Review protocol for review question: Is the addition of oral corticosteroids to oral isotretinoin of benefit for the treatment of severe acne (including acne conglobata and acne fulminans)?

Table 3: Review protocol for corticosteroids for treatment of severe acne vulgaris

Field	Content
PROSPERO registration number	CRD42019150497
Review title	Addition of oral corticosteroids to oral isotretinoin for the treatment of severe inflammatory acne vulgaris
Review question	Is the addition of oral corticosteroids to oral isotretinoin of benefit for the treatment of severe acne (including acne conglobata and acne fulminans)?
Objective	The objective of this review is to determine what the most effective oral corticosteroid agent is when combined with oral isotretinoin in the treatment of severe acne (including acne conglobata and acne fulminans).
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • Date: No restriction • Language of publication: English language only • Publication status: Conference abstracts will be excluded because these do not typically provide sufficient information to fully assess risk of bias • Standard exclusions filter (animal studies/low level publication types) will be applied • For each search (including economic searches), the principal database search strategy is quality assured by a second information specialist using an adaption of the PRESS 2015 Guideline Evidence-Based Checklist

Condition or domain being studied	• Severe nodulo-cystic acne, including
	  ○ Acne conglobata
	  ○ Acne fulminans
	  ○ Severe acne vulgaris

Population	• Inclusion: People ≥12 years-old with severe acne, including those with acne conglobata or fulminans • Exclusion: Neonatal acne vulgaris
Intervention	Oral isotretinoin plus any of the following listed oral corticosteroids: • Betamethasone • Deflazacort • Dexamethasone

	• Hydrocortisone • Methylprednisolone • Prednisone • Prednisolone Note: Oral corticosteroids can be given at the same time as, or before or after the start of, oral isotretinoin. All results will be pooled regardless of when the oral corticosteroid was administered.
Comparator	The following comparison will be considered: • Oral isotretinoin plus any listed oral corticosteroid vs oral isotretinoin • Oral isotretinoin plus any listed oral corticosteroid vs oral isotretinoin plus any other listed oral corticosteroid
Types of study to be included	• Systematic reviews/meta-analyses of randomised controlled trials (RCTs) • Randomised or quasi-randomised controlled trials (individual or cluster) If no RCT evidence is identified, the committee will make research recommendations if appropriate. Excluded study designs: • Quasi- or non-randomised controlled studies • Case-control studies • Cohort studies • Cross-sectional studies • Epidemiological reviews or reviews on associations • Non-comparative studies Note: For further details, see the algorithm in appendix H, Developing NICE guidelines: the manual.
Other exclusion criteria	• Studies with <50% completion data (that is drop-out of ≥ 50%) • Studies that do not report the level of acne severity in the study sample, or they include all ranges of severity, from mild to severe • Studies with indirect population: Where studies with a mixed population (i.e. include people with acne vulgaris and another condition, for example hirsutism) are identified, those with <66% of the relevant population will be excluded, unless subgroup analysis for acne vulgaris is reported
Context	Recommendations will apply to those receiving care in any healthcare setting (for example community, primary care, secondary care, tertiary care).

Primary outcomes (critical outcomes)	**Critical outcomes**
	
	Efficacy
	• Clinician-rated improvement
	  ○ Percentage change in acne lesion count
	  ○ Change or final score on a validated acne severity scale
	
	Note: Percentage change data will be prioritised over change or final score on a validated acne severity scale and combined into this outcome.
	• Improvement of isotretinoin-induced acne flare:
	  ○ Clinician-rated change
	  ○ Participant-reported change
	• Long-term side effects of corticosteroids

	Note: 'Long-term' defined as any side effect that occurs between 6 months and 2 years after stopping corticosteroids.
Secondary outcomes (important outcomes)	**Important outcomes** • Adverse effects of oral isotretinoin • Participant-reported improvement ○ Change in acne severity or symptoms (for example assessed using global self-assessment score) • Short-term side effects of corticosteroids • Skin-specific quality of life Note: 'Short-term' defined as any side effect that occurs between 1 week and 6 months after stopping corticosteroids. Participants may still be on course of oral isotretinoin.
Data extraction (selection and coding)	• All references identified by the searches and from other sources will be uploaded into STAR and de-duplicated. Titles and abstracts of the retrieved citations will be screened to identify studies that potentially meet the inclusion criteria outlined in the review protocol. • Dual sifting will be performed on at least 10% of records; 90% agreement is required. • Disagreements will be resolved via discussion between the two reviewers, and consultation with senior staff if necessary. • Full versions of the selected studies will be obtained for assessment. Studies that fail to meet the inclusion criteria once the full version has been checked will be excluded at this stage. Each study excluded after checking the full version will be listed, along with the reason for its exclusion. A standardised form will be used to extract data from studies including study reference, study characteristics (for example design, type of statistical analysis), participant characteristics (for example age, ethnicity, sex, acne severity, concurrent acne treatment), intervention(s) characteristics (intervention details for example dosage, length, duration, frequency, mode), outcomes, and risk of bias. One reviewer will extract relevant data into a standardised form, and this will be quality assessed by a senior reviewer.
Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the preferred checklist as described in Developing NICE guidelines: the manual.
Strategy for data synthesis	• Depending on the availability of the evidence, the findings will be summarised narratively or quantitatively. Where possible, meta-analyses will be conducted using Cochrane's Review Manager software. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios or odds ratios for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. For dichotomous outcomes, intention-to-treat (ITT) data will be used if available; if not then available data will be used. Final and change scores will be pooled and if any study reports both, change scores will be used in preference over final scores. • Sensitivity analysis will be conducted according to risk of bias of individual studies. Missing data will be accounted for in the risk of bias assessment. • Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. I^2 values of greater than 50% and 80% will be considered as serious and very serious heterogeneity, respectively. Heterogeneity will be explored as appropriate using

<table>
<tr><td></td><td colspan="3">sensitivity analyses and pre-specified subgroup analyses. If heterogeneity cannot be explained through subgroup analysis then a random effects model will be used for meta-analysis, or the data will not be pooled.
• Default MIDs will be used for risk ratios and continuous outcomes only, unless the committee pre-specifies published or other MIDs for specific outcomes
○ For risk ratios: 0.8 and 1.25.
○ For continuous outcomes: +/-0.5 times the baseline SD of the control arm. If there are 2 studies, the MID is calculated as +/- 0.5 times the mean of the SDs of the control arms at baseline. If there are 3 or more studies, the MID is calculated as +/- 0.5 times the median of the SDs of the control arms at baseline. If baseline SD is not available, then SD at follow up will be used.
• The confidence in the findings across all available evidence will be 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/
• Studies that do not use a validated scale to assess severity of acne are at high risk of bias. If appropriate, the contribution of such studies to an outcome will be accounted for using the GRADE domain of indirectness.</td></tr>
<tr><td>Analysis of sub-groups</td><td colspan="3">No sub-group analysis will be performed.</td></tr>
<tr><td rowspan="7">Type and method of review</td><td>☒</td><td colspan="2">Intervention</td></tr>
<tr><td>☐</td><td colspan="2">Diagnostic</td></tr>
<tr><td>☐</td><td colspan="2">Prognostic</td></tr>
<tr><td>☐</td><td colspan="2">Qualitative</td></tr>
<tr><td>☐</td><td colspan="2">Epidemiologic</td></tr>
<tr><td>☐</td><td colspan="2">Service Delivery</td></tr>
<tr><td>☐</td><td colspan="2">Other (please specify)</td></tr>
<tr><td>Language</td><td colspan="3">English</td></tr>
<tr><td>Country</td><td colspan="3">England</td></tr>
<tr><td>Anticipated or actual start date</td><td colspan="3">11 September 2019</td></tr>
<tr><td>Anticipated completion date</td><td colspan="3">13 January 2021</td></tr>
<tr><td rowspan="4">Stage of review at time of this submission</td><td>Review stage</td><td>Started</td><td>Completed</td></tr>
<tr><td>Preliminary searches</td><td>☑</td><td>☑</td></tr>
<tr><td>Piloting of the study selection process</td><td>☑</td><td>☑</td></tr>
<tr><td>Formal screening of search results against eligibility criteria</td><td>☑</td><td>☑</td></tr>
</table>

	Data extraction	☑	☑
	Risk of bias (quality) assessment	☑	☑
	Data analysis	☑	☑
Named contact	**5a. Named contact** National Guideline Alliance **5b Named contact e-mail** AcneManagement@nice.org.uk **5e Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and National Guideline Alliance		
Review team members	National Guideline Alliance		
Funding sources/sponsor	This systematic review is being completed by the National Guideline Alliance, which receives funding from NICE.		
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.		
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/NG198/history		
Other registration details	Not applicable		
Reference/URL for published protocol	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=150497		
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.		
Keywords	Acne; acne conglobata; acne fulminans; adverse events; corticosteroid; flare; glucocorticoid; inflammation; oral isotretinoin; severe acne.		
Details of existing review	Not applicable		

of same topic by same authors		
Current review status	☒	Ongoing
	☒	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	Not applicable	
Details of final publication	https://www.nice.org.uk	

GRADE: Grading of Recommendations Assessment, Development and Evaluation; MID: minimally important difference; NHS: National health service; NICE: National Institute for Health and Care Excellence; RCT: randomised controlled trial; SD: standard deviation