

Writing the protocol of a network meta-analysis

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The material can be found in:

Additional considerations are required when preparing a protocol for a systematic review with multiple interventions.

Chaimani A, Caldwell DM, Li T, Higgins JPT, Salanti G.
J Clin Epidemiol. 2017 Mar;83:65-74.

Protocol for a conventional review

- A **pre-specified outline of the research to address the question under consideration**
- Describes **the process** and anticipated management of the review
- Contains detail on
 - the **condition** under investigation
 - the **available evidence** in relation to that condition
 - the **methods** the review authors will follow to answer this research question
- It requires **making decisions about the population**, the **intervention** and the clinical **outcomes** of interest, the appropriate **study design**
- It outlines how the eligible studies will be **identified, assessed and statistically synthesized**.

Protocols for reviews

Can be published in PROSPERO, Systematic Reviews, online



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Chapter 4: Guide to the contents of a Cochrane protocol and review

Editors: Julian PT Higgins and Sally Green.

Key points

- Cochrane reviews have a highly structured format, and compliance with this format is facilitated by the use of RevMan. This chapter describes what an author is expected to include, a reader may expect to find, in each component of a Cochrane protocol or review.
- The chapter also serves as a guide to much of the *Handbook*, containing links to other chapters where further discussion of the methodological issues can be found.
- A 'Review information' (or 'Protocol information') section includes details of authors and important dates associated with maintaining and updating the review.
- The main text should be succinct and readable, so that someone who is not an expert in the area can understand it. The text of a protocol ends after the Methods section.
- A 'Studies and references' section provides a framework for classifying included, excluded and ongoing studies, as well as those for which insufficient information is available, and other references.
- Tables of characteristics of studies allow the systematic presentation of key descriptors of the studies considered for the review.
- A 'Data and analyses' section has a hierarchical structure, allowing data from included studies to be placed within particular subgroups of studies, which are in turn within meta-analyses particular outcomes, which are in turn within particular intervention comparisons. For each meta-analysis, forest plots and funnel plots can be generated within RevMan.
- Further tables, figures and appendices can be included to supplement the in-built tables.

Protocols for reviews

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Do help when submitting a NMA article...

Do help researchers who undertake a NMA

Protocols for reviews

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Do help when submitting a NMA article...

A template protocol for network meta-analysis

You can download it [here](#).

www.mtm.uoi.gr

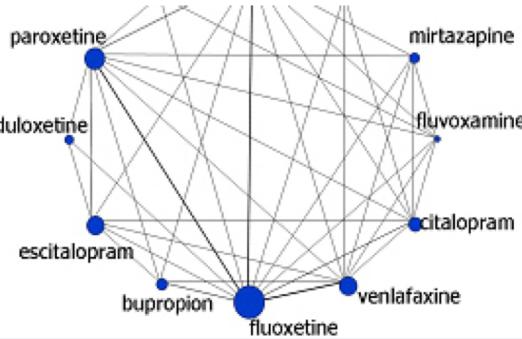
Protocols for network meta-analysis

Ongoing projects

1. Comparative efficacy and acceptability of psychological interventions in the long term treatment of bipolar disorder: a network meta-analysis ([Protocol](#) of the study)
2. Pain management strategies after total knee arthroplasty: a protocol for a network meta-analysis of randomized controlled trials ([Protocol](#) of the study)
3. Informing clinicians, patients and guidelines: network meta-analysis on 24 antipsychotic drugs and a broad range of important outcomes for schizophrenia ([Protocol](#) of the study)
4. Percutaneous coronary interventional strategies for the treatment of coronary in-stent restenosis: systematic review and network

Anecdotal evidence

- NMA projects are long, cumbersome and challenging
- Writing the protocol is a valuable opportunity to get things right from the start and get to know your collaborators
- **It involves**
 - long discussions (and disagreement!) between clinical experts
 - even longer discussions between statisticians and clinicians
- **It ensures that**
 - all needed data will be extracted and formatted in a convenient way
 - all team members learn to ‘speak the same language’
- **Steep learning curve**
 - If you work again with the same time things will be much easier and quicker



Multiple-Treatments Meta-Analysis

A Framework for Evaluating and Ranking Multiple Healthcare Tech

You are here: [Home](#) ▶ Material from Publications (software and protocols)

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Material from Publications

Software Routines, Codes and Data from Methods Research Papers and Projects

[R routine](#) and data set ([data](#)) (.R files) from the research project "Planning future studies based on the precision of network meta-analysis results"

[R routine](#) (.txt file) to simulate evidence loops, project "Statistical evaluation of inconsistency in a loop of evidence: a simulation

A template protocol for network meta-analysis

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Protocols for network meta-analysis

Ongoing projects

1. Comparative efficacy and acceptability of psychological interventions in the long term treatment of bipolar disorder: a network meta-analysis ([Protocol](#) of the study)
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4. Percutaneous coronary interventional strategies for the treatment of coronary in-stent restenosis: systematic review and network meta-analysis ([Protocol](#) of the study)
5. Comparative efficacy and tolerability of pharmacological treatments in the maintenance treatment of bipolar disorder: a multiple treatments meta-analysis ([Protocol](#) of the study, registered with PROSPERO)

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<http://cmimg.cochrane.org/comparing-multiple-interventions-cochrane-reviews>

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Comparing Multiple Interventions Methods Group

Comparing Multiple Interventions in Cochrane Reviews

Key Questions

Many Cochrane reviews compare more than two interventions, either implicitly or explicitly. Principled methods have been developed for analysing such networks so that *both direct evidence from head-to-head comparisons and indirect evidence from studies with common comparators can be utilized.*

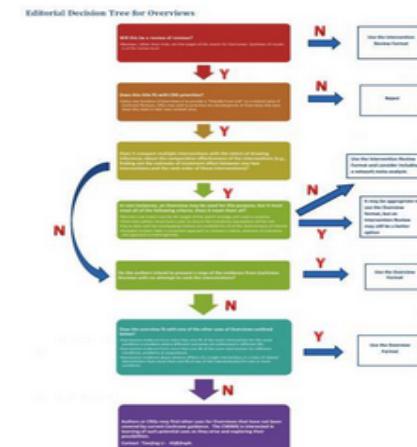
The Comparing Multiple Interventions Methods Group has received funding from the Cochrane Methods Innovation Fund to set up three working groups to address three key issues related to these comparisons.

1 - Should I use an Overview or an Intervention Review?

We have conducted a broad consultation with Collaboration partners and have produced:

- A [new set of recommendations](#)
- An [editorial decision tree](#) to assist in application of the recommendations
- A [background paper explaining the rationale](#) for each new recommendation
- A training event held in Oxford in March 2013 ([Slides available here](#))
- A [bibliography of Cochrane Overviews](#)
- A [bibliography of Cochrane Intervention Reviews and non-Cochrane systematic reviews that use network meta-analysis](#)
- A [protocol template](#) for a Cochrane Intervention Review that compares multiple interventions.

Joint work with
Anna Chaimani
Julian Higgins
Debbi Caldwell



2 - What statistical methods are available

We held a 2 day meeting of statisticians, reviewers and CEU representatives in Bristol in 2013 (minutes and selected slides from the meeting are available [here](#)) and have produced:

Updating the Cochrane protocol

- Cochrane has a protocol outline (headings, and recommended subheading) to facilitate reviewers
 - See Chapter 4, The Cochrane Handbook (online)
- This applies to pairwise meta-analysis
- Amendments and additions are needed to accommodate the needs of reviews with multiple interventions and NMA

Chapter 4: Guide to the contents of a Cochrane protocol and review

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Setting the rationale for the review: aims and objectives

- *Identify the review as one that compares multiple interventions*
- **Specify whether you aim to**
 - compare all pairs of interventions
 - rank the treatments according to each outcome
 - both
- **Clarify why a NMA is necessary**
 - lack of (many) direct comparisons between the treatments of interest
 - aim to comprehensively rank all treatments

Example

Safety of anti-epileptic drugs

“Some AEDs have been associated with increased risk of harm to the fetus and infants. For example, exposure to valporate has led to increased risk of major congenital malformations, cognitive delay, and minor congenital abnormalities. Phenobarbital has been associated with minor congenital abnormalities and developmental delay. Carbamazepine and lamotrigine have been associated with minor congenital abnormalities. However, other than studies of the use of valproate, many studies have produced inconsistent findings regarding harm to the fetus and infant with use of other agents. As such, our objective is to evaluate the comparative safety of AEDs for infants and children who were exposed in utero or during breastfeeding through a systematic review and network meta-analysis”

Frame the research question

Define

- Types of interventions
- Outcomes
- Health condition
- Type of population/settings

Specifying the eligible interventions (1)

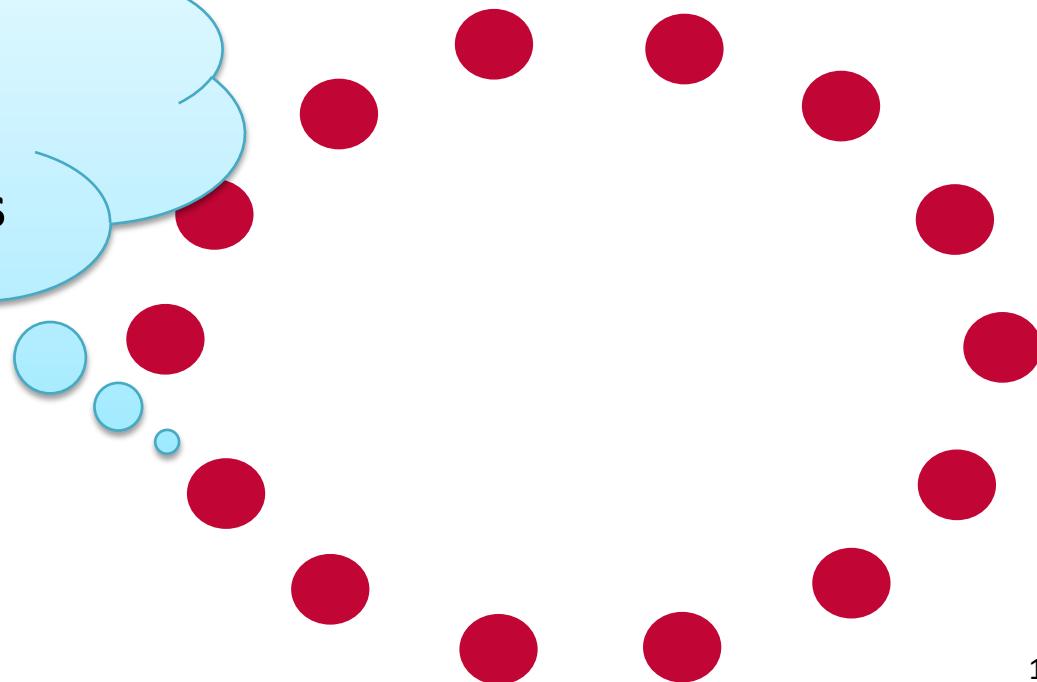
- Ideally all competing treatments for the same condition should be eligible
 - In practice researchers compare **only those that are marketed in their country or belong to a specific class**
 - If you don't plan to include all treatment options explain your rational!

Specifying the eligible interventions (2)

Defend the transitivity assumption

state that all eligible treatments are '*jointly randomizable*'

think of a multi-arm
trial including all
competing treatments



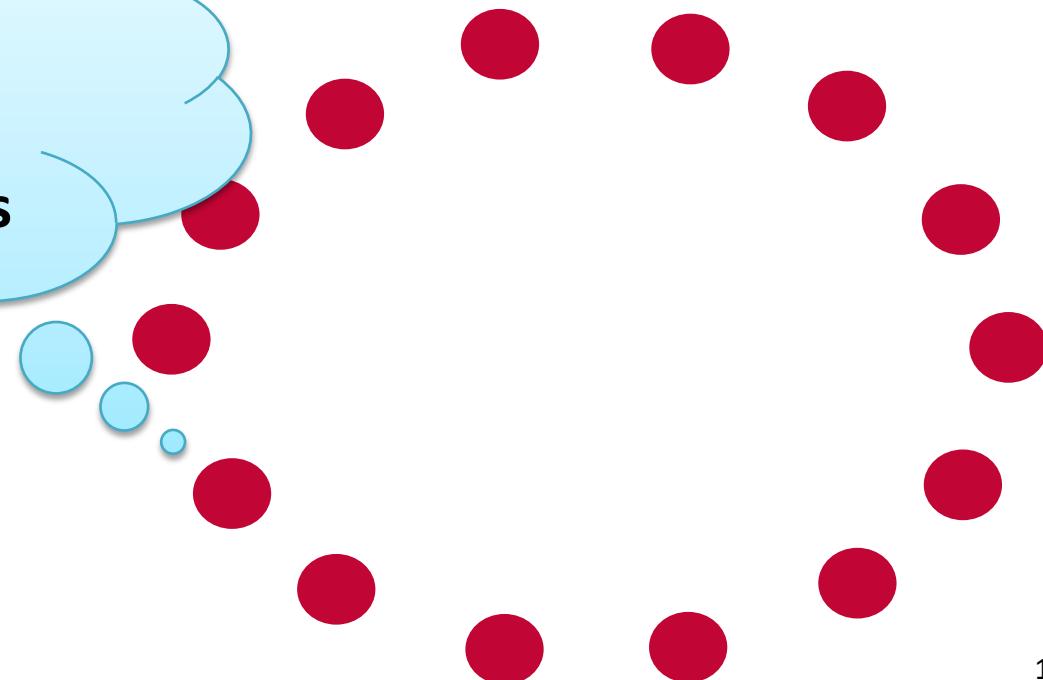
Specifying the eligible populations and study settings

Defend the transitivity assumption

state that all eligible treatments are '*jointly randomizable for the patients and study settings you consider*



think of a multi-arm trial including all competing treatments



Specifying the eligible interventions (3)

- Identify two possible categories of interventions:
 - *Interventions of direct interest* → **present the results** (those related with the research question, *decision set*)
 - *Additional interventions to supplement the analysis* those that might provide useful indirect evidence (e.g. Placebo, legacy treatments etc.)
- *What will you do if you identify new interventions while scanning the literature?*
- How to deal with different doses or drug class and co-interventions?
 - Merging versus splitting

Example

Efficacy and acceptability of psychological interventions for bipolar disorder

"We will include all psychological and psychosocial interventions, like [...]. Other potential control interventions, such as standard care involving pharmacological intervention or the use of pill placebos, will be eligible. Hence the synthesis comparator set consists of all the interventions listed above, their combinations and placebo (if we will find other eligible interventions, we will include them in the network)"

"We assume that any patient that meets all inclusion criteria is likely, in principle, to be randomized to any of the interventions in the synthesis comparator set"

Example

Bipolar disorder network: different doses were merged

“Initially, we will group interventions which have common ingredients, in other words, which share common methods, assumptions or structure (see Introduction). In order not to be biased by the retrieved evidence, we will merge -if possible- the interventions a priori through a consensus process within the review group, before selecting the final list of references to be included in the review and before carrying out the statistical analyses”.

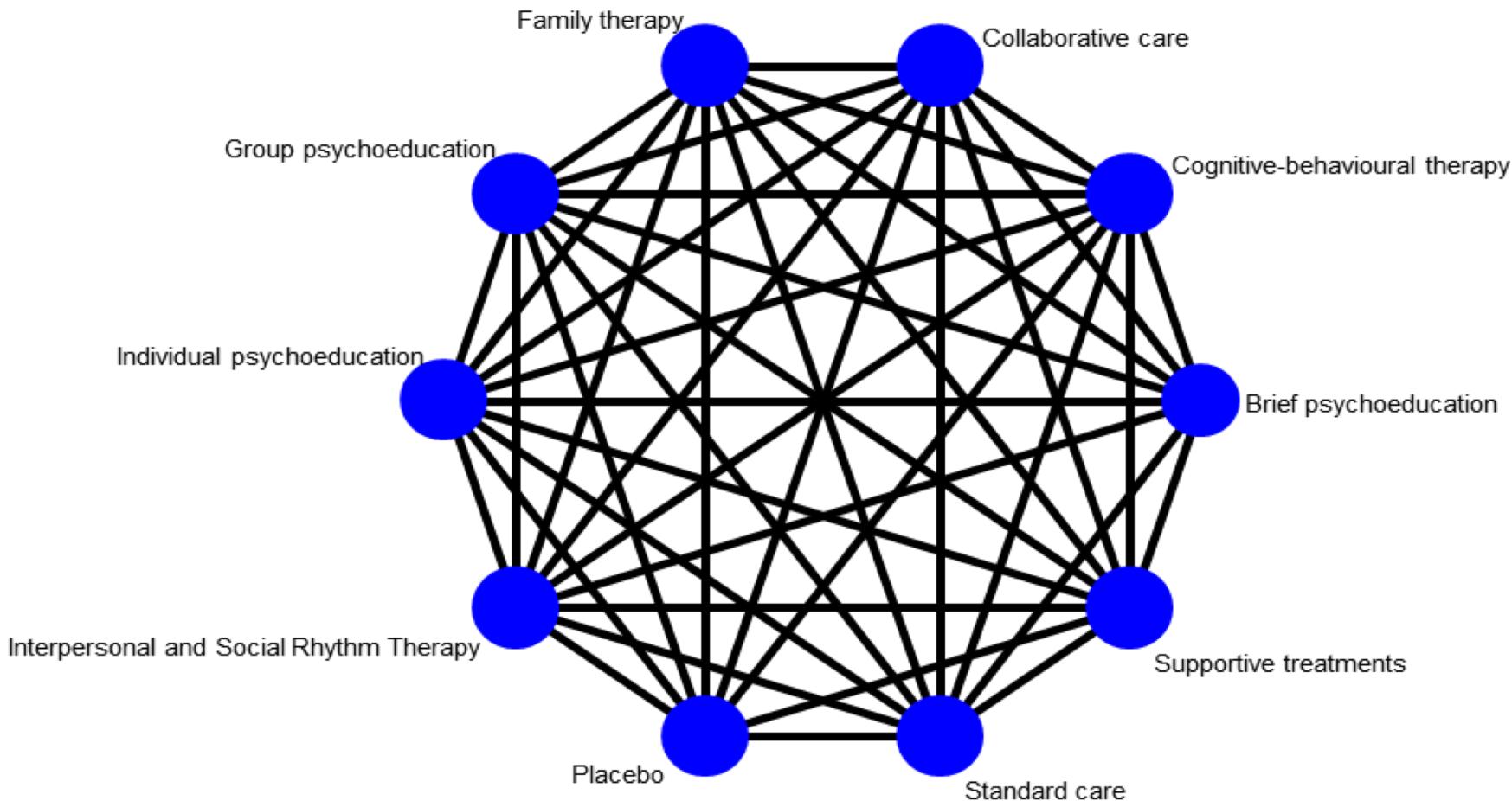
Example

The panic disorder example: dose in the included criteria

“We will include only studies where medications were used at therapeutic dosage. We define therapeutic doses as doses that are indicated for panic disorder by any of the North American/European/Japanese regulatory agencies. Where such are not available, we will follow the same dose ranges as for major depression (for antidepressants) and generalized anxiety disorder (for benzodiazepines)”.

Example

Efficacy and acceptability of psychological interventions for bipolar disorder



What to keep in mind when deciding which interventions to include

- Restricting your review to compare few interventions
 - limits its usefulness and applicability
 - you must justify your choice
 - risk to have unconnected networks
 - few data, low power (depends on the setting)
- Expanding the database too much to include many treatments
 - Jeopardizes the transitivity assumptions (or at least makes its defense challenging)
 - Renders review process long and data management difficult
- **Watch out for:** old and new treatments, ad-on treatments, intransitive legacy treatments

Outcome measures

- Define the outcomes of interest
- Define the outcomes that will be used to estimate the relative ranking of treatments
 - if it is included in the objectives of the review

Searching for studies

Search strategy should consider any study comparing at least two of the eligible interventions

i.e. all available direct comparisons between the eligible interventions should be included

Data extraction

Describe you will extract data on

- **Outcomes:** study-level or arm-level preferable?
- **Potential effect modifiers:** (population and study characteristics that may act as effect modifiers selected based on bibliography and clinical understanding) required to evaluate statistically the transitivity assumption and clinical/methodological heterogeneity
- **Other data:** any additional information (e.g. risk of bias items) that will be extracted

Example

Effectiveness and safety of treatments for panic disorders

"From each included study we will extract data on the following study, interventions and population characteristics that may act as effect modifiers:

Methods: study design, randomization (individual or cluster), total duration of study, number of study centres and location, study setting, withdrawals, and date of study.

Participants: number, setting, diagnostic criteria, presence or absence of medical and psychiatric comorbidities, presence or absence of elderly participants, percentage of patients with agoraphobia, percentage of patients with baseline depression, inclusion criteria, and exclusion criteria.

Interventions: medication dose, medication dose range, use of rescue medication.

Outcomes: primary and secondary outcomes specified and collected, and time points reported. Where possible we will extract data at the arm level, not summary effects.

Notes: sponsorship/funding for trial, and notable conflicts of interest of trial authors"

Selecting effect measures for the analysis

Usual considerations in choose between OR/RR/RD or MD/SMD

- **Be aware that** different effect measures sometimes impacts the results
- More than one effect measures might be used
 - describe how any disagreements will be handled
- Report whether the same or different measures will be used in the analyses and the presentation of results

State which **measure will be used to rank the treatments**

- Avoid probability to be the best, use mean ranks/SUCRAs instead

Evaluating the assumption of transitivity

- Describe how you will evaluate the clinical and methodological comparability of studies (**heterogeneity**)
 - As in standard meta-analysis
- Describe how you will evaluate the plausibility of the **transitivity assumption**
 - the comparability/similarity of studies evaluating *different* comparisons
 - You can compare the distribution of effect modifiers across sets of studies grouped by comparison
 - In practice this is often difficult – be prepared and remember lack of evidence is not evidence of lack

Example

Efficacy and acceptability of psychological interventions for bipolar disorder

“To infer about the assumption of transitivity:

- 1. We will assess whether the included interventions are similar when they are evaluated in RCTs with different designs; for example, whether interventions are administered the same way in studies comparing active treatments to usual care (or no treatment) and in those comparing active treatments to other active treatments.*
- 2. We will compare the distribution of the potential effect modifiers across the different pairwise comparisons (see ‘Data extraction and management’ for the list of potential effect modifiers). If the distributions are balanced across comparisons we will conclude against evidence of intransitivity.”*

not against intransitivity!

Describe the statistical analyses (1)

- **Two possible types of analyses:**
 - A series of independent pairwise meta-analyses (only as the first step of NMA)
 - Network meta-analysis
 - State whether both types of analyses will be performed
 - if the required assumptions are plausible
- Describe the **statistical model**
 - Bayesian or frequentist setting
 - fixed or random effects
 - common or different heterogeneity across the comparisons
- Report the **modelling details** (e.g whether NMA is fitted as meta-regression or hierarchical model, estimation method for heterogeneity)

Describing the statistical analyses (2)

- Explain how you will **handle variability in treatment definition** (e.g. different doses or modalities)
 - Analyze as separate treatment modes nodes
 - Model explicitly their variability
 - Additive/multiplicative models for complex interventions?
- Report the **software** of the analysis
 - e.g. STATA, R, WinBUGS
 - Give the WinBUGS code
- Give **additional details**, if analyses will be performed in a Bayesian framework
 - prior distributions, how convergence will be assessed, etc. (in an appendix)

Example

Effectiveness and safety of treatments for panic disorders

"Random-effects pairwise meta-analyses will be conducted for every treatment comparison with at least two studies, using Stata 2013. A random-effects model is considered preferable [...]

A random-effects NMA, taking into account the correlations induced by multi-arm trials, will be conducted in a Bayesian framework and implemented using WinBUGS 1.4.3.

There are three possible models that could be fitted

1. A class (lumped) model.
2. An individual treatment (possibly dose specific) model.
3. A hierarchical model where we include both class and treatments.

We will investigate models depending on the available data. The goodness of fit of the model to the data will be measured by the posterior mean of the residual deviance. [...]"

Evaluate consistency (1)

Report on methods for:

- Assessment of **statistical inconsistency locally**
 - identify pairwise comparisons or loops of evidence that might be important sources of inconsistency
 - e.g. the loop-specific or node-splitting approach
- Assessment of **statistical inconsistency globally**
 - evaluate the presence of inconsistency in the entire network
 - Q test for inconsistency
 - Compare consistency vs inconsistency models
- Use **I^2 for heterogeneity/inconsistency/both**

Evaluate consistency (2)

- Describe **how conclusions will be drawn** based on the results of each approach
 - e.g. based on the magnitude and the confidence intervals of the estimated inconsistency factors, using p-values
 - Be careful - tests for inconsistency have low power
- Explain what you will do **if important inconsistency is identified**
 - Explore sources of inconsistency?
 - Fit inconsistency models?
 - Split the network into smaller, consistent networks?
 - Do NOT exclude studies

Example

Safety of anti-epileptic drugs

“We will ensure the following factors are present prior to conducting network meta-analysis: [...] ii) consistency between direct and indirect data, which will be examined locally (i.e., in certain paths of the network) using the loop-specific method and the node-splitting method, and globally (i.e., evaluating the network as a whole), using the design-by-treatment interaction model; and iii) we will quantify the amount of variability attributed to heterogeneity and inconsistency rather than sampling error, by calculating the I^2 . [...] We will compare the magnitude of heterogeneity between consistency and inconsistency models to determine how much heterogeneity will be explained by inconsistency. We will first use the design-by-treatment model for the evaluation of inconsistency in a network as a whole and then, if inconsistency is detected, we will employ the loop-specific and node-splitting methods to identify which piece of evidence is responsible for inconsistency”

Investigating heterogeneity & inconsistency (1)

Heterogeneity & inconsistency → caused by differences in populations and study characteristics **within** and **across** comparisons

- Specify the **additional analyses** that will be performed to explain heterogeneity and inconsistency
 - e.g. **subgroup analyses, network meta-regression** (if sufficient data are available)
- **Pre-specify the variables** that will be considered as possible sources of heterogeneity and inconsistency
 - choose a subset of the potential effect modifiers listed earlier (see also Data Extraction section)

Investigating heterogeneity & inconsistency (2)

- The use of network **meta-regression** requires further details
 - e.g. *assumptions regarding the regression coefficients* and the directionality of the effect of covariates
 - if it is fitted in a Bayesian framework, prior distributions for the coefficients (in an appendix)

Example

Efficacy and acceptability of psychological interventions for bipolar disorder

"If we find important heterogeneity and/or inconsistency, we will explore the possible sources. If sufficient studies are available, we will perform meta-regression or subgroup analyses by using the following effect modifiers as possible sources of inconsistency and/or heterogeneity: (i) year of publication; (ii) study precision; (iii) baseline severity and (iv) blinding"

Reporting bias

- It is as much of a threat as in pairwise meta-analysis
- Not to be confused with small study effects
- Use **contour-enhanced funnel plots** (per comparison)
Peters J et al. *J Clin Epidemiol.* 2008 Oct;61(10):991-6J
- Use **comparison-adjusted funnel plots** (for the entire network) Chaimani A, Salanti G: *ResSynthMeth* 2012, 3:161–176.
 - Requires assumption about direction of potential small study effects
- Use **selection models** in the case of serious reporting bias Mavridis D et al. *Stat Med.* 2014 Dec 30;33(30):5399-412.
 - Example: antidepressants and placebo network

References

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