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First-line uterotonics for treating postpartum haemorrhage: a systematic review and network meta-analysis (Protocol)

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[Intervention Protocol]

First-line uterotonics for treating postpartum haemorrhage: a systematic review and network meta-analysis

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

Primary

To assess the relative effectiveness and produce a clinically meaningful hierarchy of first-line uterotonic drugs for the treatment of postpartum haemorrhage (PPH).

Secondary

To assess the relative risks and produce side effect hierarchies of first-line uterotonic drugs for the treatment of PPH.

BACKGROUND

Description of the condition

An estimated 303,000 women died in childbirth worldwide in 2015 (Alkema 2016). This equates to a 1 in 180 global lifetime risk of maternal death (WHO 2015). Postpartum haemorrhage (PPH) is the leading contributor to maternal deaths, accounting for around 27% of all cases (Say 2014). Even when death is

avoided, the risk of major maternal morbidity such as blood transfusion or hysterectomy is substantial (Penny 2007; Carroll 2016). The long-term sequelae of PPH can include anxiety, depression, and post-traumatic stress disorder (Carroll 2016).

PPH is defined as blood loss in excess of 500 mL following birth (WHO 2012). Many clinicians would identify a 500 mL blood loss as a tipping point for progression to treatment (Mavrides 2016). However, because of the poor association of 500 mL loss with morbidity, others use 1000 mL or even PPH-related morbidity to define PPH (Kerr 2016). Indeed, many clinicians report that they commence treatment as soon as they are unhappy with the rate of bleeding, rather than wait for any specific volume of loss (Hancock 2015).

The mainstay of management of PPH is to prevent it and, should prevention fail, to treat it. A comparison between uterotonic drugs to prevent PPH is covered by another Cochrane review and network meta-analysis (Gallos 2015). A comparison between uterotonic drugs to treat PPH is the subject of this review.

The World Health Organization (WHO) recommendation to use intravenous oxytocin as a first-line treatment is based on moderate-quality evidence, and recommendations to use ergometrine or prostaglandins are based on low-quality evidence (WHO 2012). The UK's National Institute for Health and Care Excellence (NICE) guidelines also highlight the lack of robust evidence to guide recommendations (NICE 2014). Consequently, in the UK there is a wide variation in the management of PPH, with several drugs used for treatment (Al Wattar 2017). Hence, there is an urgent need to define the most effective drug for the treatment of PPH.

Description of the intervention

PPH treatment is characterised by interventions to remedy the cardinal cause(s) of haemorrhage. It particularly seeks to improve uterine tone, and if necessary to repair any trauma, to remove the placenta and membranes in entirety, and to correct the clotting cascade (Coomarasamy 2016). In clinical practice uterotonic drugs are administered to improve uterine tone as a primary factor, while other issues are excluded or managed as secondary factors. Interventions such as surgery, embolization and/or compression have been described, but this review will focus entirely on uterotonic drugs because the relative treatment effects of these interventions are particularly uncertain.

How the intervention might work

Uterotonic drugs work by increasing the contractility (tone) of the uterus, thereby compressing the blood vessels of the myometrium (smooth muscle tissue in the uterus) and reducing bleeding. Each drug has its own unique side effect profile and mode of action, although the end effect is increased uterine tone.

Oxytocin, a nine-amino-acid peptide, is widely regarded as the gold standard treatment of PPH, although the optimal dose and route of administration for treatment remain unclear (WHO 2012). Furthermore, there is clinical and laboratory evidence that whilst the first dose of oxytocin is effective, repeated doses become increasingly ineffective (Weeks 2015).

An analogue of oxytocin, carbetocin, which produces sustained rather than rhythmic contraction of the uterus, is also used for the treatment of PPH, but it has been evaluated largely for prevention only (Su 2012).

Ergometrine is an ergot alkaloid that increases the muscle tone of the uterus. It has long been used in both treatment and prevention of PPH, although the optimum dose and route are debated (Liabsuetrakul 2007). Syntometrine - a combination of oxytocin and ergometrine - has been advocated in the treatment of PPH for many years (Mavrides 2016).

Misoprostol is a synthetic analogue of prostaglandin E1 with methylation at C16. The use of misoprostol to treat PPH is recognised, although the optimum route and dosage is also a matter of contention (Hofmeyr 2005). Carboprost is another synthetic prostaglandin analogue of PGF2 with uterotonic properties, often used in cases where oxytocin has already been used and a further uterotonic is indicated (Bateman 2014).

Why it is important to do this review

Across the world, maternal mortality remains unacceptably high, and excessive bleeding after childbirth is a leading cause. Although maternal mortality risks are greatest in low-income settings, in recent years a rise in the number of deaths from PPH in developed healthcare settings serves to highlight that PPH is a global problem, requiring ongoing effort to find solutions (Mehrabadi 2013). Active management of the third stage of labour may reduce the amount of bleeding and related morbidity (WHO 2012; Begley 2015), but remains unlikely to completely prevent PPH, so the need to identify effective treatment is urgent.

A Cochrane review has compared different uterotonic drugs for treating PPH (Mousa 2014). Standard pair-wise meta-analyses can only compare those treatments that have been directly compared in head-to-head trials. Standard pair-wise meta-analyses do not allow ranking of the various drugs. In the absence of a single high-quality, randomised controlled trial comparing all uterotonic agents, significant uncertainty remains about which is the most effective at treating PPH. In relation to a complex event such as PPH, with several competing treatment options, not all of which have been directly compared, a network meta-analysis may be better able to allow for comparisons and conclusions about which uterotonic drug is most effective.

A network meta-analysis simultaneously pools all the available direct and indirect evidence on relative treatment effects, to achieve a single coherent analysis (Caldwell 2005; Caldwell 2010). Indirect evidence is obtained by inferring the relative effectiveness of two

competing treatments through a common comparator. A network meta-analysis produces estimates of the relative effects of each treatment compared with every other in a network, even though some pairs may not have been directly compared, and has the potential to reduce the uncertainty in treatment effect estimates (Caldwell 2010). It also enables calculation of the probability that each treatment is the best for any given outcome, allowing ranking of the various drugs. The proposed systematic review and network meta-analysis is important; we will identify and rank first-line uterotonic drugs for the treatment of PPH and demonstrate gaps in the direct evidence to guide clinical decision making and further research.

OBJECTIVES

Primary

To assess the relative effectiveness and produce a clinically meaningful hierarchy of first-line uterotonic drugs for the treatment of postpartum haemorrhage (PPH).

Secondary

To assess the relative risks and produce side effect hierarchies of first-line uterotonic drugs for the treatment of PPH.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials including cluster trials of uterotonic drugs for the treatment of postpartum haemorrhage (PPH). Cross-over trials and quasi-randomised trials will be excluded. The cross-over study design is inappropriate to investigate the effectiveness of PPH treatment, and quasi-randomisation rather than true randomisation brings an elevated risk of bias that we wish to eliminate for the purpose of this review.

Types of participants

We will include studies involving participants delivering a baby (live or stillborn) from 24 weeks of gestation with a diagnosis of PPH within the first 24 hours (primary PPH). Studies with any participants giving birth before 24 weeks of gestation or women undergoing termination of pregnancy will be excluded.

Types of interventions

Studies of first-line uterotonic drugs administered systemically for the treatment of primary PPH will be included. These drugs may comprise oxytocin, ergot alkaloids, misoprostol, carbetocin or carboprost, or combinations of them. Systemic administration may comprise sublingual, subcutaneous, intramuscular, rectal, inhaled, nasal, oral or intravenous (both bolus and/or infusion) routes. We will include studies comparing uterotonic drugs against other uterotonic drugs or placebo. Studies comparing other interventions including non-uterotonic drugs such as tranexamic acid will be excluded.

Types of outcome measures

We will estimate the relative effects and ranking of the competing interventions according to the following primary and secondary outcomes.

Primary outcomes

- Number of participants with additional blood loss of more than 500 mL after recruitment to cessation of active bleeding.
- Composite outcome of maternal death or severe morbidity (e.g. hysterectomy, any organ dysfunction, transfer to higher level of care, coagulopathy, shock as defined by trialists).

Secondary outcomes

- Number of participant deaths.*
- Number of participants requiring additional uterotonics.*
- Number of participants with additional blood loss of more than 1000 mL after recruitment to cessation of active bleeding.*
- Number of participants having additional surgical procedures (e.g. hysterectomy, balloon insertion, pack insertion, arterial ligation, embolization and compression sutures).*
- Number of participants requiring blood transfusion or other blood products.*
- Mean additional blood loss (mL).
- Change in haemoglobin measurements before and after delivery (g/L).
- Number of participants experiencing side effects: hyperthermia (temperature above 38°C), hypothermia (temperature below 36°C), nausea, vomiting, hypertension, headache, shivering, tachycardia, arrhythmia, diarrhoea and abdominal pain.

- Number of participants reporting a sense of wellbeing, acceptability and satisfaction of the intervention.
- Number of participants breastfeeding on discharge.

(*denotes top five secondary outcomes of interest.)

Search methods for identification of studies

The following methods section of this protocol is based on a standard template used by Cochrane Pregnancy and Childbirth and the recent protocol adaption for multiple interventions suggested by Chaimani and colleagues (Chaimani 2017).

Electronic searches

We will search Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist.

The Register is a database containing over 22,000 reports of controlled trials in the field of pregnancy and childbirth. For full search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for CENTRAL, MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, please follow this link to the editorial information about Cochrane Pregnancy and Childbirth in the Cochrane Library and select the '***Specialized Register***' section from the options on the left side of the screen.

Briefly, the Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences; and
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that will be fully accounted for in the relevant review sections (Included, Excluded, Awaiting Classification or Ongoing).

In addition, we will search ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports using the search terms described in Appendix 1.

Searching other resources

We will screen the reference lists of studies identified for inclusion in the review, and seek to obtain relevant manuscripts not retrieved by the methods described above. We will also seek to obtain the full texts of studies retrieved as abstracts. In cases where published study reports do not contain sufficient information to determine eligibility for inclusion, or to extract the data required for analysis, we will approach primary authors to obtain missing details. In cases where the abstract has been published and the author incommunicado, we will extract all relevant data from the abstract. We will not apply any language or date restrictions when considering manuscripts for inclusion in this review.

Data collection and analysis

The following methods section of this protocol is based on a standard template used by Cochrane Pregnancy and Childbirth.

Selection of studies

Two review authors will independently assess for inclusion all the studies we identify as a result of the search strategy. We will resolve any disagreement through discussion or, if required, we will consult a third person.

We will create a study flow diagram to map out the number of records identified, included and excluded (Moher 2009).

Data extraction and management

We will design a form to extract data. For eligible studies, two review authors will extract the data using the agreed form. We will resolve discrepancies through discussion or, if required, we will consult a third person. We will enter data into Review Manager software (RevMan 2014) and into Microsoft Access and check for accuracy. When information regarding any of the above is unclear, we will attempt to contact authors of the original reports to provide further details. We will extract the following data.

Outcome data

We will extract primary and secondary outcomes listed above. All relevant data will be extracted per trial arm.

Data on potential effect modifiers

Most prospective clinical studies of PPH have recruited women at low risk of PPH, although most morbidity and mortality from the condition occurs among those at high risk (e.g. emergency caesareans, placental abruption, placenta praevia) (Weeks 2015). It is therefore important to describe carefully the population of each study and other effect modifiers, to identify the scope for generalisability of the review findings as well as the research gaps.

We will further extract data that may act as effect modifiers, namely: gestational age; parity of the participants; mode of delivery; prior risk of PPH; uterotonic administration prior to enrolment; dosage; route of drug administration; study setting; co-interventions such as tranexamic acid and uterine massage; and randomisation unit.

Other data

Finally, we will extract the following other data: country or countries, in which the study was performed; year of publication; number of participants randomised; exclusion criteria; type of publication (full text, abstract or unpublished data); trial registration reference; sufficient information to enable critical appraisal of the risk of bias of each study, as described below.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias of each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), modified as appropriate to the context of this review, and described below. We will resolve any disagreement by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We will describe for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups. We will assess the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We will describe for each included study the method used to conceal allocation to interventions prior to assignment and we will assess whether intervention allocation could have been foreseen in advance of, or during recruitment. We will assess the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk of bias (method unspecified).

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We will describe for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We will consider that studies are at low risk of bias if they were blinded, or if we judge that the lack of blinding would be unlikely to affect results. We will assess blinding separately for each primary outcome. We will assess the methods as:

- low, high or unclear risk of bias for participants; or
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We will describe for each included study the methods used, if any, to blind outcome assessors and study participants from knowledge of which intervention was received. We will assess blinding separately for each primary outcome. We will assess methods used to blind outcome assessment as low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We will describe for each included study, and for each primary outcome, the completeness of data including attrition and exclusions from the analysis. We will state whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. We will assess methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups or not exceeding 10% for the primary outcomes of the review);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis performed with substantial departure from the numbers of participants allocated to each group at randomisation or in excess of 10% for the primary outcomes of the review); or
- unclear risk of bias (exclusions or attrition unreported).

(5) Selective reporting (checking for reporting bias)

We will describe for each included study any inconsistency between the prespecified study protocol (if available), the study methods described in the study report, and the results listed in the study report. We will assess the methods as:

- low risk of bias (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);

- high risk of bias (where not all prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified; outcomes of interest are reported incompletely and so cannot be used; or failure to report results of a key outcome that would have been expected to have been included); or
- unclear risk of bias (prespecified study protocol unavailable).

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

(6.1) The method used to measure blood loss could generate bias. We will describe the method used and classify it as:

- low risk of other bias (objective measurement such as weighing swabs, drapes, etc.);
- high risk of other bias (subjective measurement such as visual or clinical estimation); or
- unclear risk of other bias (unspecified method of measurement).

(6.2) The source of financial support for the study could generate bias. We will describe the source of funding and classify it as:

- low risk of other bias (public funding or no external funding);
- high risk of bias (funding from individuals or institutions with material interests in the findings); or
- unclear risk of other bias (unspecified source of funding).

(6.3) We will describe for each included study any declared conflicts of interest and/or other important concerns about the risk of bias, and classify these as:

- low risk of other bias (no conflicts of interest or other concerns);
- high risk of bias (conflicts of interest that generate concern); or
- unclear risk of other bias (uncertain influence of conflicts of interest).

(7) Overall risk of bias

We will make explicit judgements about whether studies are at high risk of bias, according to the criteria given in the*Cochrane Handbook* (Higgins 2011). With reference to (1) to (6) above, we will assess the likely magnitude and direction of the bias and whether we consider it is likely to impact on the findings. We will explore the impact of the level of bias through undertaking sensitivity analyses (see Sensitivity analysis).

Measures of treatment effect

Relative treatment effects

We will summarise the relative treatment effects of dichotomous outcomes with risk ratios (RRs) and 95% confidence intervals (CIs). We will summarise the relative treatment effects of outcomes with continuous scales of measurement with mean differences (MDs). If different scales have been used we will use standardised mean differences (SMDs) with 95% CIs. In the event of the target parameter being a change in a continuous measure, such as change in haemoglobin, we will where possible account for the within-patient correlation between baseline and postpartum estimates (Dias 2013).

Relative treatment ranking

For each intervention we will estimate the ranking probabilities of being at each possible rank. We will obtain a treatment hierarchy using the Surface Under the Cumulative RAnking curve (SUCRA) (Salanti 2011). Uncertainty intervals (95% CIs) around the ranking of each treatment will be reported and considered when interpreting the results. Each outcome will be evaluated to determine confidence in the output of the network meta-analysis as described by Salanti and colleagues (Salanti 2014).

Unit of analysis issues

Cluster-randomised trials

We will include cluster-randomised trials in the analyses along with individually randomised trials. We will adjust their standard errors using the methods described in the *Cochrane Handbook*, with an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or (otherwise) from a similar trial or from a study of a similar population (Higgins 2011). If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effects of variations in the ICC. We will consider it reasonable to combine the results if there is little heterogeneity between the study designs and if the randomisation unit could not plausibly affect the effects of the interventions. However, we will perform sensitivity analyses to assess the validity of such combination.

Cross-over trials

This type of trial is not appropriate for this intervention, and will be excluded from the review.

Multi-arm trials

Multi-arm trials will be included and we will account for the correlation between the effect sizes in the network meta-analysis. Multi-arm studies will be treated as multiple independent comparisons in pair-wise meta-analyses.

Dealing with missing data

For included studies, we will note levels of attrition per primary outcome (see also 'Incomplete outcome data' in Assessment of risk of bias in included studies). We will explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analysis (see Sensitivity analysis).

For all outcomes, we will carry out analyses, as far as possible, on an intention-to-treat basis, i.e. we will attempt to include all participants randomised to each group in the analyses, and all participants will be analysed in the group to which they were allocated, regardless of whether or not they received the allocated intervention.

Assessment of transitivity across treatment comparisons

We will assess the assumption of transitivity by comparing the distribution of potential effect modifiers across the different pair-wise comparisons. We consider that the assumption of transitivity will be likely to hold given that: the common treatment used to compare different uterotonics indirectly is likely to be similar in different trials (e.g. oxytocin is administered in a similar way in studies of oxytocin versus misoprostol as it is in studies of oxytocin versus carbetocin); and pair-wise comparisons are unlikely to differ in respect of the distribution of effect modifiers (e.g. all trial designs and characteristics are similar).

The assumption of transitivity will be evaluated by comparing the clinical and methodological characteristics of sets of studies grouped by treatment comparisons.

Assessment of reporting biases

In view of the difficulty of detecting and correcting for publication bias and other reporting biases, we will aim to minimise their potential impact by ensuring a comprehensive search for eligible studies and by being alert for duplication of data. If 10 or more studies are included in the network meta-analysis, we will use a comparison-adjusted funnel plot to explore the possibility of small study effects (a tendency for estimates of the intervention effect to be more beneficial in smaller studies) (Chaimani 2013).

Data synthesis

Methods for direct treatment comparisons

We will perform standard pair-wise meta-analyses using a random-effects model in STATA for every treatment with at least two studies (DerSimonian 1986).

Methods for network meta-analysis

We will extract the sample size and number of outcome events per trial arm, to be used in the Stata network suite of commands (White 2015). Once extracted, we will set up the data using the augmented format, where all treatments are compared with a reference treatment, and studies without the reference treatment have a reference treatment arm created with a small amount of data (White 2011). The augmentation process using arm-based values will calculate the risk estimates of the comparisons with reference treatment and their variances and covariances (White 2015).

Subgroup analysis and investigation of heterogeneity

Assumptions when estimating heterogeneity

In standard pair-wise meta-analyses we will assume different heterogeneity for each pair-wise comparison. In network meta-analysis we will assume a common estimate for heterogeneity across the different comparisons.

Measures and tests for heterogeneity

We will assess statistically the presence of heterogeneity within each pair-wise comparison using the I^2 statistic and its 95% CI that measures the percentage of variability that cannot be attributed to random error. We will assess statistically the presence of heterogeneity in the entire network based on the magnitude of the heterogeneity variance parameter (T^2) estimated from the multivariate meta-analysis model. The magnitude of the heterogeneity variance will be compared to empirical distributions for dichotomous and continuous variables (Turner 2012; Rhodes 2015).

Assessment of statistical inconsistency

The statistical agreement between various sources of evidence in a network of interventions should be evaluated by global and local approaches in tandem with the evaluation of clinical homogeneity.

Local approaches for evaluation inconsistency

To evaluate the presence of inconsistency locally we will use the node-splitting approach. The node-splitting technique will allow two distinct components - direct evidence from direct comparisons or multi-arm trials and indirect evidence based on the remaining information (Dias 2010). The technique will be applied to all comparisons in the network and allow generation of graphics clearly showing the difference between combined information, direct and indirect comparisons.

Global approaches for evaluation inconsistency

To evaluate consistency in the entire network simultaneously we will use the 'design by treatment' interaction model as described by Higgins 2012, which will be implemented in STATA. This method accounts for different sources of inconsistency that can occur when studies with different designs (two-arm trials versus three-arm trials) give different results, as well as for disagreement between direct and indirect evidence. Using this approach, we will infer the presence of inconsistency from any source in the entire network based on a Chi^2 test.

Investigation of heterogeneity and inconsistency

If we find important heterogeneity and/or inconsistency, we will investigate the possible sources of such anomalies in respect of both primary outcomes and secondary outcomes. If sufficient studies are available, we will perform subgroup analyses by using the following factors as possible sources of inconsistency and/or heterogeneity.

- Population: mode of delivery; prior PPH risk (high or low) and setting (hospital delivery or community delivery including home birth).
- Intervention: dosage; route.
- Randomisation unit: cluster versus individual.
- Funding source: risk of bias.
- Methods of blood loss measurement: risk of bias.
- Overall risk of bias: studies will be ranked 'low risk of bias' if they are double-blinded, and have allocation concealment with less than 10% loss to follow up. Studies with assessor blinding and less than 10% loss to follow up will be ranked 'intermediate risk of bias'. Studies with no blinding or more than 10% loss to follow up will be ranked as 'high risk of bias'.

If these subgroup analyses do explain the heterogeneity/inconsistency we will note that the results should be treated with caution.

Subgroup analysis

Regardless of heterogeneity and/or inconsistency, in respect of primary outcomes we will perform the following subgroup analyses by evaluating the relative effects and assessment of model fit.

- Mode of delivery (vaginal versus caesarean delivery).
- Prior PPH risk (low versus high risk).
- Setting (hospital versus community births).
- Intervention: dosage and route.
- Uterotonic administration prior to enrolment.
- Co-interventions (e.g. tranexamic acid, uterine massage).

Sensitivity analysis

For the primary outcomes we will perform the following sensitivity analyses, as described previously.

- Overall risk of bias.
- Funding source.
- Objective versus subjective assessment of blood loss.
- Randomisation unit (cluster versus individual).

Differences will be assessed by evaluating the relative effects and assessment of model fit.

'Summary of findings' table

We will assess the quality of evidence using the GRADE approach outlined by Salanti and colleagues in order to assess the quality of the body of evidence relating to the primary outcomes for all comparisons (Salanti 2014). In order to create the 'Summary of findings' tables we will use GRADEpro Guideline Development Tool to import data from Revman 5 (RevMan 2014). We will use the GRADE approach to report the intervention effect for each of the above outcomes.

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As part of the prepublication editorial process, this protocol has been commented on by five peers (an editor and four referees who are external to the editorial team), a member of Cochrane Pregnancy and Childbirth's international panel of consumers and the Group's Statistical Adviser.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Search terms for ClinicalTrials.gov and ICTRP

ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP)
Third stage AND labo(u)r AND oxytocin
Third stage AND labo(u)r AND misoprostol
Third stage AND labo(u)r AND carbetocin
Third stage AND labo(u)r AND ergometrine
Third stage AND labo(u)r AND carboprost
Third stage AND labo(u)r AND syntometrine
uterotonic* AND oxytocin
uterotonic* AND misoprostol
uterotonic* AND carbetocin
uterotonic* AND ergometrine
uterotonic* AND syntometrine
uterotonic* AND carboprost
uterotonic* AND labo(u)r
uterotonic* AND h(a)emorrhage
h(a)emorrhage AND postpartum AND ergometrine
h(a)emorrhage AND postpartum AND oxytocin
h(a)emorrhage AND postpartum AND carbetocin
h(a)emorrhage AND postpartum AND misoprostol
h(a)emorrhage AND postpartum AND syntometrine
h(a)emorrhage AND postpartum AND carboprost

CONTRIBUTIONS OF AUTHORS

Ioannis D Gallos (IDG) and Arri Commarasamy (AC) conceived the idea for this study. William R Parry-Smith (WRPS) drafted the protocol. Helen M Williams (HMW), Malcolm J Price (MJP), Mariana Widmer (MW), Mubashir Angolkar (MA), Aurelio Tobias (AT), Zarko Alfirevic (ZA), Andrew Weeks (AW), G Justus Hofmeyr (GJH), A Metin Gulmezoglu (AMG), IDG and AC designed the meta-analysis. AT and MJP provided statistical advice and input. IDG, HMW, MW, MJP, AW, GJH, AC reviewed the protocol and provided critical feedback.

DECLARATIONS OF INTEREST

William R Parry-Smith (WRPS) is an Executive Board member of AmmaLife (UK registered charity 1120236), a member of The UK Membership Board of The Royal College of Obstetricians and Gynaecologists, and a Trustee of Baby Lifeline. He does not receive payment for these roles but has received payment from these organisations for travel for activities not related to this review. He has also received payment from the Liverpool School of Tropical Medicine for an invited lecture on cervical cancer and women's health. AmmaLife contributed to this review by funding literature/library costs.

Ioannis D Gallos (IDG) has received support for travel/accommodation/meeting expenses from MSD for Mothers.

Helen M Williams (HMW) none known.

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Mubashir Angolkar (MA) none known.

Aurelio Tobias (AT) none known.

Malcolm J Price (MJP) none known.

Zarko Alfirevic (ZA) has been an external adviser for Gynuity related to the charity's work on PPH.

Andrew Weeks (AW): has worked on PPH research for many years and has multiple interests in it. He voluntarily runs the not-for-profit misoprostol.org website that provides information about the optimal doses of misoprostol, including for the treatment of PPH. He also has two large clinical trial grants (from NIHR) on PPH treatment. These studies could potentially be eligible for inclusion in subsequent updates of this review, but he will not participate in decisions regarding these trials. He is also a consultant to Gynuity Health projects (unpaid) and to Azanta A/S and Monash University (both pay consultancy fees to his institution (the University of Liverpool). He is also the inventor of the PPH Butterfly device and one of the inventors of the LifeStart neonatal resuscitation trolley. He may in future receive personal payments in connection to the PPH Butterfly for which the University of Liverpool holds the patent.

G Justus Hofmeyr (GJH) is an author of trials potentially included in the review. GJH will not participate in decisions regarding these trials.

A Metin Gulmezoglu (AMG) none known.

Arri Coomarasamy (AC) is the founder of Ammalife (UK registered charity 1120236), and remains an active member of the Executive Board of this organisation. He does not receive any payment for this relationship.

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