ID	Field	Content
1.	Review title	2.1 When to suspect adrenal insufficiency
2.	Review question	When should adrenal insufficiency be suspected (for example, based on risk factors or symptoms)?
3.	Objective	To identify people who are at risk of adrenal insufficiency through risk factors or symptoms that are either strongly associated with AI or that predict its occurrence. This review will be conducted in 2 parts: 1) Signs and symptoms: this part will aim to identify the association of specific signs or symptoms that are indicative of having AI (diagnostic association) 2) Risk factors: this part will aim to identify the association and predictive accuracy of specific factors or patient characteristics that may lead to developing AI in the future (prognostic factor association)
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

		Any search filters applied (e.g. study design) will be found in the review appendix. 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: Adults and children without a diagnosis of adrenal insufficiency Exclusion: None identified
7.	Exposure	**Signs/symptoms:** • Low blood pressure (hypotension including postural hypotension) • Hyperpigmentation • Lethargy • Salt craving • Weight loss • Hyponatraemia • Hyperkalaemia • Hypoglycaemia • Nausea • vomiting • Diarrhoea

		• Failure to respond to initial treatments. **Risk factors:** <u>Drugs:</u> • checkpoint inhibitors e.g., atezolizumab, avelumab, durvalumab • opioids • glucocorticoid therapy (any route) • adrenal enzyme inhibitors: e.g. mitotane ketoconazole, itraconazole, voriconazole, metyrapone, etomidate, aminoglutethimidie, phenobarbital, phenytoin, rifampicin • mifepristone • chlorpromazine • imipramine <u>Co-existing conditions or co-morbidities:</u> • Primary hypothyroidism • Type 1 diabetes • Premature ovarian insufficiency • Autoimmune Polyendocrinopathy Syndrome type 1 • Pituitary tumours • Hypothalamic tumours or disease • Traumatic brain injury (particularly base of skull fracture) • Infections: TB, HIV/AIDS, CMV, fungal infections, syphilis, Lymphocytic hypophysitis, sarcoidosis, histiocytosis X, haemochromatosis Specific to children and neonates: • Prolonged jaundice • Hypoglycaemia

		• Ambiguous genitalia (in females) • Hypotensive crisis Any of the above, alone or in combination
8.	Reference standard/Confounding factors	**Reference standard for signs and symptoms review:** • Clinical diagnosis of adrenal insufficiency by a specialist **Confounding factors for risk factors review:** • Any exposure/risk factors listed above. • Age and sex as a minimum.
9.	Types of study to be included	**For signs and symptoms review:** • Cross sectional (single gate) diagnostic studies • If no or insufficient diagnostic accuracy studies are identified, prospective cohort studies looking at the association between individual or combinations of signs and symptoms (multivariable models/algorithms) and a confirmed diagnosis of adrenal insufficiency. • Systematic reviews of the above **For risk factor review:** • Prospective cohort studies with multivariate analysis. • Systematic reviews of the above. Studies will only be included if key confounders have been accounted for in a multivariate analysis. Key confounders will vary based on each risk factor but should at least include age and sex. Published NMAs and IPDs will be considered for inclusion.
10.	Other exclusion criteria	Non-English language studies. Retrospective cohort studies case-control (two-gate) diagnostic studies Before and after 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)	**For signs and symptoms review:**
		• Diagnostic accuracy data
		  ○ Sensitivity (prioritised)
		  ○ specificity
		If no sensitivity or specificity, LR- and LR+ if raw data unavailable and unable to calculate from 2 x 2 table.
		Diagnostic association of signs and symptoms with a confirmed diagnosis of adrenal insufficiency. Measured by:
		• Association data
		  ○ Adjusted hazard ratios, odds ratios or risk ratios.
		• Discrimination
		  ○ For example, C statistic, area under ROC curve
		• Calibration
		  ○ For example, calibration slope
		For risk factors review:
		• Diagnosis of adrenal insufficiency as defined by authors and reported as adjusted hazard ratios, odds ratios or risk ratios.
		• For risk prediction tools: sensitivity, specificity and statistical measures of discrimination and calibration including Area Under the Curve (AUC) for risk tools.

13.	Data extraction (selection and coding)	EndNote will be used for reference management, citations and bibliographies. 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. These may include: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • Nonrandomised study, including cohort studies: Cochrane ROBINS-I • Clinical prediction study (risk prediction modelling) for a prognosis or diagnosis: PROBAST • Risk factors study: QUIPs • Diagnostic association: QUADAS
15.	Strategy for data synthesis	Where possible data from diagnostic studies will be meta-analysed using Cochrane Review Manager (RevMan5) (if at least 3 studies reporting data at the same diagnostic threshold). Summary diagnostic outcomes will be reported from the meta-analyses with their 95% confidence intervals in adapted GRADE tables. Where association data allows, pairwise meta-analysis will be performed using Cochrane Review manager (RevMan5) software. A fixed-effect meta-analysis, with hazard ratios, odds ratios or risk ratios (as appropriate), and 95% confidence intervals will be calculated for each outcome.

		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. If meta-analysis is not possible, data will be presented as individual values in adapted GRADE profile tables and plots of un-pooled sensitivity and specificity from RevMan software.		
16.	Analysis of sub-groups	Subgroups that will be investigated if heterogeneity is present: None identified		
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	February 2023		
21.	Anticipated completion date	-		
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] Madelaine Zucker [Technical analyst] 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		
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