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# **BMJ Open** Methodological review to develop a list of bias items used to assess reviews incorporating network meta-analysis: protocol and rationale

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#### ABSTRACT

Introduction Systematic reviews with network metaanalysis (NMA: ie, multiple treatment comparisons, indirect comparisons) have gained popularity and grown in number due to their ability to provide comparative effectiveness of multiple treatments for the same condition. The methodological review aims to develop a list of items relating to biases in reviews with NMA. Such a list will inform a new tool to assess the risk of bias in NMAs, and potentially other reporting or quality checklists for NMAs which are being updated.

Methods and analysis We will include articles that present items related to bias, reporting or methodological quality, articles assessing the methodological quality of reviews with NMA, or papers presenting methods for NMAs. We will search Ovid MEDLINE, the Cochrane library and difficult to locate/unpublished literature. Once all items have been extracted, we will combine conceptually similar items, classifying them as referring to bias or to other aspects of quality (eg, reporting). When relevant, reporting items will be reworded into items related to bias in NMA review conclusions, and then reworded as signalling questions.

Ethics and dissemination No ethics approval was required. We plan to publish the full study open access in a peer-reviewed journal, and disseminate the findings via social media (Twitter, Facebook and author affiliated websites). Patients, healthcare providers and policymakers need the highest quality evidence to make decisions about which treatments should be used in healthcare practice. Being able to critically appraise the findings of systematic reviews that include NMA is central to informed decision-making in patient care.

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#### INTRODUCTION

Reviews with network meta-analysis (NMAs) have gained popularity due to their ability to provide comparative effectiveness of multiple treatments for the same condition.<sup>1</sup> Reviews with NMA have grown in number. Between 1997 and 2015, 771 NMAs were published in 336 journals from 3459 authors and 1258 institutions in 49 countries.<sup>2</sup> More

### Strengths and limitations of this study

- No tool for assessment of biases in reviews with network meta-analysis (NMA) currently exists.
- Our research aims to develop a list of items related to bias in the goal of developing the first tool for assessing risk of bias in the findings of NMAs.
- A comprehensive and systematic process will be followed to develop a risk of bias tool for assessing reviews with NMAs, as outlined in Whiting et al's 'Framework for Developing Quality Assessment Tools', starting with this methodological review to develop a list of bias items used to assess NMAs
- One limitation is that the items identified through this methodological review should be considered as possible contenders for inclusion in the risk of bias in NMAs tool since items have not been vetted through a Delphi exercise with experts as of yet.
- Wording of the items may change after conducting the Delphi and pilot testing exercises.

data mining, Al training, than three-quarters (n=625; 81%) of these NMAs were published in the last 5 years. Many organisations such as the National Institute for Health and Care Excellence (NICE) in the UK, the World Health Organisation (WHO) and the Canadian Agency for Drugs and Technologies in Health (CADTH) conduct NMAs as they represent the best available evidence to inform clinical practice guidelines.<sup>3–5</sup> We adopt a broad definition of **O** NMAs, specifically: a review that aims to, or & intends to, simultaneously synthesise more **g** than two heath care interventions of interest. Reviews that intend to compare multiple treatments with an NMA but then find that the assumptions are violated (eg, a disconnected network, or studies are too heterogeneous to combine) and that NMA is not feasible, will also be included in our definition.

Evidence shows that biased results from poorly designed and reported studies can

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mislead decision-making in healthcare at all levels.<sup>6-9</sup> If a review is at risk of bias and inappropriate methods are used, the validity of the findings can be compromised.<sup>10–12</sup> Evaluating how well a review has been conducted is essential to determining whether the findings are relevant to patient care and outcomes. Several empirical studies have shown that bias can obscure the real effects of a treatment.<sup>13-16</sup> Being able to appraise reviews with NMA is central to informed decision-making in patient care.

The systematic procedures required to conduct a systematic review help mitigate the risk of bias. However, bias can also be introduced when interpreting the reviews findings. For example, review's conclusions may not be supported by the evidence presented, the relevance of the included studies may not have been considered by review authors, and reviewers may inappropriately emphasise results on the basis of their statistical significance.<sup>17</sup> A wellconducted systematic review draws conclusions that are appropriate to the included evidence and can therefore be free of bias even when the primary studies included in the review have high risk of bias.

Tools are available for most study designs to make risk of bias assessment easier for a knowledge user (eg, healthcare practitioners, policymakers, patients<sup>18</sup>). Many tools and checklists can be used either when conducting a systematic review (quality of conduct), when assessing how well a study has been described (reporting), or when knowledge users want to assess the risk of bias in the conclusions of a review. The methodological quality of studies (ie, how well the study is conducted) is often confused with reporting quality (ie, how well authors describe their methodology and results). A risk of bias assessment is an assessment of review limitations, which focus on the potential of those methods to bias the study findings.<sup>17</sup>

More than 40 tools have been identified<sup>19 20</sup> for critically appraising the quality of reviews with pairwise metaanalysis. AMSTAR (A MeaSurement Tool to Assess the methodological quality of systematic Reviews)<sup>21</sup> and the OQAQ (Overview Quality Assessment Questionnaire<sup>22</sup>) have been identified as the most commonly used, and they follow a simple checklist format.<sup>20 23</sup> AMSTAR has been recently updated to AMSTAR 2, which aims to evaluate how reviews are planned and conducted.<sup>24</sup> The ROBIS (Risk Of Bias In Systematic reviews) tool is designed to assess the risk of bias in systematic reviews with or without pairwise meta-analysis.<sup>17</sup> The ROBIS tool involves assessment of methodological features in reviews known to increase the risk of bias in review conclusions. Domain-based assessment tools require a careful reading and thoughtful analysis of the study to adequately rate risk of bias, instead of simply identifying keywords reported in the article, as usually made in a checklist type of assessment.

For critically appraising reviews with NMA, several checklists exist. To assess reporting quality, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement extension for reviews incorporating network

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conducting systematic reviews Assess the quality of AN	IECIR <sup>34</sup>	Detailed methodological guidance on how to conduct a systematic review with or without pairwise meta-analysis of effectiveness, diagnostic test accuracy, individual patient data reviews and	No
		reviews in public health and health promotion	
published reviews OC	MSTAR-2 <sup>24</sup> , QAQ <sup>22</sup>	AMSTAR-2 is a critical appraisal tool to assess the quality of conduct of reviews of randomised controlled trials of interventions	ISPOR <sup>27</sup>
Assess the risk of ROBIS <sup>17</sup> bias of published reviews		ROBIS is a tool for assessing the risk of bias in reviews. It is aimed at four broad categories of reviews mainly within healthcare settings: interventions, diagnosis, prognosis, and aetiology.	No
Assess the certainty GF in evidence and the strength of recommendations	RADE <sup>39</sup>	GRADE approach defines the certainty of a body of evidence as the extent to which one can be confident that a pooled effect estimate is close to the true effect of the intervention. Five domains assessed: risk of bias, inconsistency, indirectness, imprecision and publication bias.	GRADE-NMA, <sup>40</sup> <sup>41</sup> CINeMA, <sup>42</sup> Threshold method <sup>4</sup>
Guidelines for the PF complete reporting published reviews	RISMA <sup>44</sup>	PRISMA is an evidence-based minimum set of items for reporting in reviews and meta-analyses. PRISMA focuses on the reporting of reviews evaluating randomised trials, but can also be used as a basis for reporting reviews of other types of research, particularly evaluations of interventions.	PRISMA-NMA <sup>25</sup> , NICE-DSU <sup>26</sup>

#### **Eligibility criteria**

There will be two types of studies included. Study type 1 are articles that present and describe items related to bias, reporting or methodological quality of reviews with NMA. Items related to reporting will be retained because they can potentially be translated into a risk of bias item. For example, in the PRISMA-P guideline,<sup>31</sup> one item asks whether study PICO (Population, Interventions, Comparisons, Outcomes) characteristics were used as criteria for determining study eligibility. Reporting of all outcomes in a protocol may prevent authors from only selecting outcomes that are statistically significant when publishing their systematic review. This PRISMA-P reporting item can then be translated into a bias item related to the 'selective reporting' of outcomes.<sup>32</sup> Study type 2 are studies that assess the methodological quality in a sample of reviews with NMA.

Study type 1 will meet any of these inclusion criterion

- Articles describing items related to bias or methodological quality in reviews with NMA (eg, Dias 2018<sup>33</sup>); tools that only assess general aspects of systematic reviews without focusing specifically on NMA will be excluded (eg, AMSTAR,<sup>21</sup> AMSTAR 2<sup>24</sup> or ROBIS<sup>17</sup>).
- Articles describing editorial standards for reviews with NMA (eg, similar to the Cochrane MeCIR (Methodological standards for the conduct of new Cochrane

- Articles describing items related to reporting quality in reviews with NMA (eg, PRISMA-NMA<sup>25</sup>).
- mining, AI training, and Articles identifying or addressing sources of bias and variation in NMA and published after PRISMA-NMA in 2014.

#### Study type 2 will meet any of these inclusion criterion

Articles assessing the methodological quality (or risk of bias) of reviews with NMA (ie, a sample of NMAs are assessed for methodological quality; e.g. Chambers  $2015^{35}$ ) using criteria that focus specifically on aspects of NMA not just on general aspects of systematic reviews.

We will include articles with any publication status and in any language, and where the coauthors are not fluent **g** in the language, Google Translate will be used.

If through our main search, we identify a systematic review encompassing the eligible articles, or one aspect of the eligible article, we will use the results of the systematic review and only include primary studies published subsequent to the systematic review. For example, a review by Laws *et al* in  $2019^5$  identified all guidance documents for conducting an NMA from countries throughout the world. We therefore would not search for guidance documents published before the last search date of this review.

#### Search strategy

We will search Ovid MEDLINE (January 1946 to June 2020), the Cochrane library as well as the following grey literature databases: the EQUATOR Network (http:// www.equator-network.org/reportingguidelines/), Dissertation Abstracts, websites of evidence synthesis organisations (Campbell Collaboration Cochrane Multiple Treatments Methods Group, CADTH, NICE-DSU, Health Technology Assessment International (HTAi), Pharmaceutical Benefits Advisory Committee, Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen, European Network for Health Technology Assessment, Guidelines International Network, ISPOR, International Network of Agencies for Health Technology Assessment, and [BI) as well as methods collections (ie, Cochrane Methodology Register, AHRO Effective Healthcare Programme). We will validate the MEDLINE strategy by using the PubMed IDs of 10 included studies (identified by experts prior to our eligibility screening) and evaluating whether the strategy identified the PMIDs (online supplemental appendix 2).

A systematic search strategy will be developed by two methodologists (CL and PW) without limitations to publication type, status, language or date to identify existing tools or articles. An information specialist will check the search strategy for MEDLINE Ovid and assess it using the PRESS (Peer Review Electronic Search Strategies) guidance.<sup>36</sup> The full search strategies for all databases and websites can be found in Appendix 2. To identify other potentially relevant studies, we will examine the reference lists of included studies. We will ask experts in methods for NMA to identify articles missed by our search. We will contact authors of abstracts to retrieve the full report or poster.

We will search the reference section of a bibliometric study of reviews with NMAs<sup>37</sup> and extract the name of the journals that publish NMAs. We will then contact their editors in chief and ask if they have any in-house editorial standards for reviews with NMA.

#### Process for screening, data extraction and analysis

The eligibility criteria will be piloted in Microsoft Excel by two reviewers independently on a sample of 25 citations retrieved from the search to ensure consistent application. After high agreement (>70%) is achieved, the Covidence<sup>38</sup> web-based tool (https://www.covidence.org) will be used by two reviewers to independently screen the citations based on the eligibility criteria. Disagreements will be discussed until consensus is reached. A third reviewer (CL) will arbitrate if disagreements cannot be resolved.

The data extraction form will be piloted by reviewers independently on a sample of five included papers to ensure consistent coding. Two independent authors will extract data on the characteristics of the studies and items. Any disagreements will be arbitrated by a third author.

#### **Data extraction**

The sources will first be categorised by the type of article coded as per our inclusion criteria. A table of tool characteristics will be developed with the following headings: first author, year; type of tool (tool, scale, checklist or domain-based tool); whether the tool is designed specific topic areas (specify); number of items; domains within the tool; whether the item relates to reporting or methodological quality (or other concepts such as precision, acceptability); how items and domains within the tool are rated; methods used to develop the tool (eg, review of items, Delphi study, expert consensus meeting) and the availability of an 'explanation and elaboration'.

by copyright, including Data will be extracted on items that are potentially relevant to the risk of bias or quality of reviews with NMAs. Items will be initially extracted verbatim.

#### **Data analysis**

The following steps will be used when analysing items:

1. Map to ROBIS domains

Items will be mapped to ROBIS domains (study eligibility criteria; identification and selection of studies; data **o** collection and study appraisal; and synthesis and find-ings) and specific items within the domains. The rationale for mapping items to ROBIS is that it is the only tool re to assess risk of bias in reviews. Items that do not clearly map to the existing ROBIS domains will be listed separately and grouped by similar concept. New domains may be created if items do not fit well into the established **ROBIS** domains.

2. Split items so that each item only covers a single concept

Two or more concepts grouped in one item will be split so that each item covers a single concept. A rationale as to why the item was split will be described. For example, G PRISMA-NMA item 15 ('Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies)') will be split into two items because this item is represented by **B** two items in ROBIS in the synthesis and findings domain, namely '4.5 Were the findings robust, for example, as demonstrated through funnel plot or sensitivity analyses?' and '4.6 Were biases in primary studies minimal or addressed in the synthesis?"'.

3. Group similar items

Items that are conceptually similar will be grouped together and noted with the source. We will classify **B** items as relating to bias or other aspect of quality (eg.  $\overline{\mathbf{g}}$ reporting). When relevant, items related to reporting will be reworded into items related to bias in NMA review conclusions.

4. Omit duplicate items (but keep these in a column in the table for transparency)

If items are worded vaguely or are unexplained, we will use an iterative process to interpret the item and ensure that there is a mutual understanding of the item between authors when coding. The process will be iterative, and if any gaps in items related to bias in reviews of NMA are identified, a new item will be inferred.

The final list of items deemed unique will be retained. We will reword items as signalling questions, where an answer of 'yes' suggests the absence of bias. We will provide examples to illustrate the items and write a rationale and description of each item. These items will be submitted in a multiround Delphi exercise by NMA experts who will give their opinion about each item's potential inclusion in the tool.

We will count the number of sources and unique items included. We will summarise the characteristics of included tools in tables and figures. We will calculate the median and IQR of items across all tools and tabulate the frequency of different biases identified in the tools.

#### Patient and public involvement

Patients or the public were not involved in the design of our research protocol.

#### **ETHICS AND DISSEMINATION**

No ethics approval was required as no human subjects were involved. Our research aims to develop a list of items related to bias in the goal of developing the first tool for assessing risk of bias in the findings of reviews with NMA. We plan to publish the full study open access in a peerreviewed journal, and disseminate the findings via social media (Twitter, Facebook and author affiliated websites).

Patients, healthcare providers and policy-makers need the highest quality evidence to make decisions about which treatments should be used in healthcare practice. Being able to critically appraise the findings of reviews with NMA is central to evidenced-based decision-making in patient care.

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**Contributors** CL conceived of the study; all authors contributed to the design the study; CL wrote the draft manuscript; CL, PW, ACT, BH, SD, GS, A-AV, IW and JW revised the manuscript; all authors edited the manuscript; and all authors read and approved the final manuscript.

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# Appendix 1

# PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol\*

Section and topic	Item No	Checklist item	Page #
ADMINISTRATIV	E INFO	DRMATION	
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Yes, in title, abstract and main text
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	First page
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Page 9
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Page 9
Sponsor	5b	Provide name for the review funder and/or sponsor	Page 9
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Page 9
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Page 5
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Page 4
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Page 6
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Page 6/7

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Page 7
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Page 7
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Page 7
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Page 7
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Page 7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Page 7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	N/A
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Page 7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$ , Kendall's $\tau$ )	
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	N/A
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	N/A
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

\* It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

# Appendix 2: Search strategies

**Ovid MEDLINE** (R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) (1946 - )

((network meta-analys?s or NMA or ((indirect or mixed) adj3 comparison)) adj5 (tool? or instrument? or checklist? or check list? or scale? or measure? or assess? or compar\*)).ab,ti.

# EBM Reviews - Cochrane database of Systematic Reviews (2005 -)

network meta-analys?s or NMA or ((indirect or mixed treatment? or treatment?) adj3 comparison) AND (tool? or instrument? or checklist? or check list? or scale? or assess? or Validity or bias\$ or apprais\$ or quality)

**The EQUATOR Network (**http://www.equator-network.org/reportingguidelines**/)** Study type: Systematic reviews and contl F "network"

**ProQuest Dissertations & Theses Global** 

TI(Network Meta-Analysis) AND AB(tool)

**Cochrane Comparing Multiple Interventions Methods Group** https://methods.cochrane.org/cmi/welcome https://methods.cochrane.org/cmi/relevant-publications-and-resources (Cochrane Chapter on NMA; and MECIR considerations for NMA – in development)

# **EBM Reviews - Cochrane Methodology Register (includes Cochrane Colloquium abstracts) (**3rd Quarter 2012) (includes Cochrane Colloquium abstracts)

((network meta-analys?s or NMA or ((indirect or mixed) adj3 comparison)) adj5 (tool? or instrument? or checklist? or check list? or scale? or measure? or assess? or compar\* or valid\$ or invalid or bias\$ or apprais\$ or quality)).ab,ti.

Scientific Resource Center Methods library of the AHRQ Effective Health Care Program http://www.refworks.com/refworks2/?site=027181135918800000%2F57381342557464357%2FSRC+Methods+ Library network meta-analysis

International Network of Agencies for Health Technology Assessment: https://www.inahta.org "network meta-analysis" and "mixed treatment comparison"

**Pharmaceutical Benefits Advisory Committee:** https://www.pbs.gov.au/info/industry/listing/participants/pbac "network meta-analysis" and "mixed treatment comparison"

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen: https://www.iqwig.de/en/home.2724.html "network meta-analysis" and "mixed treatment comparison"

# European Network for Health Technology Assessment:

https://eunethta.eu/methodology-guidelines/ "network meta-analysis" and "mixed treatment comparison"

# Guidelines International Network:

https://g-i-n.net/home "network meta-analysis", and "mixed treatment comparison"

# International Society for Pharmacoeconomics and Outcomes Research:

https://www.ispor.org/ AND https://tools.ispor.org/peguidelines "network meta-analysis", and "mixed treatment comparison"

# National Institute for Health and Care Excellence Decision Support Unit:

http://nicedsu.org.uk/multivariate-meta-analysis-tsd "network meta-analysis", and "mixed treatment comparison"

# Canadian Agency for Drugs and Technologies in Health:

https://www.cadth.ca/ Search study type "reports", then for "network meta-analysis", and "mixed treatment comparison"