Review protocol for the safety of peripherally administered vasopressors for guiding treatment in people aged under 16 with suspected sepsis

ID	Field	Content
1.	Review title	Safety of peripherally administered vasopressors in people aged under 16 with suspected sepsis.
2.	Review question	In people aged under 16 with suspected sepsis, how safe is the peripheral administration of intravenous vasopressors compared to central line administration?
3.	Objective	To determine the safety of peripherally administered vasopressors in people aged under 16 with suspected sepsis.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • Epistemonikos • MEDLINE Searches will be restricted by: • Studies published after 2010 • English Language • Human studies • Conference abstracts excluded • OECD countries The full search strategies will be reported in the final review in accordance with the PRISMA-S reporting guide.
5.	Condition or domain being studied	Suspected sepsis
6.	Population	Inclusion: • People aged under 16 who require vasoactive medication for treatment of hypotension or shock and who are in in-hospital* and ambulance settings

		*this could include hospital at home/virtual wards Exclusion: • People who are or have recently been pregnant** • Adults and young people aged over 16 **Someone is considered to have recently been pregnant: • in the 24 hours following a termination of pregnancy or miscarriage • for 4 weeks after giving birth.
7.	Intervention	• Any vasopressor delivered via peripheral venous access
8.	Comparator	• Any vasopressor delivered via central venous access
9.	Types of study to be included	• Systematic reviews of RCTs and cohort studies • RCTs • Cohort studies (considered if less than 3 RCTs are found at low risk of bias, or 5 at moderate or better risk of bias)
10.	Other exclusion criteria	• Conference abstracts, editorials/letters • Dissertations and theses • Studies not published in English • Pre-prints. • Studies reporting data without confidence intervals or data that cannot be used to calculate confidence intervals.
11.	Context	During the previous update to the Sepsis guideline published in January 2024, the guideline committee highlighted that clinical practice has moved to start vasopressors sooner or even concurrently with IV fluids, particularly in patients who are very hypotensive, as this can prevent people being given too much fluid which may worsen outcomes. Furthermore, they highlighted that a senior clinical decision maker should be able to start vasopressors using peripheral venous access without having to wait for a critical care clinician to undertake central line placement. These changes were reflected in the update to the guidance for people aged over 16, so this review is needed to align the guidance for people aged under 16

12.	Primary outcomes (critical outcomes)	• Blood stream infection (dichotomous)* • Extravasation (dichotomous)* • Phlebitis (dichotomous)* • Bleeding (dichotomous)* • Occlusion (dichotomous)* • Mortality related to adverse events due to method vasopressor administration at 30 days (dichotomous) • Serious adverse events (dichotomous)* • Extravasation management beyond removal of cannula (for example limb elevation or application of dressing) (dichotomous)* *Where multiple time points are reported, data will be extracted for the longest time point (or up to 7 days post treatment) only."
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: • Systematic reviews of RCTs and cohort studies: Risk of Bias in Systematic reviews (ROBIS) • Randomised controlled trials: Cochrane risk of bias (ROB) 2 tool • Cohort studies: Cochrane ROBINS-I.

16.	Strategy for data synthesis	Where possible, meta-analyses will be conducted to combine the results of quantitative studies for each outcome. RCT and non-randomised comparative studies data will be pooled separately. **Approach to meta-analysis** Pairwise meta-analyses will be performed in Cochrane RevMan Web. A pooled relative risk will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. A pooled mean difference will be calculated for continuous outcomes (using the inverse variance method) when the same scale will be used to measure an outcome across different studies. Where different studies presented continuous data measuring the same outcome but using different numerical scales these outcomes will be all converted to the same scale before meta-analysis is conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data will be analysed using standardised mean differences (SMDs, Hedges' g). Fixed effects models will be fitted unless there is significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$, when random effects models will be used instead. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically assess the potential for publication bias. **Approach to GRADE** GRADE will be used to assess the quality of any pair-wise analysis of outcomes. Data from randomised controlled trials and non-randomised comparative studies will be initially rated as high quality where they come from: • RCTs and systematic reviews of RCTs (where individual studies have been quality assessed using Cochrane risk of bias.

		• non-randomised comparative studies and systematic reviews of non-randomised studies (where individual studies have been quality assessed using the ROBINS-I assessment tool) The quality of the evidence for each outcome will then be downgraded or not from this starting point based on the other GRADE domains. To assess imprecision, where there are no defined MIDs we will set the MID as the line of no effect for all outcomes (1.0 for dichotomous outcomes and 0 for continuous outcomes). A second decision threshold will be applied where the sample size is sufficiently small that it is not plausible any realistic effect size could have been detected..		
17.	Analysis of sub-groups	None		
18.	Type and method of review	☐ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☒ Other: Safety		
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 • Senior Information specialist: Lynda Ayiku
26.	Funding sources/sponsor	This systematic review is being completed by the centre for guidelines 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, vasopressors, safety, blood stream infection, extravasation
33.	Details of existing review of same topic by same authors	This is a new review question that will update Sepsis in people aged under 16: 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