Editorial considerations in reviews with network meta-analysis

Network meta-analysis: Learning Live webinar series

Tuesday 17th March 2020

Kerry Dwan – Methods Support Unit Lead and Statistical Editor, Cochrane Editorial and Methods Department.

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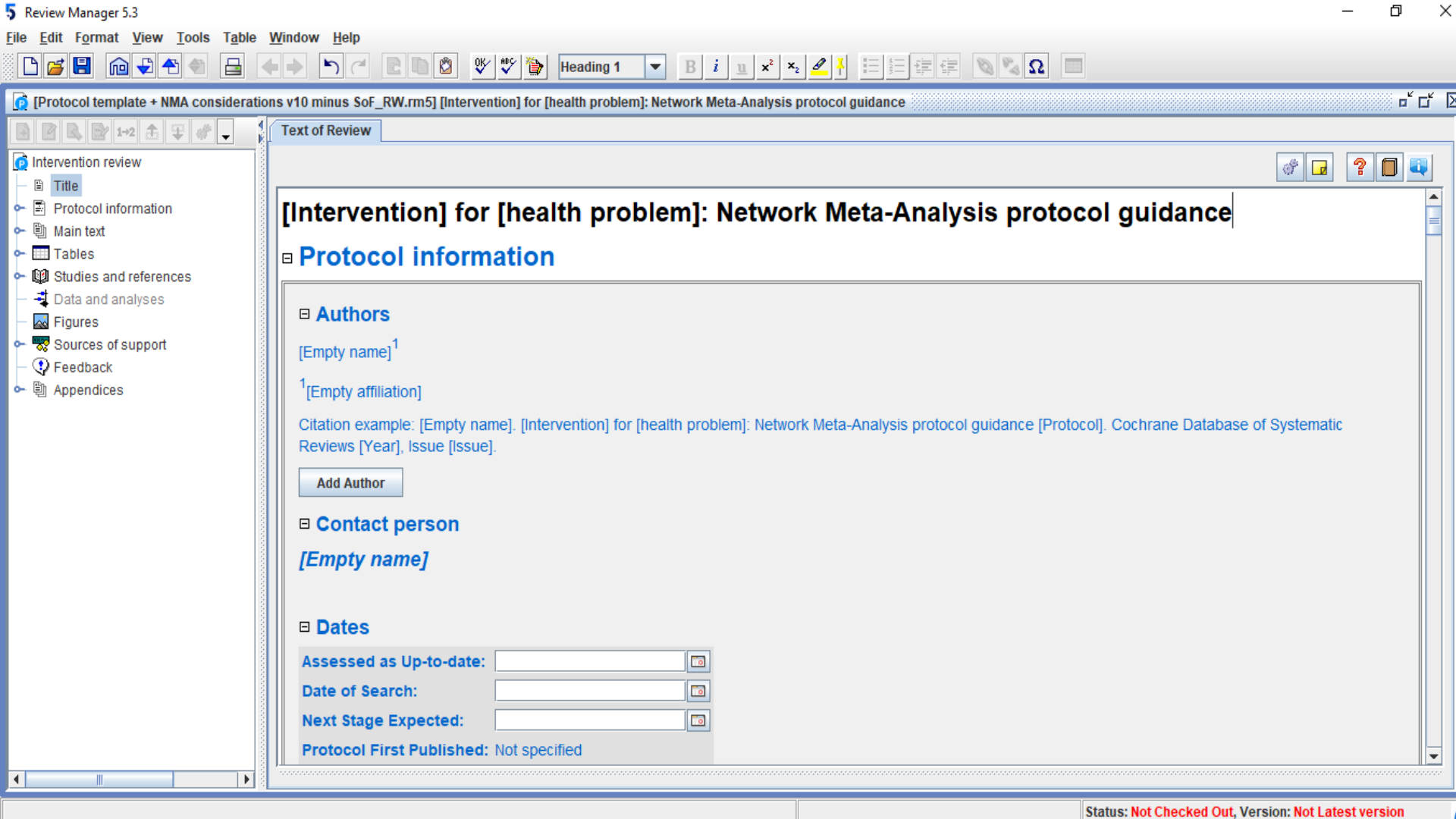
Outline

Editorial Support for NMAs

- For any Cochrane protocol or review including a network meta-analysis, CRGs should please seek methodological/ statistical input in the peer review process via Network Associate Editors.
- Support can be sought at any stage of the editorial process, but the earlier the better!
- Associate Editors will then consult with the Methods Support Unit, and other sources of advice as necessary.

NMA Template



NMA – Editorial Guiding Questions

- The following is a list of guiding questions to help editors when reviewing a NMA review.

- Answering ‘no’ to any of these questions does not automatically mean the authors have made an error. It is simply a red flag that indicates (a) authors need to provide more detail or further clarification, or (b) a deeper investigation by an experienced statistician may be needed.

- **Other typical MECIR Standards still apply to all sections of the review (but MECIR is being extended to NMA)**

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NMA – Editorial Guiding Questions

Review Section	Guiding Question
Author Team	1. Does the author team include an experienced Statistician and Clinician?
Background	2. Is an NMA justified?
Objectives	3. Is the research question clear, appropriate, and consistent with Title? Does it include NMA/ rankings in the objective?
Eligibility Criteria	4. Have the authors have considered the Transitivity Assumption? Are the interventions discussed in sufficient detail?
Data Extraction	5. Was data extracted on both 'Outcome Data' and 'Effect Modifiers'?
Measures of Treatment Effect	6. Are there separate subheadings for 'Relative treatment effects', and 'Relative treatment ranking'?
Heterogeneity	7. Is there an appropriate plan for assessing across treatment comparisons?
Data Synthesis	8. Is there a plan for both 'pairwise meta-analysis' and 'network meta-analysis'? Are details for statistical analysis reported in sufficient detail? Do the authors state which outcomes they will conduct an NMA for?

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NMA – Editorial Guiding Questions

Review Section	Guiding Question
Inconsistency	9. Was statistical inconsistency assessed both Globally and Locally?
Assessment of reporting biases	10. Have the authors constructed a comparison adjusted funnel plot?
Effects of Interventions	11. For each outcome, did the authors present; (a) A 'map' of the evidence in the network for each outcome? (b) The intervention effects in a concise and comprehensible way? (c) The ranking in a concise and comprehensible way? (d) The level of heterogeneity and incoherence in the network? (e) The certainty of the evidence?
Summary of Findings tables	12 (a) Did authors provide a clear rationale for the choice of the comparisons they report in the 'Summary of findings' tables. (b) Did they specify how confidence in the evidence was assessed?(c) Did they present the planned outcomes and comparisons?
Tables/Figures	13. Have tables and Figures been kept to a minimum?
Abstract	14. Is the evidence presented in the Abstract the most 'important' information for key decision makers?

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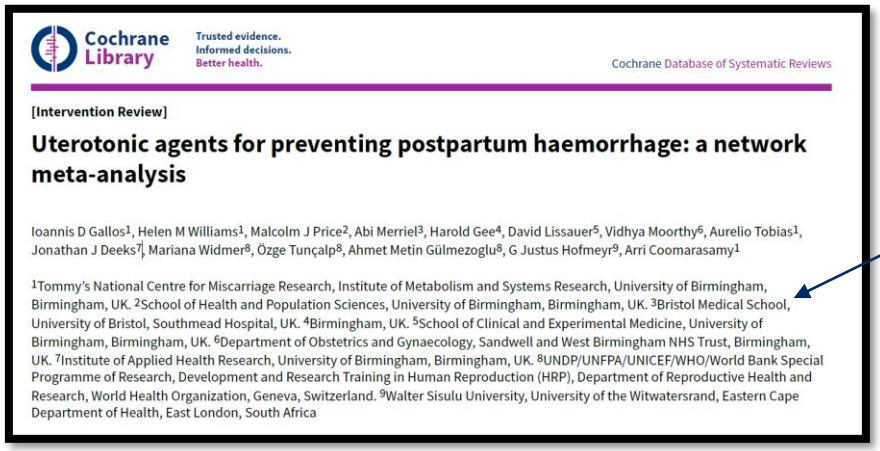
Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis (Review)

Gallos ID, Williams HM, Price MJ, Merriel A, Gee H, Lissauer D, Moorthy V, Tobias A, Deeks JJ, Widmer M, Tunçalp Ö, Gülmezoglu AM, Hofmeyr GJ, Coomarasamy A

Author Team

1. Does the author team include an experienced Statistician (with knowledge of NMA) and Clinician?



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[Intervention Review]

Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis

Ioannis D Gallos[1], Helen M Williams[1], Malcolm J Price[2], Abi Merriel[3], Harold Gee[4], David Lissauer[5], Vidhya Moorthy[6], Aurelio Tobias[1], Jonathan J Deeks[7], Mariana Widmer[8], Özge Tunçalp[8], Ahmet Metin Gülmezoglu[8], G Justus Hofmeyr[9], Arri Coomarasamy[1]

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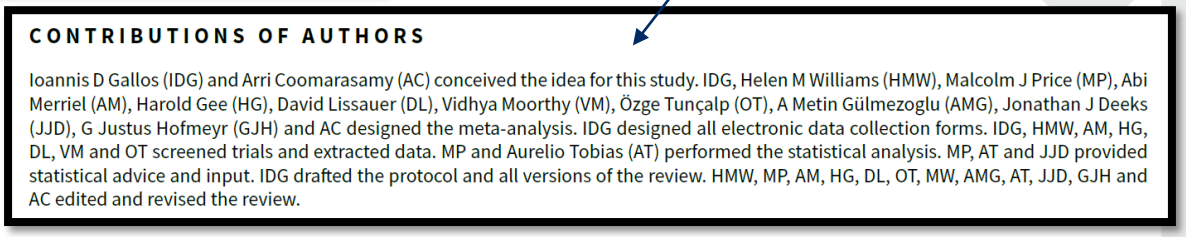
Check both author affiliations and contributions of authors



CONTRIBUTIONS OF AUTHORS

Ioannis D Gallos (IDG) and Arri Coomarasamy (AC) conceived the idea for this study. IDG, Helen M Williams (HMW), Malcolm J Price (MP), Abi Merriel (AM), Harold Gee (HG), David Lissauer (DL), Vidhya Moorthy (VM), Özge Tunçalp (OT), A Metin Gülmezoglu (AMG), Jonathan J Deeks (JJD), G Justus Hofmeyr (GJH) and AC designed the meta-analysis. IDG designed all electronic data collection forms. IDG, HMW, AM, HG, DL, VM and OT screened trials and extracted data. MP and Aurelio Tobias (AT) performed the statistical analysis. MP, AT and JJD provided statistical advice and input. IDG drafted the protocol and all versions of the review. HMW, MP, AM, HG, DL, OT, MW, AMG, AT, JJD, GJH and AC edited and revised the review.

Rationale

2. Is an NMA justified?

Check ‘Background > Why it is important to do this review’

Why it is important to do this review

Cochrane reviews have compared individual uterotonic agents against another uterotonic agent, placebo or no treatment (Begley 2015; Liabsuetrakul 2007; McDonald 2004; Su 2012; Tuncalp 2012; Westhoff 2013). Such pairwise meta-analyses can only compare two agents that have been compared directly in head-to-head trials (direct evidence). In the absence of a single randomised controlled trial comparing all available uterotonic agents, uncertainty remains over their relative effectiveness and ranking. We conducted a network meta-analysis synthesizing all direct and indirect trial evidence of relative treatment effects in a single coherent analysis for all the competing agents. Indirect evidence is obtained when the relative effectiveness of two competing drugs is inferred through a common comparator, even though this pair may not have been compared directly (Caldwell 2005; Lumley 2002). Our network meta-analysis provides effectiveness and side-effect profiles, along with the ranking for each uterotonic agent.

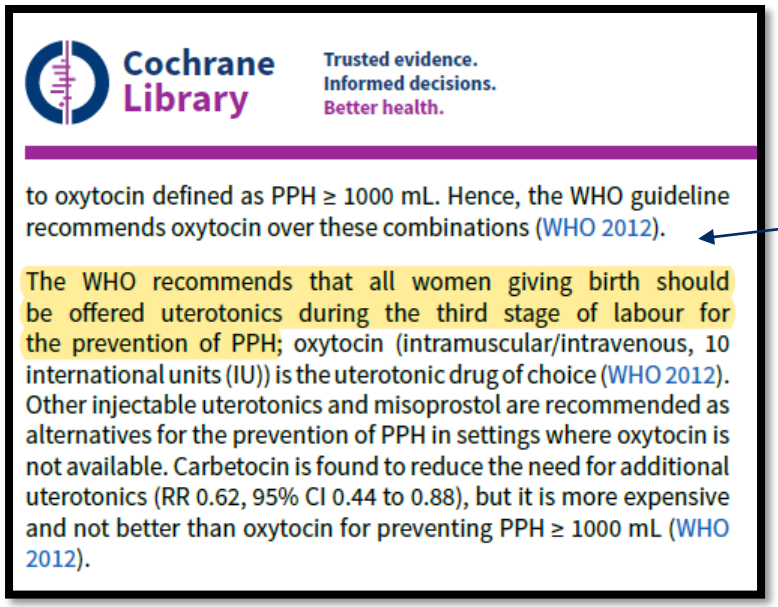
Appropriate rationales include;

1. Availability of many independent comparisons
2. Absence of head-to-head comparisons
3. Need to resolve inconsistent findings
4. Need to rank available treatment

Most important rationale = review addresses a question involving multiple interventions (comparative effectiveness of multiple interventions)

Rationale

2. Is an NMA justified?



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to oxytocin defined as PPH ≥ 1000 mL. Hence, the WHO guideline recommends oxytocin over these combinations (WHO 2012).

The WHO recommends that all women giving birth should be offered uterotonics during the third stage of labour for the prevention of PPH; oxytocin (intramuscular/intravenous, 10 international units (IU)) is the uterotonic drug of choice (WHO 2012). Other injectable uterotonics and misoprostol are recommended as alternatives for the prevention of PPH in settings where oxytocin is not available. Carbetocin is found to reduce the need for additional uterotonics (RR 0.62, 95% CI 0.44 to 0.88), but it is more expensive and not better than oxytocin for preventing PPH ≥ 1000 mL (WHO 2012).

Check 'Background' for indication that Transitivity assumption would not be violated.

(i.e., that patients equally likely to receive alternative treatments?)

Objective

3. Is the research question clear, appropriate, and consistent with Title?

Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis

OBJECTIVES

Primary

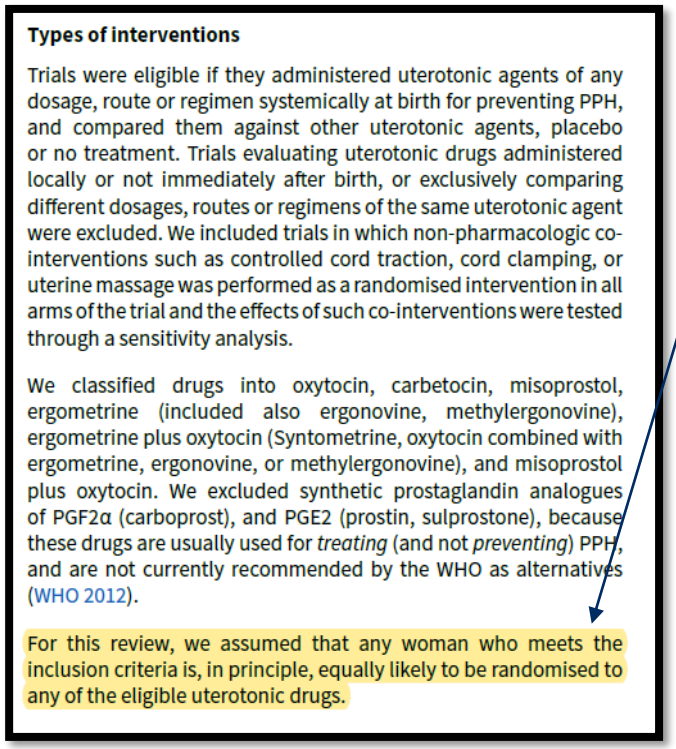
To identify the most effective uterotonic drug(s) to prevent postpartum haemorrhage (PPH) with a favourable side-effect profile, and to generate a clinically useful ranking of all available uterotonics.

Most objectives will focus on generating both 'effects estimates' and 'ranking probabilities'

The objective should also include 'conducting an NMA'

Criteria for considering studies for this review

4. Have the authors have considered the Transitivity Assumption?



Types of interventions

Trials were eligible if they administered uterotonic agents of any dosage, route or regimen systemically at birth for preventing PPH, and compared them against other uterotonic agents, placebo or no treatment. Trials evaluating uterotonic drugs administered locally or not immediately after birth, or exclusively comparing different dosages, routes or regimens of the same uterotonic agent were excluded. We included trials in which non-pharmacologic co-interventions such as controlled cord traction, cord clamping, or uterine massage was performed as a randomised intervention in all arms of the trial and the effects of such co-interventions were tested through a sensitivity analysis.

We classified drugs into oxytocin, carbetocin, misoprostol, ergometrine (included also ergonovine, methylergonovine), ergometrine plus oxytocin (Syntometrine, oxytocin combined with ergometrine, ergonovine, or methylergonovine), and misoprostol plus oxytocin. We excluded synthetic prostaglandin analogues of PGF2α (carboprost), and PGE2 (prostin, sulprostone), because these drugs are usually used for *treating* (and not *preventing*) PPH, and are not currently recommended by the WHO as alternatives (WHO 2012).

For this review, we assumed that any woman who meets the inclusion criteria is, in principle, equally likely to be randomised to any of the eligible uterotonic drugs.

Clarify that patients equally likely to receive alternative treatments?

Check number of interventions / comparisons:

(a) large enough so that the review is comprehensive and answers the question

(b) small enough so that the review is clinically meaningful, and readable.

A decision on lumping or splitting the nodes of a network should be formed on the basis of the research question of the review and the outcomes of interest

Will unspecified interventions be considered for post hoc inclusion in the network?

Data Extraction

5. Was data extracted on both ‘Outcome Data’ and ‘Effect Modifiers’?

Data extraction and management

We designed an electronic form on ©Microsoft Access to extract data. For eligible studies, at least three review authors independently extracted the data using a blank electronic form (IDG, HW, AM, DL, HG, OT). We resolved discrepancies through discussion or, if required, we consulted another person (AC). We entered data into STATA and Review Manager software (RevMan 2014) and checked for accuracy. When information was unclear, we attempted to contact authors of the original reports to provide further details. The following data were extracted.

Outcome data

From each included study we extracted: the number of participants, the gestational age and the parity of participants, and any exclusion criteria. We also extracted: the interventions being compared, and their respective primary and secondary outcomes. All relevant arm level data were extracted (e.g. number of events and number of patients for binary outcomes).

Data on potential effect modifiers

From each included study we extracted the following study, intervention and population characteristics that may act as effect modifiers:

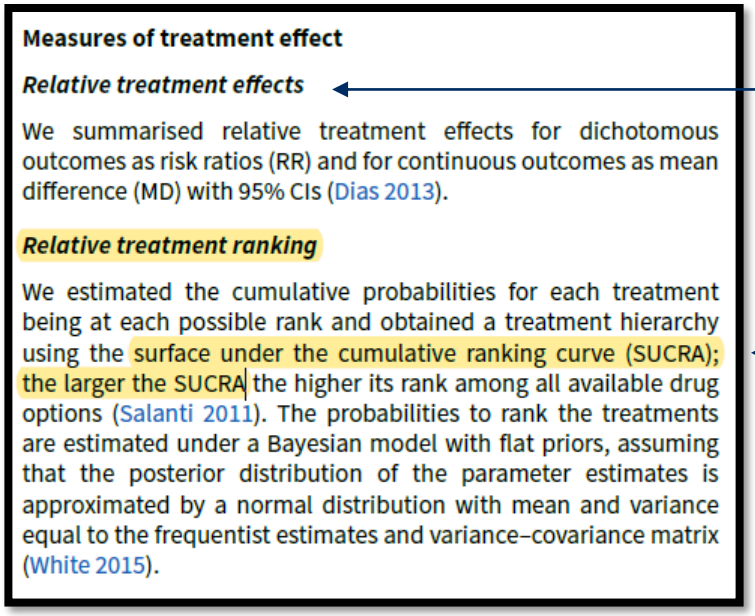
1. mode of delivery (vaginal or caesarean birth);
2. prior risk of PPH (as defined by trialists and categorised as low, high, mixed or not stated);
3. dosage, regimen, and route of drug administration (sublingual, subcutaneous, intramuscular, rectal, oral, intravenous bolus and/or infusion); and
4. setting of the study (community or hospital).

Use of subheadings is helpful

Important for checking Transitivity Assumption

Measures of Treatment Effect

6. Are there separate subheadings for ‘Relative treatment effects’, and ‘Relative treatment ranking’?



Measures of treatment effect

Relative treatment effects

We summarised relative treatment effects for dichotomous outcomes as risk ratios (RR) and for continuous outcomes as mean difference (MD) with 95% CIs (Dias 2013).

Relative treatment ranking

We estimated the cumulative probabilities for each treatment being at each possible rank and obtained a treatment hierarchy using the surface under the cumulative ranking curve (SUCRA); the larger the SUCRA the higher its rank among all available drug options (Salanti 2011). The probabilities to rank the treatments are estimated under a Bayesian model with flat priors, assuming that the posterior distribution of the parameter estimates is approximated by a normal distribution with mean and variance equal to the frequentist estimates and variance–covariance matrix (White 2015).

Relative treatment effects – as usual (RR, MD, etc)

Relative treatment ranking – Appropriate method (such as SUCRA, or mean ranks) must be cited

Heterogeneity

7. Is there a plan for assessing **across** treatment comparisons?

Assessment of transitivity across treatment comparisons

In this context we expect that the transitivity assumption holds assuming the following: 1) the common treatment used to compare different uterotonics indirectly is similar when it appears in different trials (e.g. oxytocin is administered in a similar way in oxytocin versus misoprostol trials and in oxytocin versus oxytocin plus ergometrine trials); 2) all pairwise comparisons do not differ with respect to the distribution of effect modifiers (e.g. the design and study characteristics of oxytocin versus misoprostol trials are similar to oxytocin versus oxytocin plus ergometrine trials). The assumption of transitivity was evaluated epidemiologically by comparing the clinical and methodological characteristics of sets of studies from the various treatment comparisons.

Outline the approach used to evaluate the plausibility of the transitivity (e.g. comparing the distributions of effect modifiers)

Data Synthesis

8. Is there a plan for both ‘pairwise meta-analysis’ and ‘network meta-analysis’

Data synthesis

Methods for direct treatment comparisons

Initially, we performed pairwise meta-analyses using a random-effects model in Stata for every treatment comparison with at least two studies (DerSimonian 1986).

Methods for indirect and mixed comparisons

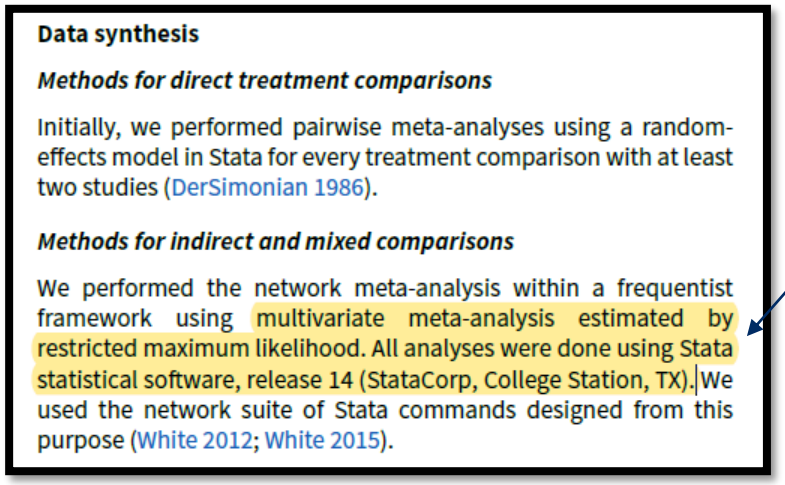
We performed the network meta-analysis within a frequentist framework using multivariate meta-analysis estimated by restricted maximum likelihood. All analyses were done using Stata statistical software, release 14 (StataCorp, College Station, TX). We used the network suite of Stata commands designed from this purpose (White 2012; White 2015).

- *Specific statistical model to fit NMA: Bayesian vs. frequentist setting;*
- *Fixed or random effects;*
- *Multivariate meta-analysis vs. hierarchical model.*

- *Account for correlated nature of multi arm studies?*
- *Assumptions about the heterogeneity variance and the method for estimating it should be reported*

Data Synthesis

8. Is there a plan for both ‘pairwise meta-analysis’ and ‘network meta-analysis’



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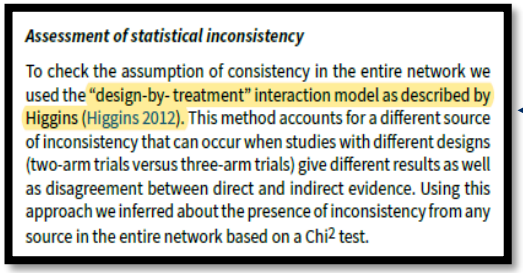
CMIMG recommends three software packages for NMA;

1. Stata using the network package by Ian White
2. R using the netmeta package by Gerta Rücker
3. Bayesian approaches using Monte Carlo Markov chain methods

Do the authors state which outcomes they will be undertaking NMA for?

Incoherence (also referred to as inconsistency)

9. Was statistical incoherence assessed both Globally and Locally?

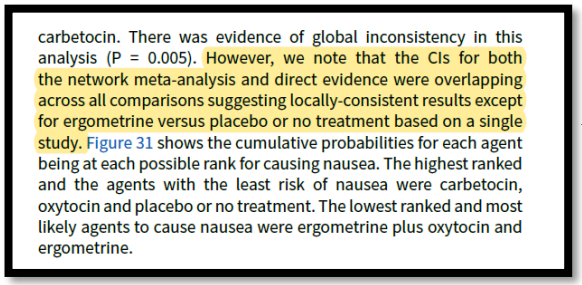


Assessment of statistical inconsistency

To check the assumption of consistency in the entire network we used the "design-by- treatment" interaction model as described by Higgins (Higgins 2012). This method accounts for a different source of inconsistency that can occur when studies with different designs (two-arm trials versus three-arm trials) give different results as well as disagreement between direct and indirect evidence. Using this approach we inferred about the presence of inconsistency from any source in the entire network based on a Chi^2 test.

Global approaches for evaluating incoherence = used to evaluate the presence of statistical incoherence in the entire network (e.g. inconsistency models or measures like the *I2* for inconsistency)

E.g., *design-by-treatment' interaction model as described by Higgins and colleagues*



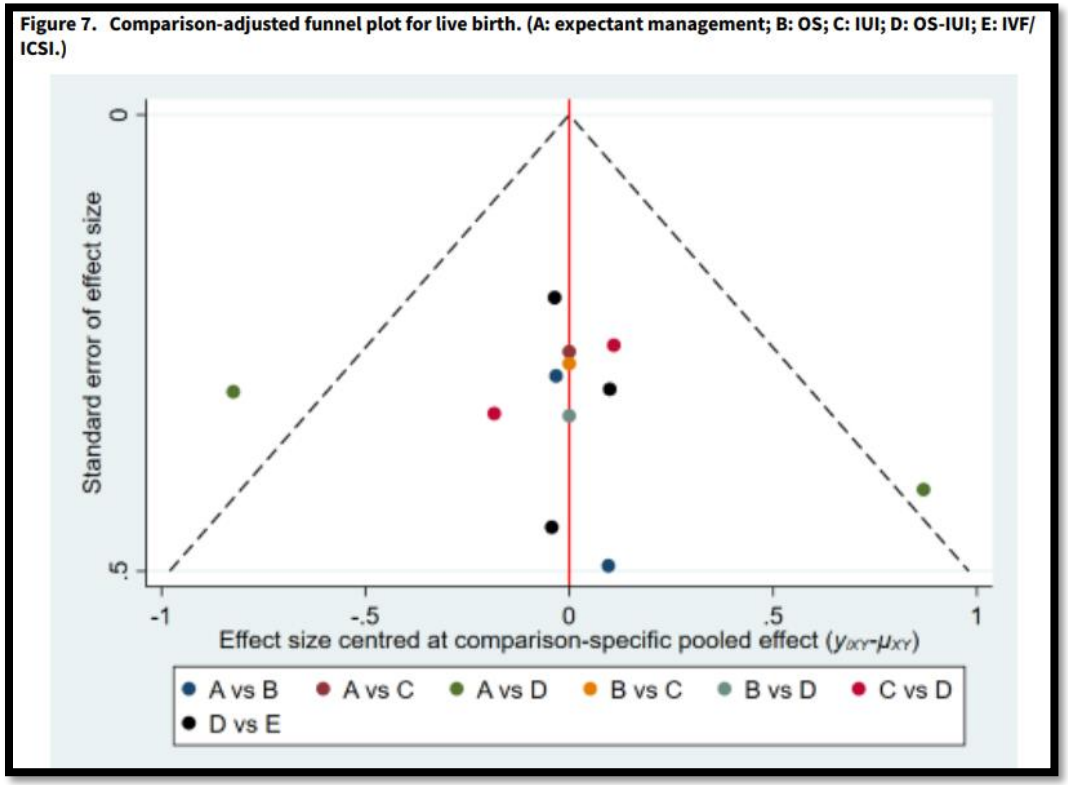
carbetocin. There was evidence of global inconsistency in this analysis (P = 0.005). However, we note that the CIs for both the network meta-analysis and direct evidence were overlapping across all comparisons suggesting locally-consistent results except for ergometrine versus placebo or no treatment based on a single study. Figure 31 shows the cumulative probabilities for each agent being at each possible rank for causing nausea. The highest ranked and the agents with the least risk of nausea were carbetocin, oxytocin and placebo or no treatment. The lowest ranked and most likely agents to cause nausea were ergometrine plus oxytocin and ergometrine.

Local approaches for evaluating incoherence = used to identify pairwise comparisons or loops formed by groups of comparisons that might be important sources of statistical incoherence in the network

E.g., *loop-specific approach, node splitting*

Assessment of reporting biases

10. Have the authors constructed a comparison adjusted funnel plot?



Like any funnel plot, there are multiple reasons for asymmetry. Be careful!

Wang R, Danhof NA, Tjon-Kon-Fat RI, Eijkemans MJC, Bossuyt PMM, Mochtar MH, van der Veen F, Bhattacharya S, Mol BWJ, van Wely M. **Interventions for unexplained infertility: a systematic review and network meta-analysis.** Cochrane Database of Systematic Reviews 2019, Issue 9. Art. No.: CD012692. DOI: 10.1002/14651858.CD012692.pub2.

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Effects of interventions

11. For each outcome, did the authors present;

(a) A ‘map’ of the evidence in the network for each outcome?
(b) The intervention effects in a concise and comprehensible way?
(c) The ranking in a concise and comprehensible way?
(d) The level of heterogeneity and incoherence in the network?
(e) The certainty of the evidence?

Effects of interventions

11 (a) Did the authors 'map' the evidence in the network for each outcome?

Network Diagram

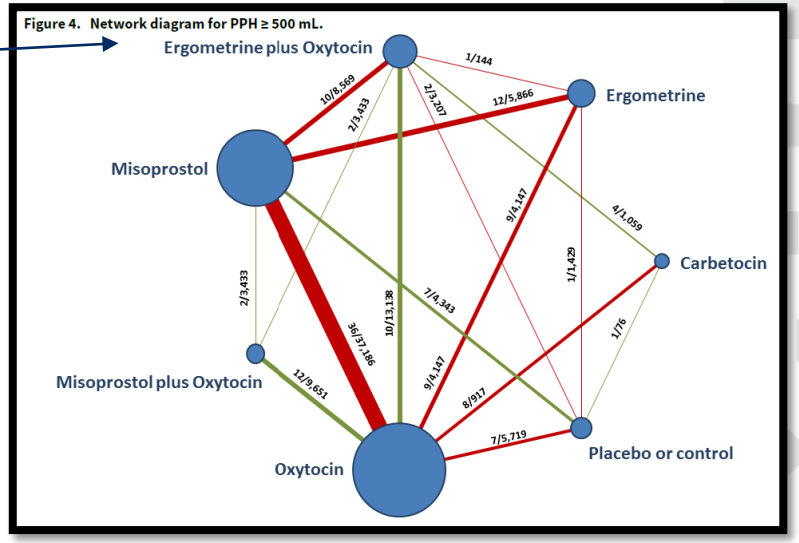
Effects of interventions

See: **Summary of findings for the main comparison**

Primary outcomes

Postpartum haemorrhage (PPH) ≥ 500 mL

The network diagram for PPH ≥ 500 mL is presented in Figure 4. Oxytocin was the most frequently investigated uterotonic agent (82%, 82 of 100 trials) (Figure 4).



Effects of interventions

11 (a) Did the authors 'map' the evidence in the network for each outcome?

Alternatives;

- Table – with columns represent the competing interventions and the rows represent the different study designs in terms of interventions being compared (best if there are too many competing interventions & study designs)

Table 11.6.a Example of table presenting a network that compares seven interventions and placebo for controlling exacerbation of episodes in chronic obstructive pulmonary disease (Baker et al 2009). Reproduced with permission of John Wiley & Sons

Number of studies	Placebo	Fluticasone	Budesonide	Salmeterol	Formoterol	Tiotropium	Fluticasone + salmeterol	Budesonide + formoterol
4	x	x		x			x	
4	x	x						
2	x		x		x			x
2	x			x		x		
2	x			x			x	
8	x			x				
2	x				x			
10	x					x		
1	x						x	
1				x		x		
1				x			x	
1					x	x		
1						x	x	

Baker WL, Baker EL, Coleman CI. Pharmacologic treatments for chronic obstructive pulmonary disease: a mixed-treatment comparison meta-analysis. Pharmacotherapy 2009; 29: 891–905.

Effects of interventions

11 (a) Did the authors 'map' the evidence in the network for each outcome?

Alternatives;

- Contribution matrix – Shows the percentage information that direct evidence contributes to each relative effect estimated in a network meta-analysis

Figure 13. Contribution matrix: Percentage contribution of each direct estimate to the NMA estimates. PVT: prevocational training; Psych care: psychiatric care only; SE: supported employment; SE+: augmented supported employment; TE: transitional employment

Direct comparisons in the network

Network meta-analysis estimates	SE + vs SE	SE + vs PVT	SE + vs TE	SE + vs Psych care	SE vs PVT	SE vs TE	SE vs Psych care	PVT vs Psych care
Mixed estimates								
SE + vs SE	30.0	8.8	21.0	4.8	8.1	21.0	5.5	0.7
SE + vs PVT	20.5	8.9	14.3	3.3	34.3	14.3	0.5	3.8
SE + vs TE	16.6	4.9	43.7	2.7	4.5	24.2	3.1	0.4
SE + vs Psych care	19.7	5.9	13.7	3.6	4.2	13.7	37.6	1.6
SE vs PVT	2.4	4.4	1.7	0.3	73.3	1.7	8.2	7.9
SE vs TE	15.4	4.5	22.4	2.5	4.2	47.8	2.8	0.4
SE vs Psych care	0.5	.	0.4	0.9	2.6	0.4	92.7	2.6
PVT vs Psych care	1.2	2.7	0.8	0.7	42.8	0.8	44.8	6.2
Indirect estimates								
PVT vs TE	8.4	5.1	14.9	1.4	35.0	29.0	2.4	3.8
TE vs Psych care	9.3	2.8	14.0	1.9	1.4	29.3	39.9	1.4
Entire network	13.0	5.0	14.8	2.3	20.5	19.1	22.5	2.8
Included studies	3	1	2	1	9	4	1	2

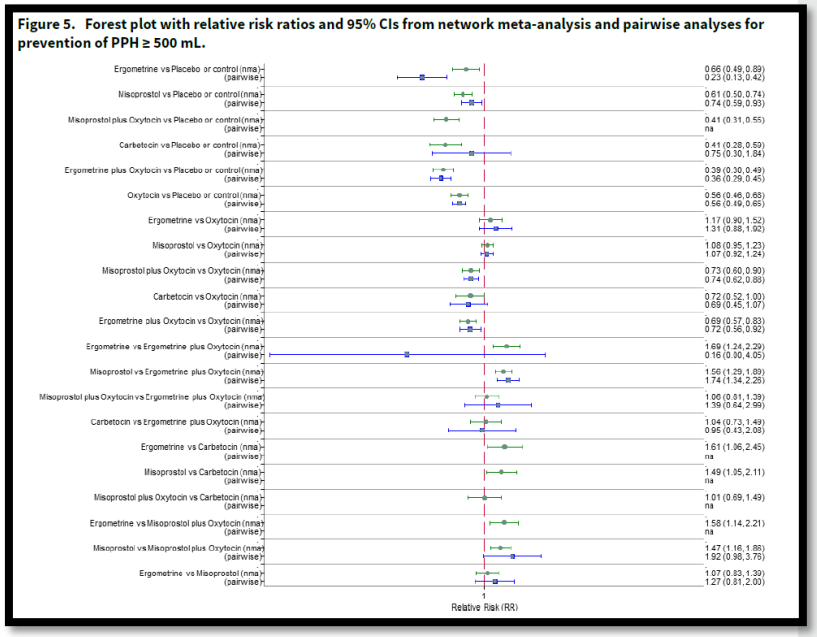
Suijkerbuijk YB, Schaafsma FG, van Mechelen JC, Ojajärvi A, Corbière M, Anema JR. **Interventions for obtaining and maintaining employment in adults with severe mental illness, a network meta-analysis.** Cochrane Database of Systematic Reviews 2017, Issue 9. Art. No.: CD011867.

Effects of interventions

11 (b) Did the authors present the intervention effects in a concise and comprehensible way?

Forest Plot

Pooled effect sizes from the network meta-analysis of 100 trials suggested that all drugs were effective for preventing PPH ≥ 500 mL when compared with placebo or no treatment (Figure 5). The three most effective options for prevention of PPH ≥ 500 mL were ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination. All three drugs more effectively reduced the risk of PPH ≥ 500 mL than oxytocin (ergometrine plus oxytocin risk ratio (RR) 0.69 (95% confidence interval (CI) 0.57 to 0.83): carbetocin RR 0.72 (95% CI 0.52 to 1.00): misoprostol plus oxytocin RR 0.73 95% CI (0.60 to 0.90), (Figure 5). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were also found to be more effective when compared with misoprostol and ergometrine when used alone. There was evidence of global inconsistency in this analysis, where the direct and network (combining direct and indirect) randomised evidence were not in agreement (P = 0.046). The inconsistency was driven by a single unblinded study of ergometrine versus no treatment (Begley 1990).



Effects of interventions

11 (b) Did the authors present the intervention effects in a concise and comprehensible way?

Alternatives;

- A table presenting direct, indirect and network summary relative effects along with their confidence ratings is a helpful format

League Table

Serious adverse events

AIL17	1.47 (0.98,2.20)	1.17 (0.83,1.64)	1.15 (0.83,1.59)	1.16 (0.73,1.86)	1.66 (0.98,2.82)	1.08 (0.82,1.42)
1.25 (0.99,1.59)	AIL23	0.79 (0.52,1.20)	0.78 (0.55,1.11)	0.79 (0.48,1.31)	1.13 (0.64,1.99)	0.74 (0.52,1.03)
1.52 (1.26,1.83)	1.21 (0.96,1.51)	AIL12_23	0.98 (0.67,1.43)	1.00 (0.60,1.66)	1.42 (0.80,2.53)	0.93 (0.66,1.30)
2.20 (1.80,2.69)	1.75 (1.45,2.12)	1.45 (1.17,1.80)	ATA	1.02 (0.66,1.57)	1.45 (0.88,2.39)	0.94 (0.74,1.21)
3.26 (2.27,4.67)	2.60 (1.81,3.72)	2.15 (1.49,3.10)	1.48 (1.07,2.04)	SM	1.43 (0.77,2.66)	0.93 (0.63,1.38)
6.31 (4.64,8.59)	5.03 (3.64,6.96)	4.16 (3.00,5.78)	2.87 (2.13,3.85)	1.94 (1.28,2.94)	CSA	0.65 (0.40,1.07)
29.33 (23.38,36.79)	23.38 (18.49,29.56)	19.34 (15.28,24.48)	13.33 (10.95,16.21)	9.01 (6.58,12.33)	4.65 (3.38,6.39)	PBO

Sbidian E, Chaimani A, Afach S, Doney L, Dressler C, Hua C, Mazaud C, Phan C, Hughes C, Riddle D, Naldi L, Garcia Doval I, Le Cleach L.

Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis.

Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD011535. DOI: 10.1002/14651858.CD011535.pub3.

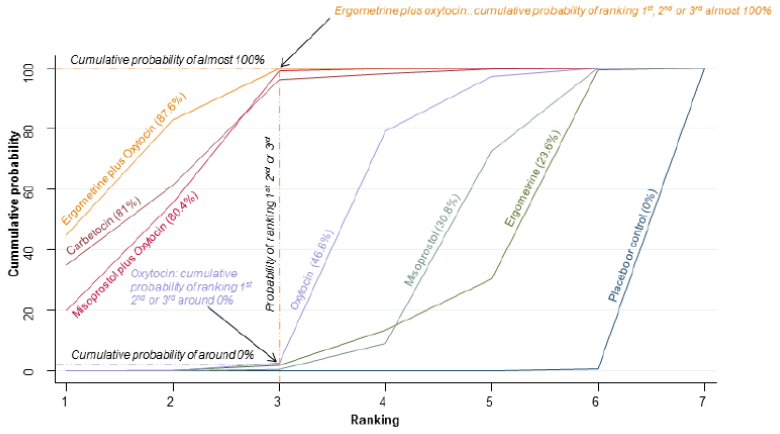
Effects of interventions

11 (c) Did the authors present the Ranking in a concise and comprehensible way?

Rankogram

The cumulative probabilities for each agent being at each possible rank for preventing PPH ≥ 500 mL are shown in Figure 6. Ranking indicates the cumulative probability of being the best drug, the second best, the third best, etc. The highest ranked agents were ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination with an almost 100% probability of these three agents being ranked first, second or third best. Oxytocin was ranked fourth and its probability of being ranked in the top three agents was close to 0%.

Figure 6. Cumulative rankograms comparing each of the uterotonic drugs for prevention of PPH ≥ 500 mL.



Effects of interventions

11 (c) Did the authors present the Ranking in a concise and comprehensible way?

Mean Ranks and SUCRA should also be considered in additional to rankogram

N.B., Ranking is **optional**

Ranking class-level analysis (Figure 8; Figure 10; Table 4)

Ranking analysis for SAE performed with SUCRA strongly suggested that conventional systemic treatment was associated with the best safety profile at class level in terms of serious adverse events (versus placebo: RR 0.65, 95% CI 0.40 to 1.07; SUCRA = 87.9), followed by anti-IL23 (versus placebo: RR 0.74, 95% CI 0.52 to 1.03; SUCRA = 81.1), anti-IL12/23 (versus placebo: RR 0.93, 95% CI 0.66 to 1.30; SUCRA = 46.5), and then small molecules (versus placebo: RR 0.93, 95% CI 0.63 to 1.38; SUCRA = 45.1). The heterogeneity τ for this network overall was 0.03, which we considered low heterogeneity.

Sbidian E, Chaimani A, Afach S, Doney L, Dressler C, Hua C, Mazaud C, Phan C, Hughes C, Riddle D, Naldi L, Garcia Doval I, Le Cleach L. **Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis.** Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD011535. DOI: 10.1002/14651858.CD011535.pub3.

Effects of interventions

11 (d) Did the authors present the level of heterogeneity and incoherence in the network of interventions

misoprostol plus oxytocin RR 0.73 95% CI (0.60 to 0.90), (Figure 5). Ergometrine plus oxytocin, carbetocin and misoprostol plus oxytocin were also found to be more effective when compared with misoprostol and ergometrine when used alone. There was evidence of global inconsistency in this analysis, where the direct and network (combining direct and indirect) randomised evidence were not in agreement (P = 0.046). The inconsistency was driven by a single unblinded study of ergometrine versus no treatment (Begley 1990).

Can be expressed via the magnitude of the between-study variance $Tau^{2,}$ and summarized in the P value of the Chi^2 statistic incoherence test and the I^2 statistic for incoherence (see Chapter 10, Section 10.10.2).

Effects of interventions

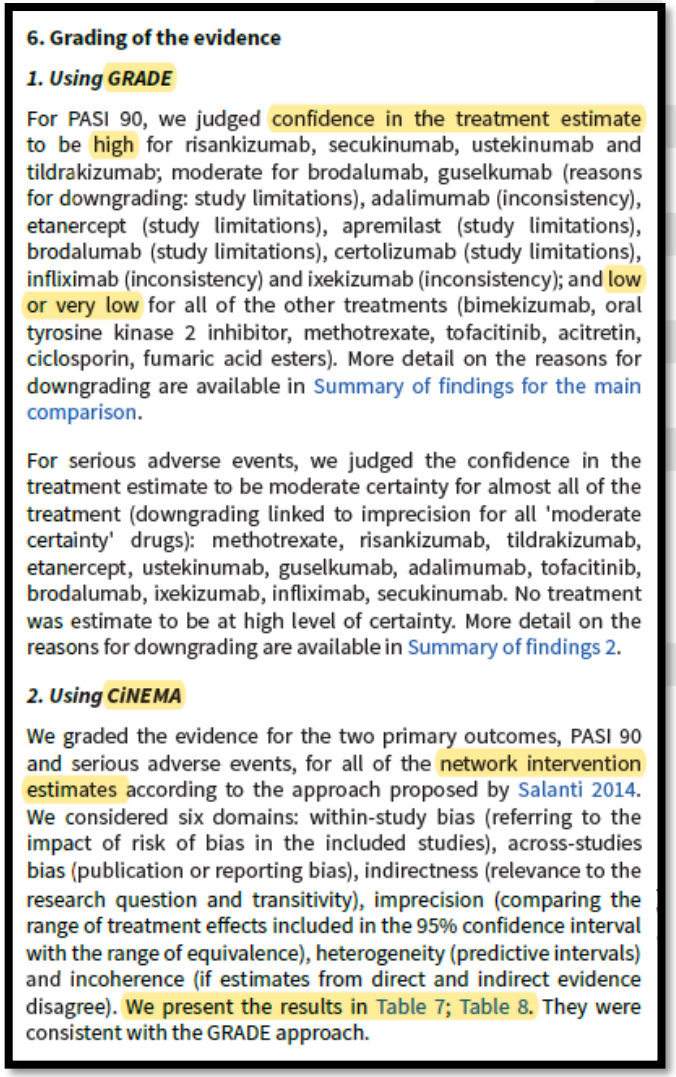
11 (e) Did the authors clearly state the certainty of the evidence

For confidence in each **pairwise** comparisons , look for use of **GRADE**

For confidence in the evidence from a **network** of interventions , look for use of either;

- **CINeMA** (Salanti et al 2014)
- **Puhan** and colleagues (Puhan et al 2014).

Sbidian E, Chaimani A, Afach S, Doney L, Dressler C, Hua C, Mazaud C, Phan C, Hughes C, Riddle D, Naldi L, Garcia Doval I, Le Cleach L. **Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis.** Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD011535. DOI: 10.1002/14651858.CD011535.pub3.



6. Grading of the evidence

1. Using GRADE

For PASI 90, we judged confidence in the treatment estimate to be high for risankizumab, secukinumab, ustekinumab and tildrakizumab; moderate for brodalumab, guselkumab (reasons for downgrading: study limitations), adalimumab (inconsistency), etanercept (study limitations), apremilast (study limitations), brodalumab (study limitations), certolizumab (study limitations), infliximab (inconsistency) and ixekizumab (inconsistency); and low or very low for all of the other treatments (bimekizumab, oral tyrosine kinase 2 inhibitor, methotrexate, tofacitinib, acitretin, ciclosporin, fumaric acid esters). More detail on the reasons for downgrading are available in Summary of findings for the main comparison.

For serious adverse events, we judged the confidence in the treatment estimate to be moderate certainty for almost all of the treatment (downgrading linked to imprecision for all 'moderate certainty' drugs): methotrexate, risankizumab, tildrakizumab, etanercept, ustekinumab, guselkumab, adalimumab, tofacitinib, brodalumab, ixekizumab, infliximab, secukinumab. No treatment was estimate to be at high level of certainty. More detail on the reasons for downgrading are available in Summary of findings 2.

2. Using CINEMA

We graded the evidence for the two primary outcomes, PASI 90 and serious adverse events, for all of the network intervention estimates according to the approach proposed by Salanti 2014. We considered six domains: within-study bias (referring to the impact of risk of bias in the included studies), across-studies bias (publication or reporting bias), indirectness (relevance to the research question and transitivity), imprecision (comparing the range of treatment effects included in the 95% confidence interval with the range of equivalence), heterogeneity (predictive intervals) and incoherence (if estimates from direct and indirect evidence disagree). We present the results in Table 7; Table 8. They were consistent with the GRADE approach.

Summary of Findings tables

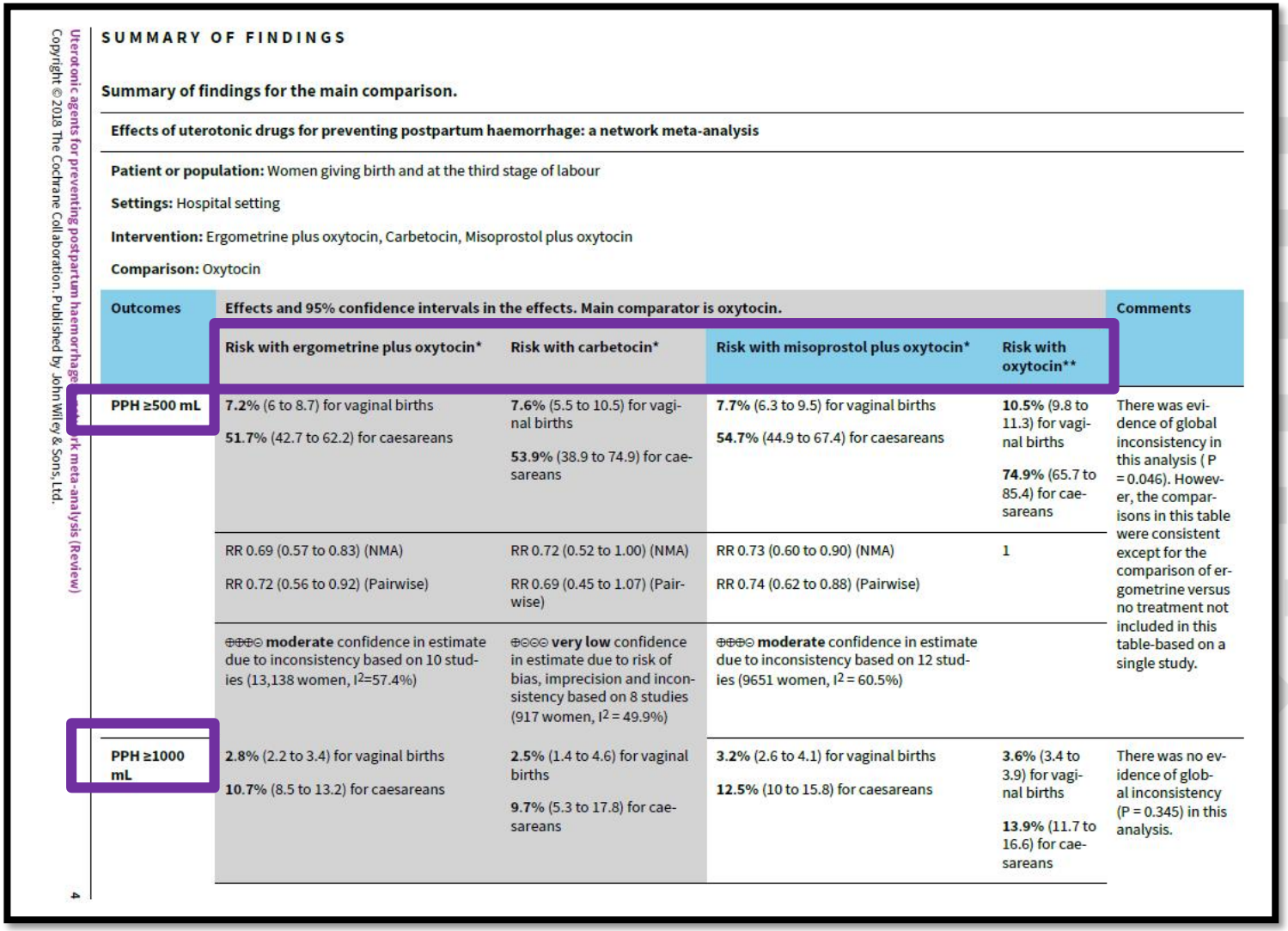
12 (a) Did authors provide a clear rationale for the choice of outcomes and comparisons they report in the 'Summary of findings' tables.

Summary of findings

A "Summary of findings" table is presented as described by Puhan et al (Puhan 2014). This table shows the overall quality of the body of evidence for the primary review outcomes and important side-effects, using GRADE criteria. GRADE ratings were determined on the basis of risk of bias, inconsistency, indirectness and imprecision. The risks of bias was assessed conventionally for each included trial. A judgement was made to downgrade the quality of the evidence if the majority of the trials for each outcome or each direct comparison were at high risk of bias. The evidence was also downgraded in quality if we found inconsistency between estimates produced by the network meta-analysis and direct estimates obtained from pairwise comparisons. Heterogeneity across studies for each pairwise meta-analysis was assessed using I^2. The evidence was downgraded for indirectness if the included trials for specific direct comparisons were considered to be more restrictive or different than the overall review question. Lastly, evidence was downgraded if there was imprecision. Imprecision relates to the overall level of confidence that may be placed in the estimated treatment effects. Each quality element considered to have 'serious' or 'very serious' limitations was rated down one or two levels respectively. GRADE assessments were made for the most effective drugs (ergometrine plus oxytocin, carbetocin, and misoprostol plus oxytocin) in comparison with the most frequently used and recommended drug (oxytocin) as a comparison for the primary outcomes and important side-effects. The risk calculated in the comparison group (oxytocin) (and its 95% confidence interval (CI)) was based on a meta-analysis of proportions from the studies included in this review. The risks (and their 95% CIs) calculated in the intervention groups were based on the assumed risk in the comparison group and the relative effects of the interventions (and their 95% CIs). The risks differed significantly by the mode of birth subgroup and they are presented separately for vaginal births and caesareans. Assessments were carried out by IDG and checked by AC.

12 (b) Did they specify how confidence in the evidence was assessed?

12 (c) Did they present the planned outcomes and comparisons?



SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Effects of uterotonic drugs for preventing postpartum haemorrhage: a network meta-analysis

Patient or population: Women giving birth and at the third stage of labour

Settings: Hospital setting

Intervention: Ergometrine plus oxytocin, Carbetocin, Misoprostol plus oxytocin

Comparison: Oxytocin

Outcomes	Effects and 95% confidence intervals in the effects. Main comparator is oxytocin.				Comments
	Risk with ergometrine plus oxytocin*	Risk with carbetocin*	Risk with misoprostol plus oxytocin*	Risk with oxytocin**	
PPH ≥500 mL	**7.2%** (6 to 8.7) for vaginal births **51.7%** (42.7 to 62.2) for caesareans	**7.6%** (5.5 to 10.5) for vaginal births **53.9%** (38.9 to 74.9) for caesareans	**7.7%** (6.3 to 9.5) for vaginal births **54.7%** (44.9 to 67.4) for caesareans	**10.5%** (9.8 to 11.3) for vaginal births **74.9%** (65.7 to 85.4) for caesareans	There was evidence of global inconsistency in this analysis (P = 0.046). However, the comparisons in this table were consistent except for the comparison of ergometrine versus no treatment not included in this table-based on a single study.
	RR 0.69 (0.57 to 0.83) (NMA) RR 0.72 (0.56 to 0.92) (Pairwise)	RR 0.72 (0.52 to 1.00) (NMA) RR 0.69 (0.45 to 1.07) (Pairwise)	RR 0.73 (0.60 to 0.90) (NMA) RR 0.74 (0.62 to 0.88) (Pairwise)	1	
	⊕⊕⊕⊖ **moderate** confidence in estimate due to inconsistency based on 10 studies (13,138 women, I^2=57.4%)	⊕⊖⊖⊖ **very low** confidence in estimate due to risk of bias, imprecision and inconsistency based on 8 studies (917 women, I^2 = 49.9%)	⊕⊕⊕⊖ **moderate** confidence in estimate due to inconsistency based on 12 studies (9651 women, I^2 = 60.5%)		
PPH ≥1000 mL	**2.8%** (2.2 to 3.4) for vaginal births **10.7%** (8.5 to 13.2) for caesareans	**2.5%** (1.4 to 4.6) for vaginal births **9.7%** (5.3 to 17.8) for caesareans	**3.2%** (2.6 to 4.1) for vaginal births **12.5%** (10 to 15.8) for caesareans	**3.6%** (3.4 to 3.9) for vaginal births **13.9%** (11.7 to 16.6) for caesareans	There was no evidence of global inconsistency (P = 0.345) in this analysis.

	RR 0.77 (0.61 to 0.95) (NMA) RR 0.73 (0.57 to 0.93) (Pairwise)	RR 0.70 (0.38 to 1.28) (NMA) RR 0.71 (0.38 to 1.35) (Pairwise)	RR 0.90 (0.72 to 1.14) (NMA) RR 0.89 (0.71 to 1.12) (Pairwise)	1	
	⊕⊕⊕⊕ **high** confidence in estimate based on 9 studies (13,038 women, I^2 = 0%)	⊕⊕◯◯ **low** confidence in estimate due to risk of bias and imprecision based on 7 studies (1026 women, I^2 = 0%)	⊕⊕⊕◯ **moderate** confidence in estimate due to imprecision based on 14 studies (9897 women, I^2 = 0%)		
Vomiting	**1.9%** (1.3 to 2.7) for vaginal births **16.1%** (11 to 23.7) for caesareans	**0.5%** (0.3 to 0.9) for vaginal births **4.6%** (2.9 to 7.4) for caesareans	**1.3%** (0.8 to 2) for vaginal births **11.2%** (7.1 to 17.6) for caesareans	**0.6%** (0.5 to 0.6) for vaginal births **5.2%** (4.9 to 5.5) for caesareans	There was no evidence of global inconsistency (P = 0.06) in this analysis.
	RR 3.10 (2.11 to 4.56) (NMA) RR 3.15 (1.72 to 5.78) (Pairwise)	RR 0.89 (0.55 to 1.42) (NMA) RR 0.88 (0.39 to 1.99) (Pairwise)	RR 2.16 (1.37 to 3.39) (NMA) RR 2.25 (1.45 to 3.48) (Pairwise)	1	
	⊕⊕⊕⊕ **high** confidence in estimate based on 8 studies (9811 women, I^2 = 48.1%)	⊕◯◯◯ **very low** confidence in estimate due to risk of bias, inconsistency and imprecision based on 10 studies (1939 women, I^2 = 59.2%)	⊕⊕⊕⊕ **high** confidence in estimate due to imprecision based on 9 studies (5015 women, I^2 = 30.1%)		
Hypertension	**.2%** (0.4 to 4) for vaginal births **29.6%** (to) for caesareans	**0.6%** (0.1 to 3.3) for vaginal births **14.2%** (2.5 to 79.7) for caesareans	Risks not available as no studies report this outcome	**0.7%** (0.7 to 0.8) for vaginal births **16.7%** (11.2 to 24.9) for caesareans	There was no evidence of global inconsistency (P = 0.481) in this analysis.
	RR 1.77 (0.55 to 5.66) (NMA) RR 0.95 (0.10 to 8.38) (Pairwise)	RR 0.85 (0.15 to 4.77) (NMA)	RR not available as no studies reported this outcome	1	
	⊕⊕◯◯ **low** confidence in estimate due to inconsistency and imprecision based on 2 studies (1039 women, I^2 = 73.2%)	⊕⊕◯◯ **low** confidence in estimate due to imprecision	Quality of the evidence cannot be assessed as no studies report this outcome		

		and based only on indirect evidence			
Fever	3% (1.5 to 6) for vaginal births **11.7**% (6.5 to 23.2) for caesareans	**3.1**% (0.8 to 12.1) for vaginal births **12**% (3.1 to 46.6) for caesareans	**11.4**% (8 to 16.4) for vaginal births **44.2**% (30.9 to 63.2) for caesareans	**3.6**% (3.4 to 3.9) for vaginal births **13.9**% (11.7 to 16.6) for caesareans	There was no evidence of global inconsistency (P = 0.352) in this analysis.
	RR 0.84 (0.42 to 1.67) (NMA) RR 1.07 (0.47 to 2.43) (Pairwise)	RR 0.86 (0.22 to 3.35) (NMA) RR 2.11 (0.18 to 24.40) (Pairwise)	RR 3.18 (2.22 to 4.55) (NMA) RR 2.96 (1.95 to 4.51) (Pairwise)	1	
	⊕⊕⊕⊖ **moderate** confidence in estimate due to imprecision based on 2 studies (1591 women, I^2 = 0%)	⊕⊖⊖⊖ **very low** confidence in estimate due to risk of bias, inconsistency and imprecision based on 3 studies (292 women, I^2 = 40.9%)	⊕⊕⊕⊖ **moderate** confidence in estimate due to inconsistency based on 15 studies (8209 women, I^2 = 77.8%)		

***The risks in the ergometrine plus oxytocin, carbetocin, misoprostol plus oxytocin groups** (and their 95% confidence interval) are based on the assumed risk in the oxytocin group and the **relative effects** of the interventions (and its 95% CI).

****The risk in the oxytocin group** (and its 95% confidence interval) is based on a meta-analysis of proportions from the studies included in this review for this group.
RR: Risk ratio

GRADE Working Group grades of evidence

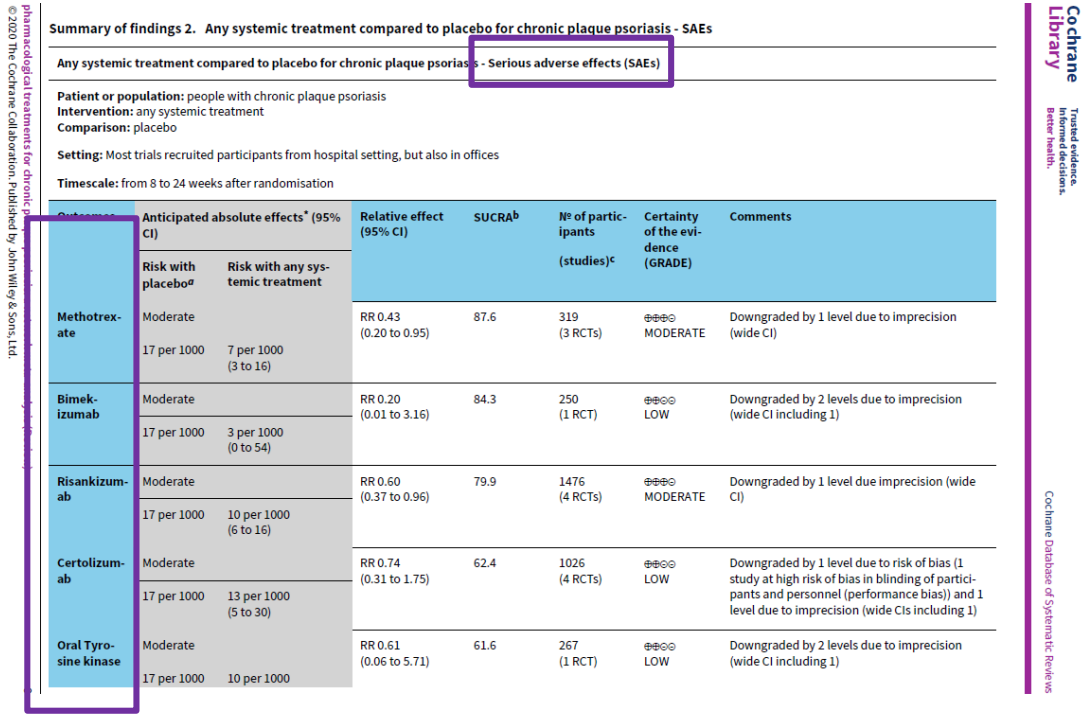
High quality:

We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Summary of Findings tables

Alternatives;

- A separate 'Summary of findings' table for each important outcome



Summary of findings 2. Any systemic treatment compared to placebo for chronic plaque psoriasis - SAEs

Any systemic treatment compared to placebo for chronic plaque psoriasis - Serious adverse effects (SAEs)

Patient or population: people with chronic plaque psoriasis
Intervention: any systemic treatment
Comparison: placebo

Setting: Most trials recruited participants from hospital setting, but also in offices

Timescale: from 8 to 24 weeks after randomisation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	SUCRA[b]	№ of participants (studies)[c]	Certainty of the evidence (GRADE)	Comments
	Risk with placebo[a]	Risk with any systemic treatment					
Methotrexate	Moderate		RR 0.43 (0.20 to 0.95)	87.6	319 (3 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due to imprecision (wide CI)
	17 per 1000	7 per 1000 (3 to 16)					
Bimekizumab	Moderate		RR 0.20 (0.01 to 3.16)	84.3	250 (1 RCT)	⊕⊕⊖⊖ LOW	Downgraded by 2 levels due to imprecision (wide CI including 1)
	17 per 1000	3 per 1000 (0 to 54)					
Risankizumab	Moderate		RR 0.60 (0.37 to 0.96)	79.9	1476 (4 RCTs)	⊕⊕⊕⊖ MODERATE	Downgraded by 1 level due imprecision (wide CI)
	17 per 1000	10 per 1000 (6 to 16)					
Certolizumab	Moderate		RR 0.74 (0.31 to 1.75)	62.4	1026 (4 RCTs)	⊕⊕⊖⊖ LOW	Downgraded by 1 level due to risk of bias (1 study at high risk of bias in blinding of participants and personnel (performance bias)) and 1 level due to imprecision (wide CIs including 1)
	17 per 1000	13 per 1000 (5 to 30)					
Oral Tyrosine kinase	Moderate		RR 0.61 (0.06 to 5.71)	61.6	267 (1 RCT)	⊕⊕⊖⊖ LOW	Downgraded by 2 levels due to imprecision (wide CI including 1)
	17 per 1000	10 per 1000					

Sbidian E, Chaimani A, Afach S, Doney L, Dressler C, Hua C, Mazaud C, Phan C, Hughes C, Riddle D, Naldi L, Garcia Doval I, Le Cleach L. **Systemic pharmacological treatments for chronic plaque psoriasis: a network meta-analysis.** Cochrane Database of Systematic Reviews 2020, Issue 1. Art. No.: CD011535. DOI: 10.1002/14651858.CD011535.pub3.

- An interactive electronic display such that the user can choose what to emphasize.

Summary of Findings tables

11.6.4.3 'Summary of findings' tables

The purpose of 'Summary of findings' tables in Cochrane Reviews is to provide concisely the key information in terms of available data, confidence in the evidence and intervention effects (see Chapter 14). Providing such a table is more challenging in reviews that compare multiple interventions simultaneously, which very often involve a large number of comparisons between pairs of interventions. A general principle is that the comparison of multiple interventions is the main feature of a network meta-analysis, so is likely to drive the structure of the 'Summary of findings' table. This is in contrast to the 'Summary of findings' table for a pair-wise comparison, whose main strength is to facilitate comparison of effects on different outcomes. Nevertheless, it remains important to be able to compare network meta-analysis results across different outcomes. This provides presentational challenges that are almost impossible to resolve in two dimensions. One potential solution is an interactive electronic display such that the user can choose whether to emphasize the comparisons across interventions or the comparisons across outcomes.

For small networks of interventions (perhaps including up to five competing interventions) a separate 'Summary of findings' table might be produced for each main outcome. However, in the presence of many (more than five) competing interventions, researchers would typically need to select and report a reduced number of pair-wise comparisons. Review authors should provide a clear rationale for the choice of the comparisons they report in the 'Summary of findings' tables. For example, they may consider including only pair-wise comparisons that correspond to the decision set of interventions; that is, the group of interventions of direct interest for drawing conclusions (see Section 11.3.2.1). The distinction between the decision set and the wider synthesis comparator set (all interventions included in the analysis) should be made in the protocol of the review. If the decision set is still too large, researchers may be able to select the comparisons for the 'Summary of findings' table based on the most important information for clinical practice. For example, reporting the comparisons between the three or four most effective interventions with the most commonly used intervention as a comparator.

Handbook v6, section 11.6.4.3

More than 5 interventions

- *Select and report a reduced number of comparisons*
- *Clear rationale for choice of comparisons*
  - *Direct interest for conclusions (pre specify)*
  - *Most important for clinical practice*

Cochrane

Table 3. NMA-SoF table template for dichotomous outcomes

Bayesian NMA-SoF table

BENEFITS

Estimates of effects, credible intervals, and certainty of the evidence for chemoprevention of colorectal cancer in individualswith previous colorectal neoplasia

Patient or population: Individuals with previous colorectal neoplasia

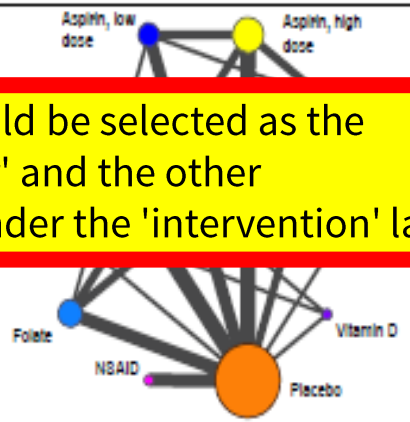
Interventions: Low and high dose aspirin, nonaspirin non-steroidal ant

calcium, vitamin D, folic acid

Comparator (reference): Placebo

Outcome: Prevention of advanced neoplasia; range of follow up between three to five years

Setting: Outpatient



One intervention should be selected as the 'reference comparator' and the other interventions listed under the 'intervention' label

Total studies: 21 RCT Total Participants: 12088	Relative effect** (95% CrI)	Anticipated absolute effect*** (95% CrI)			Certainty of evidence	Ranking**** (95% CrI)	Interpretation of Findings
		Without intervention	With intervention	Difference			
Aspirin + c vitamin D (1 RCT; 42							
Calcium + (1 RCT; 102 participants)	Network estimate						

- A placebo intervention,
- a “gold” standard treatment for the condition under review,
- the most cost-effective intervention,
- the least effective intervention.

Summary of Findings tables

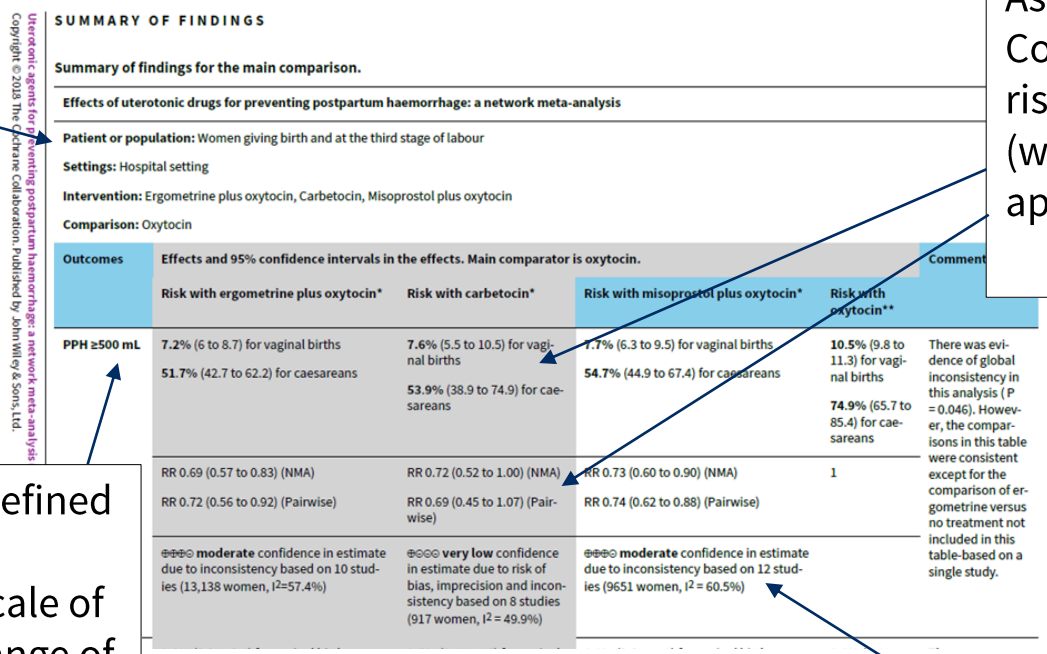
12 (d) Were all other standard recommendations for SoF tables adhered to?

PICO (including Settings) are accurate & informative

Assumed & Corresponding risks included (where appropriate)

Outcomes fully defined (i.e. time of measurement, scale of measurement, range of scores specified)

GRADE ratings presented and adequately justified



Uterotonic agents for preventing postpartum haemorrhage: a network meta-analysis

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Effects of uterotonic drugs for preventing postpartum haemorrhage: a network meta-analysis

Patient or population: Women giving birth and at the third stage of labour

Settings: Hospital setting

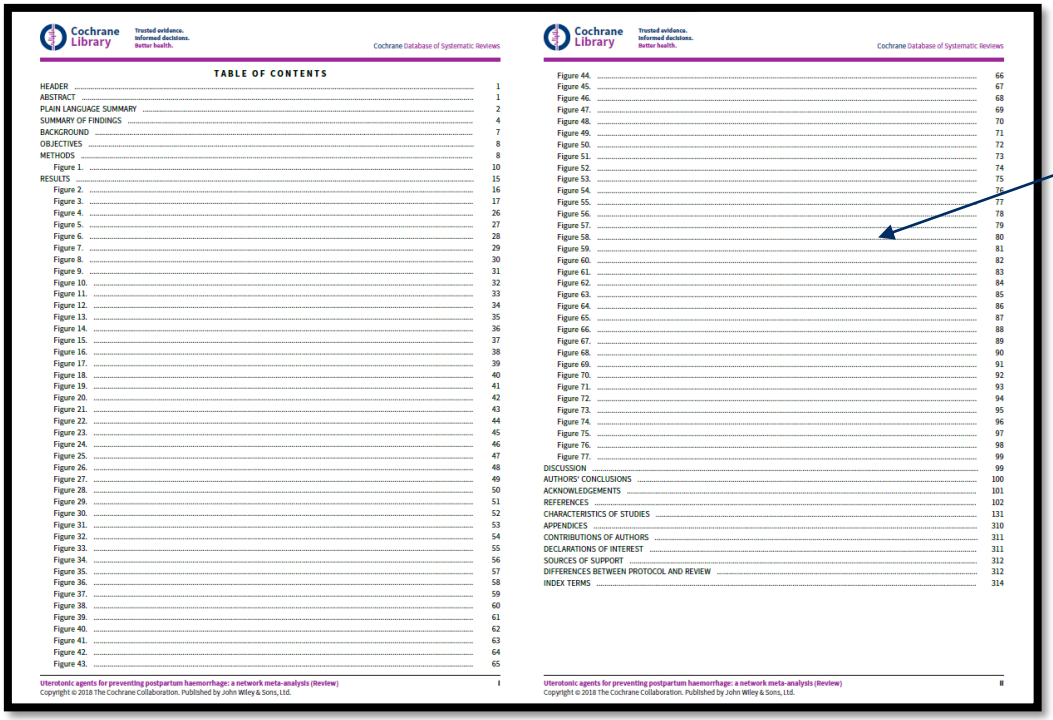
Intervention: Ergometrine plus oxytocin, Carbetocin, Misoprostol plus oxytocin

Comparison: Oxytocin

Outcomes	Effects and 95% confidence intervals in the effects. Main comparator is oxytocin.				Comment
	Risk with ergometrine plus oxytocin*	Risk with carbetocin*	Risk with misoprostol plus oxytocin*	Risk with oxytocin**	
PPH ≥500 mL	**7.2%** (6 to 8.7) for vaginal births **51.7%** (42.7 to 62.2) for caesareans	**7.6%** (5.5 to 10.5) for vaginal births **53.9%** (38.9 to 74.9) for caesareans	**7.7%** (6.3 to 9.5) for vaginal births **54.7%** (44.9 to 67.4) for caesareans	**10.5%** (9.8 to 11.3) for vaginal births **74.9%** (65.7 to 85.4) for caesareans	There was evidence of global inconsistency in this analysis (P = 0.046). However, the comparisons in this table were consistent except for the comparison of ergometrine versus no treatment not included in this table-based on a single study.
	RR 0.69 (0.57 to 0.83) (NMA) RR 0.72 (0.56 to 0.92) (Pairwise)	RR 0.72 (0.52 to 1.00) (NMA) RR 0.69 (0.45 to 1.07) (Pairwise)	RR 0.73 (0.60 to 0.90) (NMA) RR 0.74 (0.62 to 0.88) (Pairwise)	1	
	⊕⊕⊕⊖ **moderate** confidence in estimate due to inconsistency based on 10 studies (13,138 women, I^2=57.4%)	⊕⊖⊖⊖ **very low** confidence in estimate due to risk of bias, imprecision and inconsistency based on 8 studies (917 women, I^2 = 49.9%)	⊕⊕⊕⊖ **moderate** confidence in estimate due to inconsistency based on 12 studies (9651 women, I^2 = 60.5%)		

Tables and Figures

13. Have Tables and Figures been kept to a minimum?



Cochrane Library — Trusted evidence. Informed decisions. Better health. — Cochrane Database of Systematic Reviews

TABLE OF CONTENTS

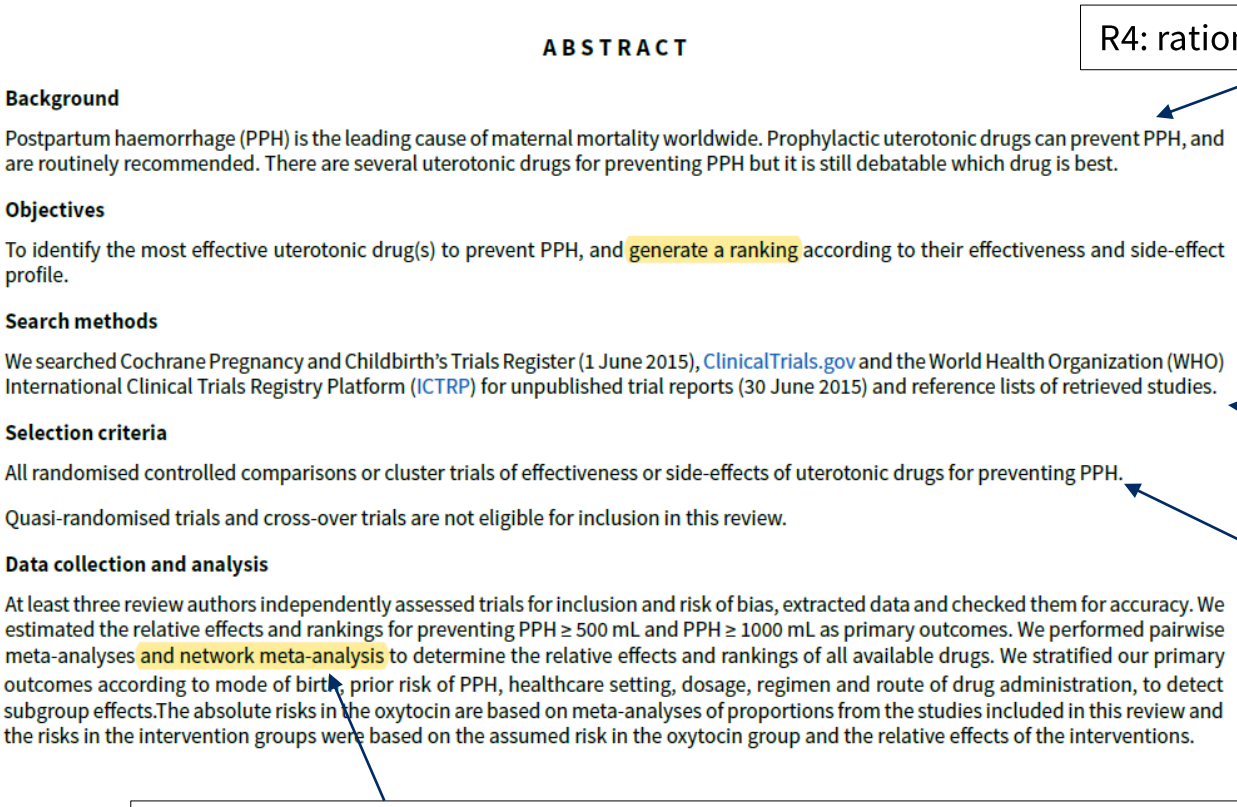
Cochrane Library — Trusted evidence. Informed decisions. Better health. — Cochrane Database of Systematic Reviews

Best to only present critical figures/tables and use either appendices or online science depository systems for the rest, such as

https://datadryad.org/stash
https://figshare.com/

Abstract

14. Were all standard recommendations for Abstract tables adhered to?



ABSTRACT

Background

Postpartum haemorrhage (PPH) is the leading cause of maternal mortality worldwide. Prophylactic uterotonic drugs can prevent PPH, and are routinely recommended. There are several uterotonic drugs for preventing PPH but it is still debatable which drug is best.

Objectives

To identify the most effective uterotonic drug(s) to prevent PPH, and generate a ranking according to their effectiveness and side-effect profile.

Search methods

We searched Cochrane Pregnancy and Childbirth's Trials Register (1 June 2015), ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) for unpublished trial reports (30 June 2015) and reference lists of retrieved studies.

Selection criteria

All randomised controlled comparisons or cluster trials of effectiveness or side-effects of uterotonic drugs for preventing PPH.

Quasi-randomised trials and cross-over trials are not eligible for inclusion in this review.

Data collection and analysis

At least three review authors independently assessed trials for inclusion and risk of bias, extracted data and checked them for accuracy. We estimated the relative effects and rankings for preventing PPH ≥ 500 mL and PPH ≥ 1000 mL as primary outcomes. We performed pairwise meta-analyses and network meta-analysis to determine the relative effects and rankings of all available drugs. We stratified our primary outcomes according to mode of birth, prior risk of PPH, healthcare setting, dosage, regimen and route of drug administration, to detect subgroup effects.The absolute risks in the oxytocin are based on meta-analyses of proportions from the studies included in this review and the risks in the intervention groups were based on the assumed risk in the oxytocin group and the relative effects of the interventions.

R4: rationale and context of the review

R5: main objective in a single concise sentence - **including the word 'NMA' (and 'rank' if applicable)**

R6: date of last search

R7: Summarize eligibility criteria, including info on study design, population and comparison

R8: Summarize **noteworthy methods** for selecting studies, collecting data, evaluating risk of bias and synthesizing findings

Abstract

14. Were all standard recommendations for Abstract tables adhered to?

Main results

This network meta-analysis included 140 randomised trials with data from 88,947 women. There are two large ongoing studies. The trials were mostly carried out in hospital settings and recruited women who were predominantly more than 37 weeks of gestation having a vaginal birth. The majority of trials were assessed to have uncertain risk of bias due to poor reporting of study design. This primarily impacted on our confidence in comparisons involving carbetocin trials more than other uterotonics.

The three most effective drugs for prevention of PPH ≥ 500 mL were ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination. These three options were more effective at preventing PPH ≥ 500 mL compared with oxytocin, the drug currently recommended by the WHO (ergometrine plus oxytocin risk ratio (RR) 0.69 (95% confidence interval (CI) 0.57 to 0.83), moderate-quality evidence; carbetocin RR 0.72 (95% CI 0.52 to 1.00), very low-quality evidence; misoprostol plus oxytocin RR 0.73 (95% CI 0.60 to 0.90), moderate-quality evidence). Based on these results, about 10.5% women given oxytocin would experience a PPH of ≥ 500 mL compared with 7.2% given ergometrine plus oxytocin combination, 7.6% given carbetocin, and 7.7% given misoprostol plus oxytocin. Oxytocin was ranked fourth with close to 0% cumulative probability of being ranked in the top three for PPH ≥ 500 mL.

The outcomes and rankings for the outcome of PPH ≥ 1000 mL were similar to those of PPH ≥ 500 mL. with the evidence for ergometrine plus oxytocin combination being more effective than oxytocin (RR 0.77 (95% CI 0.61 to 0.95), high-quality evidence) being more certain than that for carbetocin (RR 0.70 (95% CI 0.38 to 1.28), low-quality evidence), or misoprostol plus oxytocin combination (RR 0.90 (95% CI 0.72 to 1.14), moderate-quality evidence)

There were no meaningful differences between all drugs for maternal deaths or severe morbidity as these outcomes were so rare in the included randomised trials.

Two combination regimens had the poorest rankings for side-effects. Specifically, the ergometrine plus oxytocin combination had the higher risk for vomiting (RR 3.10 (95% CI 2.11 to 4.56), high-quality evidence; 1.9% versus 0.6%) and hypertension [RR 1.77 (95% CI 0.55 to 5.66), low-quality evidence; 1.2% versus 0.7%), while the misoprostol plus oxytocin combination had the higher risk for fever (RR 3.18 (95% CI 2.22 to 4.55), moderate-quality evidence; 11.4% versus 3.6%) when compared with oxytocin. Carbetocin had similar risk for side-effects compared with oxytocin although the quality evidence was very low for vomiting and for fever, and was low for hypertension.

Authors' conclusions

Ergometrine plus oxytocin combination, carbetocin, and misoprostol plus oxytocin combination were more effective for preventing PPH ≥ 500 mL than the current standard oxytocin. Ergometrine plus oxytocin combination was more effective for preventing PPH ≥ 1000 mL than oxytocin. Misoprostol plus oxytocin combination evidence is less consistent and may relate to different routes and doses of misoprostol used in the studies. Carbetocin had the most favourable side-effect profile amongst the top three options; however, most carbetocin trials were small and at high risk of bias.

R9: number of included studies and participants.

R10: Study Characteristics

R11: Risk of Bias assessment

R12-15: All important outcomes summarised (i.e., SoF table outcomes), including;

- **statistical summaries**
- **re-expressed in interpretable way**
- **certainty of evidence**

R7: Key conclusions, using language reflecting certainty

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Abstract > Main Results

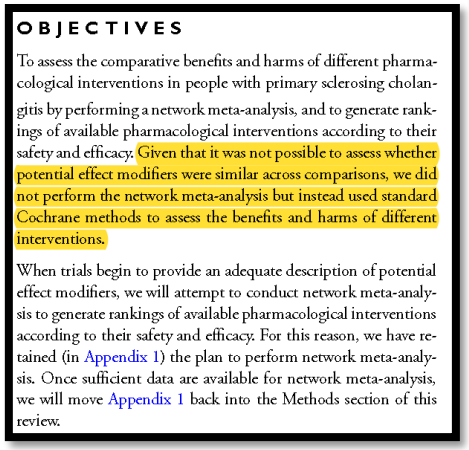
- N.B., **MECIR R12 to R15** states that the Abstract > Main Results must present;
  - All 'important' outcomes, including adverse effects
  - Summaries of statistical analyses
  - Key findings in an 'interpretable' way

All of which becomes more difficult when presenting complex results of an NMA

- Identify the **most important outcomes and comparisons (**from the SoF tables), and prioritise summarising that information in the Abstract
  - Consult with Key Stakeholders in advance, to identify what decision makers **need to know**.

When an NMA is planned, but not feasible

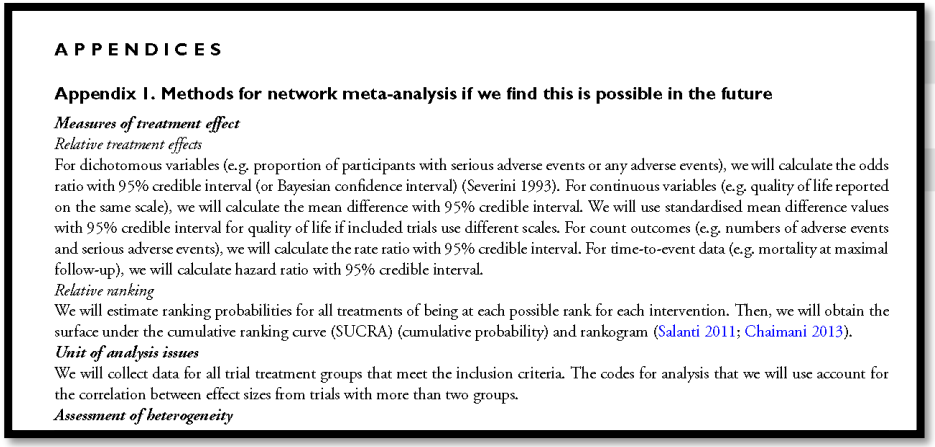
- Protocol may plan for NMA, but find it impossible in full review, due to lack of studies, or uncertainty regarding transitivity assumption etc.
- NMA methods must remain in the review in some form, e.g. as an Appendix.



OBJECTIVES

To assess the comparative benefits and harms of different pharmacological interventions in people with primary sclerosing cholangitis by performing a network meta-analysis, and to generate rankings of available pharmacological interventions according to their safety and efficacy. Given that it was not possible to assess whether potential effect modifiers were similar across comparisons, we did not perform the network meta-analysis but instead used standard Cochrane methods to assess the benefits and harms of different interventions.

When trials begin to provide an adequate description of potential effect modifiers, we will attempt to conduct network meta-analysis to generate rankings of available pharmacological interventions according to their safety and efficacy. For this reason, we have retained (in Appendix 1) the plan to perform network meta-analysis. Once sufficient data are available for network meta-analysis, we will move Appendix 1 back into the Methods section of this review.



APPENDICES

Appendix 1. Methods for network meta-analysis if we find this is possible in the future

Measures of treatment effect

Relative treatment effects

For dichotomous variables (e.g. proportion of participants with serious adverse events or any adverse events), we will calculate the odds ratio with 95% credible interval (or Bayesian confidence interval) (Severini 1993). For continuous variables (e.g. quality of life reported on the same scale), we will calculate the mean difference with 95% credible interval. We will use standardised mean difference values with 95% credible interval for quality of life if included trials use different scales. For count outcomes (e.g. numbers of adverse events and serious adverse events), we will calculate the rate ratio with 95% credible interval. For time-to-event data (e.g. mortality at maximal follow-up), we will calculate hazard ratio with 95% credible interval.

Relative ranking

We will estimate ranking probabilities for all treatments of being at each possible rank for each intervention. Then, we will obtain the surface under the cumulative ranking curve (SUCRA) (cumulative probability) and rankogram (Salanti 2011; Chaimani 2013).

Unit of analysis issues

We will collect data for all trial treatment groups that meet the inclusion criteria. The codes for analysis that we will use account for the correlation between effect sizes from trials with more than two groups.

Assessment of heterogeneity

Saffioti F, Gurusamy KS, Hawkins N, Toon CD, Tsochatzis E, Davidson BR, Thorburn D. **Pharmacological interventions for primary sclerosing cholangitis**. Cochrane Database of Systematic Reviews 2017, Issue 3. Art. No.: CD011343. DOI: 10.1002/14651858.CD011343.pub2.

Resources

- Chapter 11 in Cochrane Handbook (v6) https://training.cochrane.org/handbook/current/chapter-11
- Cochrane Comparing Multiple Interventions Methods Group (CMIMG) https://methods.cochrane.org/cmi/welcome
- Training https://training.cochrane.org/online-learning/cochrane-methodology/network-meta-analysis-nma
- Recordings from webinar series https://training.cochrane.org/network-meta-analysis-learning-live-webinar-series
- Methods Support Unit https://methods.cochrane.org/about-us/cochrane-central-executive-methods-team/methods-support-unit

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References

- Brignardello-Petersen R, Bonner A, Alexander PE, Siemieniuk RA, Furukawa TA, Rochwerg B, Puhan MA. *Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis*. Journal of Clinical Epidemiology 2018;93:36-44
- Chaimani A, Caldwell DM, Li T, Higgins JPT, Salanti G. Additional considerations are required when preparing a protocol for a systematic review with multiple interventions. *Journal of Clinical Epidemiology* 2017; **83**: 65–74.
- CINeMA: Salanti G, Del Giovane C, Chaimani A, Caldwell DM, Higgins JPT. *Evaluating the quality of evidence from a network meta-analysis*. PLoS One 2014;9(7).
- Puhan MA, Schunemann HJ, Murad MH, Li T, Brignardello-Petersen R, Singh JA, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. Bmj. 2014;349:g5630
- Yepes-Nuñez JJ, Li SA, Guyatt G, Jack SM, Brozek JL, Beyene J, Murad MH, Rochwerg B, Mbuagbaw L, Zhang Y, Flórez ID, Siemieniuk RA, Sadeghirad B, Mustafa R, Santesso N, Schünemann HJ. Development of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Summary of Findings (SoF) Table for Network Meta-analysis. Journal of Clinical Epidemiology 24 April 2019.

Extra Slides on Assessing Confidence

Two approaches……

- The confidence in each combined comparison depends on the confidence in the direct and indirect evidence that contribute to it
- The confidence in each indirect comparison depends on the pieces of the direct comparisons that contribute to it
- GRADE for direct evidence
- Two approaches diverge in the way they combine the considerations when thinking about an indirect or combined comparison

Puhan (2014)

Step 1: Presenting direct and indirect effect estimates and 95% CI

Step 2: Rating of quality of direct and indirect effect estimates

- Intransitivity

Steps 3 and 4: Presenting and rating of quality of NMA effect estimates

- higher of the direct/indirect rating

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Brignardello-Petersen (2018)

- Focus on precision of network estimate
- There is no need to rate the indirect evidence when the certainty of the direct evidence is high and the contribution of the direct evidence to the network estimate is at least as great as that of the indirect evidence
- We should not trust a statistical test of global incoherence of the network to assess incoherence at the pairwise comparison level
- In presence of incoherence between direct and indirect evidence, the certainty of the evidence of each estimate can help decide which estimate to believe.

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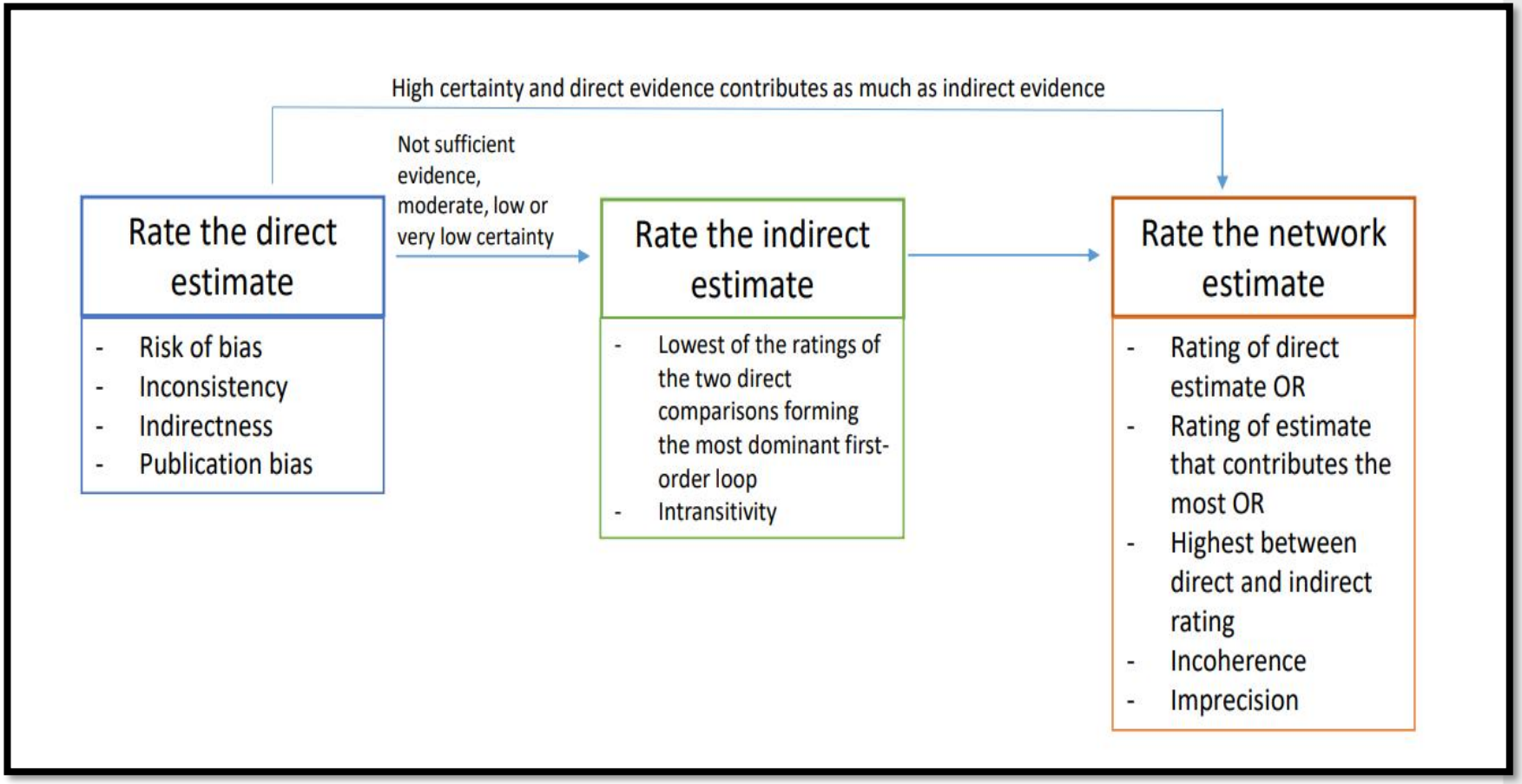
High certainty and direct evidence contributes as much as indirect evidence
Not sufficient evidence, moderate, low or very low certainty
Rate the direct estimate
- Risk of bias
- Inconsistency
- Indirectness
- Publication bias
Rate the indirect estimate
- Lowest of the ratings of the two direct comparisons forming the most dominant first-order loop
- Intransitivity
Rate the network estimate
- Rating of direct estimate OR
- Rating of estimate that contributes the most OR
- Highest between direct and indirect rating
- Incoherence
- Imprecision

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CINeMA (2014)

- https://cinema.ispm.unibe.ch
  - Currently being updated
- Confidence in each pairwise effect size
- Confidence in ranking
- Weighted sum of all the direct comparisons - Contribution matrix
  - gives % based on variance of direct estimate

Which approach should we use?

- Puhan

When indirect comparisons are built on existing pairwise meta-analyses, which have already been rated with respect to their confidence

- CINeMA

If the body of evidence is built from scratch or there are a large number of interventions

Assess confidence in relative ranking if reported