A.1 Review protocol for when to refer for specialist investigation.

ID	Field	Content
1.	Review title	When to refer for specialist investigation
2.	Review question	When should a person who is having exogenous corticosteroids withdrawn be referred for investigation and management of adrenal insufficiency related to HPA-axis suppression?
3.	Objective	To determine when a person who is having exogenous corticosteroids withdrawn be referred to a specialist for investigation of AI related to HPA-axis suppression based on specific cut-offs for cortisol tests.
4.	Searches	The following databases (from inception) will be searched: • 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	Population	Inclusion: People on long term glucocorticoids who are having them withdrawn. These include: • People on prednisolone doses > 3-5mg/day • People on dexamethasone doses > 0.3-0.5mg/day • People on glucocorticoids longer than 4 weeks Patient circumstances: ○ Those on lower doses and symptomatic ○ Those with co-morbidities ○ Those with clinical indications of AI ○ Individual risk factors ○ Speed of withdrawal e.g. rapid withdrawal vs slow tapering ○ Those who have had or are having steroids via multiple routes. Examples of populations: people with asthma, chronic obstructive pulmonary disease, rheumatoid arthritis, polymyalgia, lupus or multiple sclerosis) Exclusion: None identified.
7.	Test	Diagnostic accuracy based on cut-off: • Cortisol Tests –8- 9 am • Salivary cortisol • Salivary cortisone

		• Short Synacthen test • ACTH and cortisol Note assay specific cut-offs and which assays being used – exclude if they don't' state the assay.
8.	Reference standard	Short Synacthen Test (standard and low dose) Or Insulin tolerance test (insulin hypoglycaemia test) Or Clinical diagnosis by a specialist (a specialist will take into account the full clinical picture, including signs, symptoms, risk factors and test results)
9.	Types of study to be included	• Cross sectional (single gate) diagnostic studies • Systematic reviews of diagnostic accuracy studies • If no or insufficient diagnostic accuracy studies are identified, prospective cohort studies may be included
10.	Other exclusion criteria	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)	Diagnostic accuracy data • Sensitivity (prioritised) *[fewer false negatives i.e., very few people with the condition will be missed]* • Specificity The GC has prioritised sensitivity and specificity as the most important outcomes for their interpretation of the evidence.

		The following thresholds will be used for imprecision for DTA measures and for deciding on the usefulness of the tests in detecting adrenal insufficiency: Sensitivity • Upper 0.9 • Lower 0.6 Specificity • Upper 0.7 • Lower 0.5 Likelihood ratios or other measures such as C statistic or area under ROC curve will only be reported if they are the only measures available, sensitivity and specificity are not reported and cannot be calculated from raw data. Should this be the case, cut-offs for summarising the performance of diagnostic tests or prediction models will be agreed with the guideline committee before the analysis of the evidence is conducted and the protocol will be updated accordingly.
13.	Data extraction (selection and coding)	EndNote will be used for reference management, sifting, 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) • Non-randomised study, including cohort studies: Cochrane ROBINS-I • Cross sectional study: JBI checklist for cross sectional study • Check list for diagnostic test accuracy studies: QUADAS-2	
15.	Strategy for data synthesis	Diagnostic meta-analysis using Cochrane Review Manager (RevMan5) will be conducted where appropriate. 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. Where meta-analysis is not possible, data will be presented, and quality assessed individually per outcome. 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/	
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			
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	Sharon Swain [Guideline lead] Saoussen Ftouh [Senior systematic reviewer] [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		
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	