Items for consideration in a reporting guideline for mediation analyses: a Delphi study

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Pages: 18

Word count: 2574 (up to 3500)

Figures and tables: 2 figure, 2 tables (1 online supplementary appendix table)

SUMMARY BOX

What is already known about this subject

- Mediation analysis is a widely used quantitative method for investigating the mechanisms of interventions and exposures in randomised controlled trials and observational studies.
- Reporting of studies that use mediation analysis is often heterogeneous and incomplete.

What are the new findings?

- Nineteen international experts reached consensus on 34 items that should be reported in studies that use mediation analysis. These experts also contributed 60 qualitative comments to help refine and prioritise items for the final reporting guideline.

How might it impact on research practice in the foreseeable future?

- The level of agreement and importance of these 34 items, in addition to the experts' comments will inform a consensus meeting to confirm the final list of reporting items that will be included in a reporting guideline for studies using mediation analysis.
- Complete and transparent reporting of studies that use mediation analysis can facilitate clinical application, reproducibility, and evidence synthesis.

ABSTRACT

Objective

Mediation analysis is a widely used quantitative method for investigating how interventions and exposures in randomised controlled trials and observational studies have an effect on healthcare outcomes. This study aimed to assess the importance of items that should be considered in a consensus meeting aimed at developing a guideline for reporting mediation analyses.

Study Design and Setting

A Delphi panel of international experts were asked to rate the importance of a list of items for inclusion in a guideline for reporting mediation analyses. Thresholds for disagreement and consensus on importance for inclusion were specified *a priori*. We used the Research AND Development/University of California Los Angeles appropriateness method to quantitatively assess the importance for inclusion and panel agreement.

Results

Nineteen expert panellists (10 female) from seven countries agreed to participate. All panellists contributed to all three rounds conducted between 10/06/2019 and 06/11/2019. The panel reached consensus on 34 unique reporting items for study design, analytic procedures and effect estimates, with 3 items rated 'optional'. Panellists added one extra item and provided 60 qualitative comments for item refinement and prioritisation.

Conclusion

This Delphi study used a rigorous consensus process to reach consensus on 34 reporting items for studies that use mediation analysis. These results will inform a consensus meeting that will consolidate a core set of recommended items for reporting mediation analyses.

Key words

Mediation analysis, mechanisms, reporting guideline, Delphi

INTRODUCTION

Health exposures and interventions have their effects on outcomes through causal mechanisms.[1] Mediation analyses of randomised controlled trials and observational studies have been used to understand the mechanisms by which an intervention or exposure has an effect on a given outcome.[2,3] Mediation analysis is an analytical method that is used to separate the effect of an exposure or intervention into an ‘indirect effect’ which works through the mechanism(s) of interest, and a ‘direct effect’ which works through all other mechanisms. The results from mediation analyses are used to develop and optimise interventions, and to inform the implementation of policy and clinical care.[4–6] Research into understanding causal mechanisms has been endorsed by the UK Medical Research Council (MRC)[1] and National Institute for Health Research (NIHR) through their Efficacy and Mechanism Evaluation Programme[7] and is also recommended by other national funding bodies.

Although the application of mediation analysis to randomised trials and observational studies is increasing exponentially (Figure 1),[8] recent systematic reviews have identified inadequate reporting of mediation analyses.[9–16] Vo et al (2020) found that 96% of randomised controlled trials that use mediation did not report a sample size calculation and 70% did not report any underlying assumptions of mediation analyses.[16] There are no specific reporting guidelines for studies that use mediation analysis; and generic guidelines such as the Consolidated Standards of Reporting Trials (CONSORT) [17] and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)[18] do not cover the additional aspects of study design, analysis, and effects that should be reported in a mediation analysis. Numerous papers have highlighted the need for a specific reporting guideline for mediation analyses.[9,14–16]

In 2017 we formed an international working group to develop A Guideline for Reporting Mediation Analysis (AGReMA).[19] The AGReMA project methods are in accordance with the Guidance for Developers of Health Research Reporting Guidelines by Moher et al (2010).[20] After the completion of reviews to assess the extent of reporting inadequacies, we conducted a Delphi study to reach expert consensus on items that should be considered in a consensus meeting that will consolidate a core set of recommended items for reporting mediation analyses.

METHODS

A Delphi study is a structured method for achieving consensus among a panel of experts on a given question or topic.[21] The process involved developing an initial exhaustive list of reporting items from previous reviews and consultation with experts, followed by a series of online surveys to: (1) assess the level of agreement on the initial list of reporting items; (2) elicit additional items and

clarification on items to refine the initial list; and (3) identify which items are considered critically important in reporting mediation studies. We preregistered the protocol prior to data collection on 21 May 2019 on the *Open Science Framework*, (<https://osf.io/xwka6>). The University of New South Wales Human Research Ethics Advisory Panel granted ethical approval (HC16599).

Selection of preliminary items

We generated an exhaustive preliminary list of 33 items to be considered in the first round of the Delphi based on a scoping review of existing methods and reporting guidance documents for mediation analyses, and from the findings of our recent overview of systematic reviews.[15] In addition, we examined items from the CONSORT and STROBE checklist [17,18] to identify potential reporting items that could be adapted for mediation studies.

Selection of experts

We compiled a list of experts who had experience in the development and application of mediation analysis. Experts included those who had published original research papers involving mediation analysis or systematic reviews of mediation studies; or a methodological/statistical paper on mediation analysis; or a textbook on mediation analysis. Experts were identified through a variety of sources including an overview[15] and a scoping review of the literature, and through informal discussions with key stakeholders. Recruitment was an iterative process, with the final list of experts for the Delphi panel determined by the AGRReMA working group. The panel size for the Delphi consensus methodology[22] is best qualified in terms of its ‘expertness’ rather than its size,[23] differing to surveys which require larger sample sizes for statistical power. We, like most other Delphi studies [24,25], used the definition by Fink et al. (1984) that an expert “should qualify for selection because they are representative of their profession, have power to implement the findings, or because they are not likely to be challenged as experts in the field”. [26]

Delphi procedure

The Delphi procedure involves a series of ‘rounds’, where panellists independently and anonymously contribute and rank items until pre-defined consensus is reached. A central component of the Delphi procedure is the provision of summary feedback to panellists after each round to encourage the reflection on judgements for subsequent rounds to assist transforming individual opinion into group consensus.[21] The Delphi technique enables the anonymous contribution of experts across geographic locations while reducing the limitations imposed by group dynamics such as the dominance of a few panel members.[21,27,28] We collaborated with CLINVIVO (www.clinvivo.com), an independent company that designs and facilitates web-based Delphi studies. CLINVIVO developed a bespoke electronic data capture program and co-ordinated the data collection and analysis for each Delphi round.

The first Delphi round started on 10/06/2019 and the third (final) round concluded on 06/11/2019. Each round took 3 to 5 weeks. Panellists were sent three reminders to ensure an adequate response rate.

Round one

All panellists were sent a link that included a description of the project, demographic questionnaire, and the preliminary list of reporting items for consideration. Panellists rated the importance of each item on a 9-point Likert scale (1, 'not important', to 9, 'critically important') and scored their confidence in their ratings (1, 'not confident', to 9, 'very confident'). Panellists also provided free-text suggestions on item wording, where applicable, and proposed additional items for consideration in the subsequent round.

Round two

The link to round two included a summary of results from round one (mean scores and standard deviations, median scores and inter-percentile ranges (IPR), histograms and descriptive labels of importance and agreement level, anonymised qualitative comments), together with the panellists' own score of importance for each item.[29] Newly nominated items and suggested re-wording of items from round one were also presented. Panellists re-rated the importance of each item in the light of the round one results and re-scored their confidence in their ratings on a 9-point Likert Scale (1, 'not confident', to 9, 'very confident'). Panellists were informed that items scored for importance ≤ 3 would be excluded, and items scored ≥ 7 would be considered critically important for the draft guideline to be discussed at the consensus meeting.

Round three

The link to round three included a summary of results from round two (mean/medians and standard deviations/IPRs, histograms, descriptive labels of importance and agreement level, anonymised qualitative comments), together with the panellist's own scores on importance. Panellists were informed which items had reached a median importance score ≥ 7 to be included and which items reached a median score ≤ 3 to be excluded. Panellists categorised the remaining items for which consensus had not been reached (median score 4-6 or where disagreement exists – see analysis below) as either: 1) 'Include as optional' or 2) 'Exclude'. Panellist also scored their confidence in their ratings on a 9-point Likert Scale (1, 'not confident', to 9, 'very confident').

Data analysis

We used descriptive statistics to summarise demographic data from included panellists. We coded and thematically grouped the free text comments from round one and two to identify the key issues and

common themes. We used the Research AND Development/University of California Los Angeles (RAND/UCLA) appropriateness method to analyse the scores from each round. We modified this approach by asking panellists to rate ‘importance’ rather than ‘appropriateness’. The RAND/UCLA appropriateness method considers the median panel rating and dispersion of each panel rating to provide an index of importance and agreement.[22] This involves calculating the median score, the IPR (30th and 70th) and the inter-percentile range adjusted for symmetry (IPRAS) for each item being rated. We considered agreement to be present when the IPR was equal to or less than the IPRAS and disagreement to be present when the IPR was greater than the IPRAS.[22] For the analysis of the round one and two, we considered the RAND/UCLA definitions for consensus on items to be considered for the reporting guideline as [22]:

- ‘Include’: panel median of 7-9 for importance, without disagreement
- ‘Uncertain’: panel median of 4-6 for importance, or any median with disagreement
- ‘Exclude’: panel median of 1-3 for importance, without disagreement

For the analysis of round three, we considered consensus for items to be considered for the reporting guideline as [24]:

- ‘Include as optional’: panel majority as include
- ‘Exclude’: panel majority as exclude

RESULTS

Demographics of participants

Of the 40 invited experts, 19 consented and agreed to participate. Table 1 describes the panel demographics.

Table 1 here

Round one

In round one, the 19 panellists rated 33 items of which 30 achieved consensus (Figure 2) as ‘important items’ (median score ≥ 7), three achieved consensus of ‘uncertain importance’ (median score 4-6) and zero were considered ‘not important’ items (median score ≤ 3) (Table 2). The IPRAS was greater than the IPR for all item scores indicating no disagreement between experts in round one. The panellists provided 37 qualitative comments suggesting clarifications for 10 items and the addition of one item (Appendix, Table 1).

Table 2 here

Round two

All 19 panellists completed round two. Panellists rated a total of 14 items, including 10 items adapted from round one to improve clarity (items 1, 8, 7, 9, 12, 14, 18, 19, 24, 26, 31 in Table 2), three items

which were rated of ‘uncertain importance’ (items 7, 17, 30 in Table 2) and one newly suggested item (item 34 in Table 2). Of these 14 items, 11 achieved consensus as ‘important’ (median score ≥ 7) (items 1, 8, 9, 12, 14, 18, 19, 24, 26, 31, 34 in Table 2), three remained ‘uncertain’ (median score 4-6) (items 7, 17, 30 in Table 2) and zero were considered ‘not important’ items (median score ≤ 3). The IPRAS was greater than the IPR for all item scores indicating no disagreement between experts in round two. The panellists provided 14 qualitative comments on 9 items (Appendix, Table 1). These comments provided feedback on the revised wording, the additional item from round one, and the three ‘uncertain’ items. The experts suggested that the three ‘uncertain’ items (items 7, 17, 30, Table 2) were not specific or relevant to mediation studies and should be considered ‘optional’ items.

Round three

All 19 panellists completed round three. Panellists reached consensus to include the three remaining items (items 7, 17, 30) as ‘optional’ items. The panellists provided 9 additional qualitative comments supporting the ‘optional’ consideration for the three items (items 7, 17, 30) (Appendix, Table 1).

In summary, round one reached consensus to include 20 items, round two reached consensus to include an additional 11 items, and round three reached consensus to include the three final items as ‘optional’ (Figure 2). No item from the preliminary list reached consensus for exclusion. The final list included 34 items which achieved consensus to be considered for AGReMA.

Summary of free-text response

The panellists provided 60 item-specific and general comments during the three Delphi rounds (Appendix, Table 1). The comments helped revise 13 (39%) of the preliminary Delphi items, and introduced one additional item. Panellists comments also raised concern on the number of items and the degree of detail; “some of these questions concern overlapping topics, so I would simplify them”. Further, some panellists described the need for the guideline to be more specific to mediation; “I think some of your entries are not specific to mediation analysis but general for any scientific papers”; and the relevance of the guideline for all mediation publication types; “I think [the] reporting guideline also need to take into account whether the entire paper is on mediation, or whether this is just a secondary analysis with the primary analysis (in the same paper) being the analysis of total effects”. All item-specific and general comments were circulated to panellists in each subsequent round.

DISCUSSION

A group of international experts in mediation analysis reached consensus on a preliminary list of 34 items that should be considered in the next stage of the AGReMA project, a consensus and guideline development meeting. The Delphi method is an important step that engages key stakeholders in the

process of developing a reporting guideline.[20] We included a representative panel of experts who achieved a high level of agreement ($\geq 7/9$) and confidence ($\geq 7/9$) in item ratings. In each round of the Delphi, there was no evidence of disagreement between panellists based on the RAND/UCLA appropriateness method. This evidence generated from a group of international experts contributes to the growing literature of reporting practices in mediation analysis and will guide the development of AGReMA.

The panellists' item-specific and general comments provided valuable insights for item refinement and prioritisation. The comments also raised concerns to be further addressed at the consensus meeting, including the need for a concise, mediation specific guideline that is suitable for all mediation analysis publication types. The recent Guidance for Reporting Involvement of Patients and the Public (GRIPP2) reporting guideline produced two versions of their reporting checklist: a long form for studies where patient and public involvement is the primary focus, and a short form for studies where it is a secondary or tertiary focus.[30] This format could also be adopted in AGReMA as mediation analyses of randomised trials and observational studies are also reported as primary and secondary publications.

Although the preliminary list contained an exhaustive list of reporting items, all items eventually reached consensus for inclusion. The majority of items were related to study methods (25/34, 74%). This is in keeping with the function of reporting guidelines to describe study features that influence the risk of bias.[31] Our current list of 34 items is larger than CONSORT (25 items) and STROBE (22 items). In this Delphi, we purposefully split broad concepts into separate items. In the consensus meeting we may merge related items to reduce the number of items to enhance useability.

Strengths and limitations

We prospectively registered the protocol prior to data collection and used robust methodology to conduct this Delphi study. We used *a priori* thresholds of disagreement and consensus. We used the RAND/UCLA method to measure panel disagreement and to establish clear boundaries of 'importance' for inclusion. The Delphi rounds and data collection were externally conducted by CLINVIVO to avoid influence from the AGReMA working group.[32] Finally, we obtained 100% follow-up and completion rates at all rounds.

There are some limitations to our study. The results from this study are only as externally valid as the representation of the expert panel. We attempted to include a diverse, international panel of experts who represented key stakeholders. Nineteen (49%) of the 40 invited experts agreed to participate in this study which is consistent with other Delphi recruitment rates.[25,33] However, we cannot be sure that our sample accurately represents the experts who chose not to participate. The definition of an

expert itself has been debated. To safeguard the validity of our findings, we used systematic methodology to identify experts who meet the definition suggested by Fink et al. (1984).[26]

CONCLUSION

Based on a Delphi process, a preliminary list of 34 reporting items for studies that use mediation analysis were identified. These findings will inform a consensus meeting to develop a guideline for reporting mediation studies that is relevant across disciplines, study designs and publication types.

DECLARATIONS

List of abbreviations

None

Ethics approval and consent to participate

Ethics approval was obtained from the University of New South Wales Human Research Ethics Advisory Panel D: Biomedical, approval number HC16599.

Submission declaration and verification

This article has not been previously published

Availability of data and materials

The dataset used and analysed during this study is available from the corresponding author on reasonable request.

Funding

This work was supported by project funding from the Berkeley Initiative for Transparency in the Social Sciences, a program of the Center for Effective Global Action (CEGA), with support from the Laura and John Arnold Foundation. The funding body did not contribute to the design of the study, the collection, analysis and interpretation of data and in writing the manuscript.

Competing interests

AC is supported by the University of New South Wales Prince of Wales Clinical School Postgraduate Research Scholarship and a NeuRA PhD Candidature Supplementary Scholarship, and is a Catalyst for the Berkeley Initiative for Transparency in the Social Sciences. HL is funded by the National Health and Medical Research Council (APP1126767); National Institute for Health Research (NIHR) Collaboration for Leadership in Applied Health Research and Care Oxford at Oxford Health NHS

Foundation Trust; received project funding from the Berkeley Initiative for Transparency in the Social Sciences, a program of the Center for Effective Global Action (CEGA), with support from the Laura and John Arnold Foundation; and is a Catalyst for the Berkeley Initiative for Transparency in the Social Sciences. SK is funded by the National Health and Medical Research Council (APP1127932).

Author contributions

AC, HL and JM conceived the idea for the project and prepared the initial list of reporting items. All authors contributed to the project design and protocol development. AC and HL collected and analysed data with CLINVIVO. AC wrote the first draft of the manuscript. All authors provided substantive feedback on the manuscript and have read and approved the final version.

Acknowledgments

We thank Dr Rob Froud and the CLINVIVO team for providing their expertise and guidance in conducting and analysing this Delphi study. We are also grateful to the Delphi participants for their substantive engagement and feedback.

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FIGURES

Figure 1. An increasing trend in the publication of mediation analysis research. The figure displays publication counts from two searches in Google Scholar for articles (excluding patents and citations) with “mediation analysis” in the title or anywhere in the text. The search was conducted on 21/01/2020.

Figure 2. Flow of reporting items through the Delphi study

TABLES

Table 1. Demographics of experts

Characteristic	Number of Experts (n=19)
Age, mean (SD)	45.5 (8.7)
Female, number (%)	10 (53%)
Doctorate (PhD) qualification, number (%)	19 (100%)
<i>Country, number (%)</i>	
USA	8 (42%)
England/UK	3 (16%)
Netherlands	3 (16%)
Australia	2 (11%)
Canada	1 (5%)
Denmark	1 (5%)
Belgium	1 (5%)
<i>Academic title, number (%)</i>	
Assistant Professor	8 (42%)
Professor	7 (37%)
Researcher	3 (16%)
Associate Professor	1 (5%)
<i>Primary job title, number (%)</i>	
Statistician	6 (32%)
Epidemiologist	5 (26%)
Clinical researcher	2 (11%)
Health services researcher	1 (5%)
Other	5 (26%)
<i>Role in development and/or application of mediation analysis, number (%)</i>	
Application (applied mediation analysis)	16 (84%)#
Synthesise (review and summarise studies that apply mediation analysis)	15 (79%)#
Methodology (developed study designs)	10 (53%)#
Statistics (developed statistical methods)	9 (47%)#
Other	1 (5%)#

Counts and percentages are not cumulative, panellists were able to select more than one option

Table 2. Summary of ratings for each reporting item

Section	Item number	Final item description	Round 1		Round 2		Round 3	
			Median Importance (IPR 30 th - 70 th)	Median Confidence	Median Importance (IPR 30 th - 70 th)	Median Confidence	Include as optional n (%)	Median Confidence
Title	1	Identify the study as a mediation analysis or mechanism evaluation*	8 (8-9)	9	8 (8-9)	8	included from round 2, not rated in round 3	
Introduction	2	Specify the motivation for using mediation analysis	8 (7-9)	9	included from round 1, not rated in rounds 2 and 3			
	3	An explanation for the biological/theoretical rationale for studying the specified mechanism(s)	8 (7-9)	9	included from round 1, not rated in rounds 2 and 3			
	4	Identify whether the proposed mediation analysis is exploratory or confirmatory	7 (6-8)	8	included from round 1, not rated in rounds 2 and 3			
	5	State specific hypotheses for the mechanism(s) of interest	8 (7-9)	8	included from round 1, not rated in rounds 2 and 3			
	6	Provide preliminary evidence or theoretical explanation for why the intervention or exposure might cause change in the proposed mediator(s)	8 (6-9)	8	included from round 1, not rated in rounds 2 and 3			
	7	If applicable, provide reference(s) to any protocols/preregistrations**	6 (5-7)	8	6 (5-6)	7	18 (95%)	7
	34	Provide preliminary evidence or theoretical explanation for why there could be a relationship between the mediator(s) and outcome(s)	-	-	8 (7-9)	7	included from round 2, not rated in round 3	
Methods	8	Describe how the study design features allow for estimating indirect or direct effects*	9 (8-9)	9	9 (8-9)	9	included from round 2, not rated in round 3	
	9	A clear specification of the main effect(s) of interest (indirect effect and/or direct effect) *	8 (7-9)	8	8 (7-8)	8	included from round 2, not rated in round 3	
	10	Include a graphical representation of the model(s) being tested (<i>e.g.</i> directed acyclic graph, structural equation model)	7 (7-9)	8	included from round 1, not rated in rounds 2 and 3			

11	Report possible confounders in the specified mediation model how they were measured and adjusted	8 (8-9)	8	included from round 1, not rated in rounds 2 and 3		
12	Describe how possible interactions in the specified mediation model (e.g. exposure-mediator interaction) were handled in the analysis*	7 (7-8)	8	7 (7-8)	8	included from round 2, not rated in round 3
13	If relevant, specify the multilevel nature of the exposure, mediator, and outcome (e.g. exposure and mediator at group level, and outcome at individual level)	8 (8-9)	8	included from round 1, not rated in rounds 2 and 3		
14	Outline the causal assumptions that were made (e.g., no unmeasured confounding)*	8 (7-8)	8	8 (8-8)	8	included from round 2, not rated in round 3
15	State how the exposure, mediator and outcome variables were defined and measured	9 (9-9)	9	included from round 1, not rated in rounds 2 and 3		
16	State when the exposure, mediator and outcome variables were measured	9 (9-9)	9	included from round 1, not rated in rounds 2 and 3		
17	If the mediation analysis was preplanned, describe how sample size was determined*#	6 (5-7)	8	6 (5-7)	7	16 (85%) 7
18	Specify criteria or statistical tests used to assess mediation, with references*	8 (7-9)	9	8 (7-9)	8	included from round 2, not rated in round 3
19	Describe statistical models used for the mediator(s) and outcome(s) – i.e., the functional form*	8 (8-9)	8	8 (8-9)	8	included from round 2, not rated in round 3
20	State whether interaction between exposure and mediator was considered, and how they were modelled	7 (7-8)	8	included from round 1, not rated in rounds 2 and 3		
21	If relevant for exposure, mediator, and outcome being considered, state how the following were addressed: - clustering or repeated events - competing risks	7 (7-9)	7	included from round 1, not rated in rounds 2 and 3		
22	If there was missing data, describe how much was missing for the mediator(s) and outcome(s), and provide an explanation of how missing data was handled in the analysis	8 (7-9)	9	included from round 1, not rated in rounds 2 and 3		
23	Describe the method used to adjust for measured confounders of the exposure-mediator, exposure-outcome, mediator-outcome effects	8 (7-9)	9	included from round 1, not rated in rounds 2 and 3		
24	If sensitivity analysis was used, provide a reference to the method*	7 (7-9)	8	8 (7-8)	8	included from round 2, not rated in round 3

Results	25	Provide references to statistical software and packages used	8 (7-9)	9	included from round 1, not rated in rounds 2 and 3			
	26	Report any changes to the selected mediator or statistical model(s) after the study commenced, with reasons*	7 (6-9)	8	7 (6-7)	7	included from round 2, not rated in round 3	
	27	Unstandardized or standardized effects and precision estimates for the total, direct, and indirect effects	9 (8-9)	9	included from round 1, not rated in rounds 2 and 3			
	28	Unstandardized or standardized effects and precision estimates for the exposure-mediator effect	8 (7-9)	8	included from round 1, not rated in rounds 2 and 3			
	29	Unstandardized or standardized effects and precision estimates for the mediator-outcome effect	8 (7-9)	8	included from round 1, not rated in rounds 2 and 3			
	30	If applicable, report the proportion mediated or eliminated with precision estimates*#	6 (5-7)	7	6 (5-6)	7	14 (74%)	7
Discussion	31	Results from any sensitivity analysis (for example, the level of unmeasured confounding that would invalidate the effect of interest)*	7 (6-8)	8	7 (6-8)	8	included from round 2, not rated in round 3	
	32	Discuss limitations of the study, including sources of potential bias (<i>e.g.</i> residual confounding, statistical uncertainty, measurement error, and generalisability)	9 (8-9)	9	included from round 1, not rated in rounds 2 and 3			
	33	Implications of results considering the primary objectives, main findings, limitations, and results from relevant studies	9 (9-9)	9	included from round 1, not rated in rounds 2 and 3			

* item reworded from round 1 qualitative comments

item reworded from round 2 qualitative comments

IPR, Inter-percentile range

APPENDIX Table 1. Qualitative comments provided by panellists in each Delphi round

Section	Item #	Item Description	Qualitative Comments	Qualitative Comments	Qualitative Comments
			Round 1	Round 2	Round 3
Title	1	Identify the study as a mediation analysis or mechanism evaluation	1) "I found this question to be a bit unclear and ambiguous as the word 'identification' can have various meanings in this context." 2) "It very much depends on context" 3) "There are two aspects of theory for mediation, theory for how an intervention will change the mediator and theory for how the mediator is related to the outcome. Both are important. The questions so far conflate these two different aspects of mediation – see for example, MacKinnon 2008 Chapter 2." 4) "I felt this was less important as the answer to this should be clear from the other questions?"		
Introduction	2	Specify the motivation for using mediation analysis			
	3	An explanation for the biological/theoretical rationale for studying the specified mechanism(s)			
	4	Identify whether the proposed mediation analysis is exploratory or confirmatory			
	5	State specific hypotheses for the mechanism(s) of interest			
	6	Provide preliminary evidence or theoretical explanation for why the intervention or exposure might cause change in the proposed mediator(s)	5) "Identification and rationale for the potential mediators is crucial. If we cannot provide why we are testing mediator pathways, there is little use performing the analysis."		
	34	Provide preliminary evidence or theoretical explanation for why there could be a relationship between the mediator(s) and outcome(s)		1) "This is the crux of doing these analyses. A must!" 2) "Mediation analysis is always causal and hence a justification of one's assumption in pursuing it should be given" 3) "Not sure that researchers have to be told to do this, and post hoc reasoning cannot be prevented by rules, but it is something that should be done before running the analysis." 4) "I think this depends partly on the sort of study/what stage the science is at, i.e. earlier phase versus confirmatory. If this was a requirement, it might make doing hypothesis	

			generating studies difficult. And I don't see why it would just apply to mediator outcome and not also "independent variable" or "treatment" and mediator. It is important to provide if it exists – it would make any publication more robust.”
Methods	7	If applicable, provide reference(s) to any protocols/preregistrations#	<p>6) “I am not sure exactly what you mean”</p> <p>7) “Some of these questions concern overlapping topics, so I would simplify them to focus on:</p> <p>a) what is the target of estimation (again please less focus on testing)</p> <p>b) what estimation method was adopted and consequently which assumptions were invoked to interpret the estimates as mediation effects</p> <p>Point b) will encompass:</p> <p>(i) the modelling of confounders</p> <p>(ii) the specific model assumptions (eg independent errors vs clustering; PH assumption)</p> <p>(iii) the parametric specification of the models involved (eg inclusion of non-linearities, interactions, etc)”</p>
	8	Describe how the study design features allow for estimating indirect or direct effects	8) “I would expand the statement to include estimation, and to reduce the focus on testing”
	9	A clear specification of the main effect(s) of interest (indirect effect and/or direct effect)	<p>9) “Language differs across disciplines and terms such as natural indirect effect, natural direct effect, controlled direct effect will not be familiar to people unfamiliar with the counterfactual mediation framework.”</p> <p>5) “I found the original wording of 9 examples more compelling. Same for 14”</p>
	10	Include a graphical representation of the model(s) being tested (e.g. directed acyclic graph, structural equation model)	
	11	Report possible confounders in the specified mediation model how they were measured and adjusted	
	12	Describe how possible interactions in the specified mediation model (e.g. exposure-mediator interaction) were handled in the analysis	10) “The question on interactions seems a bit primitive. The key is not interaction, but model fit. Interactions is just one aspect of this. The designers of the Delphi review process should read up on most recent methods”

		11) "Similarly, the notion of exposure-mediation interactions may not be evident to those working outside of epidemiology."	
13	If relevant, specify the multilevel nature of the exposure, mediator, and outcome (<i>e.g.</i> exposure and mediator at group level, and outcome at individual level)		
14	Outline the causal assumptions that were made (<i>e.g.</i> , no unmeasured confounding)	<p>12) "I find it less important to discuss consistency, but crucially important to discuss exchangeability and positivity."</p> <p>13) "I think stating the assumptions are critical but I would give priority to the exchangeability/no-unmeasured-confounding assumptions over consistency, interactions, positivity. I also think how the assumptions are stated will vary according to the journal. An Epidemiology journal may be happy to see all the technical assumptions. This is NOT the case with clinical journals. With clinical journals I think it is best just to state "The methods assume that baseline covariates control for exposure-outcome-, mediator-outcome-, and exposure-mediator confounding and leave it at that. Likewise, when stating the effect of interest, I think it is good to specify "natural" vs. "controlled" in an epidemiology journal, but I think this is confusing in clinical journals. There I think it is best just to refer to "direct and indirect effects" (if effect decomposition / natural effects are of interest) and to just refer to a "direct effect" (if the controlled direct effect is of interest). Always give references to more technical work but do not necessarily include these technicalities in the methods section itself of a clinical journal"</p>	5) "I found the original wording of 9 examples more compelling. Same for 14"
15	State how the exposure, mediator and outcome variables were defined and measured		
16	State when the exposure, mediator and outcome variables were measured		
17	If the mediation analysis was preplanned, describe how sample size was determined#	14) "I don't think current sample size calculations can well reflect the real complexity of a mediation analysis, and therefore don't think they	<p>1) "I agree with the comments."</p> <p>2) "I agree that sample size is context specific and it is often not useful (small samples etc). However, mediation analysis does require larger</p>

		<p>should be enforced or that a sample size calculation is necessarily indicative of a better quality study.”</p> <p>15) “Power calculation and sample size generation should relate to mediation analysis (not original primary outcome – as is often the case)”</p> <p>16) “Again depends on context. The size of observational studies is often not controllable, eg those derived from linkage across electronic health records, hence reporting of assumptions underlying power calculations are not sensible for all studies.”</p> <p>17) “This depends on the setting and if mediation was a primary aim. I think it is important to acknowledge that power to detect indirect effects is often greater than total effects, but power to detect direct effects is often less than total effects.”</p> <p>18) “Many times these types of studies are secondary analyses of existing data from an observational study.”</p>	<p>numbers (or acknowledgement of bootstrapping etc) so I think it is important to at least acknowledge....”</p> <p>3) “It may not apply to many, and it almost seems like punishment for planning. How about reporting power to detect important effects instead”</p> <p>4) “Although this will often not be the case, I think it is advisable to at least address this issue by including it in the guide”</p>
18	Specify criteria or statistical tests used to assess mediation, with references	19) “Not sure the second sentence is necessary? The wording of the sentence is confusing (particularly "estimate exact values")”	
19	Describe statistical models used for the mediator(s) and outcome(s) – i.e., the functional form	20) “Would suggest separating "Describe statistical models used for the mediator(s) and outcome(s) (the functional form) " from "any assumptions underlying use of such models" – make this two separate criteria. The first point is critical – must describe the models used – the second part is important but not as critical as the first, in my opinion.”	
20	State whether interaction between exposure and mediator was considered, and how they were modelled	21) “Again seems [the] interaction question illustrates lack of current knowledge. Other questions are just generic. They apply to any data analysis so..... what’s the point here?”	
21	<p>If relevant for exposure, mediator, and outcome being considered, state how the following were addressed:</p> <p>- clustering or repeated events - competing risks</p>		

Results	22	If there was missing data, describe how much was missing for the mediator(s) and outcome(s), and provide an explanation of how missing data was handled in the analysis			
	23	Describe the method used to adjust for measured confounders of the exposure-mediator, exposure-outcome, mediator-outcome effects	22) “With sensitivity analysis I think it is fine just to provide the references on the approach used, rather than describe the approach itself.”		
	24	If sensitivity analysis was used, provide a reference to the method			
	25	Provide references to statistical software and packages used			
	26	Report any changes to the selected mediator or statistical model(s) after the study commenced, with reasons	23) “Regarding the changes to hypothesized mediators... I think as our fields evolve and we learn about new potential mechanisms or treatment targets, new mediators may be hypothesized for existing treatment outcomes data. Requiring everything be known from the outset of a study (ie, proposal phase), when treatment trials last years, would be overly confining and would likely restrict progress and potential innovation.” 24) “I did not understand what was meant with this statement”	6) “I do think it's important to report any changes, especially if this takes into account new findings published since the protocol was published. I think this helps strengthen any theoretical underpinnings to the planned mediation analysis.” 7) “Perhaps I am misunderstanding the concept “after the study commenced.” A controlled trial may not have initially aimed to uncover mechanisms, but if the “study” means a subsequent post hoc mediation analysis itself, then yes, changes would need to be reported.”	
	27	Unstandardized or standardized effects and precision estimates for the total, direct, and indirect effects	25) “Not sure what you mean with “Unstandardized/standardized”: does that mean marginal or conditional (on confounders)?”		
	28	Unstandardized or standardized effects and precision estimates for the exposure-mediator effect			
	29	Unstandardized or standardized effects and precision estimates for the mediator-outcome effect			
	30	If applicable, report the proportion mediated or eliminated with precision estimates#	26) “Proportion mediated is unstable unless sample size is large – See MacKinnon et al., 1995 Multivariate Behavioral Research and Miocevic et al., 2015 Behavior Research Methods. There are better effect size measures. But overall I agree it would be wonderful if everyone reported the same effect size measures even in the proportion is unstable unless effect sizes and/or sample sizes are large.”	8) “Not every mediation analysis will lead to focus on proportion mediated, so the guideline should be for precision estimates IF proportion mediated is part of the study aims” 10) “I see where raters are coming from in terms of common reporting metrics and requiring precision estimates, but I agree with the stated problems. If by precision estimates the presentation of CI's is implied, it likely needs to be acknowledged that these may not be bounded by 0 and 100 (probably related to the final rater comment above). What I tend to do is standardise	5) “There are many proposed effect sizes for mediation analysis, and all have weaknesses. The guidelines should not implicitly favour one (and one with such major problems noted in the literature) over the others until the literature can agree on one or two superior effect size measures.” 6) “Not always the point of the paper!” 7) “Agree with the comments above - proportion mediated is not the most accurate way to present results.”

		27) "I would say the issue is that they should report effects or proportion mediated, with precision estimates. I think the precision estimates is the key part so perhaps a point about "including precision estimates on indirect effect or proportion mediated" should be presented separately."	the data prior to analysis and report the standardised estimates and CI's arising from this data, with the point estimate only of the proportion mediated (for continuous mediator and outcome) as it is. I agree it would be good to suggest some sort of standard way of reporting, might standardised estimates be one way? I think it is difficult as there are different ways to standardise and a number of different effect sizes that could be chosen. Then there is the issue of non-continuous outcomes...I haven't worked with these so far so haven't fully thought this through, but does proportion mediated make sense for non-continuous outcomes?" 11) "I think either a measure of the indirect effect OR the proportion mediated is needed. And whichever is provided, it needs to be accompanied by confidence intervals or other measure of precision."	8) "I think it is more important to report the indirect effect and CIs as the CIs for the proportion mediated are a bit odd/possibly not informative. Reporting the indirect effect and CIs should be mandatory, reporting the proportion mediated optional." 9) "I disagree with removing from guidelines or including as optional. Some form of precision estimate must be included. The phrasing should be changed to indicate that precision estimate is provided for either the direct/indirect effects or the proportion mediated."
	31	Results from any sensitivity analysis (for example, the level of unmeasured confounding that would invalidate the effect of interest)	28) "I don't think that sensitivity analysis is a must – maybe re-word as "results from any sensitivity analysis"" 29) "Sensitivity analysis are recommended, but only feasible in very simple settings, so I don't think they should be imposed. Proportion mediated is usually very imprecise so I don't think it should be imposed."	12) "Sensitivity analysis is important, but I do not label it as critical because the involved parameters can be very difficult to choose, and the available sensitivity analyses can only be applied in very simple mediation analyses. This makes it difficult to strive towards enforcing it. Likewise, sensitivity analyses are not routinely considered in observational analyses of total effects because they can be overly complicated."
Discussion	32	Discuss limitations of the study, including sources of potential bias (e.g. residual confounding, statistical uncertainty, measurement error, and generalisability)		
	33	Implications of results considering the primary objectives, main findings, limitations, and results from relevant studies		
		General Comments	30) "None of the questions seems to address the question of no-exposure dep confounding. Also known as no-intertwined causal pathways. This should have been included. Also other mediators (measured or unmeasured) needs to be discussed. And the likely causal links between these mediators." 31) "There could be more about the measurement of the mediators as well, e.g., whether the mediator is a biological measure, weight, or a	General comments in relation to items 7, 17, 30: 13) "I agree with the points mentioned. I am in doubt as to what you actually ask in this round." 14) "If these items were not REQUIRED (because of all the concerns listed) – optional would be ok."

psychological measure such as self-efficacy, or individual perception of a social norm, environmental measure such as perceptions that the person is being rated by experimenters, etc. There are substantial differences in the ease of changing a mediator with an intervention – some intervention components may change a mediator quickly but others may be much more difficult to change. For many studies, the intervention is encouragement to do something, not actually changing the mediator.”

32) “I would recommend the inclusion of a table describing how intervention or treatment was designed to influence potential mediators. Ideally, this should include behaviour change strategies etc.”

33 “I think some of your entries are not specific to mediation analysis but general for any scientific papers – so not sure if you should develop guidelines that are more specific to this area, instead of revisiting gold standard of scientific reporting (eg discussing limitations and potential biases)”

34) “I think reporting guidelines also need to take into account whether the entire paper is on mediation, or whether this is just a secondary analysis with the primary analysis (in the same paper) being the analysis of total effects. If the mediation analysis is a secondary part of the paper then obviously a lot less detail can be included.”

35) “The number of mediation analyses conducted, if not all reported”

36) “Thank you for the opportunity to participate. Some of these were difficult to answer, because they might not be applicable, or because there were several questions included within one question.”

37) “This is great!”