

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

TITLE (PROVISIONAL)	The impact of patient's health related quality of life on physicians' therapy and perceived benefit in acute coronary syndromes: protocol for a systemic review of quantitative and qualitative studies
AUTHORS	Kaambwa, Billingsley; Gesesew, Hailay; Horsfall, Matthew; Chew, Derek

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Xianliang Liu Institution and Country: The Hong Kong Polytechnic University Competing interests: No.
REVIEW RETURNED	12-Oct-2018

GENERAL COMMENTS	<p>Thank you for inviting me to review this protocol. The methodology needs greater explanation.</p> <p>(1) The Background proposed by the authors to justify this review is inadequate. The aim of this review is not clear for me and the rationale for this study is unclear;</p> <p>(2) Perhaps it is better to add the search strategy as an appendix, it is not possible to review the search strategy as full details have not been included and please add the date for the database search;</p> <p>(3) One of my main concerns is the exclusion of unpublished literature. Not seeking unpublished literature is not consistent with the Cochrane approach;</p> <p>(4) Quality assessment should be more specific;</p>
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REVIEWER	Reviewer name: Mr. H. B. oshi Institution and Country: University Hospital of Wales and School of Medicine, Cardiff Competing interests: None declared
REVIEW RETURNED	28-Oct-2018

GENERAL COMMENTS	<p>This is the protocol for a proposed systematic review of qualitative and quantitative studies. There are certain issues that need clarification and might limit the study results.</p> <p>1. How do authors aim to standardise ACS and its treatments from clinical point before comparing the HRQoL associated with them.</p> <p>2. How would the impact of comorbidities, acute against chronic events, prior interventions would be evaluated before standardising the patient groups? Would there be subgroups?</p> <p>3. One major issue is heterogeneity of generic and disease specific (if any) measures used. What would be the authors' strategy to have meaningful comparisons between different domains and reported outcomes?</p>
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	4. Are there enough studies, in the literature, to establish the links between the HrQoL assessments and physician's therapy and perceptions of the benefit? How would authors separate the impact of other confounding factors (e.g. availability of resources, expertise, commercial interests) in a clear way?
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REVIEWER	Reviewer name: Michael H McGillion Institution and Country: McMaster University, Canada Competing interests: None declared.
REVIEW RETURNED	28-Oct-2018

GENERAL COMMENTS	<p>Thank you for the opportunity to review this manuscript, which addresses an important topic. I am interested in seeing the results of this unique systematic review. There are a some items to be addressed, in my view, which will serve to strengthen the manuscript and enhance the strength of the upfront argument, pertaining to the need for this review. Below, I have included narrative-based responses to most review checklist items (in cases where I had comment to offer), which I hope will be helpful to the authors:</p> <p>Is the research question or study objective clearly defined? The study objective is clearly defined. The authors of this protocol propose to synthesize all quantitative and qualitative evidence available to answer the question, "How does patients' health-related quality of life (HRQoL) influence treatment decisions and subsequent risk benefit analyses by physicians in patients with acute coronary syndrome?"</p> <p>Is the abstract accurate, balanced and complete? The abstract is structured as the following sections: Introduction, Methods & Analysis, Ethics & Dissemination. This is an appropriate structure for a systematic review protocol.</p> <p>Is the study design appropriate to answer the research question? The proposed study is a systematic review, which would be appropriate to comprehensively synthesize the available literature to answer the research question. However, the protocol as written needs requires amendment in some places in order to conform to systematic review methodology (see next question, methods).</p> <p>Are the methods described sufficiently to allow the study to be repeated? The methods need to be flushed out with further detail in some places, and require further clarification in others. Key issues are as follows:</p> <ul style="list-style-type: none"> i. It seems that Percutaneous transluminal angioplasty (PTA or PTCA) was not included in the search terms. Inclusion of all relevant search terms may impact number of available studies returned for analysis. ii. The authors state that they aim to synthesize all quantitative and qualitative literature applicable to the study topic, however, no searching of grey literature or contacting study authors is mentioned – suggest that these additional search strategies be included. iii. Suggest including a draft search for at least one database, as per PRISMA-P guidelines. iv. The authors may consider specifying the specific quality appraisal tools they plan to use.
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	<p>v. The authors should describe their plans to manage the data from this study (e.g. software programs used for analyses).</p> <p>Are research ethics (e.g. participant consent, ethics approval) addressed appropriately? The authors have included a statement that they will not seek ethics approval as no primary data will be collected.</p> <p>Are the outcomes clearly defined? Some ambiguity, I think, exists in the outcome as defined by the researchers. For instance: i) HRQoL is not defined for the purposes of the review. It may indeed be that no a priori definition is specified in order to be inclusive of a broad range of literature. If this is the case, it may be helpful for the authors to state this decision. In the background literature review, however, I think it would be helpful to at least provide common definitions of HRQoL, as a precursor to the fact that a number of definitions and measures may ultimately be included. ii) The authors only mention the use of validated tools to measure HRQoL in the conclusion, this should be brought up front to help with cohesion of argument and iii) The authors do not define how "impact" of HRQoL on physicians' treatment decisions or assessment of risk will be measured; this needs to be addressed. iv) It is not clearly presented how HRQoL may in fact impact estimation of bleeding events post-procedure. The argument in support of this statement needs to be further developed- same for mortality.</p> <p>Are the references up-to-date and appropriate? Several references are >10 years old. Suggest updating if and where possible.</p> <p>Are the study limitations discussed adequately? The authors list one study limitation at the beginning of the protocol: "The measurement of quality of life may be based on dissimilar tools and may have its own limitations on estimating outcomes." Suggest a more thorough exploration of limitations (e.g. included studies were limited to English language [if correct], etc.)</p> <p>Is the supplementary reporting complete (e.g. trial registration; funding details; CONSORT, STROBE or PRISMA checklist)? The authors have included a STROBE Statement at the end of their proposal. However, STROBE is normally used for observational study reporting. Suggest that this be changed to a PRISMA-P report, which is the usual report for systematic review protocols.</p> <p>To the best of your knowledge is the paper free from concerns over publication ethics (e.g. plagiarism, redundant publication, undeclared conflicts of interest)? Yes. The authors have declared no funding and no conflict of interest.</p> <p>Is the standard of written English acceptable for publication? Yes.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1 Reviewer Name: Xianliang Liu Institution and Country: The Hong Kong Polytechnic University The methodology needs greater explanation.

We have revised the methodology now.

(1) The Background proposed by the authors to justify this review is inadequate. The aim of this review is not clear for me and the rationale for this study is unclear;

We have added illustrations to justify more. Additionally, we clarified the aims more now. The details can be seen in the revised version.

(2) Perhaps it is better to add the search strategy as an appendix, it is not possible to review the search strategy as full details have not been included and please add the date for the database search;

We have added the search strategy now.

(3) One of my main concerns is the exclusion of unpublished literature. Not seeking unpublished literature is not consistent with the Cochrane approach;

Thank you, and we will include the 'unpublished literature'.

(4) Quality assessment should be more specific; We have revised to specifically use the Joanna Briggs Institute checklist and annexed in the appendix.

Reviewer: 2 Reviewer name: Joshi, Hrishi B. Institution and Country: University Hospital of Wales and School of Medicine, Cardiff This is the protocol for a proposed systematic review of qualitative and quantitative studies. There are certain issues that need clarification and might limit the study results.

1. How do authors aim to standardise ACS and its treatments from clinical point before comparing the HRQoL associated with them?

We have described that we will consider any of the definitions provide by the primary studies in order to include as many studies as possible.

2. How would the impact of comorbidities, acute against chronic events, prior interventions would be evaluated before standardising the patient groups? Would there be subgroups?

This is a review, and we will only assess the potential relationship between QoL and decision to prescribe a treatment strategy for ACS patients. As this is a part of a big project, these confounders might be considered in the planned primary study analysis after carrying out the systematic review. Based on the scoping exercise we have conducted, we will not have a subgroup analysis.

3. One major issue is heterogeneity of generic and disease specific (if any) measures used. What would be the authors' strategy to have meaningful comparisons between different domains and reported outcomes?

Our preliminary search showed that different tools were used to measure the QoL. Thus, we will use a standardized mean difference (SMD). Furthermore, we will also consider diseases specific tools.

4. Are there enough studies, in the literature, to establish the links between the HrQoL assessments and physician's therapy and perceptions of the benefit? How would authors separate the impact of other confounding factors (e.g. availability of resources, expertise, commercial interests) in a clear way?

Initial scoping exercise showed presence of studies. We have answered points with regards to the confounding factors in comment #2 of the reviewer.

Reviewer: 3 Reviewer Name: Michael H McGillion Institution and Country: McMaster University, Canada Are the methods described sufficiently to allow the study to be repeated? The methods need to be flushed out with further detail in some places, and require further clarification in others. Key issues are as follows: i. It seems that Percutaneous transluminal angioplasty (PTA or PTCA) was not included in the search terms. Inclusion of all relevant search terms may impact number of available studies returned for analysis.

Thanks, this was a typo—we have included it.

ii. The authors state that they aim to synthesize all quantitative and qualitative literature applicable to the study topic, however, no searching of grey literature or contacting study authors is mentioned – suggest that these additional search strategies be included.

We have included the grey literature. Please see comment#3 of reviewer 1.

iii. Suggest including a draft search for at least one database, as per PRISMA-P guidelines. iv. The authors may consider specifying the specific quality appraisal tools they plan to use. v. The authors should describe their plans to manage the data from this study (e.g. software programs used for analyses). Are the outcomes clearly defined? Some ambiguity, I think, exists in the outcome as defined by the researchers. For instance: i) HRQoL is not defined for the purposes of the review. It may indeed be that no a priori definition is specified in order to be inclusive of a broad range of literature. If this is the case, it may be helpful for the authors to state this decision. In the background literature review, however, I think it would be helpful to at least provide common definitions of HRQoL, as a precursor to the fact that a number of definitions and measures may ultimately be included.

We have added this information, and some of lists of tools used so far were also described in the introduction.

ii) The authors only mention the use of validated tools to measure HRQoL in the conclusion, this should be brought up front to help with cohesion of argument and

We have stated this.

iii) The authors do not define how “impact” of HRQoL on physicians’ treatment decisions or assessment of risk will be measured; this needs to be addressed.

We have included adequate justification now.

iv) It is not clearly presented how HRQoL may in fact impact estimation of bleeding events post-procedure. The argument in support of this statement needs to be further developed- same for mortality.

We have added this argument.

Are the references up-to-date and appropriate? Several references are >10 years old. Suggest updating if and where possible.

We have revised this, and tried to include more recent studies in the introduction. Are the study limitations discussed adequately? The authors list one study limitation at the beginning of the protocol. Suggest a more thorough exploration of limitations (e.g. included studies were limited to English language [if correct], etc.) We have added some possible limitations.

Is the supplementary reporting complete (e.g. trial registration; funding details; CONSORT, STROBE or PRISMA checklist)? The authors have included a STROBE Statement at the end of their proposal. However, STROBE is normally used for observational study reporting. Suggest that this be changed to a PRISMA-P report, which is the usual report for systematic review protocols. We have included a PRISMA-P instead of STROBE. **FORMATTING AMENDMENTS** (if any) Required amendments will be listed here; please include these changes in your revised version: - Kindly re-upload figure 1 under 'Image' file designation with at least 300 dpi resolution and at least 90mm x 90mm of width in either TIFF or JPG format.

We have uploaded the modified fig. - Please include Figure 1 legend at the end of your main manuscript.

We included a legend for Fig 1. - Please ensure that your CORRESPONDING AUTHOR in your main document and ScholarOne submission system are the same. If more than one author needs to share credit as first or senior author then to have a footnote in your main document saying 'xx and yy contributed equally to this paper' instead of listing two corresponding authors. Please refer to below sample: Corresponding author: Author 1 (name and email address) [as shown in ScholarOne]. We have fixed this out.

Author 1 and Author 2 contributed equally to this paper. - Patient and Public Involvement: Authors must include a statement in the METHODS section of the manuscript under the sub-heading 'Patient and Public Involvement'. This should provide a brief response to the following questions: How was the development of the research question and outcome measures informed by patients' priorities, experience, and preferences? How did you involve patients in the design of this study? Were patients involved in the recruitment to and conduct of the study? How will the results be disseminated to study participants? For randomised controlled trials, was the burden of the intervention assessed by patients themselves?

Patient advisers should also be thanked in the contributorship statement/acknowledgements. If patients and or public were not involved please state this.

We have added this information.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Michael McGillion Institution and Country: McMaster University, Canada Competing interests: None declared
REVIEW RETURNED	29-Nov-2018

GENERAL COMMENTS	<p>Thank you for the opportunity to re-review this paper. The authorship team has responded to the reviews satisfactorily, in my opinion, and the paper is much improved. Please see my additional remarks below:</p> <p>As a suggestion, 'Concept 2' in the search strategy should be sub divided in order to separate physician therapies from outcome events.</p> <p>Grammar needs attention in a few places. Issues are as follows:</p> <ul style="list-style-type: none"> • Page 4, line 46: interpretation is spelled incorrectly • Page 5, bottom, the word event is missing from the end of this sentence:
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	<p>"Although evidence on the relationship between bleeding and QoL is scarce, the existing evidence demonstrated worse QoL following a bleeding 26 27"</p> <ul style="list-style-type: none"> • Suggest capitalize formal names of instruments (Page 4, lines 48 to 53)
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 3

Reviewer Name: Michael McGillion

Institution and Country: McMaster University, Canada

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

Thank you for the opportunity to re-review this paper. The authorship team has responded to the reviews satisfactorily, in my opinion, and the paper is much improved. Please see my additional remarks below:

As a suggestion, 'Concept 2' in the search strategy should be sub divided in order to separate physician therapies from outcome events.

Please note that we need the 'phrase' as is for our searching 'Physician therapy', however, we modified it.

Grammar needs attention in a few places. Issues ae as follows:

- Page 4, line 46: interpretation is spelled incorrectly: Corrected
- Page 5, bottom, the word event is missing from the end of this sentence: Added

"Although evidence on the relationship between bleeding and QoL is scarce, the existing evidence demonstrated worse QoL following a bleeding 26 27"

- Suggest capitalize formal names of instruments (Page 4, lines 48 to 53) Corrected