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Development of guidelines for the conduct and reporting of systematic reviews and meta-analyses of newborn and child health research: protocol for PRISMA-PC and PRISMA-C

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Complete List of Authors:	Kapadia, Mufiza; The Hospital for Sick Children, Child Health Evaluation Sciences Askie, Lisa; The University of Sydney, Systematic Reviews & Health Technology Assessment, NHMRC Clinical Trials Centre Hartling, Lisa; University of Alberta, Pediatrics Contopoulos-Ioannidis, Despina; Stanford University School of Medicine, and Meta Research Innovation Center at Stanford (METRICS), Department of Pediatrics, Division of Infectious Diseases Bhutta, Zulfiqar; SickKids Center for Global Child Health, Soll, Roger; University of Vermont College of Medicine; Vermont Oxford Network, Pediatrics Moher, David; Ottawa Hospital Research Institute, Ottawa Methods Centre Offringa, Martin; The Hospital for Sick Children, Child Health Evaluation Sciences
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Development of guidelines for the conduct and reporting of systematic reviews and meta-analyses of newborn and child health research: protocol for PRISMA-PC and PRISMA-C

Mufiza Kapadia¹, Lisa Askie², Lisa Hartling³, Despina Contopoulos-Ioannidis⁴, Zulfiqar A. Bhutta¹, Roger Soll⁵, David Moher⁶, and Martin Offringa¹

Author emails:

mufiza.farid@gmail.com; lisa.askie@ctc.usyd.edu.au; hartling@ualberta.ca;
dcontop@stanford.edu; zulfiqar.bhutta@sickkids.ca; Roger.Soll@uvmhealth.org;
dmoher@ohri.ca; martin.offringa@sickkids.ca

Author' affiliations

1. Child Health Evaluative Sciences, Research Institute, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada
2. Systematic Reviews & Health Technology Assessment, NHMRC Clinical Trials Centre, the University of Sydney, Australia
3. Alberta Research Centre for Health Evidence, Department of Pediatrics, University of Alberta, Edmonton, Canada
4. Department of Pediatrics, Division of Infectious Diseases, Stanford University School of Medicine, Stanford, USA and Meta Research Innovation Center at Stanford (METRICS), Stanford, USA
5. Department of Pediatrics, University of Vermont College of Medicine; Vermont Oxford Network, Burlington, Vermont
6. Centres for Practice-Changing Research, Ottawa Hospital Research Institute

Corresponding author

Mufiza Kapadia, MD, MSc, PhD.
Child Health Evaluative Sciences,
Research Institute,
The Hospital for Sick Children
Toronto, Canada
E-mail: Mufiza.kapadia@sickkids.ca

ABSTRACT

Introduction: Pediatric systematic reviews differ from adult systematic reviews in several key aspects such as considerations related to child tailored interventions, justifiable comparators, valid outcomes and child sensitive search strategies. Available guidelines, including PRISMA-P (2015) and PRISMA (2009), do not cover the complexities associated with reporting systematic reviews in the pediatric population. We aim to develop a minimal set of evidence- and consensus-based PRISMA-PC (Protocol for Children) and PRISMA-C (Children) Extension to guide pediatric systematic review protocol and completed review reporting.

Methods and Analysis: This project's methodology follows published recommendations for developing reporting guidelines and involves the following six phases; i) establishment of a steering committee comprised of representation from key stakeholder groups; ii) a scoping review to identify potential Extension items; iii) three types of consensus activities including meetings of the steering committee to achieve high-level decisions on the content and methodology of the Extensions, a survey of key stakeholders to generate a list of possible items to include in the Extensions, and a formal consensus meeting to select the reporting items to add to, or modify for, the Extension; iv) the preliminary checklist items generated in phase III will be evaluated against the existing evidence and reporting practices in pediatric systematic reviews; v) extension statements and explanation and elaboration documents will provide detailed advice for each item and examples of good reporting; vi) development and implementation of effective knowledge translation of extension checklist, and an evaluation of the Extensions by key stakeholders.

Ethics and Dissemination: This protocol was considered a quality improvement project by the Hospital for Sick Children's Ethics Committee and did not require ethical review. The resultant checklists, jointly developed with all relevant stakeholder will be disseminated through peer-reviewed journals, national and international conference presentations. Endorsement of the checklist will be sought simultaneously in multiple journals.

KEYWORDS

PRISMA-PC, PRISMA-C, Protocol, Pediatric, Systematic Review

Strengths and Limitations

- The methods chosen for the development of PRISMA-PC and PRISMA-C extensions are based on evidence-based principles of reporting guideline development.
- The simultaneous development of reporting guideline for both protocol and reports of pediatric systematic reviews will ensure that relevant items in the protocol (PRISMA-PC) are reflected in the report (PRISMA-C).

- Identification of pediatric systematic reviewers from published reports for the Delphi survey will help in identifying an un-biased selection of participants than the project steering committee could provide alone.
- The involvement of various stakeholders in guideline development will ensure that a wide range of perspectives are captured and will help maximize the impact and implementation of the guideline by relevant stakeholders.

For peer review only

BACKGROUND

Systematic reviews and meta-analyses are considered the highest level in the hierarchy of scientific evidence and are of fundamental importance in decision making by healthcare providers and policy makers. Systematic reviews may also identify the need for further research to establish evidence in a particular population or a sub-set of population. Over the past decade, several evaluations of the methodological quality of systematic reviews have shown limitations, even for those published in high impact factor journals (1, 2). The Preferred Reporting Items in Systematic Review and Meta-Analysis (PRISMA 2009) (3) and PRISMA-P(rotocol-2015) (4) statements were developed to provide guidance on minimal elements needed for optimal reporting of systematic reviews and meta-analyses and their protocols, respectively, in order to maximize the completeness of reporting, transparency and replicability of such studies. An evaluation of the impact of endorsement of the PRISMA statement by specialty journals showed a significant increase of completeness of reporting and methodological quality of systematic reviews in those journals (5).

Rationale for “newborn and child specific” extension of PRISMA

Pediatric systematic reviews differ from adult systematic reviews in several key aspects, as they need to address considerations related to the age specific growth and developmental stages of the patients, newborn and child tailored interventions, justifiable comparators and valid outcomes, and newborn and child sensitive search strategies. Search strategies may need to incorporate specific age related MESH and key search terms such as “neonate”, “infant”, “adolescent”, etc. Furthermore, for systematic reviews with a mixed adult and pediatric population, statistical analyses need to consider subgroup analyses according to targeted pediatric age groups to examine differences in intervention effects (6). These pediatric specific methodological considerations play a role throughout the design, conduct and reporting of pediatric systematic reviews to permit adequate interpretation. Hence, systematic reviews relating to newborn and/or children, including those with mixed adult and pediatric population, require modified and additional standards for reporting items.

The currently available guidelines, including PRISMA-P (2015) and PRISMA (2009), do not cover the complexities associated with reporting (protocols for) systematic reviews in the pediatric population. A scoping review conducted in 2015 identified a need for pediatric extensions of PRISMA (6). This review synthesized evidence on existing evaluations of the quality of reporting of pediatric systematic review protocols and reports. The need for pediatric-specific items in reporting guidelines is also evident from a recent international Consensus meeting on Standard Protocol Items for Randomized Trials in Children (SPIRIT-C) and Consolidated Standards of Reporting Trials in Children (CONSORT-C) held in Toronto in 2014, that agreed on 8 and 14 “pediatric-specific” extension items, respectively, for the design and conduct (SPIRIT-C) and reporting (CONSORT-C) (7) of pediatric clinical trials. At the same meeting, a call was made for guidance to enable scientists to improve the conduct and reporting of systematic reviews in newborn and child health. Limited empirical evidence has shown that the quality of some domain specific pediatric systematic reviews may be low (8, 9). Furthermore, only a small

fraction of systematic reviews are done in children (10), indicating a need to improve the quantity of systematic reviews in children.

Objectives

Our primary objectives are: 1. to develop a minimal set of evidence- and consensus-based PRISMA-PC (Protocol for Children) and PRISMA-C (Children) checklist items to guide pediatric systematic review protocol development and completed review reporting, and 2. to develop and launch a knowledge translation and implementation strategy that encompasses education, dissemination, endorsement and implementation of the final PRISMA-PC and PRISMA-C checklists and accompanying guidance documents by key stakeholders.

Definition and scope of newborn and child relevant systematic reviews

PRISMA-PC and PRISMA-C have adopted the same definition of a “systematic review” and “protocol” as PRISMA-P (4) and PRISMA (3). A systematic review collates all relevant evidence that fits pre-specified eligibility criteria to answer a specific research question. It uses explicit, systematic methods to minimize bias in the identification, selection, synthesis, and summary of relevant studies. A protocol is a document that presents an explicit plan for a systematic review and details the rationale and a priori methodological and analytical approaches for the review. The PRISMA-PC and PRISMA-C checklists will be applicable to pediatric systematic reviews with or without a meta-analysis; and for systematic reviews of randomised controlled trials and/or observational studies.

Table 1: Scope of newborn and child relevant systematic reviews with examples

A newborn and/or child relevant systematic review meets one or more of the following criteria:	
i)	A systematic review with intended population of children only (0-18 years of age). Examples: “Late (> 7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants (11)” and “The effect of beta-blocker therapy on progressive aortic dilatation in children and adolescents with Marfan's syndrome: a meta-analysis (12)”.
ii)	A systematic review with intended population including both children and adult. Examples: “Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma (13)” and “Micronutrient supplementation in children and adults with HIV infection (14)”.
iii)	A systematic review of family based interventions intended to improve the health and well-being of children. Examples: “Group-based parent-training programmes for improving emotional and behavioural adjustment in children from birth to three years old (15)” and “Parent-only vs parent-child (family-focused) approaches for weight loss in obese and overweight children: a systematic review and meta-analysis” (16).
iv)	A systematic review of interventions in pregnancy with objectives to measure outcomes in the neonate. Examples: “Hepatitis B vaccination during pregnancy for preventing infant infection (17)” and “Routine iron/folate supplementation during pregnancy: effect on maternal anaemia and birth outcomes” (18).

METHODS/DESIGN

The project methodology follows published recommendations for developing reporting guidelines (19) and involves the following five phases (see also Figure 1):

Phase I – Project launch

A steering committee comprised of pediatric systematic review authors, methodologists and guidelines developers from leading research institutions (Child Health Evaluation Sciences, and Centre for Global Child Health, The Hospital for Sick Children; Ottawa Hospital Research Institute (OHRI), Alberta Research Centre for Health Evidence (ARCHE), Canada; Stanford University, USA; NHMRC Clinical Trials Centre, University of Sydney, Australia; Cochrane Child Health Field; Cochrane Childhood Cancer Group; Cochrane Neonatology Group) has been identified. The selection of the steering committee members was based on their extensive publication of pediatric systematic reviews and leadership role in systematic review methodology. The steering committee will manage the project via face-to-face (video conferencing) online meetings to discuss and finalize key steps of the guideline development process. They will also help recruit participants for the Delphi survey and Consensus meeting.

Phase II – Review of Evidence and compilation of pediatric specific topics

Based on the results of the scoping review that identified a need of pediatric extensions of PRISMA and PRISMA-P, a preliminary list of pediatric specific methodological issues will be compiled which may require detailed guidance to enhance the quality and consistency of reporting of pediatric systematic review protocols and reports. Furthermore, items that are relevant to pediatric systematic reviews will also be identified from the SPIRIT-C and CONSORT-C checklists.

Phase III – Consensus Process

The PRISMA-PC and PRISMA-C guideline development will involve three streams of consensus activities complemented by evidence gathering as follows:

Meetings of the steering committee: Steering committee meetings will be held regularly throughout the project to achieve high-level decisions on the content and methodology of the pediatric extensions of PRISMA guidelines. Following the synthesis of evidence in phase II, a formal meeting will be held with the steering committee to discuss each topic that requires further guidance. A further meeting will be held following a survey (described below) in which items will be discussed for which strong objection for their omission or inclusion has been received.

- 1. Survey:** An electronic survey of international experts in systematic reviews will lead to the preliminary list of potential pediatric extension items for conducting (PRISMA-PC) and reporting (PRISMA-C) pediatric systematic reviews. Survey methodology has been used as an initial step of guideline development in other guideline extensions, such as PRISMA-IPD (20) and PRISMA-Equity (21). Survey participants will be identified through the editorial boards of Cochrane Child Health, Cochrane Neonatal Group, leading systematic reviewers in the child health field, editorial boards of leading pediatric and other journals and through

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3 networks of our steering committee members. Potential survey participants will be invited
4 by email to complete a web-based survey. The survey will remain open for 3 weeks.
5 Eligibility criteria for survey participation will include a combination of experience in
6 pediatric clinical research and systematic reviews or guideline development. In the survey,
7 each item will be rated as “omit,” “possible,” “desirable,” or “essential” to include in the
8 final checklists (22). The ranked items will then be divided into three groups. *Group I* will
9 contain items with the highest rankings (rated as “essential” by $\geq 70\%$ participants or
10 “essential or desirable” by $\geq 90\%$), and these items will be included for a discussion in the
11 Consensus meeting. *Group II* will contain items with moderate rankings (“essential” or
12 “desirable” by $\geq 80\%$ to $< 90\%$) and will be further discussed by the Steering Committee
13 members for their inclusion or exclusion in the Consensus meeting. *Group III* will contain
14 items with low rankings (i.e., $< 80\%$ “essential” or “desirable”, or $> 70\%$ “omit” or $\geq 85\%$
15 “possible” or “omit”), and these items will be removed and will not be discussed further.
16 Participants will have the opportunity to suggest new items that will be considered by the
17 Steering Committee members to decide whether they should be discussed at the Consensus
18 meeting. In addition, participants will be given an opportunity to comment on each item’s
19 wording or provide general comments on its concept. We considered the need for several
20 (usually three) rounds of the Delphi survey as unnecessary, as a similar multi-round Delphi
21 survey exercise was recently undertaken for the development of SPIRIT-C (Children) and the
22 concepts and feedback on pediatric specific items were already captured by experts in
23 pediatric research and other stakeholders such as journal editors. The feedback for SPIRIT-C
24 items was further reviewed by the steering committee while identifying PRISMA-PC and
25 PRISMA-C relevant topics. However, a survey will establish its applicability to pediatric
26 systematic reviews from the perspective of relevant end users such as pediatric systematic
27 reviewers, clinicians and methodologists.
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2. **Systematic Review:** Two preliminary checklists for PRISMA-PC and PRISMA-C that will be compiled following the survey will then be evaluated against the existing evidence and reporting practices in pediatric systematic reviews. The proposed knowledge synthesis will be completed using a ‘conventional’ systematic review approach. The search strategy will be adopted from tested search filters developed for “systematic review”, “pediatric” and “protocol” (23). The Cochrane Database of Systematic Review and Database of Abstracts of Reviews of Effects (DARE) databases will be searched from January 2010 to December 2014. The reason for limiting the search from 2010 and beyond is because the steering committee decided to review the quality of evidence following the publication of a widely endorsed systematic review reporting guideline i.e., the PRISMA statement, which was published in 2009 (3). The titles and abstracts will be screened for the following eligibility criteria: i) a child-relevant systematic review (as per the definitions provided in Table 1); ii) published in English language; iii) not a commentary or editorial. A random sample of 300 pediatric systematic reviews will be included for this evidence synthesis. The screening of full text will continue until the desired sample size is achieved. We anticipate a limited number of published pediatric systematic review protocols, therefore, all the identified protocols that meet the inclusion criteria will be included. Data will be extracted on; i) the characteristics

of the review; ii) whether the review fulfilled the reporting criteria identified in the proposed items; iii) examples of good reporting.

3. **Consensus meeting:** A Consensus development meeting will be held to reach consensus regarding the minimum items required in a pediatric extension of PRISMA-PC and PRISMA-C. The Cochrane Colloquium will provide the ideal venue to host this Consensus meeting, since this annual meeting is attended by systematic reviewers, representatives from Cochrane and Prospective Register of Systematic Reviews (PROSPERO), and end-users of pediatric systematic reviews such as patients and clinicians, funders, methodologists, guideline developers and journal editors, allowing them to gather under one umbrella for scientific exchange regarding systematic reviews and their methodology, as well as the opportunity to further develop methods. Hence the Cochrane Colloquium will facilitate the meeting of our goals and objectives to gather a wide range of stakeholders for the Consensus process.

The voting process will follow methods used in previous Consensus meetings of guideline development. A preliminary round of voting will take place for each candidate item. Each item will be presented sequentially and debated in the light of the results from the Delphi survey and a summary of literature findings. Votes will be carried out anonymously using an online m-clicker voting system. In order to reach consensus, a classification scheme for selecting items to include in the checklists will be used, similar to the one used in developing the original PRISMA checklist. Briefly, a candidate item will be included within the final checklist if $\geq 80\%$ of voters agree on its inclusion. Items with $\leq 20\%$ votes for inclusion will be excluded from the final checklist. For items that do not reach consensus through the preliminary votes, round table discussions will be held, whereby participants will be given the opportunity to express their points of view in support for or against the inclusion of the item of interest. Discussions will be followed by a second round of voting with the same qualification criteria for inclusion. An experienced moderator not directly involved in this project (to allow unbiased facilitation of the consensus process) will facilitate the meeting.

Phase IV – Write up

Following the Consensus meeting, the proposed checklists for PRISMA-PC and PRISMA-C will be reviewed by the project Steering Committee to draft final checklists using concise, unambiguous, and comprehensive wording, taking into account of any comments obtained in the Delphi survey and the Consensus meeting regarding the wording of the items. Guideline documents will be written, separately for PRISMA-PC and PRISMA-C, including statement and an explanation and elaboration document that will provide detailed advice for each item and examples of good reporting in pediatric systematic review protocols and reports, respectively. The systematic review from Phase III will provide empirical evidence about the relevance and rationale to support pediatric specific reporting items of a systematic review. Results from this review will also provide an evidence base of studies about good reporting practice cited in an accompanying explanation and elaboration documents. Drafts of the statements and the explanation and elaboration manuscripts will be circulated to Consensus meeting participants

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3 to ensure that the documents accurately represent the decisions made during the meeting and
4 provide examples of good reporting for specific items.
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7 **Phase V – Evaluation**

8 A survey of pediatric systematic review authors will be conducted to introduce them to the new
9 items in PRISMA-PC and PRISMA-C, establish the extent to which they had historically
10 addressed those items in their own systematic reviews, and gather feedback on the usefulness
11 of the extension items, including facilitators and barriers of its use. The survey participants will
12 be identified through the database of corresponding authors maintained by Cochrane Child
13 Health.
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16 **Phase VI – Integrated Knowledge Translation and Implementation**

17 PRISMA-PC and PRISMA-C's potential for impacting clinical care in children can only be realized
18 with an effective knowledge translation (KT) and implementation plan. The Steering Committee
19 has been carefully selected to include principal knowledge users who will participate in all
20 stages of the research process. Furthermore, a knowledge translation and dissemination plan
21 will be developed and launched during the Consensus meeting that encompasses education,
22 dissemination and endorsement by various key stakeholders. A Knowledge Translation Planning
23 Template (24) will be followed to develop a KT plan for building awareness and understanding
24 of the guideline (KT goals) with identified knowledge users (e.g. researchers, funders, journal
25 editors). Active involvement of partners will be achieved by bringing representatives together
26 from diverse international stakeholder groups in the development of the checklists, keeping
27 them engaged throughout the development and evaluation process, and providing them with
28 an active role in the strategic planning of actions to amplify the impact of PRISMA-PC and
29 PRISMA-C. Beyond translating the guidelines, evidence based implementation strategies and
30 processes will be developed to encourage its use.
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37 A special session will be held in the Cochrane Colloquium to disseminate the meeting findings.
38 All known (Cochrane) systematic reviewers that are active in child health will be invited to
39 attend this KT meeting. In addition to disseminating knowledge about the need for a newborn
40 and child extension of PRISMA and the method involved in developing this extension, attendees
41 of this session will be invited to offer feedback on the checklist items and facilitators and
42 barriers of its uptake. The goal of the dissemination plan is to maximize awareness,
43 understanding, and use of the PRISMA extensions when reporting protocols and results of
44 pediatric systematic reviews. The potential KT strategies that have been used and proved
45 successful in other guideline development processes such as CONSORT, SPIRIT and PRISMA will
46 be used. These include open access publication and endorsement of the guideline in multiple
47 journals including targeted pediatric journals, endorsement by funding agencies and systematic
48 review registration portals such as PROSPERO, presentations at conferences and other
49 meetings, webinars, short (e.g. 5 minute) you-tube videos explaining each extension item with
50 examples, and a dedicated website that will facilitate feedback about the guideline by end
51 users. The findings will also be shared with the WHO guideline development group and experts
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dealing with Child & Adolescent health interventions and action plans. The final checklists will be copyrighted by the PRISMA-PC and PRISMA-C Groups under the Creative Commons License.

DISCUSSION

The methods employed in developing the PRISMA-PC and PRISMA-C checklists and the accompanying explanation and elaboration documents are based on best practice and evidence-based principles which are widely used in developing reporting guidelines (19). The selection of the Steering Committee will ensure that systematic reviewers, guideline developers and knowledge users with leadership roles in pediatric systematic reviews have actively participated throughout the project. The active recruitment of key stakeholder groups in the Delphi survey and the Consensus Meeting will ensure that a wide perspective is captured and will facilitate endorsement and implementation of the guidelines, hence maximizing their impact. Moreover, in accordance with the EQUATOR network recommendations, consensus on the checklist items will be achieved through an iterative process involving a combination of Delphi survey and Consensus meeting, thereby minimizing potential bias associated with less structured Consensus methods. The gathering of partners, health researchers, and knowledge users in the Consensus meeting will also lead to new and improved collaboration of stakeholders involved in pediatric systematic reviews, including funders, regulators, and journal editors. A systematic review informing the checklist item, with examples of best reporting practice, will ensure that evidence-based practical guidance is available to facilitate its implementation. By employing a validated framework of knowledge translation, we will enable active engagement of key stakeholders by assigning leading roles in the knowledge translation process for their respective stakeholder groups.

The resultant PRISMA-PC and PRISMA-C statements and explanation and elaboration documents will help authors write clear protocols and reports of pediatric systematic reviews and create a framework for reviewers and funders to assess publications and protocols. These checklists will be applicable to both Cochrane and non-Cochrane pediatric systematic reviews involving newborn and children. These checklists will also provide a tool for training students and researchers on pediatric systematic review methodology. Furthermore, end-users of the systematic review, such as pediatricians, policy makers, and other decision makers, will be able to evaluate systematic review validity and applicability in their evidence-based decision making process, thereby increasing the uptake of relevant evidence and ultimately improving child health outcomes.

Competing Interest

LA is a co-convenor of the Cochrane Prospective Meta-analysis Methods Group, a member of the Cochrane Individual Participant Data Meta-analysis Methods Group, an author on many (Cochrane and non-Cochrane) pediatric systematic reviews and a member of the PRISMA-IPD extension working group; RS is the Coordinating Editor of the Cochrane Neonatal Group and is President and Director of Clinical Trials of the Vermont Oxford Network; ZB was a member of PRISMA-Equity extension. There are no other competing interests to declare by the authors.

Author's Contribution

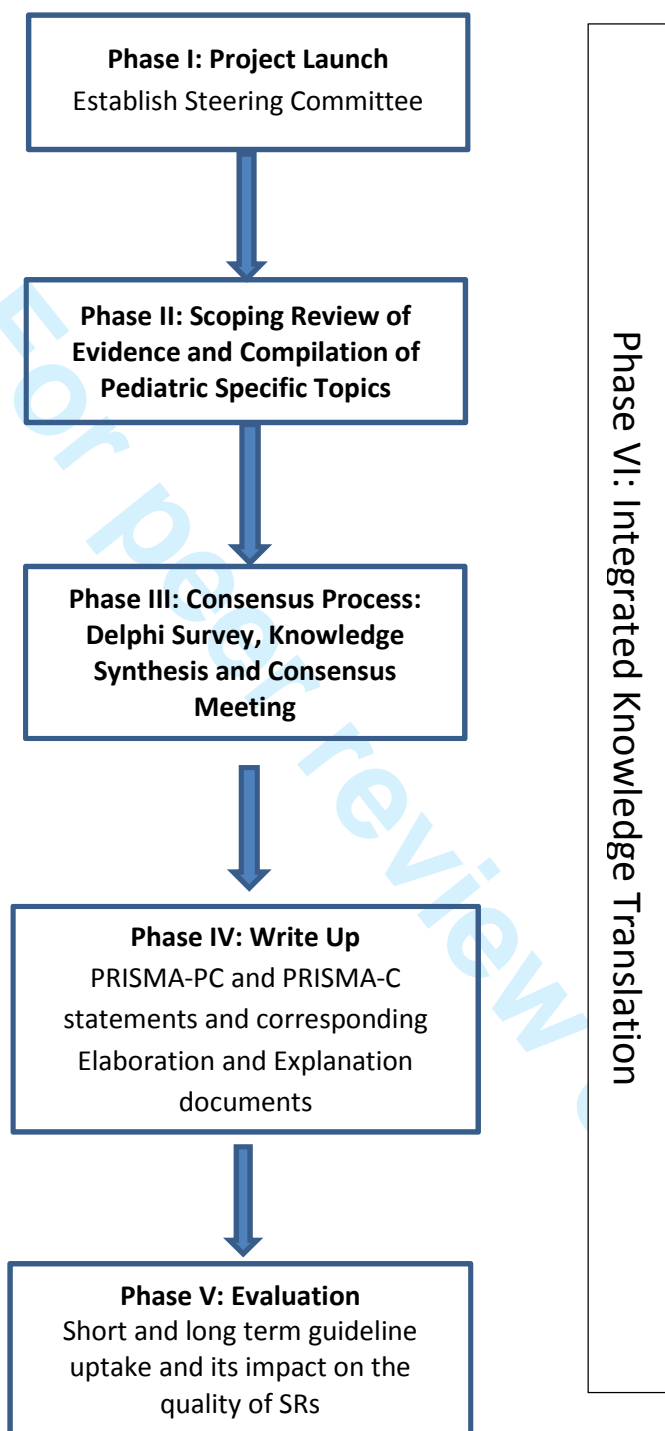
MZK conceived the study and made substantial contributions to design of the manuscript, acquisition of data; MZK and MO participated in the design and coordination to draft the manuscript, analysis and interpretation of data; MZK, MO, LA, LH, RS and DCI have been involved in drafting the manuscript or revising it critically for important intellectual content; All authors read and approved the final manuscript.

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Figure 1: Workflow for PRISMA-PC and PRISMA-C



BMJ Open

PRISMA-Children (C) and PRISMA-Protocol for Children (P-C) Extensions: A study protocol for the development of guidelines for the conduct and reporting of systematic reviews and meta-analyses of newborn and child health research.

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Complete List of Authors:	Kapadia, Mufiza; The Hospital for Sick Children, Child Health Evaluation Sciences Askie, Lisa; The University of Sydney, Systematic Reviews & Health Technology Assessment, NHMRC Clinical Trials Centre Hartling, Lisa; University of Alberta, Pediatrics Contopoulos-Ioannidis, Despina; Stanford University School of Medicine, and Meta Research Innovation Center at Stanford (METRICS), Department of Pediatrics, Division of Infectious Diseases Bhutta, Zulfiqar; SickKids Center for Global Child Health, Soll, Roger; University of Vermont College of Medicine; Vermont Oxford Network, Pediatrics Moher, David; Ottawa Hospital Research Institute, Ottawa Methods Centre Offringa, Martin; The Hospital for Sick Children, Child Health Evaluation Sciences
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Protocol

PRISMA-Children (C) and PRISMA-Protocol for Children (P-C) Extensions: A study protocol for the development of guidelines for the conduct and reporting of systematic reviews and meta-analyses of newborn and child health research

Mufiza Kapadia¹, Lisa Askie², Lisa Hartling³, Despina Contopoulos-Ioannidis⁴, Zulfiqar A. Bhutta¹, Roger Soll⁵, David Moher⁶, and Martin Offringa¹

Author emails:

mufiza.farid@gmail.com; lisa.askie@ctc.usyd.edu.au; hartling@ualberta.ca;
dcontop@stanford.edu; zulfiqar.bhutta@sickkids.ca; Roger.Soll@uvmhealth.org;
dmoher@ohri.ca; martin.offringa@sickkids.ca

Author' affiliations

1. Child Health Evaluative Sciences, Research Institute, The Hospital for Sick Children, University of Toronto, 555 University Avenue, Toronto, Ontario, M5G 1X8, Canada
2. Systematic Reviews & Health Technology Assessment, NHMRC Clinical Trials Centre, the University of Sydney, Australia
3. Alberta Research Centre for Health Evidence, Department of Pediatrics, University of Alberta, Edmonton, Canada
4. Department of Pediatrics, Division of Infectious Diseases, Stanford University School of Medicine, Stanford, USA and Meta Research Innovation Center at Stanford (METRICS), Stanford, USA
5. Department of Pediatrics, University of Vermont College of Medicine; Vermont Oxford Network, Burlington, Vermont
6. Centres for Practice-Changing Research, Ottawa Hospital Research Institute

Corresponding author

Mufiza Kapadia, MD, MSc, PhD.
Child Health Evaluative Sciences,
Research Institute,
The Hospital for Sick Children
Toronto, Canada
E-mail: Mufiza.farid@gmail.com

ABSTRACT

Introduction: Pediatric systematic reviews differ from adult systematic reviews in several key aspects such as considerations of child tailored interventions, justifiable comparators, valid outcomes and child sensitive search strategies. Available guidelines, including PRISMA-P (2015) and PRISMA (2009), do not cover all the complexities associated with reporting systematic reviews in the pediatric population. Using a collaborative, multi-disciplinary structure, we aim to develop evidence- and consensus-based PRISMA-P-C (Protocol for Children) and PRISMA-C (Children) Extensions to guide pediatric systematic review protocol and completed review reporting.

Methods and Analysis: This project's methodology follows published recommendations for developing reporting guidelines and involves the following six phases; i) establishment of a steering committee representing key stakeholder groups; ii) a scoping review to identify potential Extension items; iii) three types of consensus activities including meetings of the steering committee to achieve high-level decisions on the content and methodology of the Extensions, a survey of key stakeholders to generate a list of possible items to include in the Extensions, and a formal consensus meeting to select the reporting items to add to, or modify for, the Extension; iv) the preliminary checklist items generated in phase III will be evaluated against the existing evidence and reporting practices in pediatric systematic reviews; v) extension statements and explanation and elaboration documents will provide detailed advice for each item and examples of good reporting; vi) development and implementation of effective knowledge translation of extension checklist, and an evaluation of the Extensions by key stakeholders.

Ethics and Dissemination: This protocol was considered a quality improvement project by the Hospital for Sick Children's Ethics Committee and did not require ethical review. The resultant checklists, jointly developed with all relevant stakeholder will be disseminated through peer-reviewed journals, national and international conference presentations. Endorsement of the checklist will be sought simultaneously in multiple journals.

KEYWORDS

PRISMA-P-C, PRISMA-C, Protocol, Pediatric, Systematic Review

Strengths and Limitations

- The methods chosen for the development of PRISMA-P-C and PRISMA-C extensions are based on evidence-based principles of reporting guideline development.
- The simultaneous development of reporting guideline for both protocol and reports of pediatric systematic reviews will ensure that relevant items in the protocol (PRISMA-P-C) are reflected in the report (PRISMA-C).

- Identification of pediatric systematic reviewers from published reports for the Delphi survey will help in identifying an un-biased selection of participants than the project steering committee could provide alone.
- The involvement of various stakeholders in guideline development will ensure that a wide range of perspectives are captured and will help maximize the impact and implementation of the guideline by relevant stakeholders.

For peer review only

BACKGROUND

Systematic reviews and meta-analyses are considered the highest level in the hierarchy of scientific evidence and are of fundamental importance in decision making by healthcare providers and policy makers. Systematic reviews may also identify the need for further research to establish evidence in a particular population or a sub-set of population. In order to maximize the potential use of synthesized evidence, there had been repeated calls for transparent and consistent reporting of systematic review (1-3). The Preferred Reporting Items in Systematic Review and Meta-Analysis (PRISMA 2009) (4) and PRISMA-P (rotocol-2015) (5) statements were developed to provide guidance on key elements needed for optimal reporting of systematic reviews and meta-analyses and their protocols, respectively, in order to maximize the completeness of reporting, transparency and replicability of such studies. An evaluation of the impact of endorsement of the PRISMA statement by specialty journals showed a significant increase of completeness of reporting and methodological quality of systematic reviews in those journals (6). Although the PRISMA statement was designed to improve the completeness of reporting of systematic reviews and meta-analyses, there are still other areas e.g., network (7), equity (8) and individual patient data (9) studies that were not fully addressed by the original statement, resulting in PRISMA extensions in these areas.

Rationale for “newborn and child specific” extension of PRISMA

Pediatric systematic reviews differ from adult systematic reviews in several key aspects. Some key issues identified relate to age specific growth and developmental stages of the patients, newborn and child tailored interventions. Since placebo response rates in drug trials appear to be higher in children compared to adults (10, 11), consequently pooled response rates are higher in children than for adults with similar conditions (12). The synthesis of evidence from trials into pediatric systematic reviews is impaired by the use of outcome measurement instruments that are neither qualified nor validated in pediatric sub-populations (13). Pediatric systematic reviews have also been reported weak in terms of the comprehensiveness in their search to identify primary studies (2). Consequently, search filters have been developed to ensure comprehensiveness of pediatric search terms (14-16). Other studies have used search hedges that cover concepts using terms, i.e. neonates, infants, adolescents, harvested from standard term indices to identify more potential relevant articles (17). Furthermore, for systematic reviews with a mixed adult and pediatric population, statistical analyses need to consider subgroup analyses according to targeted pediatric age groups to examine differences in intervention effects (18). These pediatric specific methodological considerations play a role throughout the design, conduct and reporting of pediatric systematic reviews to permit adequate interpretation. The currently available guidelines, including PRISMA-P (2015) and PRISMA (2009), do not cover the complexities associated with reporting (protocols for) systematic reviews in the pediatric population. Hence, systematic reviews relating to newborn and/or children, including those with mixed adult and pediatric population, require modified and additional standards for reporting items.

The need for pediatric-specific items in reporting guidelines is also evident from a recent international Consensus meeting on Standard Protocol Items for Randomized Trials in Children

(SPIRIT-C) and Consolidated Standards of Reporting Trials in Children (CONSORT-C) held in Toronto in 2014, that agreed on 8 and 14 “pediatric-specific” extension items, respectively, for the design and conduct (SPIRIT-C) and reporting (CONSORT-C) of pediatric clinical trials (19). At the same meeting, a call was made for guidance to enable scientists to improve the conduct and reporting of systematic reviews in newborn and child health. Our goal is, therefore, to develop evidence based reporting guidelines for child relevant systematic review protocols and reports in order to improve transparency, quality and quantity of child relevant systematic review.

Objectives

Our primary objectives are: 1. to develop an evidence- and consensus-based PRISMA-P-C (Protocol for Children) and PRISMA-C (Children) checklist items to guide pediatric systematic review protocol development and completed review reporting, and 2. to develop and launch a knowledge translation and implementation strategy that encompasses education, dissemination, endorsement and implementation of the final PRISMA-P-C and PRISMA-C checklists and accompanying guidance documents by key stakeholders.

Definition and scope of newborn and child relevant systematic reviews

PRISMA-P-C and PRISMA-C have adopted the same definition of a “systematic review” and “protocol” as PRISMA-P (5) and PRISMA (4). A systematic review collates all relevant evidence that fits pre-specified eligibility criteria to answer a specific research question. It uses explicit, systematic methods to minimize bias in the identification, selection, synthesis, and summary of relevant studies. A protocol is a document that presents an explicit plan for a systematic review and details the rationale and a priori methodological and analytical approaches for the review. The PRISMA-P-C and PRISMA-C checklists will be applicable to pediatric systematic reviews with or without a meta-analysis; and for systematic reviews of randomised controlled trials and/or observational studies.

Table 1: Scope of newborn and child relevant systematic reviews with examples

A newborn and/or child relevant systematic review meets one or more of the following criteria:	
i)	A systematic review with intended population of children only (0-18 years of age). Examples: “Late (> 7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants (20)” and “The effect of beta-blocker therapy on progressive aortic dilatation in children and adolescents with Marfan's syndrome: a meta-analysis (21)”.
ii)	A systematic review with intended population including both children and adult. Examples: “Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma (22)” and “Micronutrient supplementation in children and adults with HIV infection (23)”.
iii)	A systematic review of family based interventions intended to improve the health and well-being of children. Examples: “Group-based parent-training programmes for improving emotional and behavioural adjustment in children from birth to three years old (24)” and “Parent-only vs parent-child (family-focused) approaches for weight loss in obese and overweight children: a systematic review and meta-analysis” (25).

- iv) A systematic review of interventions in pregnancy with objectives to measure outcomes in the neonate. Examples: “Hepatitis B vaccination during pregnancy for preventing infant infection (26)” and “Routine iron/folate supplementation during pregnancy: effect on maternal anaemia and birth outcomes” (27).

METHODS/DESIGN

The project methodology follows published recommendations for developing reporting guidelines (28) and involves the following five phases (see also Figure 1):

Phase I – Project launch

A steering committee, who are also the authors of the current article, comprised of pediatric systematic review authors, methodologists and guidelines developers from leading research institutions (Child Health Evaluation Sciences, and Centre for Global Child Health, The Hospital for Sick Children; Ottawa Hospital Research Institute (OHRI), Alberta Research Centre for Health Evidence (ARCHE), Canada; Stanford University, USA; NHMRC Clinical Trials Centre, University of Sydney, Australia; Cochrane Child Health Field; Cochrane Childhood Cancer Group; Cochrane Neonatology Group) has been identified. An experienced librarian from the Hospital for Sick Children, Toronto with expertise in developing search strategies for such methodological systematic reviews will be added to the steering committee. The selection of the steering committee members was based on their extensive publication of pediatric systematic reviews and leadership role in systematic review methodology. The steering committee will manage the project via face-to-face (video conferencing) online meetings to discuss and finalize key steps of the guideline development process. They will also help recruit participants for the Delphi survey and Consensus meeting.

Phase II – Review of Evidence and compilation of pediatric specific topics

Based on the results of the scoping review that identified a need of pediatric extensions of PRISMA and PRISMA-P, a preliminary list of pediatric specific methodological issues will be compiled which may require detailed guidance to enhance the quality and consistency of reporting of pediatric systematic review protocols and reports. Furthermore, items that are relevant to pediatric systematic reviews will also be identified from the SPIRIT-C and CONSORT-C checklists. The two preliminary checklists for PRISMA-P-C and PRISMA-C will then be evaluated against the existing evidence and reporting practices in pediatric systematic reviews. The proposed knowledge synthesis will be completed using a recommended methodology for systematic review. The search strategy will be adopted from tested search filters developed for “systematic review”, “pediatric” and “protocol” (14). The Cochrane Database of Systematic Review and Database of Abstracts of Reviews of Effects (DARE) databases will be searched from January 2010 to December 2014. The reason for limiting the search from 2010 and beyond is because the steering committee decided to review the quality of evidence following the publication of a the PRISMA statement in 2009 (4). The titles and abstracts will be screened for the following eligibility criteria: i) a child-relevant systematic review (as per the definitions provided in Table 1); ii) published in English language; iii) not a commentary or editorial. A random sample of 300 pediatric systematic reviews will be included for this evidence synthesis.

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3 The screening of full text will continue until the desired sample size is achieved. We anticipate a
4 limited number of published pediatric systematic review protocols, therefore, all the identified
5 protocols that meet the inclusion criteria will be included. Data will be extracted on; i) the
6 characteristics of the review; ii) whether the review fulfilled the reporting criteria identified in
7 the proposed items; iii) examples of good reporting.
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10 11 Phase III – Consensus Process

12 The PRISMA-P-C and PRISMA-C guideline development will involve two streams of consensus
13 activities as follows:
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15 **Meetings of the steering committee:** Steering committee meetings will be held regularly
16 throughout the project to achieve high-level decisions on the content and methodology of
17 the pediatric extensions of PRISMA guidelines. Following the synthesis of evidence in phase
18 II, a formal meeting will be held with the steering committee to discuss each topic that
19 requires further guidance. A further meeting will be held following a survey (described
20 below) in which items will be discussed for which strong objection for their omission or
21 inclusion has been received.
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25 1. **Survey:** An electronic survey of international experts in systematic reviews will lead to the
26 preliminary list of potential pediatric extension items for conducting (PRISMA-P-C) and
27 reporting (PRISMA-C) pediatric systematic reviews. Survey methodology has been used as
28 an initial step of guideline development in other guideline extensions, such as PRISMA-IPD
29 (9) and PRISMA-Equity (8). Survey participants will be identified through the editorial boards
30 of Cochrane Child Health, Cochrane Neonatal Group, leading systematic reviewers in the
31 child health field, editorial boards of leading pediatric and other journals and through
32 networks of our steering committee members. Potential survey participants will be invited
33 by email to complete a web-based survey. The survey will remain open for 3 weeks.
34 Eligibility criteria for survey participation will include a combination of experience in
35 pediatric clinical research and systematic reviews or guideline development. In the survey,
36 each item will be rated as “omit,” “possible,” “desirable,” or “essential” to include in the
37 final checklists (29). The ranked items will then be divided into three groups. *Group I* will
38 contain items with the highest rankings (rated as “essential” by $\geq 70\%$ participants or
39 “essential or desirable” by $\geq 90\%$), and these items will be included for a discussion in the
40 Consensus meeting. *Group II* will contain items with moderate rankings (“essential” or
41 “desirable” by $\geq 80\%$ to $< 90\%$) and will be further discussed by the Steering Committee
42 members for their inclusion or exclusion in the Consensus meeting. *Group III* will contain
43 items with low rankings (i.e., $< 80\%$ “essential” or “desirable”, or $> 70\%$ “omit” or $\geq 85\%$
44 “possible” or “omit”), and these items will be removed and will not be discussed further.
45 Participants will have the opportunity to suggest new items that will be considered by the
46 Steering Committee members to decide whether they should be discussed at the Consensus
47 meeting. In addition, participants will be given an opportunity to comment on each item’s
48 wording or provide general comments on its concept. We considered the need for several
49 (usually three) rounds of the Delphi survey as unnecessary, as a similar multi-round Delphi
50 survey exercise was recently undertaken for the development of SPIRIT-C (Children) and the
51 concepts and feedback on pediatric specific items were already captured by experts in
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3 pediatric research and other stakeholders such as journal editors. The feedback for SPIRIT-C
4 items was further reviewed by the steering committee while identifying PRISMA-P-C and
5 PRISMA-C relevant topics. However, a survey will establish its applicability to pediatric
6 systematic reviews from the perspective of relevant end users such as pediatric systematic
7 reviewers, clinicians and methodologists.
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11 2. Consensus meeting: A Consensus development meeting will be held to reach consensus regarding
12 the minimum items required in a pediatric extension of PRISMA-P-C and PRISMA-C. The Cochrane
13 Colloquium will provide the ideal venue to host this Consensus meeting, since this annual meeting is
14 attended by systematic reviewers, representatives from Cochrane and Prospective Register of
15 Systematic Reviews (PROSPERO), and end-users of pediatric systematic reviews such as patients and
16 clinicians, funders, methodologists, guideline developers and journal editors, allowing them to
17 gather under one umbrella for scientific exchange regarding systematic reviews and their
18 methodology, as well as the opportunity to further develop methods. Hence the Cochrane
19 Colloquium will facilitate the meeting of our goals and objectives to gather a wide range of
20 stakeholders for the Consensus process.
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24 Each item of the checklist will be discussed in the context of evidence synthesized through
25 the systematic review and results of the Delphi surveys. The voting process will follow
26 methods used in previous Consensus meetings of guideline development. A preliminary
27 round of voting will take place for each candidate item. Each item will be presented
28 sequentially and debated in the light of the results from the Delphi survey and a summary
29 of literature findings. Votes will be carried out anonymously using an online m-clicker voting
30 system. In order to reach consensus, a classification scheme for selecting items to include in
31 the checklists will be used, similar to the one used in developing the original PRISMA
32 checklist. Briefly, a candidate item will be included within the final checklist if $\geq 80\%$ of
33 voters agree on its inclusion. Items with $\leq 20\%$ votes for inclusion will be excluded from the
34 final checklist. For items that do not reach consensus through the preliminary votes, round
35 table discussions will be held, whereby participants will be given the opportunity to express
36 their points of view in support for or against the inclusion of the item of interest.
37 Discussions will be followed by a second round of voting with the same qualification criteria
38 for inclusion. An experienced moderator not directly involved in this project (to allow
39 unbiased facilitation of the consensus process) will facilitate the meeting.
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45 **Phase IV – Write up**

46 Following the Consensus meeting, the proposed checklists for PRISMA-P-C and PRISMA-C will
47 be reviewed by the project Steering Committee to draft final checklists using concise,
48 unambiguous, and comprehensive wording, taking into account of any comments obtained in
49 the Delphi survey and the Consensus meeting regarding the wording of the items. Guideline
50 documents will be written, separately for PRISMA-P-C and PRISMA-C, including statement and
51 an explanation and elaboration document that will provide detailed advice for each item and
52 examples of good reporting in pediatric systematic review protocols and reports, respectively.
53 The systematic review from Phase III will provide empirical evidence about the relevance and
54 rationale to support pediatric specific reporting items of a systematic review. Results from this
55 review will also provide an evidence base of studies about good reporting practice cited in an
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3 accompanying explanation and elaboration documents. Drafts of the statements and the
4 explanation and elaboration manuscripts will be circulated to Consensus meeting participants
5 to ensure that the documents accurately represent the decisions made during the meeting and
6 provide examples of good reporting for specific items.
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9 10 **Phase V – Evaluation**

11 A survey of pediatric systematic review authors will be conducted to introduce them to the new
12 items in PRISMA-P-C and PRISMA-C, establish the extent to which they had historically
13 addressed those items in their own systematic reviews, and gather feedback on the usefulness
14 of the extension items, including facilitators and barriers of its use. The survey participants who
15 were initially recruited for phase III of the project will be invited again to respond to this
16 evaluation survey. In addition, new authors will be identified through the database of
17 corresponding authors maintained by Cochrane Child Health.
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20 21 **Phase VI – Integrated Knowledge Translation and Implementation**

22 PRISMA-P-C and PRISMA-C's potential for impacting clinical care in children can only be realized
23 with an effective knowledge translation (KT) and implementation plan. The Steering Committee
24 has been carefully selected to include principal knowledge users who will participate in all
25 stages of the research process. Furthermore, a knowledge translation and dissemination plan
26 will be developed and launched during the Consensus meeting that encompasses education,
27 dissemination and endorsement by various key stakeholders. A Knowledge Translation Planning
28 Template (30) will be followed to develop a KT plan for building awareness and understanding
29 of the guideline (KT goals) with identified knowledge users (e.g. researchers, funders, journal
30 editors). Active involvement of partners will be achieved by bringing representatives together
31 from diverse international stakeholder groups in the development of the checklists, keeping
32 them engaged throughout the development and evaluation process, and providing them with
33 an active role in the strategic planning of actions to amplify the impact of PRISMA-P-C and
34 PRISMA-C. Beyond translating the guidelines, evidence based implementation strategies and
35 processes will be developed to encourage its use.
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41 A special session will be held in the Cochrane Colloquium to disseminate the meeting findings.
42 All known (Cochrane) systematic reviewers that are active in child health will be invited to
43 attend this KT meeting. In addition to disseminating knowledge about the need for a newborn
44 and child extension of PRISMA and the method involved in developing this extension, attendees
45 of this session will be invited to offer feedback on the checklist items and facilitators and
46 barriers of its uptake. The goal of the dissemination plan is to maximize awareness,
47 understanding, and use of the PRISMA extensions when reporting protocols and results of
48 pediatric systematic reviews. The potential KT strategies that have been used and proved
49 successful in other guideline development processes such as CONSORT, SPIRIT and PRISMA will
50 be used. These include open access publication and endorsement of the guideline in multiple
51 journals including targeted pediatric journals, endorsement by funding agencies and systematic
52 review registration portals such as PROSPERO, presentations at conferences and other
53 meetings, webinars, short (e.g. 5 minute) you-tube videos explaining each extension item with
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3 examples, and a dedicated website that will facilitate feedback about the guideline by end
4 users. The findings will also be shared with the WHO guideline development group and experts
5 dealing with Child & Adolescent health interventions and action plans. The final checklists will
6 be copyrighted by the PRISMA-P-C and PRISMA-C Groups under the Creative Commons License.
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10 DISCUSSION

11 The methods employed in developing the PRISMA-P-C and PRISMA-C checklists and the
12 accompanying explanation and elaboration documents are based on best practice and
13 evidence-based principles which are widely used in developing reporting guidelines (28). The
14 selection of the Steering Committee will ensure that systematic reviewers, guideline developers
15 and knowledge users with leadership roles in pediatric systematic reviews have actively
16 participated throughout the project. The active recruitment of key stakeholder groups in the
17 Delphi survey and the Consensus Meeting will ensure that a wide perspective is captured and
18 will facilitate endorsement and implementation of the guidelines, hence maximizing their
19 impact. Moreover, in accordance with the EQUATOR network recommendations, consensus on
20 the checklist items will be achieved through an iterative process involving a combination of
21 Delphi survey and Consensus meeting, thereby minimizing potential bias associated with less
22 structured Consensus methods. The gathering of partners, health researchers, and knowledge
23 users in the Consensus meeting will also lead to new and improved collaboration of
24 stakeholders involved in pediatric systematic reviews, including funders, regulators, and journal
25 editors. A systematic review informing the checklist item, with examples of best reporting
26 practice, will ensure that evidence-based practical guidance is available to facilitate its
27 implementation. By employing a validated framework of knowledge translation, we will enable
28 active engagement of key stakeholders by assigning leading roles in the knowledge translation
29 process for their respective stakeholders groups.
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37 Potential challenges and mitigation strategies

38 A key challenge is maximising both the breadth and the depth of this work to enhance
39 comprehensiveness and rigor, while ensure timely completion of tasks. We anticipate two years
40 for the completion of this project (May 2015 to April 2017) and the final PRISMA-P-C and
41 PRISMA-C statements and E&E will be published in summer 2017. We have engaged a broad
42 team of co-investigators and collaborators in pediatric systematic reviews and reporting
43 guideline development who will provide support in all aspects of this project such as early
44 critical review of the research findings. We will rely on our experience in conducting evidence
45 synthesis for reporting guideline development such as CONSORT-C and SPIRIT-C (19). Though
46 the current project examines in-depth reporting features of pediatric systematic reviews, based
47 on our intimate knowledge on the subject matter, we are confident that the systematic review
48 can be completed in a timely and efficient manner. Another challenge is ensuring integrated
49 and end of project knowledge translation of new evidence generated by the synthesis and
50 Delphi survey. Our ongoing collaborations with our knowledge users that comprised of the
51 network of our steering committee as well as the potential Delphi participants who were the
52 authors of recently published pediatric systematic review will ensure that the scope meets their
53 decision-making needs and expectations, while adhering to timelines and deliverables. Our
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team has previously completed several successful collaborative projects with diverse stakeholders, and will be a highly effective team. Finally, implementation of the new reporting standard by pediatric systematic reviewers in their future studies may present challenges. Through our involvement of key research leaders and engaging diverse stakeholders and collaborators we hope to disseminate to a large audience in a timely and effective manner.

The resultant PRISMA-P-C and PRISMA-C statements and explanation and elaboration documents will help authors write clear protocols and reports of pediatric systematic reviews and create a framework for reviewers and funders to assess publications and protocols. These checklists will be applicable to both Cochrane and non-Cochrane pediatric systematic reviews involving newborn and children. These checklists will also provide a tool for training students and researchers on pediatric systematic review methodology. Furthermore, end-users of the systematic review, such as pediatricians, policy makers, and other decision makers, will be able to evaluate systematic review validity and applicability in their evidence-based decision making process, thereby increasing the uptake of relevant evidence and ultimately improving child health outcomes.

Competing Interest

LA is a co-convener of the Cochrane Prospective Meta-analysis Methods Group, a member of the Cochrane Individual Participant Data Meta-analysis Methods Group, an author on many (Cochrane and non-Cochrane) pediatric systematic reviews and a member of the PRISMA-IPD extension working group; RS is the Coordinating Editor of the Cochrane Neonatal Group and is President and Director of Clinical Trials of the Vermont Oxford Network; ZB was a member of PRISMA-Equity extension. There are no other competing interests to declare by the authors.

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Author's Contribution

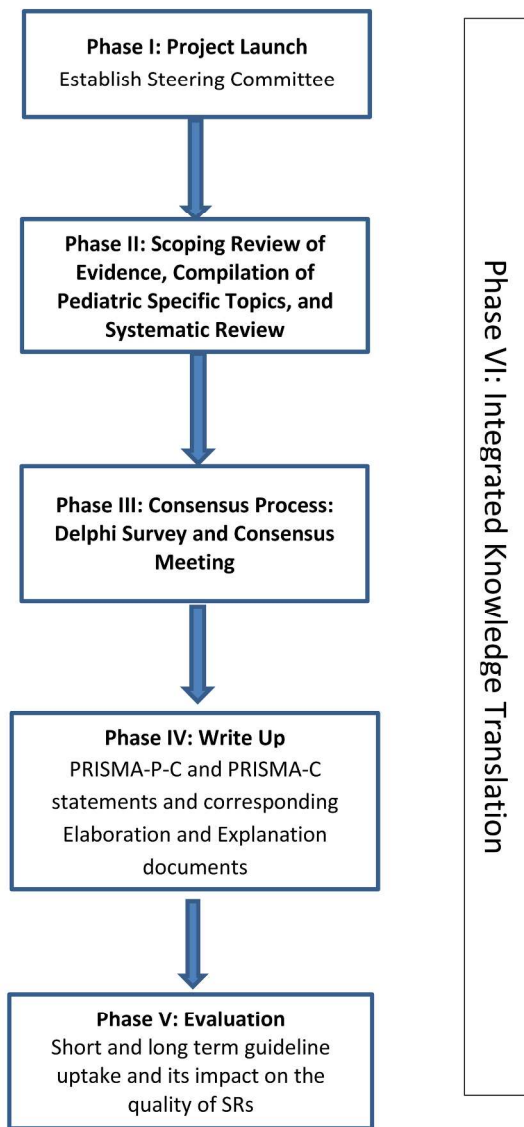
MZK conceived the study and made substantial contributions to design of the manuscript, acquisition of data; MZK and MO participated in the design and coordination to draft the manuscript, analysis and interpretation of data; MZK, MO, LA, LH, RS and DCI have been involved in drafting the manuscript or revising it critically for important intellectual content; All authors read and approved the final manuscript.

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Figure 1: Workflow for PRISMA-P-C and PRISMA-C



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