Review protocol for review question: Is intravenous administration of oxytocin more effective than intramuscular administration in the active management of the third stage of labour?

Table 3: Review protocol

Field	Content
PROSPERO registration number	CRD42021269397
Review title	Intravenous administration of oxytocin compared with intramuscular administration in the active management of the third stage of labour
Review question	Is intravenous administration of oxytocin more effective than intramuscular administration in the active management of the third stage of labour?
Objective	To draft recommendations for the route of administration of oxytocin in the active management in the third stage of labour. Surveillance has identified that, compared to the intramuscular route, intravenous administration of oxytocin (as part of active management) may be associated with significantly lower rates of severe postpartum haemorrhage, the need for blood transfusion and admission to a high dependency unit.
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • International Health Technology Assessment database Searches will be restricted by: • No date limitations • English language only

Field	Content
	• Human studies only Other searches: • Inclusion lists of systematic reviews The full search strategies for MEDLINE database will be published in the final review. For each search, the principal database search strategy is quality assured by a second information scientist using an adaptation of the PRESS 2015 Guideline Evidence-Based Checklist.
Condition or domain being studied	Labour and birth
Population	Women in the third stage of labour who have given birth (spontaneous or assisted vaginal birth) to a single baby, who went into labour at term (37 to 42 weeks of pregnancy)
Intervention	Intravenous administration of oxytocin in the third stage of labour
Comparator	Intramuscular administration of oxytocin in the third stage of labour
Types of study to be included	Include published full-text papers: • Systematic reviews of RCTs • Parallel RCTs (individual or cluster) If not enough evidence from RCTs is found: • Prospective and retrospective cohort studies • Conference abstracts will not be included because these do not typically have sufficient information to allow full critical appraisal.
Other exclusion criteria	None
Context	This guideline will partly update the following: Intrapartum care for healthy women and babies (CG190)
Primary outcomes (critical outcomes)	• Maternal admission to intensive therapy unit (ITU) or high-dependency area • Primary postpartum haemorrhage (PPH) at time of birth and up to 24 hours (PPH > 500 mL) • Severe primary postpartum haemorrhage (PPH) at time of birth and up to 24 hours (PPH > 1000 mL)

Field	Content
Secondary outcomes (important outcomes)	• Need for manual removal of placenta • Need for additional uterotonics during the third stage or within the first 48 hours • Side effects (for example, change in blood pressure, headache, nausea/ vomiting, pain analgesia) during the third stage of labour or within the first 24 hours • Women's experience of labour and birth
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. The following data will be extracted: study details (reference, country where study was carried out, type and dates), participant characteristics, inclusion and exclusion criteria, details of the interventions if relevant, setting and follow-up, relevant outcome data and source of funding. 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	Quality assessment of individual studies will be performed using the following checklists: • ROBIS tool for systematic reviews • Cochrane RoB tool v.2 for RCTs • Cochrane RoB tool v.2 for cluster randomised controlled trials • ROBINS-I tool for non-randomised (clinical) controlled trials and cohort studies The quality assessment will be performed by one reviewer and this will be quality assessed by a senior reviewer.
Strategy for data synthesis	Quantitative findings will be formally summarised in the review. Where multiple studies report on the same outcome for the same comparison, meta-analyses will be conducted using Cochrane Review Manager software. 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

Field	Content
	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. 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/ **Minimally important differences:** • Validated scales/continuous outcomes: published MIDs where available • All other outcomes & where published MIDs are not available: 0.8 and 1.25 for all relative dichotomous outcomes ; +/- 0.5x control group SD for continuous outcomes
Analysis of subgroups	Evidence will be stratified by: • BMI thresholds on booking: o Underweight range: <18.5 kg/m2 o Healthy weight range: 18.5 to 24.9 kg/m2 o Overweight range: 25 to 29.99 kg/m2 o Obesity range 1: 30 to 34.99 kg/m2 o Obesity range 2: 35 to 39.99 kg/m2 • Dosage of oxytocin (5 IU oxytocin vs 10 IU oxytocin) • Intravenous oxytocin bolus injection vs IV oxytocin slow infusion • Mode of birth (spontaneous vaginal vs instrumental vaginal) • Risk of PPH (high risk vs moderate vs low), as defined by study authors • Women who have had oxytocin in the first stage of labour vs women who have not **Amendment:** The term 'IV oxytocin slow bolus injection' originally described in the analysis of subgroups section in the protocol has been replaced for the term 'IV oxytocin slow infusion' to more accurately describe the route of administration of intravenous.

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	Stratifications will be dealt with in a hierarchy (this is, first by BMI thresholds on booking, then by dosage of oxytocin, then by oxytocin given as bolus or slow bolus injection, then by mode of birth, then by risk of PPH and then by women who have had oxytocin in the first stage of labour versus women who have not) Evidence will be subgrouped by the following only in the event that there is significant heterogeneity in outcomes: • Age of woman (<35 vs >/= 35) • Ethnicity • White • Asian/Asian British • Black/African/Caribbean/Black British • Mixed/Multiple ethnic groups • Other ethnic group • Women with disability vs not • Deprived socioeconomic group vs not Where evidence is stratified or subgrouped the committee will consider on a case by case basis if separate recommendations should be made for distinct groups. Separate recommendations may be made where there is evidence of a differential effect of interventions in distinct groups. If there is a lack of evidence in one group, the committee will consider, based on their experience, whether it is reasonable to extrapolate and assume the interventions will have similar effects in that group compared with others.	
Type and method of review	☒	Intervention
	☐	Diagnostic
	☐	Prognostic
	☐	Qualitative
	☐	Epidemiologic
	☐	Service Delivery
	☐	Other (please specify)
Language	English	

Field	Content
Country	England
Anticipated or actual start date	14/07/2021
Anticipated completion date	22/03/2023
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.

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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.
Other registration details	None
URL for published protocol	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=269397
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	Oxytocin; route of administration; third stage of labour
Details of existing review of same topic by same authors	Not applicable
Additional information	None
Details of final publication	www.nice.org.uk

BMI: body mass index; CDSR: Cochrane Database of Systematic Reviews; CENTRAL: Cochrane Central Register of Controlled Trials; DARE: Database of Abstracts of Reviews of Effects; GRADE: Grading of Recommendations Assessment, Development and Evaluation; HTA: Health Technology Assessment; MID: minimally important difference; NGA: National Guideline Alliance; NHS: National health service; NICE: National Institute for Health and Care Excellence; PPH: postpartum haemorrhage; PRESS: peer review of electronic search strategies; RCT: randomised controlled trial; RoB(IS): risk of bias (in systematic reviews); SD: standard deviation