharmacological management of physiological stress

NICE guideline NG243

Evidence reviews underpinning recommendations 1.4.1 to 1.4.9 and 1.4.12 to 1.4.21 and recommendation for research 5 in the NICE guideline

August 2024

Final

This evidence review was developed by NICE

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1. Pharmacological management at times of physiological stress

1.1. Review question:

What is the clinical and cost effectiveness of pharmacological treatments for managing periods of physiological stress in people with adrenal insufficiency including:

a) planned and emergency invasive procedures
b) pregnancy and intrapartum care
c) intercurrent illness and periods of physiological stress including minor (for example, colds) and major illnesses (for example, severe infection, cardiac events)?

1.1.1. Introduction

In times of physiological stress, the body produces additional cortisol. Under such circumstances, cortisol improves the efficiency of the heart, maintains blood pressure, ensures an adequate supply of glucose for cells to use for energy, and helps reduce inflammation.

Individuals with adrenal insufficiency are unable to produce high amounts of cortisol to meet the requirements for normal functioning during physiological stress. A failure to increase glucocorticoid replacement in times of physiological stress may place individuals at risk of adrenal crisis or even death. The amount of additional glucocorticoid required is different depending on the type of stressor, whilst severe illnesses such as sepsis, patients being in the intensive care unit or undergoing surgery require parental hydrocortisone. Although it is known that additional glucocorticoid dosing is recommended during periods of increased physiological stress, there is significant variation in clinical practice.

This review considers the clinical- and cost-effectiveness of pharmacological treatments for people with adrenal insufficiency at times of physiological stress.

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)
Intervention	**Glucocorticoids:** Any preparation, any dose and any route of administration of the following: • Hydrocortisone • Prednisolone • Dexamethasone Exclusions: Hydrocortisone acetate Long-acting methylprednisolone Prednisone (not used in the UK) For management of hypoglycaemia – specific to children • Dextrose any dose/concentration glucose oral or iv any dose/concentration usually 20% or hypogel in children
Comparison	**For glucocorticoids:**

	• Different doses • Compared to each other • Routes of administration **For Glucose for management of hypoglycaemia** • Different doses or concentrations
Outcomes	• Mortality • Health-related quality of life, for example EQ-5D, SF-36 • Incidence of adrenal crisis • Acute adverse events of drugs: (up to 2 weeks- if none at this follow up include shortest follow up time reported in paper) • Long term cumulative adverse effects: • Admission to hospital • Admission to ITU • Length of hospital stay. • Readmission to hospital • Psychological morbidities e.g., Incidence of stress or PTSD • Adverse effects of hypoglycaemia e.g., neurological damage, seizures, • Adverse effects of hyponatraemia e.g., neurological damage, seizures,
Study design	Systematic reviews of RCTs and RCTs. If not enough RCT data, non-randomised studies adjusting for at least 3-3 of the following confounders: age, sex, smoking, weight/BMI, time to treatment, doses (timing or actual dose), Iv vs im administration, comorbidities e.g., heart disease, diabetes, kidney disease. Practice guidelines that include recommendations on pharmacological management of physiological stress

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. A summary of the criteria for assessing guidelines using the AGREE II tool is included in Appendix K 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 studies comparing the administration of additional doses or corticosteroids to no additional doses or placebo at times of physiological stress in patients with adrenal insufficiency. One RCT was included in the review (Glowniak 1997[5]) and is summarised in Table 2 below. Evidence from this study is summarised in the clinical evidence summary below (Table 4).

Glowniak included 17 male patients who were on long-term corticosteroid therapy and who had secondary adrenal insufficiency as determined by results of cosyntropin testing. They were all undergoing major surgical procedures and were randomised to receive stress doses of corticosteroids or placebo.

The committee wished to look for additional evidence through searches for non-randomised studies. However, these did not identify any additional non-randomised studies for inclusion. The committee agreed that the management of physiological stress 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 pharmacological management at times of physiological stress.

Eight guidelines were identified and included in the review.

- Two guidelines were for adults with any type of AI (primary, secondary or tertiary) (Arlt 2016[2] and Simpson 2020[9])
- Two for adults and children with any type of AI (Araujo-Castro 2020[1], Woodcock 2020[11])
- Two were for adults and children with primary AI (Bornstein 2016[4] and Husebye 2014[6])
- One was for children only with any type of AI (Mushtaq 2023[7])
- One was for adults and children with primary AI due to 21-hydroxylase deficiency (Speiser 2018[10]).

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

1.1.4.2. Excluded studies.

See the excluded studies list in Appendix J.

1.1.5. Summary of studies included in the effectiveness evidence.

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

Study	Population	Intervention and comparison	Outcomes	Comments
Glowniak 1997[5] Double blind RCT USA	N=17 (18 surgical procedures) Secondary AI All male patients Patients who had been taking at least 7.5 mg prednisone daily for several months and had secondary adrenal insufficiency as defined by adrenocorticotropic hormone testing (determined by results of cosyntropin testing) and who were undergoing major surgical procedures. Conditions being treated with prednisone included: Rheumatoid arthritis, COPD, Crohn's disease, post-liver transplant, idiopathic thrombacytopenic purpura, demyelinating spastic pamparesis.	**Steroid-treated group** **n=6** <u>Before the start of operation:</u> intravenous injection of 100 mg cortisol in normal saline solution 1 hour before the start of the operation <u>After operation:</u> Iv injection 25 mg cortisol given every 6 hours for 2 days and then every 12 hours for 1 day (total of 10 postoperative injections). This regimen supplies 200 mg cortisol for the first 24 hours after operation, 100 mg cortisol on second day after operation and 50 mg on the third day in addition to patients' normal daily dose of prednisone. **Placebo group** **n=12** Identical injection amounts of normal saline solution.	Lowest blood pressure (BP) during operation Change in BP during operation. Highest pulse rate during operation Lowest BP in first 3 days after operation Other outcomes Highest pulse each day after operation	

Table 3: Summary of guidelines included in the review

Study	Population	Recommendations included in the guideline	Quality assessment with AGREE II
Arlt 2016[2] UK Society for Endocrinology Clinical Committee	Adults only Primary, secondary and tertiary AI	**Education of patients and partner/parents** regarding symptom awareness and the correct adjustment of glucocorticoid replacement dose: **Sick-Day Rule 1**: the need to double daily oral glucocorticoid dose during illness with fever that requires bed rest and/or antibiotics. Ensure they have an additional supply of hydrocortisone tablets so that they can double their dose for at least 7 days. **Sick-Day Rule 2**: the need to administer glucocorticoids per i.v. or i.m. injection during prolonged vomiting or diarrhoea, during preparation for colonoscopy or in case of acute trauma or surgery.	**Scope and Purpose** **69%** The guideline clearly states that the aim is to take the non-specialist 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%**

Study	Population	Recommendations included in the guideline	Quality assessment with AGREE II
			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.
			Editorial Independence **0%** There is no statement of funding body or competing interests of the authors.
Araujo-Castro 2020[1] Spain Spanish Society of Endocrinology and Nutrition (SEEN guidelines)	Adults and children Primary, secondary and tertiary AI	The provide a very detailed summary table of the main recommendations on how glucocorticoid doses should be adjusted in relation to stress, pregnancy and various medical or therapeutic procedures (too detailed to reproduce here). In summary, the following is recommended: • Increasing the doses of hydrocortisone, sometimes doubling (fever >38oC) or even tripling it (fever >39oC).	**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

Study	Population	Recommendations included in the guideline	Quality assessment with AGREE II
		• An awareness of those situations that can trigger hormone deficiency and of the reasons why early treatment is so important. • Education and regular follow-up (annually or more often in patients with a recent history of AAI), reviewing how to increase the GC dose according to the severity of intercurrent illness, and when and how to administer hydrocortisone via the intramuscular, subcutaneous, or rectal route at home.	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 of what the key recommendations are. **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**

Study	Population	Recommendations included in the guideline	Quality assessment with AGREE II
			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[4] Multinational	Adults and children Primary AI	For the prevention of adrenal crisis, we suggest adjusting glucocorticoid dose according to severity of illness or magnitude of the stressor. We suggest patient education concerning glucocorticoid adjustments in stressful events and adrenal crisis-prevention strategies including parenteral self- or lay-administration of emergency glucocorticoids. 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. We recommend that every patient should be equipped with a glucocorticoid injection kit for emergency use and be educated on how to use it.	**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. There was no patient or lay member involvement. **Rigour of Development** **11%**

Study	Population	Recommendations included in the guideline	Quality assessment with AGREE II
		Treatment during pregnancy We suggest that, based on the individual clinical course, an increase in hydrocortisone dose should be implemented, in particular during the third trimester. (Ungraded best practice statement) In pregnant women with PAI, we suggest using hydrocortisone over cortisone acetate, prednisolone, or prednisone and recommend against using dexamethasone because it is not inactivated in the placenta. We recommend hydrocortisone stress dosing during the active phase of labour, similar to that used in major surgical stress.	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 included in the guideline	Quality assessment with AGREE II
			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[7] UK British Society of Paediatric Endocrinology & Diabetes (BSPED) 2022	Children up to 15 years Primary, secondary and tertiary paediatric AI	The authors recommend additional doses of hydrocortisone during intercurrent illness in line with sick-day rules. If the child is taking a glucocorticoid at over 30 mg/m2/day of a hydrocortisone equivalent dose, then further sick-day doses with additional hydrocortisone may not be necessary in principle but they should have a bespoke plan for the management of AI. For those on regular prednisolone, our recommendation is for sick-day dosing with hydrocortisone. If this is not practical, then prednisolone 7.5/mg/m2/day given in two divided doses can be used. If the existing prednisolone dose is greater than the required sick-day dose, then the prescribed prednisolone should be split into two doses given at 12-hourly intervals. The relatively short half-life of Deflazacort necessitates the use of sick-day dosing with hydrocortisone. The authors also provide a detailed table of how to adjust hydrocortisone in different situations from minor	**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 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.

Study	Population	Recommendations included in the guideline	Quality assessment with AGREE II
		procedures to major surgery (too detailed to reproduce here).	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%** 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%**

Study	Population	Recommendations included in the guideline	Quality assessment with AGREE II
			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	The authors provide a detailed table of how to adjust hydrocortisone in different situations from minor procedures to major surgery (too detailed to reproduce here). In summary, they recommend that surgery and invasive medical procedures often require intravenous or intramuscular hydrocortisone and increased oral doses. Small adjustments to hydrocortisone and fludrocortisone doses may be needed during	**Scope and Purpose** **39%** The document very briefly describes the aim as being the 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.

Study	Population	Recommendations included in the guideline	Quality assessment with AGREE II
		pregnancy, particularly during the last trimester; parenteral doses if hydrocortisone should be given during delivery. An increase in hydrocortisone should also be considered if embarking on unaccustomed, intense or prolonged exercise. **Treatment in pregnancy** Surgery and invasive medical procedures often require iv or im HC and increased oral doses. Small adjustments to HC and fludrocortisone doses may be needed during pregnancy, particularly during the last trimester; parenteral doses of hydrocortisone should be given during delivery	**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%** The guideline does not provide any information on how the recommendations may be implemented such as facilitators and

Study	Population	Recommendations included in the guideline	Quality assessment with AGREE II
			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.
Speiser 2018[10]	This guideline focusses solely on CAH caused by 21-hydroxylase deficiency.	In all patients with congenital adrenal hyperplasia who require glucocorticoid treatment, for situations such as febrile illness (>38.5°C), gastroenteritis with dehydration, major surgery accompanied by general anaesthesia, and major trauma we recommend increasing the glucocorticoid dosage. In patients with congenital adrenal hyperplasia under everyday mental and emotional stress and minor illness and/or before routine physical exercise we recommend against the use of increased glucocorticoid doses. In patients with congenital adrenal hyperplasia who require treatment, we recommend always wearing or	**Scope and Purpose** **56%** The authors state that the aim of the guideline is to update their previous clinical practice guideline on management of CAH due to steroid 21-hydroxylase deficiency. However, no clear health questions included. **Stakeholder Involvement** **58%**

Study	Population	Recommendations included in the guideline	Quality assessment with AGREE II
		carrying medical identification indicating that they have adrenal insufficiency. In patients with congenital adrenal hyperplasia, we recommend educating patients and their guardians and close contacts on adrenal crisis prevention and increasing the dose of glucocorticoid (but not mineralocorticoid) during intercurrent illness. We recommend equipping every patient with congenital adrenal hyperplasia with a glucocorticoid injection kit for emergency use and providing education on parenteral self-administration (young adult and older) or lay administration (parent or guardian) of emergency glucocorticoids. **Treatment in pregnancy** In women with non-classic congenital adrenal hyperplasia who are infertile or have a history of prior miscarriage, we recommend treatment with a glucocorticoid that does not traverse the placenta. In women with congenital adrenal hyperplasia who are pregnant, we advise management by an endocrinologist familiar with congenital adrenal hyperplasia. In women with congenital adrenal hyperplasia who become pregnant we recommend continued pre-pregnancy doses of hydrocortisone/ prednisolone and fludrocortisone therapy, with dosage adjustments if	The Writing Committee consisted of 10 content experts representing the following specialties: endocrinology, paediatric urology, and psychology. Two of the committee members brought an international perspective to this guideline topic. The Writing Committee also included a clinical practice guideline methodologist. The guideline was subject to internal and external review to include stakeholder views such as Endocrine Society members, representatives of cosponsoring organisations and an Expert Reviewer. However, there is no patient involvement or representation. **Rigour of Development** **40%** Part of the guideline is evidence based using GRADE but no search strategies or methods for evidence selection are available. Some of the recommendations have considerations of benefits and harms but not the recommendations on stress dosing. There is a clear description of the internal and external review process and how views were taken into account in the final guideline document. Where there was evidence a description of the link to recommendations was included.

Study	Population	Recommendations included in the guideline	Quality assessment with AGREE II
		symptoms and signs of glucocorticoid insufficiency occur. Technical remark: Clinicians should evaluate the need for an increase in glucocorticoid during the second or third trimester and administer stress doses of glucocorticoids during labour and delivery. In women with congenital adrenal hyperplasia who are pregnant, or trying to become pregnant, we recommend against using glucocorticoids that traverse the placenta, such as dexamethasone.	**Clarity of Presentation** **72%** Recommendations were clear and key recommendations identifiable. There weren't many suggested management options for different situation. **Applicability** **13%** The guideline didn't include any discussion of facilitators and barriers or consideration of resource impact. There were no criteria for auditing or monitoring. **Editorial Independence** **100%** This guideline was exceptional in the description of conflicts of interest providing clear statements on how these are used in selection of members and there is also a clear table of each member and the interests they declared. Funding bodies and how they were involved are also clearly stated.
Simpson 2020[9]	Adults only All AI	**Sick-day rule 1**	**Scope and Purpose** **81%**

Study	Population	Recommendations included in the guideline	Quality assessment with AGREE II
UK Royal College of Physicians	(some recommendations for children included)	Moderate intercurrent illness (e.g., fever, infection requiring antibiotics), surgical procedure under local anaesthetic. Double usual daily glucocorticoid use **Sick-day rule 2** Severe intercurrent illness (eg persistent vomiting from GI viral illnesses), preparation for colonoscopy, acute trauma or surgery Hydrocortisone 100 mg intravenously at onset, followed by initiation of a continuous infusion of hydrocortisone 200 mg.24 h-1 Or hydrocortisone 100 mg intramuscularly followed by 50 mg every 6 h i.m. or i.v.	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. 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.

Study	Population	Recommendations included in the guideline	Quality assessment with AGREE II
			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 competing interests of the authors.
Woodcock 2020[11] UK Association of Anaesthetists, the Royal College of Physicians and	Adults and children All types of AI	Hydrocortisone 100 mg by intravenous (i.v.) injection should be given at induction of anaesthesia in adult patients with adrenal insufficiency from any cause, followed by a continuous infusion of hydrocortisone at 200 mg.24 h, until the patient can take double their usual oral glucocorticoid dose by mouth. This regimen is preferred above others due to enhanced safety. This should then be tapered back to the appropriate maintenance dose, in most cases within 48 h, although for up to a week if surgery is more major/complicated	**Scope and Purpose** **100%** The authors clearly state that the aim is to ensure that patients with adrenal insufficiency are identified and adequately supplemented with glucocorticoids during the peri-operative period. It also clearly states

Study	Population	Recommendations included in the guideline	Quality assessment with AGREE II
the Society for Endocrinology		clinical judgement should be used to guide this. Intramuscular (i.m.) administration may be prescribed in circumstances where i.v. infusion therapy is impractical. The authors also provide a detailed table of how to adjust hydrocortisone in different situations (too detailed to reproduce here). **Treatment in pregnancy** Maternal glucocorticoid supplementation in obstetric patients with adrenal insufficiency represents another group who require special mention; women may require a higher maintenance dose during the later stages of pregnancy (20th week onwards), and stress dose supplementation using hydrocortisone 100 mg at the onset of labour, and then either by continuous i.v. infusion of hydrocortisone 200 mg.24 h-1 or 50 mg intramuscularly every 6 h until after delivery.	the target population and the expected benefit. **Stakeholder Involvement** **67%** Group membership and target users are clearly stated. However, there is no indication that stakeholder views were sought. **Rigour of Development 0%** This is a consensus guideline and does not include any details about methodology. **Clarity of Presentation** **97%** Key recommendations are prominent in the guideline document. More specific recommendations are clearly presented in tables with different management options for different situations. **Applicability** **6%** The guideline does not provide any information on how the recommendations may be implemented such as facilitators and

Study	Population	Recommendations included in the guideline	Quality assessment with AGREE II
			barriers or potential resource implications.
			Editorial Independence **100%** The authors clearly state the source of funding (National Institute for Health Research (NIHR) through the Birmingham and Oxford NIHR Biomedical Research Centres) and clarify that the views expressed are those of the authors and not of the sponsors. Competing interests were included in the document (none of the authors had any to declare).

Table key:: i.v. intraveneous .m. intramustular PAI: Primary Adrenal Insufficiency

See Appendix D for full evidence tables.

1.1.6. Summary of the effectiveness evidence

Table 4: Clinical evidence summary: glucocorticoids versus placebo

See Appendix F for full GRADE tables.

Outcomes	№ of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with Hydrocortisone
Lowest systolic BP during operation	18 (1 RCT)	⊕◯◯◯ Very low [a,b,c]	-	The mean lowest systolic BP during operation was 102 mmHg	MD 13 mmHg higher (13.49 lower to 39.49 higher)
Lowest diastolic BP during operation	18 (1 RCT)	⊕◯◯◯ Very low [a,b,d]	-	The mean lowest diastolic BP during operation was 63 mmHg	MD 3 mmHg higher (10.1 lower to 16.1 higher)
Change in systolic BP during operation	18 (1 RCT)	⊕◯◯◯ Very low [a,b,e]	-	The mean change in systolic BP during operation was 34 mmHg	MD 5 mmHg higher (17.92 lower to 27.92 higher)
Change in diastolic BP during operation	18 (1 RCT)	⊕◯◯◯ Very low [a,b,f]	-	The mean change in diastolic BP during operation was 18 mmHg	MD 3 mmHg lower (14.84 lower to 8.84 higher)
Highest pulse rate during operation	18 (1 RCT)	⊕◯◯◯ Very low [a,b,g]	-	The mean highest pulse rate during operation was 103 BPM	MD 10 BPM lower (22.76 lower to 2.76 higher)
Lowest Systolic BP in first 3 days after operation	18 (1 RCT)	⊕◯◯◯ Very low [a,b,h]	-	The mean lowest Systolic BP in first 3 days after operation was 109 mmHg	MD 3 mmHg higher (18.52 lower to 24.52 higher)
Lowest diastolic BP in first 3 days after operation	18 (1 RCT)	⊕◯◯◯ Very low [a,b,i]	-	The mean lowest diastolic BP in first 3 days after operation was 69 mmHg	MD 3 mmHg lower (20.61 lower to 14.61 higher)

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID = 11 (0.5 x median baseline standard deviations)

d. MID = 6.5 (0.5 x median baseline standard deviations)

e. MID = 10.75 (0.5 x median baseline standard deviations)

f. MID = 5.75 (0.5 x median baseline standard deviations)

g. MID = 7.75 (0.5 x median baseline standard deviations)

h. MID = 9.75 (0.5 x median baseline standard deviations)

i. MID = 8.25 (0.5 x median baseline standard deviations)

1.1.7. Economic evidence

1.1.7.1. Included studies.

No health economic studies were included.

1.1.7.2. Excluded studies.

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

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

1.1.8. Economic model

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

1.1.9. Unit costs

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

Table 5: Unit costs for pharmacological interventions for physiological stress in children

Resource[a]	Dose per day	Cost per day	Cost per month
Hydrocortisone	***8mg/m² - 15 mg/m²***		
Neonate	2mg – 2.5mg		
Standard release	2mg – 2.5mg[b]	£0.29	£8.68
Alkindi	2mg – 2.5mg	£2.70 - £3.38	£82.13 - £102.66
Combination	n/a		
1 year	3.5mg – 4.5mg		
Standard release	3.5mg – 4.5mg[b]	£0.29	£8.68
Alkindi	3.5mg – 4.5mg	£4.73 - £6.08	£143.72 - £184.78
Combination	3.5mg – 4.5mg[c]	£2.04 - £3.39	£62.02 - £103.08
2 years	4.5mg – 5.5mg		
Standard release	4.5mg – 5.5mg[b]	£0.29	£8.68
Alkindi	n/a		
Combination	4.5mg – 5.5mg[d]	£3.39 - £4.74	£103.08 - £144.14
5 years	6mg – 7.5mg		
Standard release	6mg – 7.5mg[b]	£0.21	£6.51
Alkindi	n/a		
Combination	6mg – 7.5mg[e]	£5.41 - £4.75	£164.68 - £144.57
10 years	9mg – 11mg		
Standard release	9mg – 11mg[f]	£0.21 - £2.17	£6.51 - £66.10
Alkindi	n/a		
Combination	9mg – 11mg[g]	£3.51 - £3.52	£106.73 - £107.16
12 years	9.5mg – 12mg		
Standard release	9.5mg – 12mg[f]	£0.21 - £2.17	£6.51 - £66.10
Combination	9.5mg – 12mg[h]	£4.18 - £4.87	£127.26 - £148.22
14 years	12mg – 15mg		
Standard release	12mg – 15mg[i]	£0.21 - £2.97	£6.51 - £90.28

Resource[a]	Dose per day	Cost per day	Cost per month
Combination	12mg[j]	£4.87	£148.22
16 years	13mg – 17mg		
Standard release	13mg – 17mg[i]	£0.21 - £2.97	£6.51 - £90.28
Combination	13mg – 17mg[k]	£3.54 - £3.57	£107.58 - £108.48

(a) Source of costs from The British National Formulary (BNF);[3] date accessed: 05/11/2023. Dosage based committee expert opinion. For children over 1 year assumed the largest dose is given in the morning and the smallest in the evening, mimicking the normal daily rhythm of cortisol secretion.
(b) One 10mg tablet used for each dose, assuming four doses daily until age 4 and three doses daily from age 5. Each tablet is crushed and dissolved in water allowing for correct dose to be drawn up and administered. For older children tablets can be split to make up doses. Assumes drug wastage.
(c) 3.5mg costed as one 2.5mg standard release tablet and 1mg Alkindi granules in capsules; 4.5mg costs as one 2.5mg standard release tablet and 2 mg Alkindi granules in capsules.
(d) 4.5mg costs as one 2.5mg standard release tablet and 2mg Alkindi granules in capsules;5.5mg costed as one 2.5mg standard release tablet and 3mg Alkindi granules in capsules.
(e) 6mg costs as one 2.5mg standard release tablet and 3.5mg Alkindi granules in capsules;7.5mg costed as two 2.5mg standard release tablets and 2.5mg Alkindi granules in capsules.
(f) Either one 10mg tablet used for each dose, assuming three doses daily, tablets can be split to make up doses or 10mg costed as one 5mg and two 2.5mg standard release tablets.
(g) 9mg costs as one 2.5mg and one 5mg standard release tablets and 1.5mg Alkindi granules in capsules;11mg costed as one 5mg and two 2.5mg standard release tablets and 1mg Alkindi granules in capsules.
(h) 9.5mg costs as one 2.5mg and one 5mg standard release tablets and 2mg Alkindi granules in capsules;12mg costed as one 5mg and two 2.5mg standard release tablets and 2mg Alkindi granules in capsules.
(i) Either one 10mg tablet used for each dose, assuming three doses daily, tablets can be split to make up doses or 15mg costed as two 5mg and two 2.5mg standard release tablets.
(j) Costed as one 5mg and two 2.5mg standard release tablets and 2mg Alkindi granules in capsules.
(k) 13mg costs as three 2.5mg and one 5mg standard release tablets and 0.5mg Alkindi granules in capsules;17mg costed as one 10mg and one 5mg standard release tablets and 2mg Alkindi granules in capsules.

Table 6: Unit costs for pharmacological interventions for physiological stress in adults

Resource[a]	Dose per day	Cost per day	Cost per month
Hydrocortisone	***15mg – 25mg[b]***		
Prescribed as one and a half 10mg tablets a day	15mg	£0.11	£3.25
Prescribed as two 10mg tablets a day	15mg – 20mg[c]	£0.14	£4.34
Prescribed as one 10mg tablet and one 15mg tablet a day	25mg	£1.19	£36.23
Prescribed as three 10mg tablets a day	15-mg – 25mg	£0.21	£6.51
Modified release hydrocortisone (Plenadren)	***15mg – 25mg***		
Prescribed as three 5mg tablets a day	15mg	£14.55	£442.56
Prescribed as four 5mg tablets a day	20mg	£19.40	£590.08
Prescribed as one 20mg tablet a day	20mg	£8.00	£243.33
Prescribed as one 5mg tablet and one 20mg tablet a day	25mg	£12.85	£390.85
Prednisolone	***3mg – 6mg***		
Prescribed as three 1mg tablets a day	3mg	£0.08	£2.51
Prescribed as one 1mg tablet and one 5mg tablet a day	6mg	£0.06	£1.86
Dexamethasone			
Dexamethasone	0.25mg – 0.5mg[d]	£0.05 - £0.10	£1.59 - £3.18

(a) Source of costs from The British National Formulary (BNF);[3] date accessed: 05/10/2023

(b) Standard release hydrocortisone is taken either 2 or 3 times a day.
(c) For a 15mg dose of hydrocortisone the additional 5mg is wasted.
(d) Cost available in the BNF is for 0.5mg per day. The cost for 0.25mg a day assumes people take half a 0.5mg tablet daily and there is no drug wastage.

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

1.2.1. The outcomes that matter most

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

The only evidence found was on blood pressure during surgical procedures and up to 3 days after. These were reported separately as lowest systolic and lowest diastolic blood pressure and change in systolic and diastolic blood pressure. The study was in a small group of male patients with secondary adrenal insufficiency and therefore the committee did not think this was enough evidence to support recommendations. Further literature searches for non-randomised studies did not retrieve any additional evidence.

The committee considered pharmacological management of physiological stress a priority area where recommendations would be highly valuable to healthcare professionals. They were aware of the existence of several national and international guidelines and wished to consider them in this review to assess their quality and consolidate the recommendations across them. Therefore, an additional systematic review of the literature was conducted to identify published guidelines that include recommendations on the pharmacological management of adrenal insufficiency at times of physiological stress.

1.2.2. The quality of the evidence

The clinical evidence for all outcomes in the included RCT was graded very low. This was largely due to the very serious risk of bias arising from the randomisation process and very serious imprecision. The study was in a small group of people and there was very low certainty in the evidence it provided. Therefore, the committee did not consider these results in their decision making.

A further systematic review of the literature was conducted to identify adrenal insufficiency guidelines that include recommendations on pharmacological management at times of physiological stress. Eight guidelines were identified and included in this review. Five guidelines covered all types of AI (primary, secondary and tertiary). Two of those were specifically for adults although one included some recommendations for children, one was for children only and two were 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 included 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 not assessed as having 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 (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 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 100% 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 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 would normally be 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 pharmacological treatment at times of physiological stress. They were also in line with the committee's expertise and current practice. Therefore, the committee wished to make their own consensus recommendations, informed by these guidelines. The committee found that the Woodcock guideline[11] which included recommendations from the Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology UK included the most comprehensive and clear recommendations on pharmacological management in the perioperative period. The guideline had scored 67% for stakeholder involvement and was directly applicable to UK settings. The committee wished to cross refer to some of the recommendations in the guideline if it was deemed to be of high enough quality. Therefore, the guideline recommendations were further assessed using the NICE second stage assessment process for evaluating the applicability and acceptability of recommendations from external guideline developers. This includes additional considerations such as inequality and cost impact considerations (see Appendix L for full details).

In the NICE second stage assessment, the committee further scrutinised the Woodcock recommendations and confirmed that they are up to date, in line with current practice and unlikely to change in the near future as no new significant research was being conducted in this area. Although the guideline was found to lack patient views, the committee did not have any concerns about its compatibility with cultures and no health inequality issues were identified. The guideline did not include any health economic evidence or economic modelling. In addition, no economic evaluations were identified in the health economic literature review for the NICE guideline nor was it feasible to undertake any economic modelling. Therefore, unit costs were presented to the committee to aid consideration of cost-effectiveness.

The Woodcock recommendations were found to be of high quality using the AGREE II tool, as well as acceptable and applicable to the NHS setting using the NICE second stage assessment of recommendations. Therefore, the committee were confident in cross-referring to Woodcock guidelines for recommendations on glucocorticoid supplementation in the pre-intra- and postoperative period.

Children under 16yrs

The BSPED guideline[7] 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 had 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 was conducted using the NICE process for assessing applicability and acceptability (see Appendix M for full details).

In the NICE 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. In addition, no health inequality issues were identified. They did not have any concerns about compatibilities with cultures and values and no health inequality issues were identified. They noted that no health economic evidence or economic modelling was considered but were aware from the 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 NICE second stage assessment of recommendations. Therefore, the committee were confident in cross-referring to the BSPED website recommendations for pharmacological management at times of physiological stress in children and young people (sections 2-5).

The committee recognised that there is limited data directly comparing outcomes between different glucocorticoid supplementation strategies at times of physiological stress. They wanted to highlight the importance in the post-operative period for in-patients undergoing invasive procedures. Further research comparing these different strategies may provide evidence of benefit of one strategy over the other in terms of the clinical and cost effectiveness. This would help clinicians develop the most effective and pragmatic approach to adrenal replacement during major stress. Therefore, the committee made a research recommendation in this regard (see Appendix N).

1.2.3. Benefits and harms

Adults

All of the reviewed guidelines included recommendations on the importance of patient education on sick-day rules and the provision of additional supplies of glucocorticoids to cover periods of physiological stress. This was in line with committee recommendations that had already been discussed as part of the information and support review. Therefore, the committee made a cross-reference to those recommendations (see review A information and support and recommendations in section 1.1 of the guideline).. The committee highlighted that some people find it difficult to obtain additional supplies of corticosteroids and it is important that health professionals are aware of the importance of this to prevent adrenal crisis. They also highlighted that additional supplies of hydrocortisone should be provided in an immediate release formulation even to people who are on the modified release formulation to ensure faster replacement of cortisol levels.

The committee discussed that there is variation in practice regarding doubling a dose of hydrocortisone versus increasing the frequency of dosing. They recommended an increase to at least 40 mg a day because on balance this is easier for people to manage. The committee agreed a dose of oral hydrocortisone 2-4 times a day is the preferred option because it's a shorter-acting glucocorticoid. However, the committee noted that significant intercurrent illness such as fever > 39^{o}C, diarrhoea and vomiting, 4 times a day would be preferential. Four times a day is preferable because diarrhoea and vomiting means that hydrocortisone will not be absorbed adequately leading to a significant risk of adrenal crisis.

The committee discussed that for emergency management, hydrocortisone should be given as this is a lifesaving replacement therapy with no toxic dose. Therefore, the benefits of

taking it far outweighed the risk of not taking it and having a potentially fatal adrenal crisis. However, , the committee wanted to highlight that increasing dosing too frequently or for prolonged periods of time can lead to symptoms of glucocorticoid excess such as Cushing's syndrome. They were unable to define the duration of the increase in dosing as this varied according to the type of physiological stress and factors related to the individual.

For people who are already taking 10 mg of oral prednisolone, the committee did not recommend increasing the dose but considered splitting it into 2 equal doses across the day. This is to ensure there is some glucocorticoid cover over 24 hours because there can be a loss of diurnal variation in cortisol overnight in intercurrent illness.

The committee discussed that if absorption of oral glucocorticoids is difficult due to vomiting and/or diarrhoea then an injection of intramuscular or intravenous hydrocortisone could be given and medical help should be sought. Admission to hospital may be required and treatment should be provided in accordance with recommendations on emergency management (see section 1.7 of the guideline).

For adults having planned or emergency or invasive medical procedures, the committee endorsed the recommendations from the Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology UK. The committee decided to cross refer to this as the two-stage quality assessment using AGREE II and the NICE checklist had increased their confidence in the recommendations and they agreed that they reflected current practice. The recommendations are summarised in tables 1 and 2 of the guideline (Woodcock et al).

Children under 16yrs

The committee reviewed the recommendations from the BSPED guideline[8] and found them to be in line with their clinical expertise. They agreed that as the BSPED guideline was methodologically robust and had achieved high scores using the AGREE tool and the NICE second stage assessment checklist, a cross-reference should be made to the BSPED website recommendations for pharmacological management of physiological stress (sections 2-5).

Pregnancy care

There was limited evidence for women or people with adrenal insufficiency who are pregnant or planning pregnancy. Where guidelines made recommendations on pregnancy, an increase in glucocorticoid dosing was recommended particularly during the third trimester and labour. Therefore, the committee made consensus recommendations based on their experience, current best practice and the expert advice of a co-opted Consultant Obstetrician, Gynaecologist & Maternal Medicine Specialist.

Normal pregnancy is associated with increases in cortisol binding globulin (oestrogen induced), total plasma cortisol, free cortisol and aldosterone which combat the anti-glucocorticoid and anti-mineralocorticoid effect of progesterone, and therefore continuation of replacement doses of glucocorticoid and mineralocorticoid are essential in pregnancy to prevent adrenal crisis. Despite these increases in cortisol and aldosterone which are more apparent by the third trimester, few women with adrenal insufficiency routinely require increases in their replacement steroid doses. Clinical signs including symptoms of adrenal insufficiency, postural hypotension and hyponatraemia justify increases in replacement doses. Indiscriminate increases in glucocorticoids can result in unnecessary steroid excess which can cause maternal complications. Minimal hydrocortisone or prednisolone crosses the placenta to the foetus as they are inactivated by placental 11β-hydroxysteroid dehydrogenase**.** The committee noted it was important to advise women on the safety of hydrocortisone during pregnancy.

Sick-day rules apply in pregnancy as they do outside pregnancy. Many women will experience nausea and vomiting during pregnancy and may not be able to keep their medications down. Advice on taking glucocorticoids during periods of pregnancy related vomiting should be provided.. Some women experience hyperemesis gravidarum (HG) where nausea and vomiting are associated with pre-pregnancy weight loss, dehydration and electrolyte imbalance requiring intravenous fluid replacement and anti-emetics. Many units manage HG in an ambulatory setting. This is not appropriate for those with adrenal insufficiency who will usually require parenteral replacement of increased doses of replacement steroids, intravenous fluid replacement and closer monitoring of blood pressure and serum electrolytes, more suited to an inpatient setting.

For guidance during the birth, the committee reviewed the recommendations on steroid replacement regimens within the NICE guideline on intrapartum care for women with existing medical conditions or obstetric complications and their babies and agreed to cross-refer to this.

Glucocorticoid requirements decline following delivery and if replacement doses have been increased in pregnancy, they should be decreased to pre-pregnancy levels providing no complications which may require continuation of increased dosing.

Due to the limited research evidence in this area, the committee agreed to make a research recommendation (see Appendix N.1).

1.2.4. Cost effectiveness and resource use

No economic evaluations were identified for this review therefore unit costs were presented to aid the committee's consideration of cost-effectiveness, these were the daily and monthly costs of hydrocortisone, prednisolone, and dexamethasone.

The committee made recommendations reflective of best clinical practice. They noted that best clinical practice is not current practice for all and fatalities as a result of people experiencing adrenal crisis in periods of physiological stress have occurred due to the lack of sick-day dosing. The committee noted that in instances where best clinical practice is not being employed – providing people with additional medication to cover periods of physiological stress is highly likely to be a cost-effective strategy. People with adrenal insufficiency experiencing physiological stress are at increased risk of adrenal crisis, which is not only life-threatening but also incurs high costs to the NHS as these people will most likely require a hospital admission. This hospital admission will include the cost of an inpatient stay in addition to intravenous hydrocortisone and fluids. These recommendations are not expected to have a significant resource impact.

No specific recommendation was made on the sick-day dosing regimen for those on dexamethasone as they considered that very few people are on this drug and therefore the dosing should decided upon on a case by case. It was noted that people who normally take modified release hydrocortisone, they should receive a prescription of immediate release hydrocortisone for the purposes of sick-day dosing. The sick-day dosing recommendations included recommendations to admit a person to hospital during periods of physiological stress if they are unable to absorb oral glucocorticoids, for example, during prolonged diarrhoea and vomiting; and give 100 mg intramuscular or intravenous hydrocortisone. There is a cost associated with an admission to hospital, however the committee highlighted that this was necessary to avert the risk of adrenal crisis, which is not only life-threatening but also incurs high costs to the NHS as these people will most likely require a hospital admission.

For those already in hospital for another reason and are severely unwell (for example with sepsis or in intensive care) they also would require intravenous or intramuscular hydrocortisone. The committee noted that health care professionals should consider seeking

endocrinology specialist advice for these people as they may require further guidance on sick-day dosing.

Recommendations were made relating specifically to pregnancy care. These were based on committee expert opinion and overall reflect current practice and therefore are not expected to result in a significant resource impact. The exception to this is the recommendation to manage hyperemesis gravidarum in an inpatient setting rather than an outpatient setting. This is not current practice and the committee noted that deaths have been reported following outpatient management of hyperemesis gravidarum in people with adrenal insufficiency. The committee highlighted the importance of inpatient care and noted that although this is more costly than outpatient care, the population for whom this recommendation would apply is small and therefore this should not result in a significant resource impact. It was also noted that once vomiting is controlled, hyperemesis gravidarum can be managed in an outpatient setting with anti-emetics.

1.2.5. Recommendations supported by this evidence review.

This evidence review supports recommendations 1.4.1 – 1.4.9 and 1.4.12 – 1.4.21 and the recommendation for research on the clinical and cost-effectiveness of glucocorticoid treatment in the post-operative period for people with known or at risk of adrenal insufficiency undergoing in-patient invasive procedures.

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Appendices

Appendix A Review protocols

A.1 Review protocol for pharmacological management at times of physiological stress

ID	Field	Content
1.	Review title	Pharmacological management of physiological stress
2.	Review question	What is the clinical and cost effectiveness of pharmacological treatments for managing periods of physiological stress in people with adrenal insufficiency including: a) planned and emergency invasive procedures b) pregnancy and intrapartum care c) intercurrent illness and periods of physiological stress including minor (for example, colds) and major illnesses (for example, severe infection, cardiac events)?
3.	Objective	To determine the optimal pharmacological strategy for managing periods of physiological stress in people with adrenal insufficiency.
4.	Searches	The following databases (from inception) will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • Epistemonikos Searches will be restricted by: • English language studies • Human studies

		The searches may be re-run 6 weeks before the final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
5.	Condition or domain being studied	Adrenal insufficiency
6.	Population	Inclusion: People with adrenal insufficiency (primary, secondary, or tertiary) who are diagnosed or presumed adrenal insufficiency including the following groups: Strata: • Adults (aged ≥16 years) • Children aged ≥ 5up to 16 years. • Infants aged 1-5 years because of more frequent dosing. • Infants aged <1 year including neonates. Note: will need to note severity of physiological stress, for example, major surgery, illness with fever, labour and birth, dental surgery. Exclusion: None specified

7.	Intervention	**Glucocorticoids:**
		Any preparation, any dose and any route of administration of the following:
		• Hydrocortisone including:
		  ○ Oral (where possible, note oral granules, oral suspension, or crushed tablets)
		  ○ Modified release hydrocortisone (separate to normal release hydrocortisone)

		○ Injected forms • Prednisolone • Dexamethasone Exclusion: Hydrocortisone acetate Long-acting methylprednisolone Prednisone (not used in the UK) **For management of hypoglycaemia – specific to children** • Dextrose any dose/concentration glucose oral or iv any dose/concentration usually 20% or hypogel in children **Notes**: Dextrose and glucose interchangeable terms so don't compare to each other just doses comparison. Weight-based regimens should also be included. Be aware some are not licensed for children. **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:**

		• Different doses • Compared to each other • Routes of administration **For Glucose for management of hypoglycaemia** • Different doses or concentrations **For timing:** • Early vs delayed (as defined by authors) • In ambulance vs at home • In ambulance (pre-hospital) vs in hospital **For settings:** • Compared to each other (all interventions for any given setting)
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 considered 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 that include recommendations on pharmacological management of physiological stress
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** • **Incidence of adrenal crisis** • **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 • **Long term cumulative adverse effects:** – impact on weight – impact on growth

		– Hypertension – Obesity/weight gain – Osteoporosis – Fracture – Heart disease/CVS – Cushingoid features: e.g stretch marks – Diabetes (newly diagnosed or exacerbated) – Impact on sleep- poor sleep due to overnight high cortisol levels – stunted growth in children – Hb1ac – Psychological effects (depression, anxiety) – Fluid retention – Increased risk of glaucoma/high pressure in the eyes – Effects on concentration – Stomach ulcers • **Admission to hospital** • **Admission to ITU** • **Length of hospital stay.** • **Readmission to hospital** • **Psychological morbidities e.g., Incidence of stress or PTSD** • **Adverse effects of hypoglycaemia e.g., neurological damage, seizures,** • **Adverse effects of hyponatraemia e.g., neurological damage, seizures,** Follow up.

		>12 months but will report other time points if 12 months not available
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
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) • For settings- by intervention	
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	Sharon Swain [Guideline lead] Saoussen Ftouh [Senior systematic reviewer]	

		Maheen Qureshi [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, physiological stress

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 7: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions, and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2007, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[8] **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.[8]

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

B.1 Clinical search literature search strategy

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

Table 8: Database parameters, filters and limits applied.

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 26 September 2023	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 9: 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

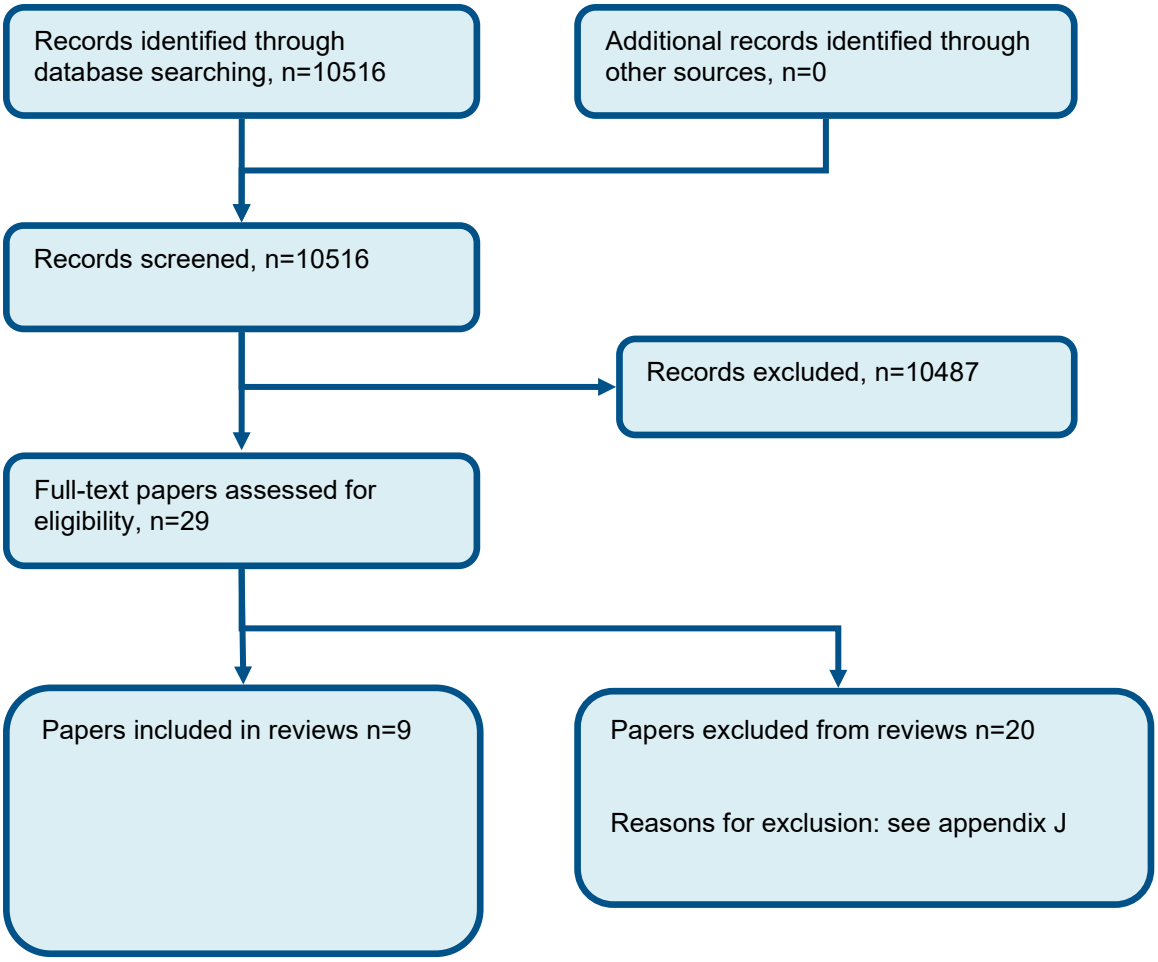
#1.	MeSH DESCRIPTOR Adrenal Insufficiency EXPLODE ALL TREES
#2.	MeSH DESCRIPTOR Adrenal Hyperplasia, Congenital EXPLODE ALL TREES
#3.	(addison* disease or addisonian)
#4.	(adrenal*) AND (insufficien* or inadequa* or deficien* or hypofunction* or disorder* or underactiv* or dysfunction* or abnormal* or 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 pharmacological management at times of physiological stress



Appendix D Effectiveness evidence

Glowniak, 1997

Bibliographic Reference	Glowniak, J. V.; Loriaux, D. L.; A double-blind study of perioperative steroid requirements in secondary adrenal insufficiency; Surgery; 1997; vol. 121 (no. 2); 123-9

Study details

Secondary publication of another included study- see primary study for details	Not applicable
Other publications associated with this study included in review	Not applicable
Trial name / registration number	Not reported
Study location	Portland, Oregon, USA.
Study setting	Surgical service Veterans Affairs Medical Center.
Study dates	Not reported
Sources of funding	Not reported
Inclusion criteria	Patients taking prednisone daily for at least 2 months and in a stable medical condition to be able to give consent. None of the patients had primary adrenal insufficiency or pituitary disease.

Exclusion criteria	Not reported
Recruitment / selection of participants	Patients were recruited from the surgical service at a Veterans Affairs Medical Center Patients taking prednisone for at least 2 months were screened for adrenal insufficiency with a rapid ACTH stimulation test using cosyntropin (Cortrosyn, ACTH l-24). A baseline cortisol level was drawn for each, and 0.25 mg Cortrosyn was injected intravenously. A blood sample for cortisol was drawn 60 minutes later. Adrenal insufficiency was defined as a 60-minute cortisol level below 20 pg/dl (550 nmol/L)s Patients whose 60-minute values were below this level were entered into the study.
Intervention(s)	Before the start of operation: intravenous injection of 100 mg cortisol in normal saline solution 1 hour After operation: Iv injection 25 mg cortisol given every 6 hours for 2 days and then every 12 hours for 1 day (total of 10 postoperative injections). This regimen supplies 200 mg cortisol for the first 24 hours after operation, 100 mg cortisol on second day after operation and 50 mg on the third day in addition to patients' normal daily dose of prednisone.
Population subgroups	Not reported
Comparator	Identical procedure and injection amounts as the intervention group but using normal saline solution.
Number of participants	17 patients/ 18 surgical procedures
Duration of follow-up	3 days
Indirectness	None
Additional comments	Not reported

Study arms

Hydrocortisone (N = 6)

- Intravenous injection of 100 mg cortisol in normal saline 1 hour before the start of operation

Placebo (N = 12)

- Intravenous injection of normal saline

Characteristics

Study-level characteristics

Characteristic	Study (N = 18)
% Female Sample size	n = 0 ; % = 0
Ethnicity Nominal	NR
Comorbidities Nominal	NR

Arm-level characteristics

Characteristic	Hydrocortisone (N = 6)	Placebo (N = 12)
Age Mean (SD)	65 (11)	57 (12)
Daily prednisone dose (mg) Mean (SD)	11.7 (2.35)	15.8 (13.9)
Duration of steroid use (Months) Mean (SD)	16.8 (14.1)	57.5 (73.8)

Outcomes

- Hydrocortisone compared to placebo during operation.

Outcome	Hydrocortisone, , N = 6	Placebo, , N = 12
Lowest systolic BP during operation (mmHg) Mean (SD)	115 (32)	102 (12)
Lowest diastolic BP during operation (mmHg) Mean (SD)	66 (14)	63 (12)
Change in systolic BP during operation (mmHg) Mean (SD)	39 (26)	34 (17)
Change in diastolic BP during operation (mmHg) Mean (SD)	15 (13)	18 (10)
Highest pulse rate during operation (BPM) Mean (SD)	93 (11)	103 (20)

- Hydrocortisone compared to placebo 3 days post operation.

Outcome	Hydrocortisone, , N = 6	Placebo, , N = 12
Lowest Systolic BP in first 3 days after operation (mmHg) Mean (SD)	112 (25)	109 (14)
Lowest diastolic BP in first 3 days after operation (mmHg) Mean (SD)	66 (20)	69 (13)

Appendix E Forest plots

E.1 Hydrocortisone vs placebo

Figure 2: Lowest systolic BP during operation

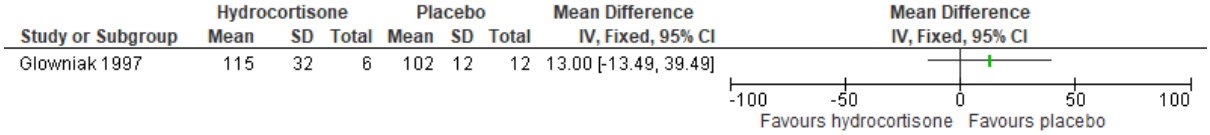


Figure 3: Lowest diastolic BP during operation

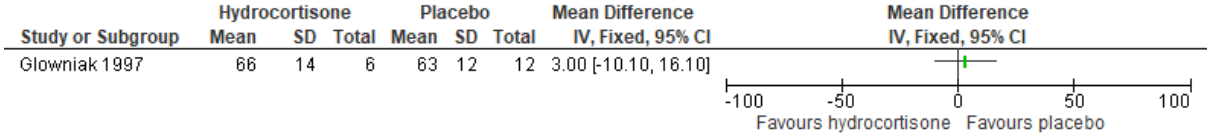


Figure 4: Change in systolic BP during operation

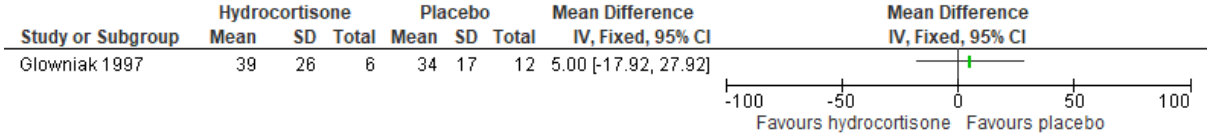


Figure 5: Change in diastolic BP during operation

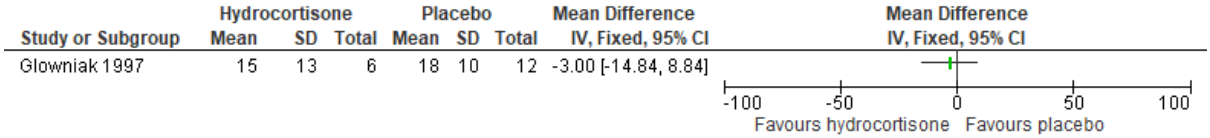


Figure 6: Highest pulse rate during operation

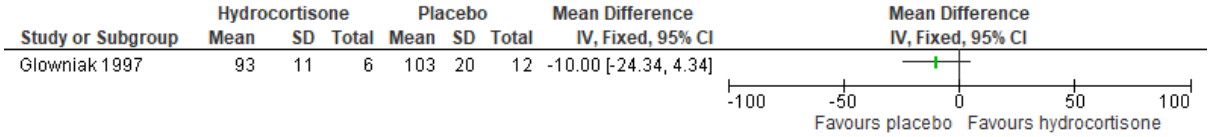


Figure 7: Lowest Systolic BP in first 3 days after operation

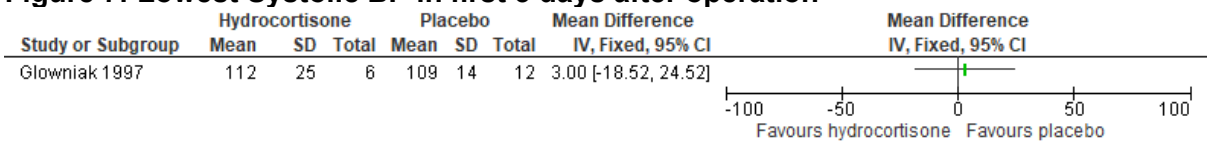
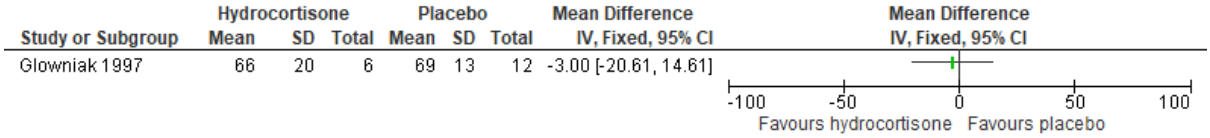


Figure 8: Lowest diastolic BP in first 3 days after operation



Appendix F GRADE tables

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydrocortisone	placebo	Relative (95% CI)	Absolute (95% CI)		
Lowest systolic BP during operation												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,c]	none	6	12	-	MD **13 mmHg higher** (13.49 lower to 39.49 higher)	⨁◯◯◯ Very low	CRITICAL
Lowest diastolic BP during operation												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,d]	none	6	12	-	MD **3 mmHg higher** (10.1 lower to 16.1 higher)	⨁◯◯◯ Very low	CRITICAL
Change in systolic BP during operation												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydrocortisone	placebo	Relative (95% CI)	Absolute (95% CI)		
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,e]	none	6	12	-	MD **5 mmHg higher** (17.92 lower to 27.92 higher)	⊕◯◯◯ Very low	CRITICAL
Change in diastolic BP during operation												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,f]	none	6	12	-	MD **3 mmHg lower** (14.84 lower to 8.84 higher)	⊕◯◯◯ Very low	CRITICAL
Highest pulse rate during operation												
1	randomised trials	very serious[a]	not serious	not serious	serious[b,g]	none	6	12	-	MD **10 BPM lower** (22.76 lower to 2.76 higher)	⊕◯◯◯ Very low	CRITICAL
Lowest Systolic BP in first 3 days after operation												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hydrocortisone**	**placebo**	**Relative (95% CI)**	**Absolute (95% CI)**		
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,h]	none	6	12	-	MD **3 mmHg higher** (18.52 lower to 24.52 higher)	⨁◯◯◯ Very low	CRITICAL
Lowest diastolic BP in first 3 days after operation												
1	randomised trials	very serious[a]	not serious	not serious	very serious[b,i]	none	6	12	-	MD **3 mmHg lower** (20.61 lower to 14.61 higher)	⨁◯◯◯ Very low	CRITICAL

a. Downgraded by 2 increments as the majority of the evidence was of very high risk of bias (due to bias arising from the randomisation process)

b. Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

c. MID = 11 (0.5 x median baseline standard deviations)

d. MID = 6.5 (0.5 x median baseline standard deviations)

e. MID = 10.75 (0.5 x median baseline standard deviations)

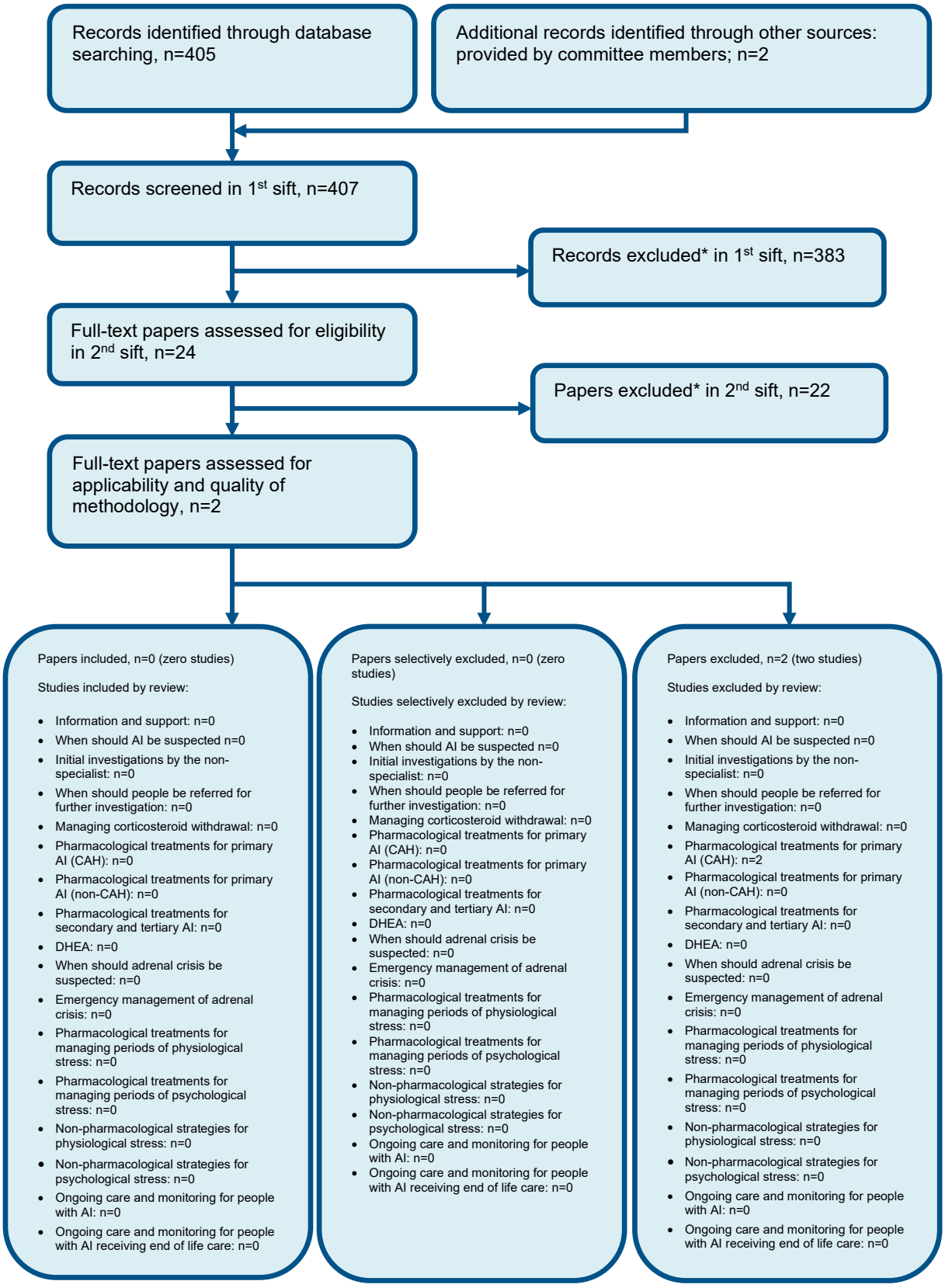
f. MID = 5.75 (0.5 x median baseline standard deviations)

g. MID = 7.75 (0.5 x median baseline standard deviations)

h. MID = 9.75 (0.5 x median baseline standard deviations)

i. MID = 8.25 (0.5 x median baseline standard deviations)

Appendix G Economic evidence study selection



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

Appendix H Economic evidence tables

None

Appendix I Health economic model

No original health economic modelling was undertaken for this review question.

Appendix J Excluded studies.

J.1 Clinical studies

Table 10: Studies excluded from the clinical review.

Study	Reasons for exclusion
Arafah, Baha M (2020) Perioperative Glucocorticoid Therapy for Patients with Adrenal Insufficiency: Dosing Based on Pharmacokinetic Data. The Journal of clinical endocrinology and metabolism 105(3)	- Study does not contain outcomes of interest *Pharmacokinetic outcomes e.g., cortisol half life*
Aso, K., Izawa, M., Higuchi, A. et al. (2009) Stress doses of glucocorticoids cannot prevent progression of all adrenal crises. Clinical Pediatric Endocrinology 18(1): 23-27	- Study does not include a multivariate analysis *Retrospective analysis of 24 cases of adrenal crises in 9 patients with no multivariate analyses.*
Bannon, C. A., Gallacher, D., Hanson, P. et al. (2020) Systematic review and meta-analysis of the metabolic effects of modified-release hydrocortisone versus standard glucocorticoid replacement therapy in adults with adrenal insufficiency. Clinical Endocrinology 93(6): 637-651	- Systematic review used as source of primary studies
Blavin, L. R. and French, L. (1997) Perioperative steroids for secondary adrenal insufficiency. Journal of Family Practice 44(6): 532-3	- Commentary article *Summary and comment on Glowniak*
Britt, R.C., Devine, A., Swallen, K.C. et al. (2006) Corticosteroid use in the intensive care unit: At what cost?. Archives of Surgery 141(2): 145-149	- Population not relevant to this review protocol
Bromberg, J S, Baliga, P, Cofer, J B et al. (1995) Stress steroids are not required for patients receiving a renal allograft and undergoing operation. Journal of the American College of Surgeons 180(5): 532-6	- Commentary article *Summary and commentary on Glowniak 1997*
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	- Study design not relevant to this review protocol
Chacko, Shireen R, Abraham, Ananth P, Asha, Hesarghatta Shyamasunder et al. (2020) Selective perioperative steroid supplementation protocol in patients undergoing endoscopic	- Study design not relevant to this review protocol

Study	Reasons for exclusion
transsphenoidal surgery for pituitary adenomas. Acta neurochirurgica 162(10): 2381-2388	
Chihaoui, M., Mimita, W., Oueslati, I. et al. (2020) Prednisolone or hydrocortisone replacement in patients with corticotrope deficiency fasting during Ramadan result in similar risks of complications and quality of life: a randomized double-blind controlled trial. Endocrine 67(1): 155-160	- Study does not contain an intervention relevant to this review protocol *Study compares prednisolone to hydrocortisone during fasting. No stress dosing.*
El-Maouche, Diala, Hargreaves, Courtney J, Sinaii, Ninet et al. (2018) Longitudinal Assessment of Illnesses, Stress Dosing, and Illness Sequelae in Patients with Congenital Adrenal Hyperplasia. The Journal of clinical endocrinology and metabolism 103(6): 2336-2345	- Study does not contain an intervention relevant to this review protocol *Intervention is stress dosing education.*
El-Sibai, Katia, Rajpal, Aman, Al-Aridi, Ribal et al. (2017) The impact of peri-operative dexamethasone administration on the normal hypothalamic pituitary adrenal response to major surgical procedures. Endocrine 58(1): 134-142	- Population not relevant to this review protocol *Participants with normal HPA function*
Fleming, Louise Kathleen; Rapp, Carla Gene; Sloane, Rick (2011) Caregiver knowledge and self-confidence of stress dosing of hydrocortisone in children with congenital adrenal hyperplasia. Journal of pediatric nursing 26(6): e55-60	- Study does not contain an intervention relevant to this review protocol - Population not relevant to this review protocol
Key, S J, Hodder, S C, Davies, R et al. (2003) Perioperative corticosteroid supplementation and dento-alveolar surgery. Dental update 30(6): 316-20	- Study design not relevant to this review protocol
Marik, P. E. and Varon, J. (2008) Requirement of perioperative stress doses of corticosteroids: a systematic review of the literature. Archives of Surgery 143(12): 1222-6	- Systematic review used as source of primary studies
Miller, C. S.; Little, J. W.; Falace, D. A. (2001) Supplemental corticosteroids for dental patients with adrenal insufficiency: reconsideration of the problem. Journal of the American Dental Association 132(11): 1570-9quiz1596	- Systematic review used as source of primary studies
Miller, Netanella, Asali, Aula Atamna, Agassi-Zaitler, Moran et al. (2019) Physiological and psychological stress responses to labor and	- Population not relevant to this review protocol

Study	Reasons for exclusion
delivery as expressed by salivary cortisol: a prospective study. American journal of obstetrics and gynecology 221(4): 351e1-351e7	
Mouri, Hideyuki, Jo, Taisuke, Matsui, Hiroki et al. (2020) Impact of glucocorticoid supplementation on reducing perioperative complications in patients on long-term glucocorticoid medication: A propensity score analysis using a nationwide inpatient database. American journal of surgery 220(3): 648-653	- Population not relevant to this review protocol *Patients on long term glucocorticoid supplementation but excludes patients who had adrenal insufficiency at admission.*
Nilsson, A. G., Marelli, C., Fitts, D. et al. (2014) Prospective evaluation of long-term safety of dual-release hydrocortisone replacement administered once daily in patients with adrenal insufficiency. European Journal of Endocrinology 171(3): 369-77	- Study does not contain an intervention relevant to this review protocol
Owa, Takao, Mimura, Kazuya, Kakigano, Aiko et al. (2017) Pregnancy outcomes in women with different doses of corticosteroid supplementation during labor and delivery. The journal of obstetrics and gynaecology research 43(7): 1132-1138	- Population not relevant to this review protocol
Plener, Paul L, Zohsel, Katrin, Hohm, Erika et al. (2017) Lower cortisol level in response to a psychosocial stressor in young females with self-harm. Psychoneuroendocrinology 76: 84-87	- Population not relevant to this review protocol
Simunkova, K., Jovanovic, N., Rostrup, E. et al. (2016) Effect of a pre-exercise hydrocortisone dose on short-term physical performance in female patients with primary adrenal failure. European Journal of Endocrinology 174(1): 97-105	- Study does not contain outcomes of interest *Looks at effects of stress dosing on physical performance and outcomes are all exercise performance related.*
Wang, Xiao, Heinrich, Daniel A, Kunz, Sonja L et al. (2021) Characteristics of preoperative steroid profiles and glucose metabolism in patients with primary aldosteronism developing adrenal insufficiency after adrenalectomy. Scientific reports 11(1): 11181	- Study does not contain an intervention relevant to this review protocol.
Weise, M., Drinkard, B., Mehlinger, S. L. et al. (2004) Stress dose of hydrocortisone is not beneficial in patients with classic congenital adrenal hyperplasia undergoing short-term, high-intensity exercise. Journal of Clinical Endocrinology & Metabolism 89(8): 3679-84	- Data not reported in an extractable format or a format that can be analysed

Study	Reasons for exclusion
Whittle, E. and Falhammar, H. (2019) Glucocorticoid Regimens in the Treatment of Congenital Adrenal Hyperplasia: A Systematic Review and Meta-Analysis. Journal of the Endocrine Society 3(6): 1227-1245	- Systematic review used as source of primary studies
Yau, Mabel, Jacob, Marianne, Orton, Sarah et al. (2021) Perioperative stress dose steroid management of children with classical congenital adrenal hyperplasia: Too much or too little?. Journal of pediatric urology 17(5): 654e1-654e6	- Study does not contain outcomes of interest
Zaghiyan, Karen N, Murrell, Zuri, Melmed, Gil Y et al. (2012) High-dose perioperative corticosteroids in steroid-treated patients undergoing major colorectal surgery: necessary or overkill?. American journal of surgery 204(4): 481-6	- Population not relevant to this review protocol
Zaghiyan, Karen, Melmed, Gil, Murrell, Zuri et al. (2011) Are high-dose perioperative steroids necessary in patients undergoing colorectal surgery treated with steroid therapy within the past 12 months?. The American surgeon 77(10): 1295-9	- Population not relevant to this review protocol
Zaghiyan, Karen, Melmed, Gil, Murrell, Zuri et al. (2012) Safety and feasibility of using low-dose perioperative intravenous steroids in inflammatory bowel disease patients undergoing major colorectal surgery: A pilot study. Surgery 152(2): 158-63	- Population not relevant to this review protocol

J.2 Health Economic studies

None.

Appendix K 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 recommendations & 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
Score % - 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
Score % - 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
Score % - 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
Score % - 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
Score % - Simpson 2020 (RCP)				**81**				**19**									**8**				**86**					**19**			**0**
R1 - Speiser 2018	5	2	6	13	7	2	5	14	1	1	5	4	5	3	7	1	27	6	4	6	16	1	2	3	1	7	7	7	14
R2 - Speiser 2018	6	1	6	13	7	1	5	13	1	1	5	4	5	3	7	1	27	6	4	6	16	1	2	3	1	7	7	7	14

	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 recommendations & 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 %**
Score % - Speiser 2018				**56**				**58**									**40**				**72**					**13**			**100**
R1 - Woodcock 2020	7	7	7	21	7	1	7	15	1	1	1	1	1	1	1	1	8	7	7	7	21	1	3	1	1	6	7	7	14
R2 - Woodcock 2020	7	7	7	21	7	1	7	15	1	1	1	1	1	1	1	1	8	6	7	7	20	1	2	1	1	5	7	7	14
Score % - Woodcock 2020				**100**				**67**									**0**				**97**					**6**			**100**

Appendix L Woodcock et al: Discussion points for assessing recommendations pharmacological management at times of physiological stress

	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 includes recommendations for perioperative management rfrom the Association of Anaesthetists, the Royal College of Physicians and the Society for Endocrinology UK but does not state if there was an established development process that was followed. However, two reviewers from the NICE team assessed the guideline using the AGREE II tool. The guideline had scored highly (67%) for stakeholder involvement and was directly applicable to UK settings. Therefore, the GC wished 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 have been reviewed and discussed by the committee and were found to be in line with current clinical practice.
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 seen and approved by the Board of Directors of the Association of Anaesthetists (RCoA), the Council of the RCoA, and the Royal College of Physicians (RCP) Executive. It has also been endorsed by the British Society for Paediatric Endocrinology and Diabetes (BSPED) and the Society for Endocrinology. 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? • This guideline is 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 agreed 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.

	• Research in this area 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 recommendations have been reviewed by the committee and 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 this guideline. In addition, no economic evaluations were identified in the health economic literature review for the NICE guideline nor was it feasible to undertake any economic modelling. 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 recommendations required to address the unmet need or should the committee develop their own recommendations?	The external guideline recommendations were reviewed against the inequality issues identified by the GC and were not found to have any adverse impact
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 haven't sought the views of any patient views or had any patient involvement. 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 M BSPED - Discussion points for assessing recommendations on pharmacological management at times of physiological stress

	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	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.

example qualitative or signs and symptoms questions]	
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 recommendations required to address the unmet need or should the committee develop their own recommendations?	The external guideline recommendations were reviewed against the inequality issues identified by the GC and were not found to have any adverse impact.
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 N Recommendation for research

N.1 Research question

What is the clinical and cost effectiveness of glucocorticoid treatment in the post operative period for people with known or at risk of adrenal insufficiency undergoing in-patient invasive procedures.

N.1.1 Why this is important.

Patients with adrenal insufficiency undergoing in-patient invasive procedures need to be identified and adequately supplemented with glucocorticoids in the post-operative period to prevent adrenal crisis. Based on current evidence both continuous intravenous (IV) infusion of hydrocortisone and repeated delivery of intramuscular (IM) hydrocortisone are recommended management strategies. However, there is limited data directly comparing outcomes between these strategies. Direct comparison may provide evidence of benefit of one strategy over the other. Comparison of clinical and cost benefits are important as is assessment of both patient preference and practical consideration with regards to feasibility of one strategy over the other to ensure development of a pragmatic approach to adrenal replacement during major stress.

N.1.2 Rationale for research recommendation

Importance to 'patients' or the population	This may provide evidence to change current care by recommending hydrocortisone delivery in post operative period by continuous IV infusion or repeated IM delivery should one be found to improve outcome over the other. Assessment of patient preference is essential to ensure patient related outcome measures are taken into consideration.
Relevance to NICE guidance	This question would potentially change guidance in terms of which hydrocortisone delivery strategy should be utilised in the post operative period for those with known or at risk of adrenal insufficiency undergoing in-patient invasive procedures (planned or emergency).
Relevance to the NHS	Potential impacts on the NHS include on service delivery in hospital, and emergency department settings.
National priorities	None.
Current evidence base	A single study was met criteria for review at this time (Glowniak 1997). This small study (n=17) sampled males with secondary adrenal insufficiency only and so limited conclusions can be drawn.
Equality considerations	In addition to the broader group of patients this research recommendation highlights the need for understanding corticosteroid use in specific subgroups (including but not exclusive to) people < 16 years of age.

N.1.3 Modified PICO table

Population	Inclusion: Anyone, any age with established primary, secondary or tertiary adrenal insufficiency. Stratified by: 1. Age <16 years old ≥16 years old 2. Aetiology Adrenal insufficiency due to adrenal pathology (Primary)

	Adrenal insufficiency secondary to hypothalamic/pituitary disease (secondary) Adrenal insufficiency secondary to previous corticosteroid or opiate use (tertiary) 3. Pregnancy i.e., Pregnant patients undergoing labour / caesarean section 4. Surgical procedure On stable hydrocortisone/prednisolone replacement for at least 4 months On stable additional hormone replacement (thyroid hormone, oestrogen or testosterone, growth hormone) for at least 4 months Willing and able to provide written informed consent. Exclusion: Unable or unwilling to provide written informed consent
Intervention	Repeated hydrocortisone injections (IM adults/IM or IV children)
Comparison	Hydrocortisone continuous IV infusion
Outcomes	All-cause mortality at ≤30 days. Length of hospital stay. Serious adverse event(s). Incidence of adrenal crisis. Symptoms of adrenal insufficiency. Haemodynamic measures: Blood pressure, heart rate. Serum cortisol levels. Need for intervention (additional steroid dosing, fluid replacement). Patient preference. Nurse preference. Outcomes measured at: <1h, 0h,1h,2h,3h,4h, 6h,12h,24h,48h.
Study design	RCT
Timeframe	Medium term – in time for the next update
Additional information	None