Review protocol for indicators of organ hypoperfusion to guide the administration of intravenous fluids for resuscitation in people aged under 16 with suspected sepsis.

ID	Field	Content
1.	Review title	Indicators of organ hypoperfusion used to guide the administration of intravenous fluids for resuscitation in people aged under 16 with suspected sepsis.
2.	Review question	In people aged under 16 with suspected sepsis, what indicators of organ hypoperfusion should be used (in addition to the PEWS score) to guide the administration of intravenous fluids for resuscitation?
3.	Objective	To determine which indicators of organ hypoperfusion should be used to guide the administration of intravenous fluids for resuscitation in people aged under 16
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE in process Searches will be restricted by: • Studies from 2014 • English Language • Human studies • Conference abstracts excluded Other searches: • Reference searching The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Suspected or confirmed sepsis
6.	Population	Inclusion:

		• People aged under 16 with suspected or confirmed sepsis in in-hospital* and ambulance settings *this could include hospital at home/virtual wards Exclusion: • Adults and young people aged 16 or over • People who are of have recently been pregnant
7.	Prognostic indicator	The following indicators of organ hypoperfusion (in addition to PEWS): • Oliguria (defined as urine output less than 1ml/kg/hour in neonates and infants and 0.5 ml/kg/hour in children older than one year) • Peripheral shutdown (defined as cool, mottled extremities, prolonged capillary refill time, weak and thready peripheral pulse) • Development of acute kidney injury (high serum creatinine measured by SOFA criteria or KDIGO) • Increasing lactate (rise above normal level, range can be >1.6, 1.8 or >2 mmol/l) • Base deficit (low base excess) • Delayed capillary refill (defined as ≥ 3 seconds)
8.	Comparator	The prognostic indicator compared against people without that indicator/other indicator/PEWS score
9.	Types of study to be included	• Systematic reviews of prospective cohort studies • Prospective cohort studies • Retrospective cohort studies
10.	Other exclusion criteria	• All other study types. • Studies reporting data without confidence intervals or data that cannot be used to calculate confidence intervals. • Studies that haven't controlled/matched for pre-existing comorbidities, age, sex, BMI, ethnicity
11.	Context	During the last update of the sepsis guideline committee members agreed that waiting for someone's lactate or blood pressure to reach a certain level before giving them fluids or escalating their care could not be justified in all circumstances and that instead

		a range of indicators should be considered. This was reflected in the recommendations made for adults aged 16 and over, so the guideline for people aged under 16 also needs to address this.
12.	Primary outcomes (critical outcomes)	• Length of Hospital stay • Mortality • Administration of IV fluids • Admission to ICU • Length of stay in ICU • Change in PEWS score • Acute Kidney Injury (AKI) • Administration of vasopressors • Invasive ventilation
13.	Secondary outcomes (important outcomes)	None
14.	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 6.2). Study investigators may be contacted for missing data where time and resources allow. Where appropriate, this review will make use of the priority screening functionality within the EPPI-reviewer software. At least 50% of the data set will be screened and we will stop screening after that if we screen more than 250 records without an include
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	**Approach to meta-analysis**

		Association data will be defined as measures of association between one or more factors (which could be either a single variable or a group of variables) and an outcome variable, where the data are not reported in terms of outcome classification (i.e. diagnostic/predictive accuracy). Examples could include (but were not limited to) data assessing the association between variables and diagnosis (diagnostic association studies) or data assessing the association between variables and a future outcome (prognostic association studies). Data will be reported as hazard ratios (if measured over time) or odds ratios or risk ratios (if measured at a specific time-point). Where appropriate, hazard ratios will be pooled using the generic inverse-variance method. Adjusted odds ratios, hazard ratios and risk ratios from multivariate models will only be pooled if the same set of factors are used across multiple studies and if the same thresholds to measure factors are used across studies. Random effects models will be fitted when significant between-study heterogeneity in methodology, population, intervention or comparator is identified by the reviewer in advance of data analysis. This decision will be made and recorded before any data analysis is undertaken. For all other syntheses, fixed- and random-effects models will be fitted, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model is clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results will be presented. Fixed-effects models are deemed to be inappropriate if there is significant statistical heterogeneity in the meta-analysis, defined as $I2 \geq 50\%$. However, in cases where the results from individual pre-specified subgroup analyses is less heterogeneous (with $I2 < 50\%$) the results from these subgroups will be reported using fixed effects models. This may lead to situations where pooled results are reported from random-effects models and subgroup results are reported from fixed-effects models. **Approach to GRADE**

		A modified approach will be applied using the GRADE framework. Data from cohort studies will be initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point. These criteria will be used to apply preliminary ratings, but will be overridden in cases where, in the view of the analyst or committee the uncertainty identified is unlikely to have a meaningful impact on decision making.		
17.	Analysis of sub-groups	Where data allows, subgroup analysis may be conducted considering: • Age • People who are immunosuppressed		
18.	Type and method of review	☐ Intervention		
		☐ Diagnostic ☒ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	January 2026		
22.	Anticipated completion date	tbc		
23.	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	☐	☐
24.	Named contact	**5a. Named contact** sepsisupdate@nice.org.uk **5b Named contact e-mail** sepsisupdate@nice.org.uk **5e Organisational affiliation of the review**		

		National Institute for Health and Care Excellence (NICE) and Guideline Development Team B
25.	Review team members	From the Centre for Guidelines: • Guideline lead: Robby Richey • Technical analysts: Michellie Young and Rachel Gick • Senior Technical analyst: James Jagroo • Health Economics Adviser: Eric Slade • Information specialist: Lynda Ayiku
26.	Funding sources/sponsor	This systematic review is being completed by the guideline development team which receives funding from NICE.
27.	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.
28.	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: tbc
29.	Other registration details	N/A
30.	Reference/URL for published protocol	tbc
31.	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.
32.	Keywords	Sepsis, Organ Hypoperfusion, critical care, IV Fluids
33.	Details of existing review of same topic by same authors	This is a new review question that will update Sepsis in under 16s: recognition, diagnosis and early management
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	N/A
36.	Details of final publication	www.nice.org.uk