Writing network meta-analysis 1

Building the network

Anna Chaimani

Network meta-analysis

A project-based course using R

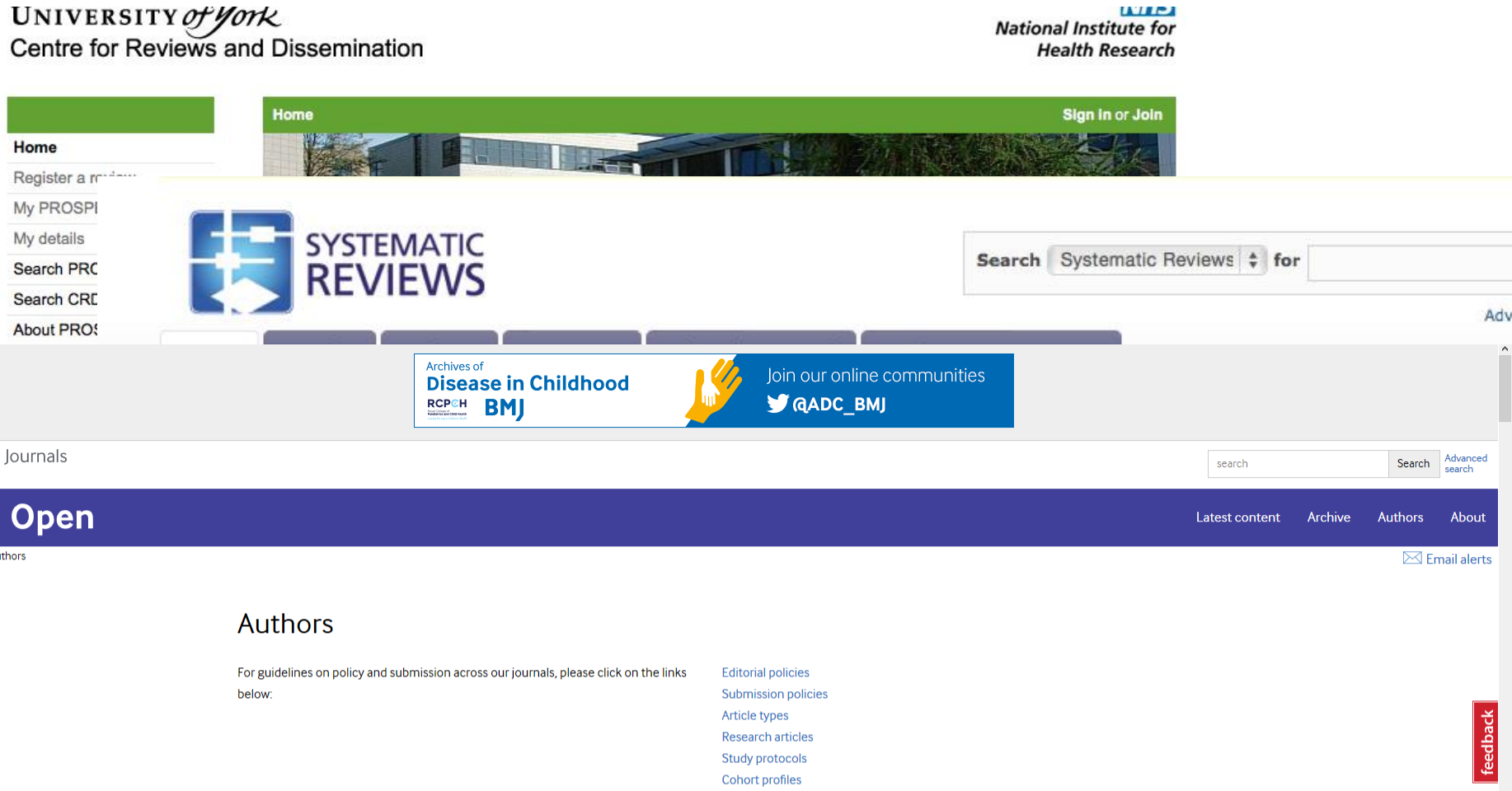
Kea island, April 2018

Protocol for a conventional review

- **A pre-specified outline of the review 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*, *BMJ Open*, online



Content of standard systematic review protocols

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, and w 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 of 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.

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 much easier and quicker

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

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, and w 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.

Content of systematic review protocols with multiple interventions

ELSEVIER

CrossMark

Journal of Clinical Epidemiology 83 (2017) 65–74

Journal of Clinical Epidemiology

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

Anna Chaimani[a,*], Deborah M. Caldwell[b], Tianjing Li[c], Julian P.T. Higgins[b], Georgia Salanti[a,d,e]

[a]*Department of Hygiene and Epidemiology, University of Ioannina School of Medicine, University Campus, Ioannina 45110, Greece*
[b]*School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol BS8 2PS, UK*
[c]*Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, 615 North Wolfe Street, E6011, Baltimore, MD 21205, USA*
[d]*Institute of Social and Preventive Medicine (ISPM), University of Bern, Finkenhubelweg 11, Bern 3012, Switzerland*
[e]*Institute of Primary Health Care (BIHAM), University of Bern, Gesellschaftsstrasse 49, Bern CH-3012, Switzerland*

Accepted 30 November 2016; Published online 11 January 2017

Abstract

Objectives: The number of systematic reviews that aim to compare multiple interventions using network meta-analysis is increasing. In this study, we highlight aspects of a standard systematic review protocol that may need modification when multiple interventions are to be compared.

Study Design and Setting: We take the protocol format suggested by Cochrane for a standard systematic review as our reference and compare the considerations for a pairwise review with those required for a valid comparison of multiple interventions. We suggest new sections for protocols of systematic reviews including network meta-analyses with a focus on how to evaluate their assumptions. We provide example text from published protocols to exemplify the considerations.

Conclusion: Standard systematic review protocols for pairwise meta-analyses need extensions to accommodate the increased complexity of network meta-analysis. Our suggested modifications are widely applicable to both Cochrane and non-Cochrane systematic reviews involving network meta-analyses.

Keywords: Comparative effectiveness review; Eligibility criteria; Transitivity; Network meta-analysis; Indirect comparison; Mixed treatment comparison

1. Introduction

component, network meta-analysis (NMA). The popularity

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"

Tricco et al. Syst Rev 2014

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*'

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

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"

Cipriani et al. PROSPERO 2015:CRD42015016085

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".

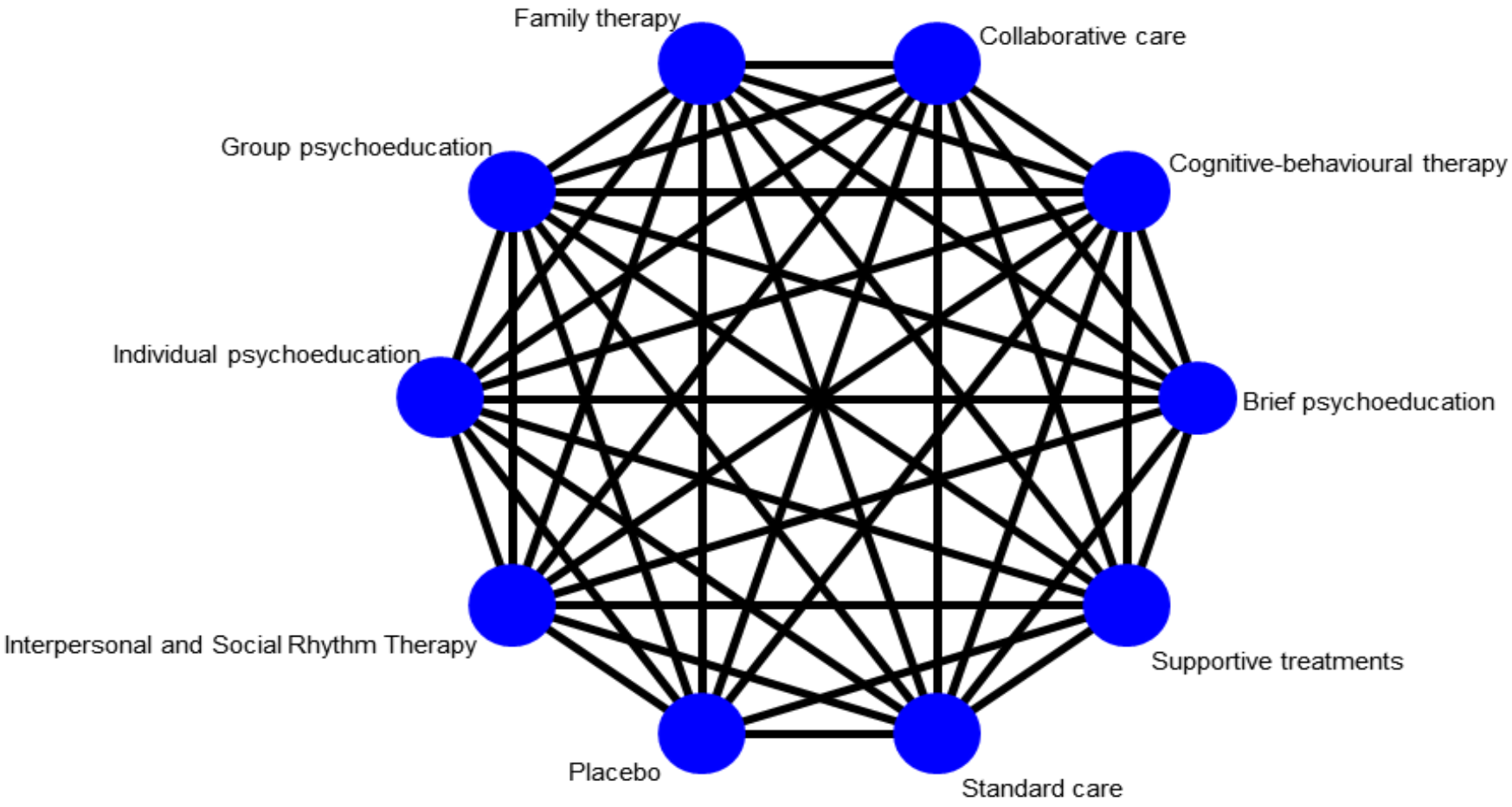
Example

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



Cipriani et al. PROSPERO 2015:CRD42015016085

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)

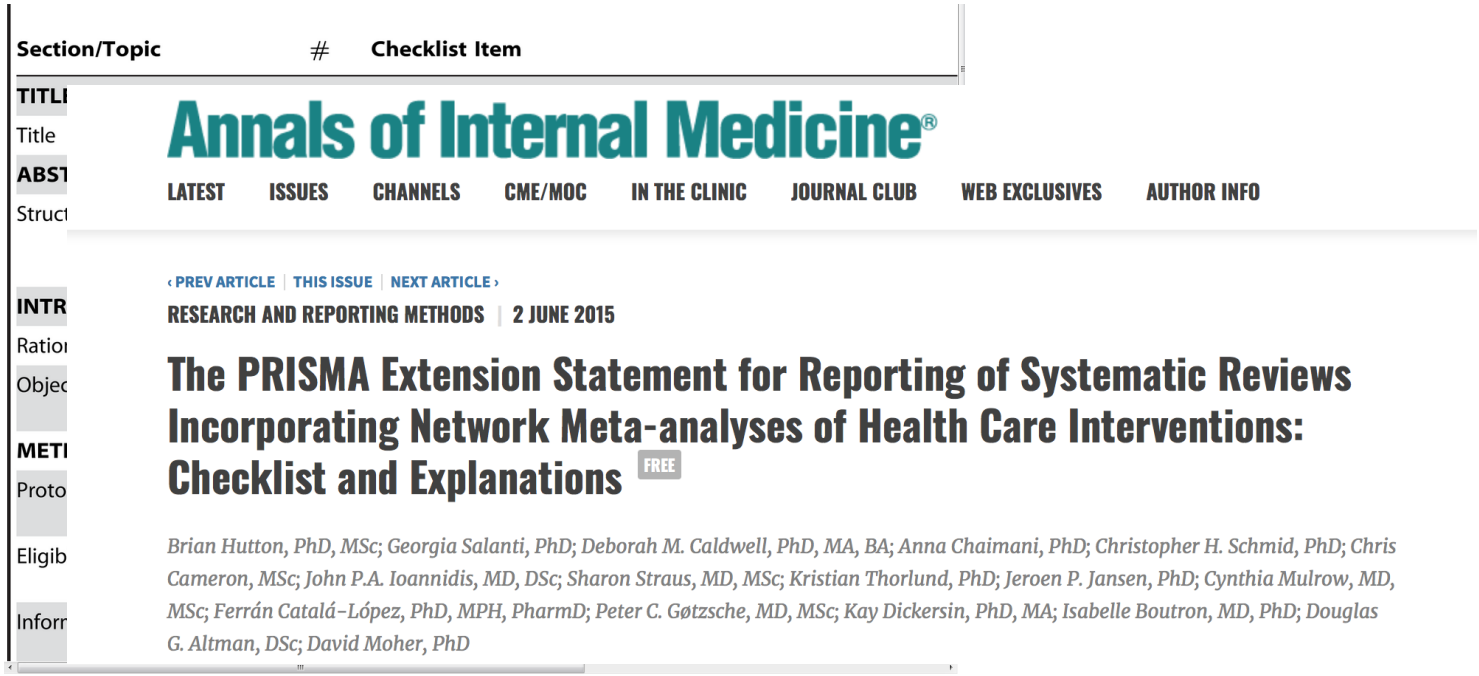
- Expanding the database too much to include many treatments
  - Jeopardizes the transitivity assumptions (or at least makes its defense challenging)
  - Renders review process long and data management difficult

- **Watch out for:** old and new treatments, ad-on treatments, intransitive legacy treatments

Preparing the manuscript

Follow the PRISMA statement

PRISMA items to report in meta-analysis (Moher at al PLoS 2009)
Network meta-analysis needs more information



Section/Topic # Checklist Item

TITLE
Title
ABST
Struct
INTR
Ratio
Objec
METH
Proto
Eligib
Inform

Annals of Internal Medicine®

LATEST ISSUES CHANNELS CME/MOC IN THE CLINIC JOURNAL CLUB WEB EXCLUSIVES AUTHOR INFO

‹ PREV ARTICLE | THIS ISSUE | NEXT ARTICLE ›

RESEARCH AND REPORTING METHODS | 2 JUNE 2015

The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-analyses of Health Care Interventions: Checklist and Explanations FREE

Brian Hutton, PhD, MSc; Georgia Salanti, PhD; Deborah M. Caldwell, PhD, MA, BA; Anna Chaimani, PhD; Christopher H. Schmid, PhD; Chris Cameron, MSc; John P.A. Ioannidis, MD, DSc; Sharon Straus, MD, MSc; Kristian Thorlund, PhD; Jeroen P. Jansen, PhD; Cynthia Mulrow, MD, MSc; Ferrán Catalá-López, PhD, MPH, PharmD; Peter C. Gøtzsche, MD, MSc; Kay Dickersin, PhD, MA; Isabelle Boutron, MD, PhD; Douglas G. Altman, DSc; David Moher, PhD

Rationale for network meta-analysis

- Title
  - Identify the report as a systematic review incorporating a network meta-analysis
- Introduction
  - Describe the rationale for the review in the context of what is already known, why a network meta-analysis was necessary
  - Describe explicitly the questions being addressed by the review

Eligibility criteria

- Methods
  - Specify study characteristics and report characteristics used as criteria for eligibility, giving rationale.
  - Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).
- Results
  - Provide a network graph of the included studies