

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Long-term economic outcomes for interventions in early childhood: Protocol for a systematic review
<b>AUTHORS</b>	Geelhoed, Elizabeth; Mandzufas, Joelle; George, Phoebe; Strahan, Ken; Duffield, Alison; Li, Ian; Cross, Donna

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Gemma Shields The University of Manchester, UK
<b>REVIEW RETURNED</b>	16-Jan-2020

<b>GENERAL COMMENTS</b>	<p>Thank you to the authors for submitting this protocol. It is an interesting topic and I appreciate that they are attempting to find evidence from a range of sectors.</p> <p>I feel it would benefit from some substantial redrafting and revisions. My feedback is below:</p> <ul style="list-style-type: none"><li>• The title and protocol frequently refer to return on investment (ROI), which leads me to believe you are only identifying ROI studies. However, you are including other types of analysis. Wording it as “economic evidence” would be more appropriate.</li><li>• The introduction section would benefit from a clear paragraph briefly explaining the types of economic evaluation included and how these are interpreted. Cost-effectiveness analysis and cost-utility analysis are very different to cost-benefit analysis and return on investment, I’m wary from the text within the paper that it’s not clear to me that the authors understand this or the differences between each type of analysis. In addition, the paper should be accessible to readers who may not be familiar with the topic.</li><li>• Heterogeneity across study methods means that it will most likely be highly inappropriate to attempt to convert study results into the same measurement unit as the authors suggest (assuming I am interpreting the methods correctly). Whilst converting currencies and inflating to common price years is fine, results should be compared separately for study types with different outcomes and conclusions drawn narratively. This narrative approach is quite typical for systematic reviews of economic evidence.</li><li>• The introduction states “determining the optimal timing, duration and threshold of intensity of intervention is an important focus of this review”. This is noted prior to the general aim and does not appear in keeping with the rest of the protocol.</li><li>• Some of the wording in the methods section is quite vague, e.g. “considered” and “may be”, and should be more certain.</li><li>• I would suggest a table is used to present the inclusion and exclusion criteria in the methods section.</li></ul>
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	<ul style="list-style-type: none"> <li>• Why is public health written in speech marks? In addition, could you provide some examples of types of public health interventions that you expect to identify?</li> <li>• The methods section needs to specify which outcomes will be included in the review.</li> <li>• The methods section describes “experimental and quasi-experimental studies”. It would make more sense to me if you focused on the types of economic studies included (by analysis type with is discussion more in the introduction and methods). E.g. will you include trial-based analysis and modelling studies? Or only trial analysis? It is not clear to me.</li> <li>• The title specifies long-term; however, it is not obvious to me where you will consider this. E.g. what if the economic evaluation has a time horizon of 6 months, will it be excluded? What cut-off will you use for study timeframes?</li> <li>• Search terms to identify economic evidence seem very brief. Why not use published search terms for economic evaluation? Examples here: <a href="https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/filters-to-find-i">https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/filters-to-find-i</a></li> <li>• Likewise, why not use a published checklist for critically appraising the studies?</li> <li>• Will there be any language restriction for included papers?</li> <li>• Will a PRISMA diagram and checklist be included when the review is written up?</li> <li>• Rearranging the text in the introduction would be useful as it jumps around a bit, e.g. first sentence followed by paragraph 2 followed by the remainder of paragraph 1.</li> <li>• The introduction of the abstract is a bit wordy and I am not immediately clear why you want economic evidence.</li> <li>• The strengths and limitations section is too brief and quite messy, I imagine this was written in a hurry prior to submission and just needs to be revisited.</li> </ul> <p>I hope these comments are helpful in improving the protocol.</p>
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<b>REVIEWER</b>	Anita Patel Anita Patel Health Economics Consulting Ltd, UK
<b>REVIEW RETURNED</b>	30-Jan-2020

<b>GENERAL COMMENTS</b>	<p>This paper sets out a protocol for a systematic review. Building on a broader evidence base that indicates that investment in early childhood generates positive individual and societal returns, the rationale for the review is clear and straightforward. It aims to systematically review literature on economic returns from investments in early childhood across multiple sectors. Key objectives are to identify the most beneficial investments to inform policy and practice, and to highlight gaps in current research. If done well, the results of this review will be helpful for a range of stakeholders across multiple service sectors.</p> <p>The paper is easy to read and covers the broad elements one would expect to find in a systematic review protocol. However, the diversity of sectors and broad scope of interventions brings a particular complexity to the review (e.g. handling differences in methodological approaches, metrics used to assess value etc.). While this is acknowledged as one of the potential limitations of the review, my main concern is that there is insufficient planning for these eventualities – or at least insufficient detail to judge to what extent these issues have been considered. In its current form, the protocol leaves some scope for variation/deviation, particularly with</p>
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	<p>regards to eligibility criteria and how results will be synthesised for the purpose of comparison (since one of the key aims is to identify which interventions provide the best returns). So while various items are marked off the methods section of the attached PRISMA checklist, I'm not sure that the protocol overall meets the spirit of those guidelines. Specific examples of gaps are as follows:</p> <p>Page 6, lines 40-44: While I understand why the authors want to focus on "public health" interventions, this criterion may need to be a bit more specific for operational purposes, otherwise there is too much scope for subjectivity regarding what interventions will be included/excluded.</p> <p>Page 6, lines 47-52: Plans for assessing study quality could be more specific. Currently, there is mention of "a set template" to assess study design and some specific elements are later mentioned in relation to data extraction. Will these assessments be developed specifically for this review or will the authors draw more directly from existing measures of quality for experimental and quasi-experimental studies?</p> <p>Page 6, lines 54-59: "Studies will be excluded if costs unrelated to outcomes for young children are the primary outcome measure or if outcomes are not included in the publication." Does this disqualify studies that have published costs and outcomes in separate publications? Also, I am not quite clear on which outcomes will/won't be considered - a more detailed and informed basis for this decision would be helpful.</p> <p>Page 7: Information sources: It would be helpful to have more details on the selection and justification of the information sources. I am not familiar with databases for the non-health sectors so am unsure whether those listed are appropriate and sufficient. Were other education-related databases considered? Will evidence on social care interventions be picked up within the listed databases? For example, just a quick search led me to a university library webpage (<a href="https://subjects.library.manchester.ac.uk/education/databases/">https://subjects.library.manchester.ac.uk/education/databases/</a>) which lists various other (non-US) education-related databases and leads me to wonder whether the authors have considered these and ruled these out.</p> <p>Page 7: Search strategy: This is fairly brief, general and not repeatable, as per the criteria in the PRISMA checklist. Currently, the wording could imply that non-monetary outcomes for non-health interventions will not be considered, which is contrary to statements elsewhere in the paper. If there is an intention to consider non-monetary outcomes other than QALYs and DALYs, how will these be picked up – just through the abstract screening or in a more targeted way through the search strategy?</p> <p>Page 11, lines 10-18: Synthesis/comparisons: I think the authors would benefit from expanding the methods for this section. While I understand that there will be significant heterogeneity in the presentation of costs and outcomes between studies, advanced planning can only help. For example, there is no detail on how DALYs and other outcomes (other than QALYs) would be monetised for the purpose of comparisons. The global perspective adds another complexity to this. While some of these issues are picked up within the Discussion section, there is an impression that</p>
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	there will be somewhat of a 'wait and see' approach. I think the authors would benefit from a little more forethought on this e.g. developing/adopting an overall framework for categorising and handling the different type of outcomes and the potential methodological approaches to each.
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<b>REVIEWER</b>	Stacey George Flinders University, Australia
<b>REVIEW RETURNED</b>	02-Feb-2020

<b>GENERAL COMMENTS</b>	A very important study. Its very logical and detailed.
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### VERSION 1 – AUTHOR RESPONSE

In response to reviewer 1 comments:

- We have reviewed the use of the term return on investment and have reworded where it has been used to broadly describe economic evaluation.
- The terms cost-effectiveness analysis and cost-utility analysis are briefly described in the fourth paragraph of the introduction. As described in the limitations, our cross-sectoral approach inevitably includes all of the ratios listed by the reviewer and will require careful comparison. We believe that further detail within the introduction would distract the reader from the main aims of the review. We agree that the information should be accessible to a broad readership and will ensure that the review paper will carefully describe the ratios used in analysis.
- As in the comment above, we will definitely report findings by subgroup to ensure we do not draw misleading conclusions. We accept that the heterogeneity will preclude general meta-analysis. It will be interesting however to compare the value of investment across different sectors (for example education and health) and to identify the methodological barriers in quantitative comparison.
- We have deleted the sentence "determining the optimal timing, duration and threshold of intensity of intervention is an important focus of this review". We do hope to gain insight into optimal timing and intensity of interventions, but this is not reflected as a major focus.
- The methods section has been reviewed and amended for clearer text.
- A table has been added to present the inclusion and exclusion criteria in the methods section.
- The reference to "public health" has been removed. The search online is deliberately broad to include all public health interventions where investment has been compared with long term outcomes.
- The words "experimental and quasi-experimental studies" have been removed for clarity. Because we are assessing long term outcomes of early childhood investment, we expect that almost all studies will include some modelling and that some models will be based on trials.
- Studies will be included where outcomes have been presented that extend can be extrapolated to lifetime or late adulthood , either through modelling or long term leads.
- Thank you for the reference for published search terms for economic evaluation. The variability presented by the ISSG Search Filter Resource illustrates the difficulty in applying search terms. This resource has a particular focus on health and because our intention was to scope as broadly across disciplines as possible, we sought assistance from two librarians – one generalist and one specialist (business and economics). We also sourced input from our advisory group, which included economists across disciplines. To translate the search strategies across different databases we took advice from the librarians. The UWA health and medical librarians used the Flinders guide for most databases- <http://flinders.libguides.com/systematicreview/building>.
- We sourced a number of checklists for potential application to our review, including CHEERs and The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews. However, as recently reported 'A standardised approach on how to best summarise cost-effectiveness evidence is lacking..' (Jacobsen, E., et al.. Challenges of Systematic Reviews of Economic Evaluations: A Review

of Recent Reviews and an Obesity Case Study. *PharmacoEconomics* 38, 259–267 (2020).  
<https://doi.org/10.1007/s40273-019-00878-2>)

Given the challenges unique to this review, we developed a checklist that best represented the information we intend to collate including data that will provide information about the quality of the study in addition to simply checking whether or not methodological components have been included.

- We did not include a language restriction in our search strategy.
- The PRISMA diagram and checklist will be included when the review is written up; and this is now noted under Synthesis.
- The text in the introduction has been reviewed and rearranged.
- The wording of the abstract has been tightened.
- The strengths and limitations section has been reworded.

In response to Reviewer 2 comments:

- As noted in previous comments, the protocol has been developed in consultation with economists across education, welfare, labour and health. Pilot reviews have indicated the heterogeneity in methodological approaches, so we will have to carefully address comparison. The limitations are not only sector specific. We are aware of additional challenges, such as different discount factors which tend to be country-specific; different comparators which alter incremental cost-effectiveness according to available infrastructure; different cost-effectiveness according to prevalence of disease. We believe however that the aim to address a review of the international data will provide a valuable platform both to identify how comparable the data is and to develop a roadmap for future economic reviews requiring intersectoral study.
- page 6, lines 40-44: We have endeavoured to reword for better clarification. Our search strategy is deliberately broad and the reference to public health aimed to encapsulate interventions that target prevention or amelioration.
- The plans for assessing study quality: (as per reviewer 1 comment) We sourced a number of checklists for potential application to our review, including CHEERs and The Joanna Briggs Institute Critical Appraisal tools for use in JBI Systematic Reviews. However, as recently reported 'A standardised approach on how to best summarise cost-effectiveness evidence is lacking..' (Jacobsen, E., et al.. *Challenges of Systematic Reviews of Economic Evaluations: A Review of Recent Reviews and an Obesity Case Study. PharmacoEconomics* 38, 259–267 (2020). <https://doi.org/10.1007/s40273-019-00878-2>). Given the challenges unique to this review, we developed a checklist that best represented the information we intend to collate including data that will provide information about the quality of the study in addition to simply checking whether or not methodological components have been included.
- page 6, lines 54-59: We have reworded to make this less confusing. Note that if studies publish costs and outcomes in separate publications, they will not fulfil the criteria for inclusion.
- page 7 information sources: (per response to reviewer 1 comment) Because our intention was to scope as broadly across disciplines as possible, we sought assistance from two librarians – one generalist and one specialist (business and economics). We also sourced input from our advisory group, which included economists across disciplines. To translate the search strategies across different databases we took advice from the librarians. The UWA health and medical librarians used the Flinders guide for most databases- <http://flinders.libguides.com/systematicreview/building>
- page 7 search strategy: this has been reworded to reflect that only standard economic evaluation outcomes will be included, ie QALYs, DALYs, LYG – other non monetary outcomes will not be included.
- page 11, lines 10-18: The primary outcomes will present cost-effectiveness within subgroups using comparative methodology. We will explore the potential for monetising health outcomes using willingness-to-pay thresholds, but we recognise the limitations of such methods. Given our innovative approach which includes all sectors, few published studies have aggregated such data. Our pilot work so far indicates significant heterogeneity as expected, however we will seek advice from experts as required.

## VERSION 2 – REVIEW

<b>REVIEWER</b>	Gemma Shields The University of Manchester, United Kingdom
<b>REVIEW RETURNED</b>	30-Mar-2020

<b>GENERAL COMMENTS</b>	I am pleased to see the authors have addressed reviewer comments well. My only remaining comment would be that an alternative title e.g. "Economic evaluations for interventions in early childhood: protocol for a systematic review" would be more suitable.
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<b>REVIEWER</b>	Anita Patel Anita Patel Health Economics Consulting Ltd, UK
<b>REVIEW RETURNED</b>	05-May-2020

<b>GENERAL COMMENTS</b>	<p>The authors' reply to the editor makes it clear that they understand and have considered the various challenges associated with this review, possibly more so than is conveyed in the paper. There are however some points which may warrant further attention. For example, their response regarding the use of quality checklists seems to conflate two separate points (how to summarise the results of economic evaluations in a review and how to quality assess different types of studies). E.g. Even if the already available quality checklists are not relevant to all studies, this shouldn't necessarily prevent their use for the subset that are relevant. So it would be a shame to discard well used/tested tools just because they aren't applicable to all studies.</p> <p>Another is that including only those studies that have 'standard economic outcomes' may end up excluding informative evidence, especially given the broad scope of the interventions under review. So while they have addressed key issues raised by both reviewers, my final suggestion would be to ensure that key nuances related to the design and implementation of this review are discussed in the paper as fully as possible.</p>
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## VERSION 2 – AUTHOR RESPONSE

Thank you for the opportunity to make revisions to our previous submission. Please see our actions in response to editorial and reviewer comments.

1. We have added a sentence with search start and planned end date in the abstract.
2. We have added a sentence describing the publication plan in the abstract.
3. We have added an Ethics and Dissemination section to the main text.
4. Title: The reviewers challenged the terminology 'return on investment' so the title has been amended to: Long term economic outcomes for interventions in early childhood: protocol for a systematic review.

(The long term outcomes are a pivotal component of the aim of the review and we believe important to include in the title.)

5. An extra sentence on page 8 of the manuscript addresses comments regarding checklists.

6. Further clarification of the 'standard economic outcomes' nuances are added on page 10.