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Interventions to prevent spontaneous preterm birth in high-risk women with singleton pregnancy: a systematic review and network meta-analysis (Protocol)

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[Intervention Protocol]

Interventions to prevent spontaneous preterm birth in high-risk women with singleton pregnancy: 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:

To compare the efficacy of current, relevant interventions to prevent preterm birth in women with singleton pregnancy and high individual risk of spontaneous preterm birth. We will consider interventions for women with a history of spontaneous preterm birth or short cervical length and women with asymptomatic vaginal infections.

BACKGROUND

Description of the condition

Preterm birth is birth before 37 weeks' gestation, or 259 days of pregnancy (Anonymous 1977). Preterm birth and its complications contribute to neonatal deaths worldwide (Blencowe 2013), and surviving infants may suffer long-term disability, including increased risk of autism and problems with cognitive function and learning even into adulthood (Johnson 2014; Linsell 2018; Liu 2015; Mackay 2010). Provider-initiated preterm birth occurs when pregnant women undergo labour induction or caesarean section for severe maternal or fetal complications during pregnancy. In contrast, spontaneous preterm birth is unplanned birth and should be prevented, provided it is safe to do so (Villar 2012). Many clinical interventions aim to prevent spontaneous preterm birth, and pregnant women and healthcare providers alike may consider the benefits and risks of several different treatment options. Both the United Nations and the World Health Organization view preterm birth research as a priority (Lawn 2016; Yoshida 2016). The UK Government also recognises that a reduction in preterm births is critical for achieving the national Maternity Safety Ambition (DHSC 2017).

Several known characteristics of pregnant women are associated with higher risk of preterm birth. Pregnant women with a short cervix, less than 25 mm detected on ultrasound between 18 and 24 weeks' gestation, women with a previous pregnancy that ended in preterm birth, and those identified as having an asymptomatic vaginal infection would each be at 'high risk' of preterm birth (Iams 1996). Our systematic review and network meta-analysis will focus on treatments to prevent preterm birth for women with singleton pregnancy and high risk of preterm birth.

Description of the intervention

Our study will include interventions that work in different ways to prevent spontaneous preterm birth in high-risk pregnant women. To manage the number of possible interventions we include in the network, we conducted a preliminary (or scoping) of the trial reports allocated to the preterm birth prevention section of the Cochrane Pregnancy and Childbirth topics list. We considered interventions to be 'active' areas for preterm birth research if we found three potentially relevant trials of an intervention to prevent preterm birth published within the last 10 years; these are the interventions we will include in our network, as named below.

Examples of current, relevant interventions that are well known as active areas for preterm birth research include cervical cerclage and cervical pessary; both of these treatments aim to support the cervix mechanically to prevent cervical dilation and consequent preterm birth. Another commonly evaluated intervention to prevent preterm birth is progesterone, a hormone responsible for maintaining pregnancy. Progesterone may be administered to women orally, via an intramuscular injection or as a vaginal gel or tablet. Other interventions of interest aim to discourage uterine contractions (e.g. prophylactic tocolytics or bed rest) or to treat the vaginal infections that may be associated with spontaneous preterm birth (e.g. antibiotics or probiotics). Finally, we will include omega 3, zinc and aspirin because each is an active area for preterm birth research. A recent Cochrane systematic review of omega 3 showed potential to prevent preterm birth (Middleton 2018). A recent Cochrane overview of preterm birth interventions identified zinc supplementation to have clear evidence of benefit and aspirin as a new area of research interest (Medley 2018).

Our review will not include interventions administered to a community, or to an unselected, general population of pregnant women. We want to review treatments that aim to prevent preterm birth in women identified to be at high risk. Our network will not include public health treatments like malaria prophylaxis or vitamin supplements when distributed to whole communities to improve the health of all pregnant women.

How the intervention might work

Current understanding of the biology of preterm birth is incomplete (Ferrero 2016). Preterm birth is as a result of diverse factors, including genetics (Villar 2012). Many interventions for spontaneous preterm birth target local or systemic inflammation or infection; examples include antibiotics, probiotics and even possibly omega 3. The precise mechanisms of infection-related preterm birth are not known, but experts agree that different pregnant women may have different responses to treatment of vaginal infections. There may be no straightforward relationship between 'fewer bugs' and fewer preterm births (Klebanoff 2018). Other interventions in our network target uterine muscle contraction or the early, mechanical opening of the cervix; examples are tocolytics, cervical cerclage and cervical pessary. Progesterone is a hormone responsible for maintaining pregnancy, and its absence is believed to initiate labour. The rationale for investigating low-dose aspirin to prevent preterm birth involves its anti-inflammatory properties and its success in reducing pre-eclampsia and associated preterm birth (Andrikopoulou 2018).

Future updates of this review may incorporate new interventions along these uterine-contraction or infection-related biological pathways or follow new pathways that emerge with more sophisticated phenotyping and a better understanding of the causes of preterm birth. Experts view new translational research into the biology of preterm birth and the development of new clinical interventions as critically important and urgent (Martin 2017).

Why it is important to do this review

There are multiple potential treatments for women with singleton pregnancy and high risk of spontaneous preterm birth. Our review will rank interventions to identify the most effective strategies for two populations of women at risk: pregnant women with a history of spontaneous preterm birth or short cervical length, and pregnant women at risk due to the presence of asymptomatic vaginal infections. We aim to synthesize all relevant evidence to inform clinical decision making and to improve women's antenatal care.

OBJECTIVES

To compare the efficacy of current, relevant interventions to prevent preterm birth in women with singleton pregnancy and high individual risk of spontaneous preterm birth. We will consider interventions for women with a history of spontaneous preterm birth or short cervical length and women with asymptomatic vaginal infections.

METHODS

Criteria for considering studies for this review

Types of studies

Eligible study types are randomised controlled trials (RCTs), including quasi-RCTs and cluster-RCTs. We will include studies published in abstract form only and eligible unpublished data obtained directly from trial investigators. We will exclude trials of cross-over study design.

Types of participants

Inclusion criteria

Population inclusion criteria

Network 1

Eligible pregnant women who are at high risk of spontaneous preterm birth due to individual risk factors, including:

1. pregnancy history, such as prior spontaneous preterm birth, midtrimester loss, or cervical insufficiency due to cervical surgery or any known uterine anomalies;
2. biomarkers relevant to spontaneous preterm birth, such as short cervical length on ultrasound.

Network 2

Eligible pregnant women who have risk factors for preterm birth directly linked to vaginal infection:

1. a positive urine culture or vaginal swab indicating asymptomatic infection during pregnancy;
2. eligible vaginal infections are bacterial vaginosis, chlamydia, ureaplasma, gonorrhoea, group B streptococcus or trichomonas vaginalis;
3. pregnant women with symptomatic infections are not eligible.

Trial inclusion criteria

To be eligible, clinical trials must test a named intervention listed below to prevent preterm birth in a population of pregnant women at risk of preterm birth due to pregnancy history or to the presence of an asymptomatic vaginal infection. Clinical trials of community and public health-level interventions and trials that target an unselected or mixed-risk population of pregnant women are not eligible. Trials of interventions applied before conception are not eligible; nor are trials of clinical assessment strategies.

Clinical trials with biomarkers as the primary or only collected trial outcome are not eligible (i.e. the effect of an agent on cytokines as a proxy for elevated preterm birth risk, or trials of antibiotic treatment for bacterial vaginosis that collect and report only cure rate). Clinical trials of the named interventions used for other purposes than preterm birth prevention will also be excluded (i.e. trials of omega 3 for glycaemic control or gestational diabetes).

Network inclusion criteria

We do not expect any included clinical trials to be eligible for inclusion in both network analyses, because the networks outline different pregnant populations. As described above, Network 1 will include women with a history of spontaneous preterm birth or short cervical length on ultrasound, or both. Network 2 will compare treatments for women with the named, asymptomatic vaginal infections.

Exclusion criteria

Women with the following characteristics are excluded.

1. Women with multiple pregnancy
2. Women with signs of preterm labour (e.g. regular contractions or vaginal bleeding)
3. Women with preterm prelabour rupture of membranes (PPROM)
4. Women with obvious symptoms of infection
5. Women with pre-eclampsia or other known maternal conditions during pregnancy that may lead to planned preterm birth

Women at risk of preterm birth solely due to population risks are not eligible. Women at risk of preterm birth solely due to elevated fetal fibronectin alone are also not eligible. Women who have undergone artificial reproductive technologies (ART) during the current pregnancy are eligible if they have a history- or infection-related risk factor for spontaneous preterm birth.

Types of interventions

Interventions of direct interest

We plan to include trials of the following treatments for pregnant women at high risk of spontaneous preterm birth who meet the inclusion criteria above.

1. Antibiotic treatment for asymptomatic vaginal infections, including bacterial vaginosis, chlamydia, ureaplasma, gonorrhoea, group B streptococcus or trichomonas vaginalis
2. Aspirin (low-dose)
3. Bed rest
4. Cervical cerclage (described as McDonald, Shirodkar or simply 'cerclage'; we will exclude trials of 'double cerclage', 'cerclage with occlusion' or cerclage trials comparing suture materials)
5. Cervical pessary (Arabin pessary or similar)
6. Fish oils or omega fatty acids
7. Nutritional supplements (zinc)
8. Probiotics
9. Progesterone (intramuscular, oral or vaginal)
10. Prophylactic antibiotics
11. Prophylactic tocolytics (excluding maintenance therapies)
12. Combinations of eligible interventions

For all included treatments, where feasible we will consider differences in type, dose and route of administration as separate nodes in the network (i.e. type of cerclage, progesterone, antibiotic, nutritional supplement or tocolytic). Eligible trials may compare single or combined active interventions with other active interventions, with placebo or with no treatment.

We will combine the placebo and no treatment as a single 'control' node in the networks.

Types of outcome measures

We will summarise clinical trial evidence for the core outcome domains identified in the core outcome set (COS) for preterm birth (Van't Hooft 2016). For pregnant women these are: maternal mortality, maternal infection or inflammation, prelabour rupture of

membranes, and harm to mother from the intervention. For offspring, outcome domains include: gestational age at birth, offspring mortality, birthweight, early neurodevelopmental morbidity, late neurodevelopmental morbidity, gastrointestinal morbidity, infection, respiratory morbidity, and harm to offspring from the intervention.

Review primary outcomes are two preterm birth time points: preterm birth less than 34 weeks' gestation and spontaneous preterm birth less than 34 weeks' gestation, both reported as a proportion.

Outcome measures to capture COS domains for pregnant women:

1. preterm birth less than 37 weeks' gestation;
2. preterm birth less than 34 weeks' gestation;
3. spontaneous preterm birth less than 34 weeks' gestation;
4. preterm birth less than 28 weeks' gestation;
5. maternal death;
6. preterm prelabour rupture of membranes;
7. maternal infection (maternal sepsis or any infection requiring antibiotics other than sepsis, or both);
8. maternal harm from the intervention (as reported in trials).

Outcome measures to capture COS domains for offspring:

1. perinatal death (fetal death at 22 weeks or later excluding termination of pregnancy for medical reasons; and neonatal death as defined below);
2. neonatal death (death of the neonate of 22 weeks' gestation or later, from birth to 28 days);
3. gestational age at birth;
4. low birthweight, less than 2500 g;
5. neonatal respiratory distress syndrome;
6. neonatal pulmonary disease (defined as the need for ventilation ≥ 24 hours, duration of ventilation in days, or oxygen therapy ≥ 36 weeks);
7. intraventricular haemorrhage (or severe lesions on transfontanellar ultrasonography);
8. periventricular leukomalacia;
9. necrotising enterocolitis;
10. proven neonatal sepsis;
11. admission to neonatal intensive care unit;
12. neonatal harm from the intervention (as reported in trials).

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.

Electronic searches

We will attempt to identify all relevant studies regardless of language or publication status (published, unpublished, in press, ongoing). We will search Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist.

The Register is a database containing over 25,000 reports of controlled trials in the field of pregnancy and childbirth. It represents over 30 years of searching. For full current 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.

Briefly, 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;
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 to searches via the Information Specialist, we will search ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform (ICTRP) for unpublished, planned and ongoing trial reports using transparent search methods based on key terms (see: Appendix 1 for draft search methods. We will report the full search methods in the review).

Searching other resources

Conference proceedings

The standard searches described above include conference proceedings, but we will ensure that the search includes abstracts for the following conferences: the Society for Maternal and Fetal Medicine, the International Federation of Gynecology and Obstetrics and the American College of Obstetrics and Gynecology.

Reference lists

We will check the reference lists of eligible studies and of similar systematic reviews identified through the above methods.

We will not apply any language or date restrictions.

Data collection and analysis

Selection of studies

N Medley (NM) and L Goodfellow (LG) will independently screen the search results for potentially relevant citations. The authors will cross check their results and resolve any differences through discussion among review authors. We will retrieve the full article for titles deemed to be potentially eligible and NM and LG will independently assess the full articles for eligibility using the above criteria and document reasons for exclusion in tables. We will cross check

eligibility assessment results and discuss and resolve differences. We will contact trial authors for more information if eligibility is unclear. We will scrutinise included trials to ensure that multiple publications from the same study are grouped appropriately. A study flow diagram will report the number of included and excluded studies at each stage of the selection process.

Data extraction and management

NM will extract data for the included trials using data extraction forms designed in Excel. The extracted data will be independently checked and verified by LG with discrepancies resolved by discussion. We will contact trial authors for additional information where necessary. We will extract data regarding the general characteristics, study design, participants, interventions, outcomes and 'Risk of bias' details. We will report characteristics of included studies and 'Risk of bias' decisions in tables and figures. Outcome data will be reported in forest plots and tables as appropriate.

We plan to cross-check data extracted from trial publications with publications based on individual patient data (IPD). For example, we are aware of a study of trials of progesterone by the EPPPIC collaboration (Stewart 2017).

Trials that randomised individuals

For each outcome, we will extract the number of participants randomised and the number of participants analysed for each study arm. For dichotomous outcomes, we will also extract the number of participants with the event for each study arm. For continuous outcomes, we will extract the mean and standard deviation for each study arm. We will extract change scores rather than end values when they are reported. For count outcomes, we will extract the number of events and the total person time at risk for each study arm. If this information is not reported, we will extract the summary statistics that are presented (e.g. medians and ranges for each study arm).

Trials that randomised clusters

For cluster-RCTs, we will extract the number of clusters randomised and number of clusters analysed per study arm as well as the number of participants randomised and analysed for each arm. We will also extract the average cluster size and the intra-cluster correlation coefficient. When trials correctly adjusted the analyses for clustering, we will extract the cluster-adjusted measure of treatment effect and its variance. However, we will extract the same data as for trials that randomise individuals when trials do not adjust for clustering.

Potential effect-modifying characteristics

We will extract the following characteristics that have the potential to alter the intervention effect estimate:

1. previous spontaneous preterm birth (Yang 2016);
2. maternal smoking (Shah 2000);
3. cervical length less than 25 mm (or another cut-off) (Iams 1996);
4. nulliparity (Salihu 2010);
5. caesarean delivery in the first pregnancy (Wong 2015);
6. birth interval shorter than 18 months (Wong 2015);
7. income in the most deprived 10% group (DHSC 2017; Taylor-Robinson 2011);
8. black race (Goldenberg 2008; Schaaf 2013);
9. periodontal disease (Goldenberg 2008).

Assessment of risk of bias in included studies

Two review authors will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2017). We will resolve any disagreement by discussion or by involving a third review author. In addition to the domains explained below, for cluster-RCTs we will assess recruitment bias, baseline imbalance, loss of clusters, incorrect analysis, and comparability with RCTs that randomised individuals (Higgins 2017).

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);
- 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 will assess whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

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);
- unclear risk of bias.

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 different outcomes or classes of outcomes.

We will assess the methods as:

- low, high or unclear risk of bias for participants;
- 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 from knowledge of which intervention a participant received. We will assess blinding separately for different outcomes or classes of outcomes.

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 outcome or class of outcomes, 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. Where sufficient information is reported, or can be supplied by the trial authors, we will re-include missing data in the analyses which we undertake.

We will assess methods as:

- low risk of bias (e.g. no or low missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

5. Selective reporting (checking for reporting bias)

We will describe for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We will assess the methods as:

- low risk of bias (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

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

We will describe for each included study any important concerns we have about other possible sources of bias.

We will assess whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

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 for Systematic Reviews of Interventions* (Higgins 2017). 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 report results in 'Risk of bias' tables, 'Risk of bias' summaries and 'Risk of bias' graphs.

We will explore the impact of the level of bias through undertaking sensitivity analyses (see Sensitivity analysis).

Assessment of the quality of the evidence using the GRADE approach

There are currently no widely agreed methods for applying the GRADE approach to the results of NMA. However, we do plan to assess the credibility of the evidence in the review and produce a 'Summary of findings' table for the main comparisons for both planned networks.

We will carry out a threshold analysis to explore how robust the treatment recommendations are to plausible degrees of bias (Caldwell 2016). For each pairwise treatment effect for which direct evidence is available, we will replace the observed treatment effect with a series of 20 alternative values using appropriate step sizes. For each alternative value, we will determine whether the treatment recommendation from the NMA would be affected.

We will also apply an alternative approach, as proposed by Salanti 2014, to assess the quality of the evidence using a procedure that is based on methods developed by the GRADE Working Group. After assessing the quality of pairwise meta-analyses results using the methods of the GRADE Working Group, we will assess the results from NMA. We will assess the quality of the treatment effects and the treatment rankings separately. For pairwise meta-analyses and NMA, we will assess five key domains: study limitations, indirectness, inconsistency, imprecision, and publication bias. We will rate each pairwise meta-analysis and NMA result as high, moderate, low or very low certainty (Guyatt 2011a; Schünemann 2013).

Measures of treatment effect

We will present all results with their 95% credibility intervals. All review outcomes listed above are dichotomous and presented as proportions, with the exception of 'gestational age at birth', which is a continuous outcome reported in trials as days or weeks.

Dichotomous data

For dichotomous outcomes, we will use the odds ratio to compare treatments.

Continuous data

We will use mean differences for continuous outcomes.

Count data

We have identified no count outcomes. However, if we include these in future updates of the review, for count outcomes we will compare treatments using rate ratios.

Relative treatment ranking

For each outcome, we will also calculate the probability that each treatment is the best (i.e. most effective), second best, third best, etc. We will report results in rankograms, with one plot per intervention; each plot shows the possible ranks on the x-axis and the probability on the y-axis.

Unit of analysis issues

Cluster-randomised trials

If a cluster-RCT did not adjust for clustering in its analysis, we will attempt to adjust for clustering by multiplying the standard error of the treatment effect by the square root of the design effect, where the design effect is calculated as 1+(1+m)*ICC where m is the average cluster size and ICC is the intra-cluster correlation coefficient. Equivalently, to adjust for clustering, an effective sample size may be calculated by dividing the original sample size by the design effect. For dichotomous outcomes, we will divide the number of events and the number of participants by the design effect. If the average cluster size is unknown, it will be estimated by the total number of clusters and participants. If the ICC is unknown, it will be estimated from external sources, such as trials with similar cluster sizes and features. If the standard error adjusted for clustering (adjusted SE), the standard error that is not adjusted for clustering (SE) and the average cluster size (m) can be obtained from a similar trial, then we will calculate an approximate ICC.

We will present results from cluster-RCTs that cannot be adjusted for clustering in an additional table, only because their standard errors will be artificially narrow.

Studies with multiple treatment groups

We will include trials with multiple arms. If the same trial is included in the same pairwise meta-analysis more than once, we will split the control groups to report a relative effect for each intervention against the control. NMA models will account for the correlation between treatment effects from multi-arm trials.

Cross-over trials are not eligible for inclusion in this review. Cross-over trials are only appropriate for evaluating interventions with a temporary effect on stable, chronic diseases such as asthma. Cross-over study designs are not appropriate for the named interventions above as tested in pregnant women.

Dealing with missing data

We will carry out an available case analysis, such that the analysis is based on the number of women for whom the outcome was obtained in the trial. For many trials, the denominator used to calculate effectiveness will be the number randomised minus any known exclusions or missing participants. Using the number of women analysed as the denominator avoids making assumptions about whether or not missing women had the outcome.

Assessment of heterogeneity

Fixed-effect and random-effects NMA and pairwise meta-analysis models will be fitted and compared in terms of the model fit and complexity. We will assess model fit and complexity of models using the deviance information criterion DIC (Spiegelhalter 2002). A model with a smaller DIC will be preferable to a model with a larger DIC but we will not consider meaningful differences of less than five units. When there is little difference in DIC, we will choose the simplest model. We will also use the posterior mean of the residual deviance to compare model fit, with small values indicating an improved fit.

We will estimate the posterior, mean, between-trial variance from the random-effects models and report it with its 95% credibility interval, with large values indicating heterogeneity.

For each pairwise comparison, we will also assess heterogeneity by visual inspection of the forest plots to detect qualitative or quantitative heterogeneity, calculation of the I^2 statistic (Higgins 2003), and the Chi^2 test (Deeks 2017), with a cutoff of $P < 0.1$ used to indicate statistically significant heterogeneity. In the event of substantial quantitative or qualitative heterogeneity we will not carry out meta-analysis. Substantial heterogeneity is generally an I^2 statistic greater than 80%, but we will consider analyses on a case-by-case basis.

For each comparison, we will compare key trial and patient characteristics listed previously as potentially treatment-effect modifying, to identify clinical heterogeneity.

Assessment of inconsistency

For each comparison, we will summarise across trials, key trial and patient characteristics that could potentially modify the treatment effects (as listed previously), and tabulate them so that we can compare the characteristics. If the characteristics differ across trials for a particular comparison, the consistency assumption may not be feasible.

We will apply node-splitting models for each comparison for which direct evidence and indirect evidence exists to assess local inconsistency and provide estimates of the treatment effects based on direct evidence and indirect evidence separately (Dias 2010a). We will assess consistency by comparing the NMA model and node-splitting models in terms of goodness of fit and the size of the between-trial variances, and by calculating the Bayesian probability that the direct and indirect evidence agrees.

We will also fit inconsistency models to assess global inconsistency and compare them with the NMA model in terms of model fit, the resulting treatment effects and the between-trial variance. We will apply the unrelated mean effects model, which is equivalent to the NMA model but does not make the assumption of consistency (Dias 2013a).

If inconsistency is detected or suspected, we will not report NMA results; instead, we will explore the cause of the inconsistency and resolve it, or instead present results from pairwise meta-analysis.

Assessment of reporting biases

For each pairwise comparison, we will assess publication bias by constructing funnel plots showing trials from direct evidence. For NMA, we will assess publication bias by applying a regression model that adjusts for reporting biases. The regression model allows for an interaction between the observed variance and the treatment effect (Trinquart 2012). We will also apply an appropriate selection model to account for publication bias (Mavridis 2014).

Data synthesis

We will construct two different networks as described above, Network 1 and Network 2. The data synthesis methods described below apply to each network.

For each outcome, we will construct a network diagram to display the treatment comparisons for which direct evidence is available and the number of trials.

We will apply NMA models and pairwise meta-analysis models to study arm data except when cluster-RCTs are included in the analy-

sis. When a cluster-RCT is included, we will meta-analyse the cluster-adjusted estimate of the treatment effect and its standard error with treatment effects and standard errors from other trials. Model specifications and computer codes are described elsewhere (Dias 2013b).

Models will be fitted using WinBUGS 1.4.3 and the R2WinBUGS package in R. We will assume the between-trial variance to be equal across comparisons in NMA models. The parameterisation of the model will be chosen to be the same for each outcome.

Following a Bayesian framework, we will choose a non-informative uniform prior distribution for the between-trial standard deviation of random-effects models. Non-informative Normal prior distributions will be chosen for all other model parameters. For each model, we will run three chains with different initial values until convergence is achieved and then we will run a further 100,000 iterations on which to base results. We will thin results if needed. We will assess convergence of the chains by inspecting plots of the draws.

Subgroup analysis and investigation of heterogeneity

If we detect heterogeneity, we will apply pairwise meta-regression models; likewise, if we find inconsistency in NMA models, we will use network meta-regression. Characteristics that we will explore are listed as potentially treatment-effect modifying in the Data extraction and management section. We will use the size of the regression coefficients for the treatment by covariate interaction and its credibility interval to determine whether an interaction exists and, therefore, whether the covariate modifies the treatment effect. We will also compare model fit statistics (i.e. residual deviance and the DIC) from meta-regression with the meta-analysis model to determine the best model. We will tabulate results, including posterior median treatment effects, regression coefficients and their credibility intervals, and presented them graphically (Donegan 2018a). We will assess the consistency assumptions that underlie network meta-regression models using node-splitting models and inconsistency models (Donegan 2018b).

Sensitivity analysis

We will carry out sensitivity analyses for the following outcomes: any preterm birth less than 34 weeks; spontaneous preterm birth less than 34 weeks, and perinatal death.

As sensitivity analyses, we will also apply an NMA model that accounts for uncertainty because of missing data by modelling both the observed and missing data; we will assume no prior information with regard to the probability of an event in the missing participants (Turner 2015). In a separate analysis, we will also assume a fixed proportion of those missing has the event (i.e. 10%).

When we have adjusted the results from cluster-RCTs ourselves, we will carry out sensitivity analyses, excluding the trial for which the approximation was made.

The NMA models we will apply will assume homogeneous variances across comparisons. We will also apply an NMA model that assumes heterogeneous variances and compare the model fit (Lu 2009).

We will estimate and adjust for bias, in terms of risk of bias components, such as, allocation concealment, in the network by applying NMA models that includes bias parameters and a covariate for 'Risk of bias' judgement (Dias 2010b). We will also carry out sensitivity analyses based on 'Risk of bias' components (i.e. excluding trials with high and unclear risk of bias for sequence generation and allocation concealment).

We will explore novel agent bias, where bias always favours the newer treatment, by fitting an NMA model that includes bias parameters and a covariate indicating whether a study arm is receiving the newer drug for that particular study (Salanti 2010).

We will assess industry sponsorship bias by applying a similar NMA bias model with funder (industry versus other) as a covariate (Naci 2014).

Finally, where relevant we will assess the impact of including quasi-randomised trials or those reported as abstracts only.

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APPENDICES

Appendix 1. Draft search methods for ICTRP and ClinicalTrials.gov

ClinicalTrials.gov

Advanced search

prevention | Interventional Studies | Preterm birth

risk | Interventional Studies | Preterm Labor

ICTRP

We will run each line separately

risk AND preterm

risk AND premature

CONTRIBUTIONS OF AUTHORS

The study was conceived and planned by Z Alfirevic, N Medley and L Goodfellow, and with L Hampson these authors conducted the scoping for eligible interventions. L Hampson will conduct all trial searches. Statistical methods were planned by S Donegan, with review and comments by S Nevitt, C Tudur Smith and D Caldwell. All named authors contributed to writing the protocol.

NM, LG and SD will conduct eligibility assessment and data extraction to prepare the data file. The methodologists on the author team (SD, SN, CT-S, DC) will conduct all statistical analyses and create graphs and tables to represent findings. The clinicians (ZA, LG) will interpret the findings and, with NM, write the review. All named authors will contribute to the final version of the review.

N Medley is the contact person and guarantor of the review.

DECLARATIONS OF INTEREST

NM: N Medley's work was financially supported by the University of Liverpool's Harris-Wellbeing of Women Preterm Birth Centre research award.

SD: none

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LG: This work was funded by a charitable grant that founded the Harris-Wellbeing Preterm Birth Research Centre, University of Liverpool.

LH: is employed by the University of Liverpool as an Information Specialist with Cochrane Pregnancy and Childbirth. Her employment is supported by the National Institute for Health Research, via Cochrane Infrastructure funding to Cochrane Pregnancy and Childbirth. She had no involvement with the editorial processes for this protocol.

DC: none

CT-S: none

ZA: my employer (University of Liverpool) has received grants from UK National Institute of Health Research, Wellbeing of Women charity and Perkin Elmer to support my research group's work related to preterm birth prevention and my Cochrane editorial work.

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