A.1 Review protocol for 4.6: pharmacological management of periods of psychological stress

ID	Field	Content
1.	Review title	Pharmacological management of psychological stress
2.	Review question	4.6 What is the clinical and cost effectiveness of pharmacological treatments for managing periods of psychological stress in people with adrenal insufficiency?
3.	Objective	To determine the optimal pharmacological strategy for managing periods of psychological 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 suspected of having an adrenal crisis 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. 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 (sub cut and iv)
		• Prednisolone
		• Dexamethasone
		For management of hypoglycaemia – specific to children
		• Dextrose any dose/concentration glucose oral or iv any dose/concentration usually 20% or hypogel in children

		Exclusion: Hydrocortisone acetate Long-acting methylprednisolone Prednisone (not used in the UK) **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 • Compared to not increasing the dose • Routes of administration **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 - IV vs IM - comorbidities e.g., heart or kidney disease Published NMAs and IPDs will be considered for inclusion.
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 (may be 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) • Non-randomised 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	From NICE: Sharon Swain [Guideline lead] Saoussen Ftouh [Senior systematic reviewer] Meena Tafazzoli [Systematic reviewer] Alexandra Bannon [Health economist] Stephen Deed [Information specialist]		
25.	Funding sources/sponsor	Development of this systematic review is being funded by NICE.		
26.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.		
27.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10237.		
28.	Other registration details	-		

29.	Reference/URL for published protocol	-	
30.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.	
31.	Keywords	Hypoadrenalism, adrenal insufficiency, congenital adrenal hyperplasia, glucocorticoids, pharmacological management, hydrocortisone, dexamethasone, prednisolone, glucose, dextrose, psychological 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	