

Stakeholder opinions on the structure and development of a new risk of bias tool to assess systematic reviews with network meta-analysis (RoB NMA tool): a cross-sectional survey

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Abstract

Introduction: Network meta-analysis (NMA) is increasingly used in guideline development and other aspects of evidence-based decision-making. We engaged with stakeholders in early phases of the development of a new tool to assess risk of bias (RoB) in NMA to facilitate its later use and potentially widen its impact.

Methods: We surveyed stakeholders' views and preferences about the importance, utility, and willingness to use the RoB NMA tool to evaluate evidence in practice and in policymaking. We included 12 closed and 10 open-ended questions, and followed a knowledge translation plan to disseminate the survey through social media and professional networks.

Results: A total of 298 stakeholders participated in the survey (14% respondent rate) which took on average 2 minutes to complete. 75% of stakeholders indicated that their organization produced NMAs, and 78% of respondents showed high interest in the tool. Most stakeholders (84%) reported they would use the tool to assess an NMA if they had received adequate training, while half reported they preferred a tool to assess *both* bias in individual NMA results *and* authors' conclusions. Twelve (8%) stakeholders said they would use the tool to conduct an overview of reviews, while 24 (17%) respondents indicated that they would use the tool to distinguish between NMAs at high and low risk of bias.

Conclusions: This survey informs the development of a RoB tool for NMAs and is a pillar in an integrated knowledge translation approach. Stakeholders preferred a tool to assess both bias in individual NMA results and authors' conclusions.

Summary Box

What is already known about this subject?

The development of new tools to inform evidence-based medicine requires the feedback of all users of the tool including stakeholders. Several reviews report that the interaction between researchers and stakeholders is a key factor associated with the impact of the research. The purpose of the survey was to ask stakeholders about the structure of a proposed tool for assessing biases in an NMA, and about their potential use of the tool in evidence-informed practice, policymaking, guideline development, or research.

What are the new findings?

The majority of stakeholders reported they would prefer a tool to assess the bias both in individual NMA results and in authors' conclusions. In their work, stakeholders indicated that they used NMAs to: (i) to inform the development of clinical practice guidelines, Health Technology Assessments, or policy; (ii) in academic research or clinical decision making; or (iii) to produce new NMAs.

How might it impact clinical practice in the foreseeable future?

Our proposed tool to assess the risk of bias in an NMA has several uses, it can help knowledge users: (i) decide whether to believe the results from a single NMA; (ii) help choose between NMAs on the same question with discordant results or conclusions. With the proposed risk of bias in NMA tool, knowledge users will be able to evaluate an NMA for important biases for use in their evidence-based decision-making. The tool has the potential to increase uptake of relevant high-quality evidence and ultimately improve patient outcomes.

Introduction

Studies have shown that stakeholders are users of quality assessment tools [1–3]. Stakeholders in research are people or organizations who have an interest in in, who affect or who are affected by the outcomes of the research, such as guideline developers, patients, funders, healthcare professionals, government employees, or industry workers. A recent survey of 107 guideline developers reported that 74% used at least one tool in the development, reporting, or critical appraisal of systematic reviews or guidelines within their organization [3]. More than half reported using the Appraisal of Guidelines for Research & Evaluation (AGREE) I/II to appraise guidelines, and one fifth used AMSTAR 1 or 2 to assess the methodological quality of systematic reviews.

The development of new quality assessment tools to inform evidence-based medicine benefits from the feedback from representative knowledge users of the tool, which may include healthcare providers, researchers, academics, patients, and stakeholders. Nonetheless, in practice, these tools are often produced without engaging stakeholders in the research process [4]. Identifying relevant stakeholders early in the research process can inform their degree of interest in the project's goals and outcomes and their potential involvement in knowledge translation activities. Clarity about stakeholders' needs and concerns helps to manage their expectations, and ensures active and constructive engagement in the project and its evaluation.

Integrated knowledge translation describes the process of partnered research between different stakeholders with the goal of producing research that ultimately achieves a greater impact when put into practice. The importance of stakeholder engagement in research is increasingly recognised [5] and several reviews indicate that the interaction between researchers and decision-makers is a key factor associated with knowledge translation and the reduction of research waste [1, 6–10]. Specifically, the benefits of engaging stakeholders early in the development of such tools include: greater public acceptance [11]; identifying and prioritising topics for research [12]; providing feedback on the tool's usability [12]; wider dissemination, uptake and communication of findings [12]; and increased likelihood of impact [12, 13]. Engaging with stakeholders during development ensures that new tools will be relevant and applicable.

The risk of bias in network meta-analysis (NMA) tool project aims to develop the first tool to assess risk of bias (RoB) in a review with NMA. The RoB NMA tool is being developed by an international steering committee of experts in tool development, bias, and NMA methodology. The RoB NMA tool will assess

NMA biases and limitations regarding how the analysis was planned, data were analysed, and results were presented, including the way in which the evidence was assembled and interpreted. Our proposed RoB NMA tool has several uses. It can help knowledge users: (i) decide whether to believe the results from a single NMA; and (ii) help choose between NMAs on the same question with discordant results or conclusions.

We aimed to engage with stakeholders in early phases of the development of the tool to facilitate its later use, and potentially widen its impact. The purpose of the survey was to ask stakeholders about the structure of a proposed tool for assessing biases in an NMA and about their potential use of the tool in evidence-informed practice, policymaking, guideline development, or research.

Methods

We used a cross-sectional survey design which was informed by established approaches for conducting systematic needs assessment surveys [14, 15]. We published our study protocol, and all data are freely available on the Open Science Framework at <https://osf.io/da4uy/>. We complied with the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) when preparing our manuscript for publication (**Appendix A**) [16]. Important definitions and concepts are found in **Box 1**.

Box 1. Important definitions and concepts

Network meta-analysis (NMA)

We adopted a broad definition of an NMA as a method that aims to, or intends to, synthesise simultaneously the evidence from multiple studies investigating more than two health care interventions of interest. Reviews that intend to compare multiple treatments with an NMA but then find that the expectations or assumptions are violated (e.g. the network is 'disconnected', studies are too heterogeneous to combine, underlying assumptions of the method are not met), and hence an NMA is not possible or optimal, are also considered in our definition.

NMA risk of bias assessment

A risk of bias assessment would evaluate limitations in the way in which the NMA analysis was planned, analysed, and presented. If these methods are inappropriate, the validity of the findings can be compromised. Our tool aims either/or to assess the biases in the individual results of the NMA, and the authors' conclusions.

Bias in results of an NMA

Network meta-analysis of effect estimates from primary studies can result in over-estimation or under-estimation of the effects of specific intervention comparisons [17, 18]. For example, Chaimani et al. conducted a network meta-epidemiological study and found that, in the majority of the 32 networks they analysed, small studies tended to exaggerate the true effect estimate of the intervention, possibly due to small study effects and publication bias. Inadequate randomization and lack of blinding in randomized trials may also lead to exaggeration of pooled effect estimates [19]. Our tool will focus on the results of an NMA [e.g. network characteristics (including geometry, effect modifiers) [20]. This is the approach taken in tools such as the RoB 2 tool for assessing risk of bias in randomized trials [21].

Bias in the conclusions of an NMA

Bias may be introduced when interpreting the NMA results to draw conclusions. Conclusions may include 'spin' (e.g. biased mis-representation of the evidence, perhaps to facilitate publication) or (erroneous) mis-interpretation of the evidence [22]. Ideally, potential biases identified in the results of the NMA might be addressed appropriately when drawing conclusions. In the same way that a well conducted 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.

Development of the survey and questionnaire design

A survey with 15 questions was developed by the investigative team. Five members of the group piloted the survey and modified it iteratively to improve clarity, face validity, and content validity. We used a web-based survey platform (Qualtrics Labs, Provo, UT, USA). Survey questions were presented in closed response (12 questions) and open-ended formats (10 questions), following an introductory explanation regarding the background and purpose of the survey. Participants were allowed to skip questions they did not wish to answer. The survey was written in English.

There were two main parts to the survey: (1) demographic information and information about whether the stakeholder or the stakeholder's organization used or produced NMAs; (2) purpose of the RoB-NMA tool, namely whether stakeholders preferred to assess the bias in the results, the authors' conclusions of an NMA, or both. Further sections (found in **Appendices**) asked about additional NMA bias concepts that might have been missed from our list; and interest and engagement in development, piloting, dissemination, and training. We did not randomise or alternate items in the survey to avoid answer option order bias. Respondents were able to review and change their answers by going back.

The full survey questionnaire is provided in **Appendix B**. We included two questions (Q9 and Q10) that were identical in concept but were worded differently. These items can be used to assess whether different forms of a question yield comparable responses. To do this, we checked whether the univariate frequency distributions were the same.

Consent

All responses were rendered anonymous. Approval from the University British Columbia Ethics Board was obtained before conducting the study, and consent was implied when participants completed the online survey. Unique site visitors were identified via IP address and personal information was collected on a voluntary basis from participants (no incentives were offered) who wished to be contacted about the survey's results and to be involved in dissemination and training. We quoted responses by participants, but they were not attributed to the specific person.

Email list development

We created an email list of journal editors publishing NMAs, using one bibliometric study of NMAs [23]. From this list, we extracted the journals that publish NMAs, and names of authors of NMAs. We also developed a list of organizations and institutions producing NMAs (Cochrane Multiple Treatments Methods Group, Guidelines International Network, JBI – formally the Joanna Briggs Institute, Campbell Collaboration, U.S. Agency for Healthcare Research & Quality's Evidence-based Practice Centre program, Centre for Reviews and Dissemination, Canadian Agency for Drugs and Technologies in Health [CADTH], Evidence for Policy and Practice Information and Co-ordinating Centre [EPPI-Centre], Centre for Implementation Research at the Ottawa Hospital Research Institute, the GRADE NMA group, and CINeMA [Confidence In Network Meta-Analysis] developers; **Appendix C**). We also included in the email list participants from a UBC Methods Speaker Series on evidence synthesis methods (<https://www.ti.ubc.ca/2022/01/01/methods-speaker-series-2022/>).

Email list recruitment

All potential survey respondents were sent an email describing the purpose of the study, requesting their participation and providing a link to the survey (**Appendix D**). We welcomed and included all knowledge users of NMAs, including stakeholders, to participate in the survey, irrespective of the level of their familiarity with NMA.

Dissemination through social media

A knowledge translation plan was followed to disseminate and advertise the survey (**Appendix E**). Anonymous links were included in LinkedIn and Twitter posts which were circulated through targeted Twitter accounts, such as the Knowledge Translation Program, SPOR (Strategy for Patient-Oriented Research) Evidence Alliance, and the DSEN (Drug Safety and Effectiveness Network) Methods and Applications Group for Indirect Comparisons. Tweets were retweeted amongst followers. We used twitter cards (i.e. advertisements with pictures) and targeted hashtags to increase awareness of the survey (see

the Twitter Campaign in **Appendix F**). In addition, we advertised through the e-newsletters of Knowledge Translation Canada, SPOR Evidence Alliance and Therapeutics Initiative.

Timing

The stakeholder survey ran from June 28 to August 1, 2021. Qualtrics email reminders were scheduled at two-week intervals throughout this period to unfinished or non-respondents. We estimated that the survey would take approximately *10 minutes* to complete of a respondents' time.

Data analysis

Prior to data analysis, the responses were transferred from Qualtrics to MS Excel and cleaned to ensure data quality. Questionnaires that were terminated early, for example, where users did not go through all questionnaire pages, were included in analyses where available, but those that were entirely blank were excluded. We measured the time respondents took to fill in a questionnaire regardless of whether it was complete.

Descriptive statistics were calculated for each closed response question including count, frequency and percentage response distributions, with denominators taken as the number who provided a response to the question. One researcher coded the open-ended questions independently by identifying themes. Respondents' comments on questions 9 and 10 were merged as they were similar in nature.

Results

Recruitment results

A total of 2,821 emails were sent out to advertise the survey. Of these, 87 emails failed to reach the recipients due to incorrect addresses, no longer at the related job post, etc., resulting in a total of 2,734 email links that reached the intended individual (Fig. 1). Most respondents completed the survey through our Qualtrics email survey link ($n = 390$, response rate = 14%) compared to those clicking and completing an anonymous link distributed over social media and e-newsletters ($n = 27$).

After consolidating duplicates (using IP addresses, $n = 33$) and blank responses ($n = 86$), a total of 298 responses were included in the analysis.

Six tweets were sent out which resulted in 28 retweets and 4 comments (**Appendix G Figure**). One LinkedIn advertisement was sent out.

Of the 298 respondents, 252 (85%) answered all the survey questions, and 46 (15%) completed half of the questions. The mean time taken to complete the survey over all respondents was 2.27 minutes (SD 1.33).

Characteristics of respondents

Characteristics of respondents are summarized in **Table 1**. Of the 298 respondents, 136 (45.6%) self-identified as a systematic review expert, 122 (40.9%) as a guideline developer, 98 (32.9%) as a clinician or health care professional, and 44 (14.8%) as a guideline developer (**Table 1**). Half of the respondents had primary affiliations at a university (50%). Other affiliations included working at a hospital (21%), non-profit organization (8%), or government (6%). The majority (75%) of these institutions/organizations produced systematic reviews with NMAs. Most respondents resided in North America (41%) and/or Europe (34%) (**Table 1**). A total of 175 (59%) respondents reported their specific organization of employment.

Three quarters (75%) of respondents indicated that their organization produced systematic reviews with NMAs, but only 54% of stakeholders said they used an NMA in their work (**Table 1**).

Table 1
Stakeholders' characteristics and familiarity with NMAs

Characteristics of the stakeholders	Overall (N = 298)
Primary and current roles*	
Systematic reviewer	136 (45.6%)
Academic	122 (40.9%)
Clinician or health care professionals	98 (32.9%)
Graduate student/postdoctoral researcher	60 (25.1%)
Epidemiologist	54 (18.1%)
Guideline developer	44 (14.8%)
Independent researcher	42 (14.1%)
Health Technology Assessment (HTA) producer or specialist	39 (13.1%)
Statistician	38 (12.8%)
Journal editor	31 (10.4%)
Research support	19 (6.4%)
Decision/policymaker	9 (3.0%)
Information scientist/medical librarian	6 (2.0%)
Funding agency representative and clinician	3 (1.0%)
Patient partner	3 (1.0%)
Other (methodologist, NGO worker, knowledge translation specialist, Scientific officer, health economist, etc.)	11 (3.7%)
Primary affiliation	
University	149 (50.0%)

Characteristics of the stakeholders	Overall (N = 298)
Hospital and university hospital	61 (20.5%)
Research institute	25 (8.4%)
Government	19 (6.4%)
Non-profit organization (e.g., NGO, charity)	23 (7.7%)
For-profit private organization (e.g. industry)	10 (3.4%)
Other (e.g. clinic, HTA organization, blood service, independent researcher)	11 (3.7%)
Geographic location	
North America/Central America	121 (40.6%)
Europe	101 (33.9%)
Asia	50 (16.8%)
South America	17 (5.7%)
Africa	2 (0.67%)
Pacific Islands	1 (0.34%)
Australia	4 (1.3%)
Other (i.e. Middle East, Oceania)	2 (0.67%)
Does your organization or institution (or work colleagues) produce systematic reviews with NMA?	
Yes	223 (75.1%)
Unsure	32 (10.8%)
No	42 (14.1%)
Missing	1 (0.3%)
Have you used systematic reviews with NMA as a source of evidence in decision making?	
Yes	193 (65.4%)

Characteristics of the stakeholders	Overall (N = 298)
No	73 (24.7%)
Unsure	29 (9.83%)
Missing	3 (1.0%)
Have you used a systematic review with NMA in your work?	
Yes	160 (54.2%)
No	160 (54.2%)
Unsure	75 (25.4%)
Missing	3 (1.0%)
If you have used one or more systematic reviews with NMA in your work, did you use:	
Both individual results of NMAs and conclusions	127 (57.7%)
Individual analysis results from the NMA to draw your own conclusions (e.g. pooled effect estimate)	72 (32.7%)
NMA authors' conclusions	21 (9.55%)
Missing	78 (26.2%)

*Percentages add to more than 100% because participants could provide more than one response.

HTA: Health Technology Assessment; NGO: Non-governmental organization; NMA: Network meta-analysis

Interest and type of tool preferred

Most stakeholders (84%) reported they would use a risk of bias tool to assess an NMA if they had received adequate training on how to use it (Fig. 2). When asked about their level of interest in a tool for appraising the risk of bias in NMAs, 182/298 (61.1%) had high interest, 53/298 (17.8%) had low interest, and only one person had no interest. Many respondents said they would use the RoB NMA tool's bias assessment when conducting an overview of reviews, Health Technology Assessment (HTA), or guideline; and to distinguish between NMAs at higher or lower risk of bias.

When we asked stakeholders about the type of tool that might be useful to them or their organization, half of the respondents (145/298) reported they preferred a tool to assess *both* the bias in individual NMA results and authors' conclusions (Fig. 2). In total, 220/298 (73.8%) thought the tool should assess results (summed across just results and both) and 165/298 (55.4%) proportion thought the tool should assess conclusions (summed across just conclusions and both).

Open-ended questions

Open-ended questions are summarised in **Appendix H Tables 1 to 4**.

How were systematic reviews with network meta-analysis used in a stakeholder's work

Of 160 respondents indicating that they used systematic reviews with NMA in their work, 137 (86%) respondents described how they did this (**Appendix H Table 1**). We grouped the ways in which systematic reviews with NMAs were used into 8 categories. The largest number (52/137; [38%]) used NMAs to inform the development of clinical practice guidelines, HTAs or policy; academic research; or clinical decision making. One quarter (31/137; [25%]) of the responders produced NMAs. Less frequently NMAs were used in teaching (3%); were used to inform economic modelling (3%); were included and used in an 'overviews of reviews' (2.5%); or were included in registries, databases or websites (1%). Open ended comments in **Appendix H Table 2** supported the quantitative finding that most participants believed both bias in the individual results of NMA and the authors' conclusions are important to assess.

How would you use the results of your risk of bias assessment?

Of the 298 survey respondents, 145 (47%) reported how they would use a completed risk of bias assessment using our RoB NMA tool (**Appendix H Table 3**). We grouped the ways in which stakeholders would use a completed risk of bias assessment into 12 categories. Of these, 32 respondents (22%) said they would use the tool to assess the certainty in the body of evidence (e.g. using CINeMA [24] or GRADE [25]). Twelve (8%) said they would use the RoB NMA tool in an overview of reviews; and 24 (17%) said they would use it to distinguish between NMAs at high or low risk of bias.

We also report in **Appendix H Table 4** participants' interest in dissemination and engagement activities. The majority of respondents (153/231; 66%) said they would want to read the final study reports, receive updates (147/231; 64%), and receiving training in using the new tool (140/231; 61%).

Discussion

A majority of stakeholders had high interest in the RoB NMA tool and said they would use the tool to distinguish between NMAs at higher or lower risk of bias, and to assess an NMA in an overview of reviews, HTA, or guideline. The survey responses indicated that stakeholders need clear guidance on what would be the intended purpose of a RoB NMA tool assessment. Many thought the assessment could be incorporated into an evaluation of the certainty of the evidence (e.g. CINeMA [24] or GRADE [25]), although our tool in development is intended for the assessment of the potential biases in an NMA, much

like ROBIS [26] is used to assess a systematic review with pairwise meta-analysis, and is not used in a certainty of the evidence evaluation. Only the quantitative results of an NMA (i.e. the analysis) are used in a certainty of the evidence evaluation. This result highlights the need for clear and easy to understand elaboration and explanation materials plus training, better understanding of the purpose and use of the tool itself, and perhaps the development of more structured guidelines for reaching domain-based RoB judgements (for example algorithms) [27].

We aimed to engage stakeholders early in the tool development process for multiple reasons. Engaging with stakeholders should ensure that our tool will be relevant, useable and accepted [11]. The responses provided us with feedback on the training needs of the users of the tool [12] and it will help with future dissemination and communication of findings as stakeholders may be aware that a tool is under development [12, 13]. Finally, the survey is part of an integrated knowledge translation plan to producing research that ultimately achieves a greater impact when put into practice [11].

Implications of this study

Stakeholder surveys have been used to inform the development of other types of tools, systematic reviews and guidelines with success [3, 8, 9, 28–30]. Online surveys have been used to evaluate the reliability and face validity of tools, and the use of a risk of bias tool in practice [27]. However, we are not aware of similar surveys conducted prior to the development of a risk of bias or quality appraisal tool, targeted specifically at stakeholders and other future users of the tool.

Strengths and limitations

A strength of our research was that we conducted it in accordance with a systematic review protocol (<https://osf.io/da4uy/>). We combined newsletter, email distribution lists, and social media to reach a wide range of stakeholders from across the globe. We attempted to maximise the response rate by sending email reminders and repeating messages through social media, and we ended up with a 14% response rate. Response bias in our sample is a major limitation as stakeholders working in higher income countries were more represented. Additionally, the sample represented in this survey, namely individuals involved in guideline development and policymaking, may have been more likely to have responded to a survey about a new tool to assess the bias in NMAs.

A limitation is we did not ask stakeholders to define what their role was and whether they considered themselves: (i) decision makers; (ii) purchasers of services/pharma products; (iii) professional service providers; (iv) evidence generators; or (v) advocates of health promotion. Another limitation is that our targeted emails and social media advertisement may have missed important stakeholders that use NMAs (e.g. members of the Canadian Institutes of Health Research [CIHR] Drug Safety and Effectiveness Network [DSEN] Methods and Applications Group for Indirect Comparisons [MAGIC] Group).

Future research

The results of the survey will inform a new tool to assess biases in NMAs. We will also consider feedback from experts in NMA bias from a Delphi survey. We will use the results of the stakeholder and Delphi surveys to choose and refine the concepts in the tool. The new tool will then be pilot tested in several different user groups: patients, healthcare providers, stakeholders, and researchers. Further research will involve reliability and validity testing.

Conclusions

This survey provided feedback from stakeholders on their preferences for the structure, focus and concepts of a proposed RoB NMA tool, which is under development. Stakeholders preferred a tool to assess both the bias in individual NMA results and authors conclusions. The majority had high interest in the tool and reported they would use the tool to assess an NMA if they had received adequate training on how to use it. With the proposed RoB NMA tool, stakeholders will be able to evaluate an NMA for important biases in the results and conclusions. This tool has the potential to increase the uptake of relevant, higher quality evidence and ultimately improve patient outcomes.

Declarations

Availability of data and materials

The datasets used and/or analysed during the current study are available freely at <https://osf.io/da4uy/>.

Competing interest

AAV was an Associate Editor for the journal, but was not involved with the decision or peer-review process. All other authors declared that they had no competing interests. Brian Hutton has previously received honoraria from Eversana Incorporated for the provision of methodologic advice related to the conduct of systematic reviews and meta-analysis.

Patient and Public Involvement

No patients were involved in our study.

Ethics approval

This study involved human participants but the University of British Columbia Behavioural Research Ethics Board exempted this study (ID H20-02013).

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Authors' contributions

CL conceived of the study; ACT, AAV, BH, CL, IW, JPTH, JMW, PW, SD contributed to the design of the study; CL drafted the survey; CL, LC, and SST inputted the questions into Qualtrics; CL, SS, SST analysed the data; CL wrote the draft manuscript; ACT, AAV, BH, CL, IW, JPTH, JMW, PW, SD revised the manuscript; all authors edited the manuscript; and all authors read and approved the final manuscript.

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Figures

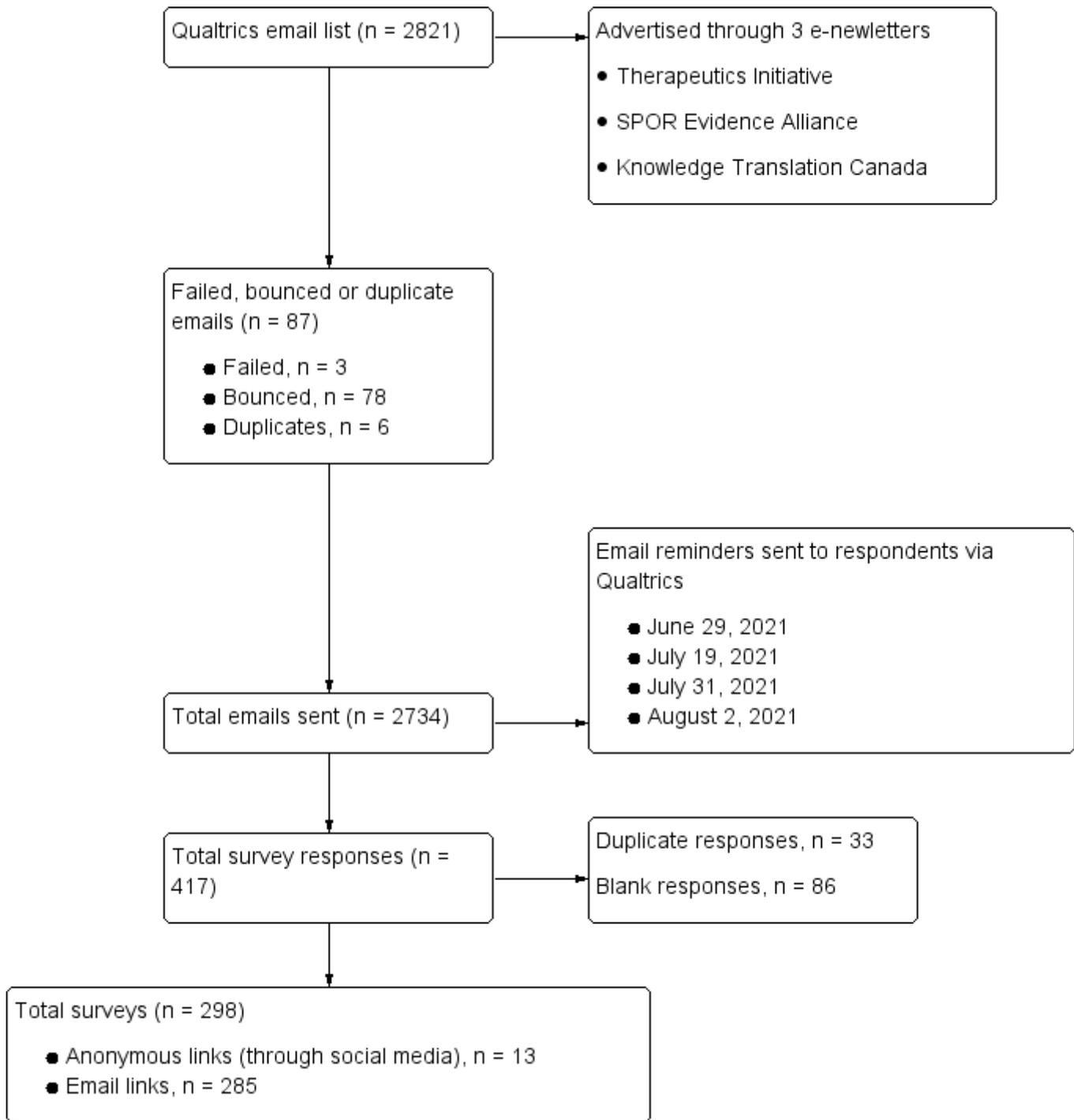


Figure 1

Flowchart of emails sent and responses

Legend: Flowchart of emails sent and responses

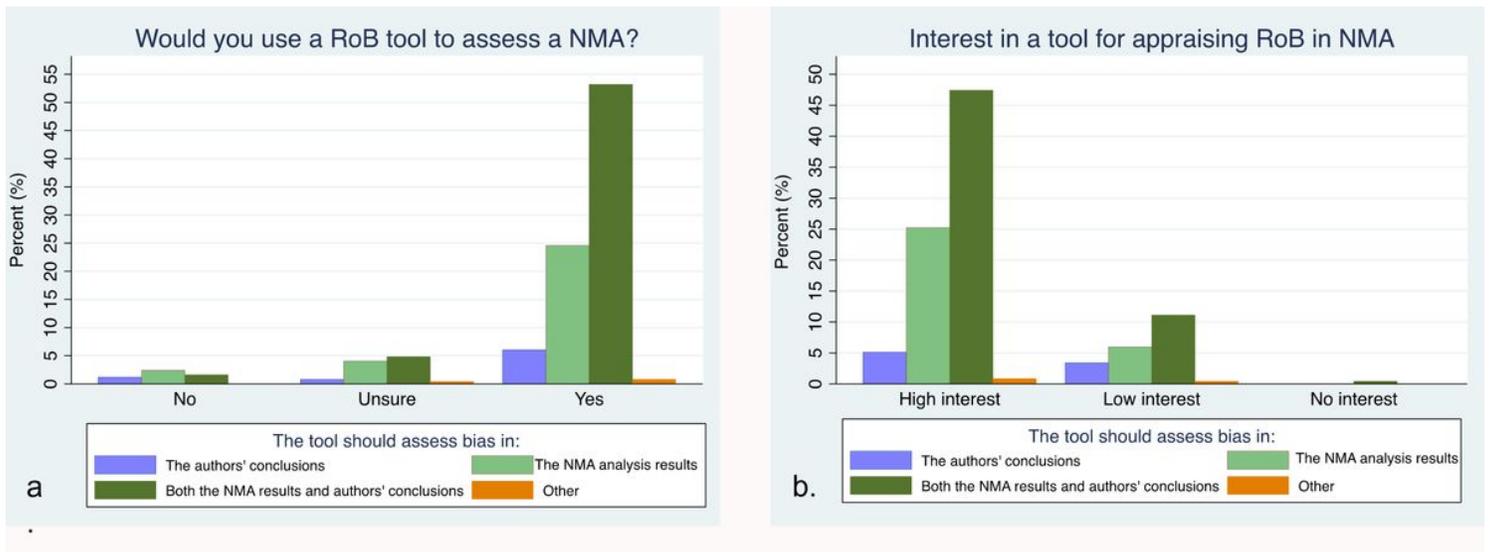


Figure 2

Production and use of NMAs in stakeholders work (a), and interest in a RoB NMAs tool (b)

Legend: Production and use of NMAs in stakeholders work (a), and interest in a RoB NMAs tool (b)
 Legend: Figure 2(a) depicts the proportion of responses to the question of whether stakeholders would use our proposed RoB NMA tool to assess the NMA analysis results, the authors conclusions, or both results and conclusions. Figure 2(b) shows the proportion of responses to the question about interest in a tool for appraising RoB in NMAs.

Supplementary Files

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- [AppendicesAtoH20220214.pdf](#)