Assessing topics, geometry and reporting quality of network meta-analyses involving CAM interventions (study protocol)

1. Introduction

While traditional pairwise meta-analysis has long been a vital component of evidence based medicine, it is increasingly common for clinicians and decision-makers to need answers to research questions which require the comparison of more than two interventions. Traditional meta-analytic methods are not able to answer such questions because the corresponding statistical framework is limited to comparison of two treatments at a time. ***Network meta-analysis*** (NMA) is a widely used approach to derive comparisons of treatment effects between interventions that may not have been compared directly in head-to-head clinical trials, or for which both direct and indirect evidence is available for synthesis.[1-3] It can be described as a generalization of pairwise meta-analysis which enables the use of both direct and indirect evidence, and its framework enables the combination of this evidence to compare many treatments in a unified analysis, as long as there exists sufficient randomized trials to link all of the interventions together.

The Knowledge Synthesis Group at the Ottawa Hospital Research Institute (OHRI KSG) is a CIHR-funded center for the performance of network meta-analysis. Amongst our current projects, we are currently performing two network meta-analyses which involve Complementary and Alternative Medicine (CAM) interventions: one review comparing a broad range of natural health products, physical activities and pharmacologics to manage hot flashes in breast and prostate cancer, and another which compares pharmacologic and non-pharmacologic interventions for attention deficit hyperactivity disorder.[4,5] The frequency and quality of use of NMA methods to compare CAM interventions has not yet been assessed, and the OHRI KSG and the Cochrane Complementary and Alternative Medicines Group have interest in addressing these knowledge gaps to begin planning potential future research in this area. Objectives related to this work are described below.

2. Objectives for this Work

The following objectives have been drafted for this methodologic research to perform in collaboration with the Cochrane Complementary Medicines Group:

1. To establish a ***repository of existing systematic reviews*** in the peer reviewed literature that have incorporated network meta-analyses and indirect comparisons to compare CAM interventions against each other or against other non-CAM interventions for a medical condition.

2. To ***assess and document the network geometry*** (i.e. the existing comparisons available, the groupings of therapies assessed, and possibly other factors related to treatment effect and included study lists) of published evidence networks comparing CAM interventions using NMA.

- Two particular sub-questions of interest regarding geometry shall be the following:
    1. Do NMAs involving CAM interventions typically focus strictly on comparisons of CAM interventions, or do the research questions in these reviews seek to compare CAM and non-CAM interventions?
    2. Do identified NMAs involving both CAM and non-CAM interventions have geometries which suggest there commonly exists sequestration of evidence for CAM interventions?

Reviewing the literature to answer these questions will also allow us to establish what comparisons between treatments to be performed in future trials could prove helpful in establishing greater connectivity in treatment networks.

3. To assess the ***completeness of reporting*** of identified NMAs that have involved CAM interventions using the PRISMA Extension Statement for Network Meta-Analysis[6]; this will be based upon the 32-item checklist published by Drs. Hutton and Moher in the Annals of Internal Medicine in 2015 (see Appendices). Variations in other features of these reviews will also be gathered (including numbers of treatments and patients included, statistical methods used, and other factors).

4. To ***identify potential priority topics*** where an NMA may be of high impact for patient treatment. In addition to the formulation of the repository of existing NMAs of CAM interventions to establish questions that have been recently answered, a survey of a set of clinical experts (implemented using Survey Monkey software) could be performed to identify key topics/research questions involving CAM interventions which would be well served by performance of an NMA. This exercise could identify possible NMA topics for members of the Cochrane Complementary Medicine Group and/or the OHRI KSG in the near future.

There is a knowledge gap with regard to awareness of currently available applications of NMA for CAM interventions in the published literature. In working to establish a preliminary repository of such studies while also assessing their characteristics and reporting quality, the OHRI KSG and the Cochrane Complementary Medicines group can work together to establish a baseline awareness of the use of NMA for assessment of CAM interventions. To supplement this baseline assessment, the proposed survey can use input from CAM experts to help the group identify possible topics to consider for systematic reviews incorporating NMAs for performance in the near future that can have an important impact on patient care.

3. Preliminary Methods (Objectives 1-4)

1. Repository of NMAs - Literature Search to Identify Reviews

A full de novo search to identify published network meta-analyses involving CAM interventions will not be performed. Drs. Georgia Salanti, Areti Angeliki-Veroniki and Andrea Tricco maintain an up-to-date database of all published network meta-analyses since 1999 (when such publications first began). Dependent upon review and approval of the objectives planned for this work, these researchers have agreed to share their database of published NMAs with our team in order to facilitate our identification of all NMAs which involve CAM interventions. We will also search the PROSPERO database to identify ongoing reviews involving forms of CAM interventions and perform an updated search if necessary should the existing database not be current into 2016. The selection of published studies identified will be used for Objectives 2 and 3 described next. ***A robust list of CAM interventions of interest is provided in Appendix 1 and can be used for screening purposes to identify relevant published NMAs.*** Regarding the types of network meta-analyses that are eligible, the following specific will be used:

- has used a valid comparison method (ie., Bucher method, adjusted indirect comparison, Bayesian model, meta-regression, multivariate meta-analysis);
- has included at least 4 nodes (i.e. 4 interventions) in the network;
- has included a greater number of studies than there were nodes in the network (# of included studies > # of nodes);
- has included data from RCTs only.

2. Assessment of Network Geometry Features and Related Data

Once the repository of existing CAM NMA reviews has been established as per Objective 1, a detailed data extraction form will be designed by members of the research team to gather information from each review related to the following details:

- Review authors, year of publication, research question addressed;
- Number of interventions compared and patients studied; types of interventions compared based on the research question (CAM only, CAM and non-CAM); sequestration of CAM vs presence of comparisons with general medicine/non-CAM therapies;
- Geometric features of the network (i.e. graphical representation, patterns of present and missing comparisons with direct data);
- Methods used (i.e. types of study designs included; lumping/splitting of treatments; analytic framework (Bayesian vs frequentist); appropriateness of methods to perform NMAs and check the consistency assumption; endpoints analyzed; and other details to be considered during drafting of a complete protocol for this work).
- Summary of key review findings, which may also include generation of rank heat plots[7] to summarize results across clinical endpoints (if sufficient data is provided in the report).

The data collection form will be piloted by two independent reviewers who will be responsible for independent data collection from all included reviews. A mixture of figures, tables and a narrative

summary will be employed to summarize all of the findings relevant to the questions posed regarding the geometry in network meta-analyses involving CAM interventions.

3. Assessment of Reporting Quality of Published NMAs

The PRISMA Extension Statement for Network Meta-Analysis[6] (2015) was published to provide researchers with examples of adequate reporting for systematic reviews involving NMA; a key element was also the reporting checklist for use (see Appendix), which can be used to establish rigor of reporting for the set of CAM-related network meta-analyses identified for the purposes of this study. The checklist modified 10 of the existing core PRISMA items and added an additional 5 items in order to address a variety of nuances that are associated with this type of review. In addition to developing a repository of the existing CAM topics studied (Objective 1), studying past patterns of evidence network geometries assessed and rigor/completeness of methods for NMAs performed (Objective 2), it will be of interest to establish the rigor of reporting in this field using what can currently be considered the most robust tool to guide NMA reporting. This will help to establish a baseline level of quality of reporting.

4. Survey of Experts to Identify future CAM Topics for NMA

To establish a list of topics, the following steps will be taken in the format of a two-part survey:

- ***Participant Identification***. Establish a list of potential respondents based on the list of members of the Cochrane Complementary Medicines Network, as well as their group of contracted experts (e.g. Beijing Centre for Evidence-Based Chinese Medicine, the Academic Consortium for Evidence-Based Medicine & Health and others); dependent upon the number of respondents identified from these sources, efforts based on approaching CAM-focused journals' editorial boards can also be taken. Ideally a total of 30-40 experts or more will be sought.
- ***Stage 1 survey***. Contact the members identified in the previous step and ask them to complete the first component of the survey which proposes the following basic questions to develop a preliminary list of possible topics for future NMA work to assess the benefits and harms of CAM interventions:
    1. *Are there clinical indications that you foresee as being of greatest need (to impact clinical practice) and greatest interest (e.g. associated with large amounts of clinical equipoise; condition is commonly diagnosed and has notable quality of life impact on patients) for a Network Meta-Analysis to address a current knowledge gap? If yes, please specify these indications.*

    2. *For indications listed in response to question 1, provide a preliminary list of interventions that you believe should be considered as comparators in a possible future network meta-analysis.*

    3. *Would you agree to participate in a second survey wherein you can review all proposed topics and rank them in terms of importance and feasibility?*

- ***Derive list of candidate topics***. Compile a list of all proposed topics suggested during round 1 of the survey.
- ***Conduct second survey of experts***. Prepare a short second survey where respondents are then asked to rank the clinical importance of each topic (i.e. potential to influence practice) as well as the feasibility of an NMA in this area (i.e. does the respondent feel a variety of studies for key treatments of interest exist).

The OHRI KSG includes three team members with extensive expertise in use of delphi panels and nominal group theory for topic selection and refinement which is directly relevant to the proposed approach to compiling a database of possible topics for future research, and they will participate in the design of both surveys. The initial survey mailout as well as 3 additional mail-based reminders (beginning two weeks after the initial mailout, with 1 week between reminders) will be sent to all invitees.

4. Deliverables

The detailed data collection planned for this work can be used to summarize various aspects regarding the use of NMA for CAM interventions to be shared with NCCAM. The research team will prepare a peer-reviewed publication describing the findings from the work performed to address objectives 1-3; this will provide readers with a robust baseline understanding of the use of network meta-analysis to study the benefits and harms of CAM interventions as currently available in the published literature. The current protocol will be made publicly available online through the University of Ottawa Health Sciences Library's online repository. The survey performed to address objective 4 will be summarized in a separate report and shared with the Cochrane Complementary Medicine group for discussions and considerations regarding possible future topics for network meta-analyses in the CAM field.

Preliminary Listing of Team Members:

- Misty Pratt (research assistant)
- Becky Skidmore (information specialist)
- Susan Wieland (Cochrane Complementary Medicine Group representation)
- Roxanne Ward (Program Manager)
- David Moher (Scientist)
- Brian Hutton (Scientist)

Reference List

(1) Caldwell D, Ades A, and Higgins J. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 331[7521], 897-900. 2005.

(2) Catala-Lopez F, Tobias A, Cameron C, Moher D, and Hutton B. Network meta-analysis for comparing treatment effects of multiple interventions: an introduction. Rheumatology International 34[11], 1489-1496. 2014.

(3) Ioannidis J. Integration of evidence from multiple meta-analyses: a primer on umbrella reviews, treatment networks and multiple treatments meta-analyses. CMAJ 181[8], 488-493. 2009.

(4) Hutton B, Yazdi F, Bordeleau L, Morgan S, and et al. Comparison of physical interventions, behavioral interventions, natural health products, and pharmacologics to manage hot flashes in patients with breast or prostate cancer: protocol for a systematic review incorporating network meta-analyses. Systematic Reviews 4[114]. 2015.

(5) Catala-Lopez F, Hutton B, Nunez-Beltran A, Mayhew A, and et al. The pharmacological and non-pharmacological treatment of attention deficit hyperactivity disorder in children and adolescents: protocol for a systematic review and network meta-analysis of randomized controlled trials. Systematic Reviews 4[19]. 2015.

(6) Hutton B, Salanti G, Caldwell D, Schmid C, Chaimani A, Cameron C, Ioannidis J, and et al. The PRISMA Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Healthcare Interventions: Checklist and Explanations. Annals of Internal Medicine In press. 2015.

(7) Veroniki AA, Straus S, Fyraridis A, and Tricco A. The rank-heat plot is a novel way to present the results from a network meta-analysis including multiple outcomes. Journal of Clinical Epidemiology 4356[16]. 2016.

Appendix 1: CAM Interventions List

The table below provides a comprehensive list of CAM interventions that would be of relevance to the work being carried out in collaboration with the Cochrane Complementary Medicines Group. While the list is not exhaustive, it represents a vast majority of available CAM therapies. For the work outline above, network meta-analyses involving any of the therapies listed below are of interest. NMAs comparing strictly CAM therapies or CAM therapies with other more traditional healthcare interventions are of interest.

CAM interventions, A-D	CAM interventions, E-K	CAM interventions, L-R	CAM interventions, S-Z
Açaí / Euterpe oleracea	Echinacea	Laetrile	S-Adenosyl methionine (SAM-e)
Acupressure	EDTA (ethylenediaminetetraacetic acid) when used in chelation therapy as described above (see Chelation therapy)	Laser acupuncture	Safflower Yellow injection (a Chinese herbal medicine)
Acupuncture	Eicosapentaenoic acid (EPA) (an omega-3 fatty acid) supplements	Laughter therapy	Salacia oblonga
Acustimulation / acupoint stimulation	Electric stimulation therapy	Lentinan (derived from Shitake)	Salvia (miltiorrhiza)(injection) (a Chinese herbal medicine)
African prune / Prunus Africana / Pygeum africanum)	Electroacupuncture	Light therapy / phototherapy (exclude for treatment of seasonal affective disorder, eczema, psoriasis, neonatal jaundice)	Sanchi preparations (a Chinese herbal medicine)
Aiyishu (a Chinese herbal medicine)	Electroacupuncture according to Voll (a diagnostic method)	Linoleic acid (an omega-6 fatty acid) supplements	Saw palmetto / serenoa repens
Alexander technique	Electromagnetic stimulation therapy	L-isoleucine (an amino acid) supplements	Selenium supplements
Alpha-linolenic acid (ALA) (an omega-3 fatty acid) supplements	Electromagnetic therapy (exclude electromagnetic field therapy for delayed- and non-union fractures)	Liuwei dihuang pill (a Chinese herbal medicine)	Shamanistic medicine / Shamanism
Amino acid supplements	Electrotherapy	L-leucine (an amino acid) supplements	Shark cartilage
Angelica	Elemental diet	Low fat diets	Shengmai / shenmai (a Chinese herbal medicine)
Anthroposophic medicine	Energy field work	Low protein diets	Shenqi Fuzheng (a Chinese herbal medicine)
Antioxidant supplements	Essiac formula	Low-glycemic index diets	Shensu / shenfu (a Chinese herbal medicine)
Arachidonic acid (AA or ARA) (an omega-6 fatty acid) supplements	Estrogen (exclude for treatment of natural or surgical menopause) supplements	L-threonine (an amino acid) supplements	Shexiang (injection) (a traditional Chinese medicine]

CAM interventions, A-D	CAM interventions, E-K	CAM interventions, L-R	CAM interventions, S-Z
Aromatherapy	Evening primrose oil	L-valine (an amino acid) supplements	Shiatsu
Art therapy	Expressive writing therapy / journaling therapy	Macrobiotic diet	Shitake
Artichoke leaf	Eye Movement Desensitization and Reprocessing (EMDR)	Magnesium supplements	Shuanghuanglian (a Chinese herbal medicine)
Astragalus / Milkvetch (a Chinese herbal medicine)	Feldenkrais	Magnetic therapy / magnetic field therapy / biomagnetic therapy	Sidda medicine (a type of Indian (East Asian) traditional medicine)
Auricular acupuncture / ear acupuncture	Feng shui	Marijuana, marihuana / cannabis / cannabinoids / C. sativa / C. indica (exclude for purely psychoactive uses)	Soy / soybeans
Ayurveda / Ayurvedic medicine (a type of Indian (East Asian) traditional medicine)	Feverfew	Massage therapy	Speleotherapy
Bach flower remedies	Fish oil (omega-3 fatty acids) supplements	Meditation	Spinal manipulation
Baduanjin	Flor·Essence formula / flower essences	Mediterranean diet	Spiritual healing
Balneotherapy	Folic acid / folate (Vitamin B9) supplements (many people would not include for prevention of neural tube defects)	Melatonin	St. John's wort (Hypericum perforatum L.)
Bee stings / bee venom	Free and Easy Wanderer (a Chinese herbal medicine)	Mesotherapy	Structural integration
Beta-sitosterol (a component of saw palmetto)	Gamma-linolenic acid (GLA) (an omega-6 fatty acid) supplements	Milk thistle	Suxiao jiuxin wan (a Chinese herbal medicine)
Bibliotherapy	Garlic	Mindfulness	Tai chi / tai ji
Bioenergetics	Gerovital H3 (primary ingredient is procaine hydrochloride)	Moxibustion	Testosterone
Biofeedback	Gerson therapy	Music therapy / sound therapy	Therapeutic touch / healing touch
Biofunctional diagnostic testing	Gestalt therapy	Myofascial release	Thiamine (Vitamin B1) supplements
Biotin (Vitamin B7) supplements	Ginger	Naprapathy	Tianmadingxian capsule (a Chinese herbal medicine)
Botanical supplements	Ginkgo biloba	Nature therapy	Traditional African healing
Bovine cartilage	Ginseng	Naturopathy / naturopathic medicine	Traditional Arabic medicine

CAM interventions, A-D	CAM interventions, E-K	CAM interventions, L-R	CAM interventions, S-Z
Breathing exercises in mind-body medicine (e.g., breathwork) (exclude for physical therapy, eg treatment of cystic fibrosis)	Glucosamine supplements	Neuromuscular therapy	Traditional Chinese medicine
Calcium supplements (many people would not include for prevention of osteoarthritis)	Glutamine supplements	Niacin / Nicotinamide/ Niacinamide (Vitamin B3) supplements	Traditional Indian medicine
Calendula	Gluten-free diet	Omega-3 fatty acids	Traditional Japanese medicine
Calorie restriction	Green tea / Camellia sinensus)	Osteopathic manipulation	Traditional Korean medicine
Carnitine supplements	Guiling pa'an wan (a Chinese herbal medicine)	Ozone therapy	Traditional Tibetan medicine
Cayenne	Hair analysis	Pantothenic acid (Vitamin B5) supplements	Transcranial magnetic stimulation (exclude for treatment of depression)
Chelation therapy (exclude for treatment of medically diagnosed heavy metal poisoning (eg, mercury or lead) and for medically diagnosed excess iron (eg, thalassemia))	Helminth therapy / trichuris suis ova / Trichuris trichiura ova	Passiflora	Transcutaneous electrical stimulation
Chinese herbal medicine	Hemp oil	Peppermint	Trigger point myotherapy
Chiropractic manipulation	Herbal medicine / herbalism	Phytoestrogens	Tui na
Chitosan supplements	High-fiber diet	Phytomedicines / Phytotherapy	Ultrasound / ultrasonic therapy (exclude diagnostic ultrasound)
Chondroitin sulfate	Hippotherapy / equine-assisted therapy (exclude when physical therapy only)	Pilates	Unani medicine / Yunani medicine (a type of Arabic or Indian (East Asian) traditional medicine)
Clinical ecology	Holistic therapy / holistic medicine	Plant medicines	Valerian
Cold laser therapy	Homeopathy	Play therapy	Vega testing
Colon cleansing / colon irrigation	Homoharringtonine (HHT) (a plant alkaloid)	Prayer	Vegan diet
Color therapy / chromotherapy	Honey	Prebiotics	Vegetarian diet
Cranberry	Horse chestnut	Probiotics	Visualization techniques
Craniosacral massage / Craniosacral therapy	Huangqi (a Chinese herbal medicine)	Procaine (only when used for aging)	Vitamin A supplements
Dance therapy	Huperzine A (a Chinese herbal medicine)	Prolotherapy	Vitamin B complex supplements
Danshen (a Chinese herbal medicine)	Hydrazine sulfate	Propolis	Vitamin B12 supplements

CAM interventions, A-D	CAM interventions, E-K	CAM interventions, L-R	CAM interventions, S-Z
Deep tissue bodywork	Hydrotherapy	Protein supplements	Vitamin C supplements
Dehydroepiandrosterone (DHEA) supplements	Hyperbaric oxygen therapy (exclude for treatment of burns, wounds or infections, radiation injury, embolism, decompression disorders or carbon monoxide poisoning)	Psychotherapies incorporating mindfulness	Vitamin D supplements
Dengzhanhua preparations (a Chinese herbal medicine)	Hypnosis / hypnotherapy	Psychotherapies incorporating spirituality	Vitamin E supplements
Devil's claw	Imagery / guided imagery	Puerarin (a Chinese herbal medicine)	Vitamin K supplements
Devil's nettle	Iridology	Pulsed electromagnetic field therapy (see Electromagnetic therapy)	Vojta method / Reflexlocomotion
Devil's root / Siberian ginseng / acanthopanax senticosus / ci wu jia	Iron supplements	Pyridoxine / Pyridoxal / Pyridoxamine (Vitamin B6) supplements	White willow bark
Dianxianning pill (a Chinese herbal medicine)	Jin Li Da liquor (a Chinese herbal medicine)	Qi Gong / chi-kung	Xiaxingci granule (a Chinese herbal medicine)
Dietary supplements	Kampo (a type of traditional Japanese medicine)	Radiesthesia	Yarrow / Achillea millefolium extract
Dihomogammalinolenic acid (DGLA) (an omega-6 fatty acid) supplements	Kava	Reflexology	Yoga therapy
Dimethylaminoethanol / dimethylethanolamine / Deanol (DMAE)	Ketogenic diet	Reflexotherapy	Zero balancing
Docosahexaenoic acid (DHA) (an omega-3 fatty acid) supplements	Kinesiology / applied kinesiology	Reiki	Zhixian I pill (a Chinese herbal medicine)
Doman Delacato patterning therapy	Kneipp therapies	Relaxation techniques	Zinc supplements
	Krestin / PSK / PSP (Coriolus Versicolor extracts)	Riboflavin (Vitamin B2) supplements	Zishen Tongli Jianonang (a Chinese herbal medicine)
		Rolfing®Structural Integration	Zone therapy

Appendix 2:
PRISMA NMA Checklist

PRISMA NMA Checklist of Items to Include When Reporting a Systematic Review Involving a Network Meta-analysis

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).*	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: **Background:** main objectives **Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.* **Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.* **Discussion/Conclusions:** limitations; conclusions and implications of findings. **Other:** primary source of funding; systematic review registration number with registry name.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, *including mention of why a network meta-analysis has been conducted.*	
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) 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).
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Geometry of the network	**S1**	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.*
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: • *Handling of multi-arm trials;* • *Selection of variance structure;* • *Selection of prior distributions in Bayesian analyses; and* • *Assessment of model fit.*
Assessment of Inconsistency	**S2**	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).

Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: • Sensitivity or subgroup analyses; • Meta-regression analyses; • *Alternative formulations of the treatment network; and* • *Use of alternative prior distributions for Bayesian analyses (if applicable).*	
RESULTS†			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Presentation of network structure	**S3**	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	
Summary of network geometry	**S4**	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.*	
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented.	
Exploration for inconsistency	**S5**	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	

Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, *alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses*, and so forth).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).*	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicates wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.
† Authors may wish to plan for use of appendices to present all relevant information in full detail for items in this section.