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

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The PRISMA statement is a reporting guideline designed to improve the completeness of reporting of systematic reviews and meta-analyses. Authors have used this guideline worldwide to prepare their reviews for publication. In the past, these reports typically compared 2 treatment alternatives. With the evolution of systematic reviews that compare multiple treatments, some of them only indirectly, authors face novel challenges for conducting and reporting their reviews. This extension of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement was developed specifically to improve the reporting of systematic reviews incorporating network meta-analyses.

A group of experts participated in a systematic review, Delphi survey, and face-to-face discussion and consensus meeting to establish new checklist items for this extension statement. Current PRISMA items were also clarified. A modified, 32-item PRISMA extension checklist was developed to address what the group considered to be immediately relevant to the reporting of network meta-analyses.

This document presents the extension and provides examples of good reporting, as well as elaborations regarding the rationale for new checklist items and the modification of previously existing items from the PRISMA statement. It also highlights educational information related to key considerations in the practice of network meta-analysis. The target audience includes authors and readers of network meta-analyses, as well as journal editors and peer reviewers.

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For author affiliations, see end of text.

Systematic reviews and meta-analyses are fundamental tools for the generation of reliable summaries of health care information for clinicians, decision makers, and patients. Systematic reviews provide information on clinical benefits and harms of interventions, inform the development of clinical recommendations, and help to identify future research needs. In 1999 and 2009, respectively, groups developed the Quality of Reporting of Meta-Analyses (QUOROM) statement (1) and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (2, 3) to improve the reporting of systematic reviews and meta-analyses. Both statements have been widely used, and coincident with their adoption, the quality of reporting of systematic reviews has improved (4, 5).

Systematic reviews and meta-analyses often address the comparative effectiveness of multiple treatment alternatives. Because randomized trials that evaluate the benefits and harms of multiple interventions simultaneously are difficult to perform, comparative effectiveness reviews typically involve many studies that have addressed only a subset of the possible treatment comparisons. Traditionally, meta-analyses have usually compared only 2 interventions at a time, but the need to summarize a comprehensive and coherent set of comparisons based on all of the available evidence has led more recently to synthesis methods that address multiple interventions. These methods are commonly referred to as *network meta-analysis, mixed treatment comparisons meta-analysis, or multiple treatments meta-analysis* (6–8). In recent years, there has been a notable increase in the publication of articles using these methods (9). On the basis of our recent overview (10) of reporting challenges in the field, as well as findings from our Delphi exercise involving researchers and journal editors, we believe that reporting guidance for such analyses is sorely needed.

In this article, we describe the process of developing specific advice for the reporting of systematic reviews that incorporate network meta-analyses, and we present the guidance generated from this process.

Development of the PRISMA Network Meta-analysis Extension Statement

We followed an established approach for this work (11). We formed a steering committee (consisting of Drs. Hutton, Salanti, Moher, Caldwell, Chaimani, Schmid, Thorlund, and Altman); garnered input from 17 journal editors, reporting guideline authors, and researchers with extensive experience in systematic reviews and network meta-analysis; and performed an overview of existing reviews of the reporting quality of network meta-analyses to identify candidate elements important to report in network meta-analyses (10). We also implemented an online Delphi survey of authors of network meta-analyses in mid-2013 (215 invited; response rate, 114 [53%]) by using Fluid Surveys online software (Fluidware, Ottawa, Ontario, Canada) to deter-

See also:

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mine consensus items for which either a new checklist item or an elaboration statement would be required, and to identify specific topics requiring further discussion.

Next, we held a 1-day, face-to-face meeting to discuss the structure of the extension statement, topics requiring further consideration, and publication strategy. After this meeting, members of the steering committee and some of the meeting participants were invited to contribute specific components for this guidance. All participants reviewed drafts of the report.

SCOPE OF THIS EXTENSION STATEMENT

This document provides reporting guidance primarily intended for authors, peer reviewers, and editors. It may also help clinicians, technology assessment practitioners, and patients understand and interpret network meta-analyses. We also aim to help readers develop a greater understanding of core concepts, terminology, and issues associated with network meta-analysis.

This document is not intended to be prescriptive about how network meta-analyses should be conducted or interpreted; considerable literature addressing such matters is available (6, 12–51). Instead, we seek to provide guidance on important information to be included in reports of systematic reviews that address networks of multiple treatment comparisons. For specific checklist items where we have suggested modification of instructions from the PRISMA statement, we have included examples of potential approaches for reporting different types of information. However, modified approaches to those presented here may also be feasible.

HOW TO USE THIS DOCUMENT

This document describes modifications of checklist items from the original PRISMA statement for systematic reviews incorporating network meta-analyses. It also describes new checklist items that are important for transparent reporting of such reviews. We present an integrated checklist of 32 items, along with elaborations that demonstrate good reporting practice. The elaboration (**Appendix**, available at www.annals.org) describes each item and presents examples for new or modified items. Although new items have been added in what was deemed the most logical place in the core PRISMA checklist, we do not prescribe an order in which these must be addressed. The elaboration also includes 5 boxes that highlight methodological considerations for network meta-analysis.

The **Table** presents the PRISMA network analysis checklist that authors may use for tracking inclusion of key elements in reports of network meta-analyses. The checklist has been structured to present core PRISMA items and modifications of these items where needed, as well as new checklist items specific to network meta-analysis. Checklist items are designated "New Item" in the main text if they address a particular aspect of reporting that is novel to network meta-analyses; these are labeled S1 through S5. The heading "Addition" indicates discussion of an issue that was covered by the original PRISMA statement but requires additional considerations for reviews incorporating network meta-analyses. Examples with elaborations have been provided for checklist items in these 2 categories.

WHAT IS A TREATMENT NETWORK?

Systematic reviews comparing the benefits and harms of multiple treatments are more complex than those comparing only 2 treatments. To present their underlying evidence base, reviews involving a network meta-analysis commonly include a graph of the network to summarize the numbers of studies that compared the different treatments and the numbers of patients who have been studied for each treatment (**Figure 1**). This *network graph* consists of *nodes* (points representing the competing interventions) and *edges* (adjoining lines between the nodes that show which interventions have been compared among the included studies). The sizes of the nodes and the thicknesses of the edges in network graphs typically represent the amounts of respective evidence for specific nodes and comparisons. Sometimes, additional edges are added to distinguish comparisons that may be part of multigroup studies that compare more than 2 treatments.

The graphs also allow readers to note particular features of the shape of a treatment network. This includes the identification of *closed loops* in the network; a closed loop is present in a treatment network when 3 or more comparators are connected to each other through a polygon, as in **Figure 1** for treatments A, B, and C. This shows that treatments A, B, and C have all been compared against each other in existing studies, and thus each comparison in the closed loop (AB, AC, BC) is informed by both direct and indirect evidence (see the **Box** for definitions of direct and indirect evidence and **Figure 2** for a graphical representation of terms in the **Box**).

DISCUSSION

All phases of the clinical research cycle generate considerable waste, from posing irrelevant questions to inappropriate study methods, bad reporting, and inadequate dissemination of the completed report. Poor reporting is not an esoteric issue. It can introduce biased estimates of an intervention's effectiveness and thus affect patient care and decision making. Journals regularly publish new evidence regarding some aspect of inadequate reporting (52). Improving the completeness and transparency of reporting research is a low-hanging fruit to help reduce waste, and possibly explains the rise in developing reporting guidelines (53, 54) and such initiatives as the EQUATOR Network.

The PRISMA statement was aimed at improving the reporting of traditional pairwise systematic reviews and meta-analyses; it has been endorsed by hundreds of

Table. 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 multigroup 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 prespecified. 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).*	

(*Continued on following page*)

Table–Continued

Section/Topic	Item # *	Checklist Item†	Reported on Page #
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., health care providers, researchers, and policymakers).	
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.	

* Boldface indicates new items to this checklist.
† 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.

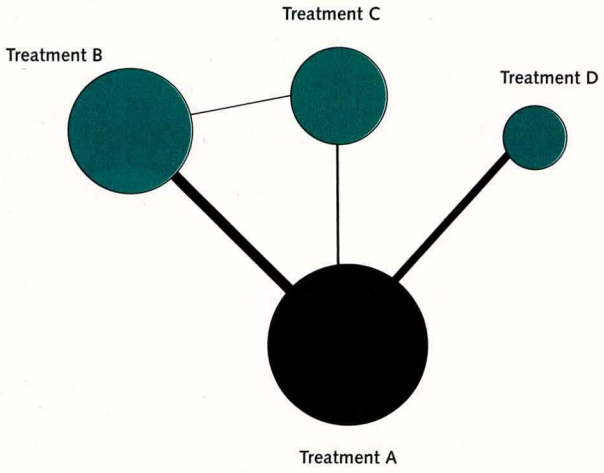
journals and editorial groups. Some extensions have been developed, including PRISMA for reporting abstracts (55) and equity (56). Other extensions are in various stages of development, including those for individual patient–data meta-analyses and harms.

Here, we describe a PRISMA extension for reporting network meta-analyses, which includes a 32-item checklist and flow diagram. This extension adds 5 new items that authors should consider when reporting a network meta-analysis, as well as 11 modifications to existing PRISMA items. Some of these are minor, whereas others are more complex, such as items 20 and 21, which ask authors to describe the results of individual studies and the corresponding syntheses thereof.

For network meta-analysis, in which it is likely that more studies and treatments will be included compared with traditional pairwise reviews, this added reporting might require authors to prepare several supplemental files as part of the manuscript submission process. Journal editors will need to make allowances for these additional materials.

Certain modifications included in some of the checklist items (for example, assessment of model fit, rationale for lumping of interventions, and presentation of tabulated study characteristics) involve considerations that are equally applicable to traditional meta-analyses of 2 treatments. Although it could be suggested that these do not warrant listing as modifications, we believe this is worthwhile; several of these

Figure 1. Overview of a network graph.



A network graph presenting the evidence base for a hypothetical review of 4 interventions is shown. Treatments are represented by *nodes* and head-to-head studies between treatments are represented by *edges*. The sizes of edges and nodes are used to visually depict the available numbers of studies comparing interventions and the numbers of patients studied with each treatment.

items were not explicitly addressed in the PRISMA statement and could be more commonly encountered when dealing with networks of treatments. Several coauthors of this reporting guidance are also members of the authorship team of the PRISMA statement and will bring these items forward when the PRISMA statement is updated in the future.

Optimally, we would like journals to endorse this extension in much the same way they have done for the PRISMA statement. Endorsement is probably best achieved through unambiguous language in the journal's instructions to authors; example wording is provided in the Appendix.

Endorsement is important, but it is less potent without implementation. At the simplest level, implementation can involve asking authors to populate the PRISMA network meta-analysis checklist with appropriate text from their report, and not accepting a submission unless this is provided. Some editors–particularly of those smaller journals, where most systematic reviews are published (57)–may perceive any endorsement and implementation as a barrier to receiving network meta-analyses reports. There are few data to support this perception. Editors can promote reporting guideline endorsement and implementation as an important way to improve the completeness and transparency of what they publish (58, 59), thus upholding one of the central tenets of the Declaration of Helsinki (60). In addition, this will reduce waste in reporting research.

There has been a steep upward trajectory of published network meta-analysis (8, 9) and methods research as the field rapidly gains momentum and interest. To help keep this PRISMA extension as up-to-date and evidence-based as possible, we invite readers to let us know about emerging evidence to help inform future updates.

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Box. Terminology: Reviews With Networks of Multiple Treatments

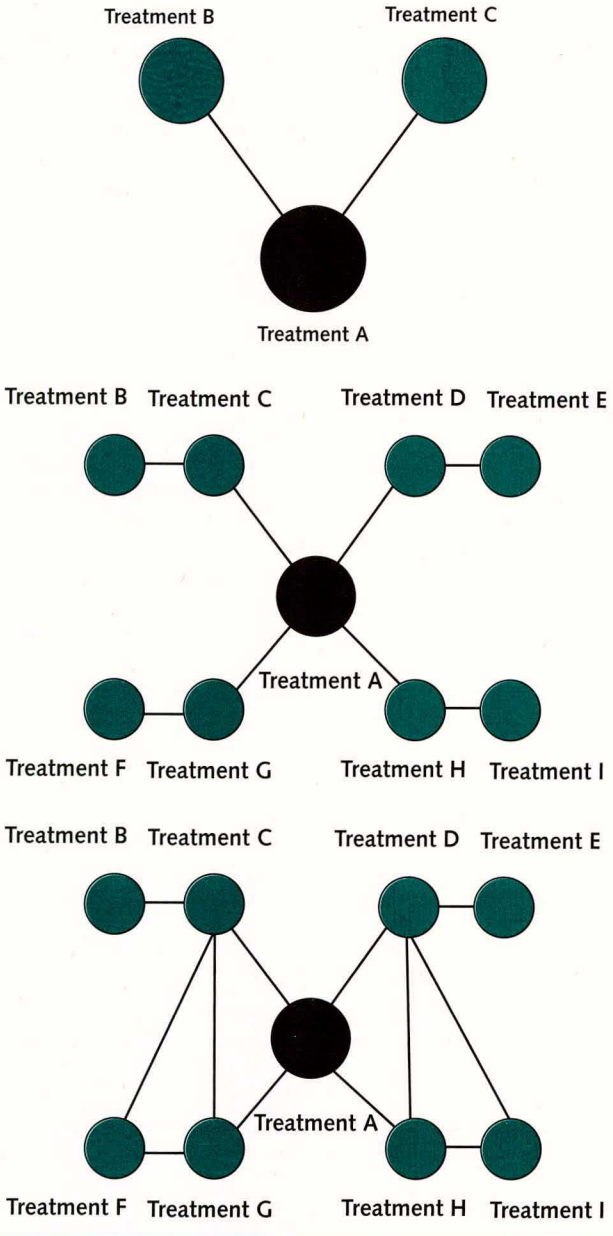
Different terms have been used to identify systematic reviews that incorporate a network of multiple treatment comparisons. A brief overview of common terms follows.

Indirect treatment comparison: Comparison of 2 interventions for which studies against a common comparator, such as placebo or a standard treatment, are available (i.e., indirect information). The direct treatment effects of each intervention against the common comparator (i.e., treatment effects from a comparison of interventions made within a study) may be used to estimate an indirect treatment comparison between the 2 interventions (**Figure 2**, *top panel*). An indirect treatment comparison (ITC) may also involve multiple links. For example, in the middle panel of **Figure 2**, treatments B and D may be compared indirectly on the basis of studies encompassing comparisons of B versus C, A versus C, and A versus D.

Network meta-analysis or mixed treatment comparison: These terms, which are often used interchangeably, refer to situations involving the simultaneous comparison of 3 or more interventions. Any network of treatments consisting of strictly unclosed loops can be thought of as a series of ITCs (**Figure 2**, *top and middle panels*). In mixed treatment comparisons, both direct and indirect information is available to inform the effect size estimates for at least some of the comparisons; visually, this is shown by closed loops in a network graph (**Figure 2**, *bottom panel*). Closed loops are not required to be present for every comparison under study. "Network meta-analysis" is an inclusive term that incorporates the scenarios of both indirect and mixed treatment comparisons.

Network geometry evaluation: The description of characteristics of the network of interventions, which may include use of numerical summary statistics. This does not involve quantitative synthesis to compare treatments. This evaluation describes the current evidence available for the competing interventions to identify gaps and potential bias. Network geometry is described further in **Appendix Box 4** (available at www.annals.org).

Figure 2. Graphical overview of the terminologies that are related to the study of treatment networks.



Terms are discussed further in the **Box. Top.** Adjusted indirect treatment comparison of treatments B and C based on studies that used a common comparator, treatment A. **Middle.** A network of 8 treatments and a common comparator, with a mix of comparisons against the control treatment and a subset of all possible comparisons between active treatments. **Bottom.** A treatment network similar to that shown in the middle panel, but with study data available for an additional 4 comparisons in the network which form closed loops.

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