Review protocol for review question: What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?

Table 29: Review protocol

Field	Content
PROSPERO registration number	Not applicable
Review title	Uterotonics for the prevention of PPH
Review question	What is the effectiveness of uterotonics for the prevention of postpartum haemorrhage?
Objective	To update the recommendations in CG190 (2014) for the use of uterotonics for prevention of postpartum haemorrhage
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE & MEDLINE In-Process • International Health Technology Assessment (IHTA) database Searches will be restricted by: • Date limitations: May 2018 (date when the search was last run for Gallos 2018) • English language studies • Human studies Other searches: • Inclusion lists of systematic reviews The full search strategies for the MEDLINE database will be published in the final review. For each search,

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	the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist. Key papers: ○ Cochrane NMA (Gallos 2018) https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011689.pub3/full ○ IMOX trial https://pubmed.ncbi.nlm.nih.gov/30606246/ ○ CHAMPION trial https://www.nejm.org/doi/full/10.1056/nejmoa1805489
Condition or domain being studied	Prevention of postpartum haemorrhage
Population	• Women in the third stage of labour following a vaginal or caesarean birth
Intervention	The following uterotonic agents: • Carbetocin • Ergometrine (includes also ergonovine, methylergonovine) • Injectable prostaglandins (carboprost, tromethamine, sulprostone) • Misoprostol ○ Dose ≤600 mcg ○ Dose >600 mcg to ≤800 mcg ○ Dose >800 mcg to ≤1000 mcg ○ Dose >1000 mcg • Oxytocin ○ Dose ≤1 iu ○ Dose >1 iu to ≤ 5 iu ○ Dose >5 iu to ≤ 10 iu ○ Dose > 10 iu • The following combination agents: ○ Syntometrine ® as a fixed-combination agent containing 5 international units (IU) of oxytocin and 500 mcg of ergometrine; any oxytocin dose and route when combined with any dose and

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	route of ergometrine, ergonovine, or methylergonovine ○ Misoprostol plus oxytocin (any oxytocin dose and route when combined with any dose and route of misoprostol) The uterotonic or combination agents noted above will be eligible if they are administered systemically by a healthcare professional for preventing PPH at birth. Any dosage, route and regimen will be included.
Comparator	• Any uterotonic agent listed as part of the interventions compared to another • Placebo • No treatment
Types of study to be included	Include published full-text papers: • RCTs • Cluster RCTs • Conference abstracts in which sufficient information can be retrieved Quasi-randomised trials will be excluded
Other exclusion criteria	• Trials evaluating uterotonics agents not administered systemically, such as intrauterine administration, or not immediately after birth • Trials exclusively comparing different dosages, routes or regimens of the same uterotonic agent
Context	This review will update the following guideline: Intrapartum care for healthy women and babies (CG190) and it is based on the Cochrane NMA Gallos 2018 https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011689.pub3/full
Primary outcome (critical outcome)	• Primary PPH ≥1000 mL
Secondary outcomes (important outcomes)	• Severe maternal morbidity: intensive care admissions • Additional uterotonics

Field	Content
	• Number of blood transfusions • Mean volumes of blood loss (mL)
Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI 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 in excel. The following data will be extracted: study details (study ID, first author, publication year, number of arms, number randomised), participant characteristics, intervention characteristics, dose and route and relevant outcome data. Data will be extracted independently by 2 reviewers into a standardised form, and any disagreements will be resolved via discussion and consultation with senior staff. For dichotomous outcomes, an intention-to-treat (ITT) approach will be taken and where possible ITT data will be extracted; if both ITT and completer data are reported, the former will be preferred; completer data will be used only if ITT data are not reported. For continuous outcomes, completer data will be preferred, unless some method of adjusting for missing data has been used, in which case, an ITT approach will be preferred.
Risk of bias (quality) assessment	Risk of bias of individual studies will be assessed using the relevant version of the Cochrane RoB tool, v1. checklist
Strategy for data synthesis	**Method of analysis** <u>Network meta-analysis (NMA)</u> • Network meta-analysis will be conducted within a Bayesian framework using WinBUGS. • The exact model structure will be agreed with the NICE Technical Support Unit (TSU) following the review of available clinical evidence. Fixed and random effects NMA models will be fitted to the data and

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	compared based on the posterior mean residual deviance and DIC. The model with the best fit and meaningfully lower DIC will be selected. Differences of at least 3 will be considered meaningful. • For dichotomous outcomes, posterior median ORs and 95% credible intervals (CrIs) will be used to report the results • For continuous outcomes, mean differences will be used to report the results • Ranking of treatments will be provided (i.e. posterior median ranks and 95% CrIs, rankograms, probability being best). • Inconsistency checks will be conducted by comparing the posterior mean residual deviance, DIC, and where appropriate (i.e., random effects models), posterior median between study standard deviation, of the base case NMA model and unrelated mean effects (UME) model. Plots of contributions to the residual deviance for the UME vs the NMA model will be inspected to identify lack of consistency for particular studies / comparisons. If these checks indicate potential inconsistency, further checks will be conducted using node splitting analysis. Pairwise estimates will be obtained from the UME model to aid comparison of the direct estimates with the NMA estimates. • Threshold analysis will also be conducted if a clear decision rule between linking the recommendations to the NMA estimates can be identified. <u>Pairwise meta-analysis</u> For outcomes with insufficient data for NMA, standard pair-wise meta-analysis will be conducted using Cochrane Review Manager. A fixed effect meta-analysis will be conducted and data will be presented as risk ratios if possible or odds ratios when required (for example, if only available in this form in included studies) for dichotomous outcomes, and mean differences or standardised mean differences for continuous outcomes. Heterogeneity in the effect estimates of the individual studies will be assessed using the I^2 statistic. Alongside visual inspection of the point estimates and confidence intervals, I^2 values of greater than 50% and 80% will be considered as significant and very significant heterogeneity, respectively. Heterogeneity will be explored as appropriate using 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.
Analysis of subgroups	Subgroup analysis: • Mode of birth:

Field	Content			
	○ Vaginal birth ○ Caesarean birth			
Type and method of review	☒	Intervention		
	☐	Diagnostic		
	☐	Prognostic		
	☐	Qualitative		
	☐	Epidemiologic		
	☐	Service Delivery		
	☐	Other (please specify)		
Language	English			
Country	England			
Anticipated or actual start date	Not applicable			
Anticipated completion date	Not applicable			
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		☑	☑

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Named contact	5a. Named contact Guideline Development Team National Guideline Alliance (NGA) 5b. Named contact e-mail IPCupdate@nice.org.uk 5c. Organisational affiliation of the review Guideline Development Team NGA, Centre for Guidelines, National Institute for Health and Care Excellence (NICE)
Review team members	From the Guideline Development Team: • Senior Systematic Reviewer • Systematic Reviewer
Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team NGA, Centre for Guidelines, which is part of the National Institute for Health and Care Excellence (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/indevelopment/gid-ng10174
Other registration details	None
URL for published protocol	Not applicable
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

Field	Content	
	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	[Give words or phrases that best describe the review.]	
Details of existing review of same topic by same authors	Not applicable	
Current review status	☒	Ongoing
	☐	Completed but not published
	☐	Completed and published
	☐	Completed, published and being updated
	☐	Discontinued
Additional information	None	
Details of final publication	www.nice.org.uk	

CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; CrIs: credible interval; DARE: Database of Abstracts of Reviews of Effects; Development and Evaluation; IHTA: International Health Technology Assessment; ITT: intention to treat; IU: international units; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; NMA: network meta-analysis; OR: odds ratio; PPH: postpartum haemorrhage; PRESS: Peer Review of Electronic Search Strategies; RCT: randomised controlled trial; RoB: risk of bias; SD: standard deviation; TSU: technical support unit; UME: unrelated mean effects