A.1 Review protocol for 4.2: pharmacological management of secondary and tertiary adrenal hyperplasia

Table 12: Clinical review protocol

ID	Field	Content
1.	Review title	Routine pharmacological management of secondary and tertiary adrenal insufficiency
2.	Review question	What is the clinical and cost effectiveness of pharmacological treatments for the routine management of secondary and tertiary adrenal insufficiency?
3.	Objective	To determine the clinical effectiveness of pharmacological treatments for routine management of secondary 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	Secondary and tertiary adrenal insufficiency
6.	Population	Inclusion: People with adrenal insufficiency (secondary or tertiary) who are diagnosed or suspected of having an adrenal crisis including the following groups: • Adults (aged ≥16 years). • Children aged ≥5 up to 16 years. • Infants aged 1-5 years (because of more frequent dosing). • Infants aged <1 year including neonates. Exclusion: None specified

7.	Intervention /	Any preparation, any dose and any route of administration of the following:
		Glucocorticoids:
		• 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
		Androgen replacement (in women only):

		DHEA replacement (unlicensed) may be prescribed in certain circumstances (such as persistent fatigue). Usually prescribed for adults and sometimes teenagers. Note: Weight-based regimens should also be included. Be aware that some of these interventions may not be licensed for this indication. Exclusions: Hydrocortisone acetate Long-acting methylprednisolone Prednisone (not used in the UK)
8.	Comparator	**For glucocorticoids:** Glucocorticoids compared to each other including different doses, routes of administration and preparations (e.g., modified release compared to standard, crushed tablets compared to whole tablets or oral suspensions) **For DHEA:** Comparisons of different DHEA regimens including doses and routes of administration **For all:** Comparisons to standard care as defined by authors
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 - Type 2 diabetes (small numbers) - Hypothalamic syndrome or associated symptoms - Hypertension - Lipids - Smoking - Growth hormone - Testosterone or oestrogen replacement, desmopressin, thyroid hormone replacement - Other treatments for underlying diseases such as radiotherapy brain or pituitary - Neurosurgery related e.g., craniotomy. - Neurocognitive issues - Hydrocephalus - Ventricular shunt - Steroid doses for underlying conditions - Underlying conditions e.g., RA Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Studies comparing glucocorticoids and DHEAs to each other as each type of drug is given for different indications and therefore a patient would not be prescribed one drug or the other. Comparisons of glucocorticoids or mineralocorticoids to placebo or no treatment Non comparative cohort studies Before and after studies Non-English language studies.

		Conference abstracts will be excluded because they are unlikely to contain enough information to assess whether the population matches the review question in terms of previous medication use, or enough detail on outcome definitions, or on the methodology to assess the risk of bias of the study.
11.	Context	-
12.	Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • **Mortality** • **Health-related quality of life, for example EQ-5D, SF-36** • **Complications of adrenal insufficiency** – growth related issues in children – Low blood sugar/ hypoglycaemia – Early satiety • **Fatigue** as measured using specific fatigue scales such as National Fatigue Index (NFI), fatigue Severity Scale (FSS) • **Incidence of adrenal crisis** (as defined by authors) • **Complications of adrenal crisis**- for example neurological complications, psychological, hypoglycaemia, shock, acute kidney injury may be as part of shock and related to hypovolaemia. • **Admission to hospital and/or ITU** • **Readmission to hospital** • **Length of hospital stay.** • **Treatment-related adverse events:** – Hypertension – Obesity/weight gain – Osteoporosis – Fracture

		– Heart disease/CVS – Cushingoid features: e.g., stretch marks. – Diabetes – 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 – Specific to subcutaneous routes: sites reactions, infections, pumps breaking. – Stomach ulcers • **Activities of daily living** – Social participation – Participation in education (School/university) – Participation in physical activity (measured by any validated scale such as Barthel Index, the Katz Index, or the Functional Independence Measure). Note: there is some overlap between outcomes. For example, hypoglycaemia may be due to either complications of AI or be a complication of adrenal crisis. We will note which outcome these relate to. **Follow up:**

		Any time point as this will be different for different variables. Most will be short term (within 30 days) except for weight or growth-related outcomes, QoL and activities of daily living. We will prioritise data from similar timepoints in order to increase the possibility of conducting a meta-analysis (if appropriate)
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. For Intervention reviews: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Randomised Controlled Trial: Cochrane RoB (2.0) • Non-randomised studies, 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: • Patients on exogenous steroids for underlying condition – may have been on bigger doses before studies	
17.	Type and method of review	☒	Intervention
		☐	Diagnostic
		☐	Prognostic
		☐	Qualitative
		☐	Epidemiologic
		☐	Service Delivery
		☐	Other (please specify)

18.	Language	English		
19.	Country	England		
20.	Anticipated or actual start date	June 2022		
21.	Anticipated completion date	April 2024		
22.	Stage of review at time of this submission	Review stage	Started	Completed
		Preliminary searches	☑	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
23.	Named contact	5a. Named contact Guideline Development Team NGC 5b Named contact e-mail Hypoadrenalism@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
24.	Review team members	From NICE: Sharon Swain [Guideline lead]		

		Saoussen Ftouh [Senior systematic reviewer] Meena Tafazzoli [Systematic reviewer] Alexandra Bannon [Health economist] Stephen Deed [Information specialist] Madelaine Zucker [Technical analyst]
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, glucocorticoids, pharmacological management, DHEA, androgen replacement, hydrocortisone, dexamethasone, prednisolone	
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	