

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a systematic review of the financial burden experienced by people affected by head and neck cancer
AUTHORS	McCaffrey, Nikki; Engel, Lidia

VERSION 1 – REVIEW

REVIEWER	Spencer, Jennifer University of North Carolina at Chapel Hill, Health Policy and Management
REVIEW RETURNED	24-Aug-2021

GENERAL COMMENTS	<p>This manuscript reports the protocol for a systematic review seeking to synthesize literature describing the financial burden faced by individuals with head and neck cancer. I appreciate the value of publishing protocols separately, as it allows authors to both pre-register their analyses and describe in more detailed elements of study methods that might be too dense for a readable manuscript to a wide audience. To be successful at this later goal in the case of a systematic review, I believe the protocol should describe the study in such a way that a reader could reasonably repeat the study if they were seeking to replicate the study or update the systematic review in five or ten years' time for example. At present, I believe this protocol fails at this objective, but could succeed upon revision.</p> <p>My primary concern is that the search criteria are not described in a way that they are at present repeatable – this seems to me to be the single most important part of a systematic review and therefore essential to a protocol paper. The style of the provided Table 1 is excellent for building the search terms in a readable way, however it is presented as a “draft search strategy” and “example search strategy” which feels inadequate for a publishable protocol. The search strategy is decided on fairly early in the systematic review process, as the bulk of the work is in screening and synthesizing the articles, therefore I don't think it's unreasonable for the authors to provide in a format similar to table 1 the exact search terms used for each of their databases.</p> <p>Smaller notes:</p> <ul style="list-style-type: none"> -ability to “continue or maintain paid employment”. If “continue” and “maintain” are different concepts here, they need to be further distinguished. If they are not, only one of those words is needed. -Authors suggest out-of-pocket expenses are “irrespective of universal health coverage status” which seems like an overstatement. Certainly, individuals with insurance may still
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	<p>experience high out-of-pocket costs, but the extent of financial burden and the nature of financial burden definitely vary by insurance status – as described in one of the studies cited in this point. I think the authors can make a point that insurance is not fully protective against financial burden, but it is wrong to suggest (as the word “irrespective” does) that burden is similar for the insured/uninsured (or for individuals living in universal coverage settings vs. non-universal settings). Certainly the authors will explore the role that study setting has in the primary categories and overall extent of financial burden.</p> <p>Methods:</p> <p>-“studies before 2010 were considered less relevant due to changes in HNC management” – This wording makes it sound as though you did consider these studies but just down-weighted their importance. I think it needs to be said here that they were excluded for this reason rather than “considered less relevant”.</p> <p>-Risk of bias: Again, for a study proposal it feels adequate to say “critical appraisal checklists such as...” but when publishing a protocol study, it feels that the uncertainty on which checklists will be used should be resolved.</p> <p>-Otherwise, the methods are sound. In particular, I am enthusiastic about the authors categorizing the expenses into formal healthcare sector, informal healthcare sector, and non-healthcare sector. I think this format will provide really useful insight.</p>
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REVIEWER	González, José Antonio Barcelona-Tech, Statistics and Operations Research Department
REVIEW RETURNED	11-Oct-2021

GENERAL COMMENTS	<p>I have little to comment on this protocol, since its authors have fulfilled the checklist for PRISMA-P, the reporting guidelines for protocols of systematic reviews. I find that the manuscript is covering substantially all the relevant parts demanded for this kind of protocols, with the necessary detail and rigor, although there are a couple of points they should address.</p> <p>Search strategy, page 7/18, lines 54-56. I was not able to find a clear justification for this precise threshold (year 2010) in these studies (Refs 29-31), perhaps because I'm not an expert in the field. Just in case, I would recommend the authors to relax a little their constraints, and be open to consider research made before 2010. Specially if they expected to find a low number of studies.</p> <p>Selection process, pages 8,9/18. Please clarify and rewrite the section. Several sentences appear repeated, maybe by mistake, or perhaps referring to similar steps. Make the flow clearer, and differentiate better between the lone researcher and the others.</p> <p>Data collection, page 9/18. This section made me wonder what about the studies involving two or more groups (possibly, different interventions). It seems that this case was not anticipated. Consider adding the group descriptor to the list of variables.</p> <p>Data synthesis, page 9/18. The authors renounce to make a meta-analysis because they anticipate high heterogeneity in the data. This is a respectable position for a scientific work like this, but most systematic reviews find heterogeneity and face it properly,</p>
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	which means that those authors try to estimate the amount of heterogeneity present between the studies, so they can differentiate between
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REVIEWER	Longo, Christopher McMaster University, DeGroote School of Business
REVIEW RETURNED	24-Oct-2021

GENERAL COMMENTS	<p>This is a well written protocol to perform a systematic review of patient costs and lost income for head and neck cancer since January 2010. This is an area in need of further study. Most of my comments are minor in nature. They include a few suggestions and some minor grammar advise.</p> <p>Details: Pg 5 of 26 lines 39-41. Each of three researchers reviewed 30% of citations. Do you mean 33%, hence all citations are covered?</p> <p>Pg 7 of 26 line 34 Should read " ...fatigue and depression"</p> <p>Pg 10 of 26 line 27 Should read "...used to manage records..." line 42-43 as above 30% or 33%?</p> <p>Pg 11 of 26 line 44-45 I would advise having separate categories for lost patient income and lost caregiver income as this is not covered in the second panel</p> <p>Pg 12 of 26 line 8-9 I wonder if you have considered the OECD purchase price parity dataset rather than CCEMG-EPPI centre cost converter.</p> <p>I look forward to reading the published outcome of this work.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

This manuscript reports the protocol for a systematic review seeking to synthesize literature describing the financial burden faced by individuals with head and neck cancer. I appreciate the value of publishing protocols separately, as it allows authors to both pre-register their analyses and describe in more detailed elements of study methods that might be too dense for a readable manuscript to a wide audience. To be successful at this later goal in the case of a systematic review, I believe the protocol should describe the study in such a way that a reader could reasonably repeat the study if they were seeking to replicate the study or update the systematic review in five or ten years' time for example. At present, I believe this protocol fails at this objective, but could succeed upon revision. Response: Thank you for the opportunity to revise the systematic review protocol to enable others to reasonable repeat the study.

My primary concern is that the search criteria are not described in a way that they are at present repeatable – this seems to me to be the single most important part of a systematic review and therefore essential to a protocol paper. The style of the provided Table 1 is excellent for building the search terms in a readable way, however it is presented as a “draft search strategy” and “example search strategy” which feels inadequate for a publishable protocol. The search strategy is decided on

fairly early in the systematic review process, as the bulk of the work is in screening and synthesizing the articles, therefore I don't think it's unreasonable for the authors to provide in a format similar to table 1 the exact search terms used for each of their databases.

Response: The search strategies for all the databases have been included as a supplementary file in a similar style to Table 1 and the methods section has been updated accordingly (p8):

"The search strategies are described in the online supplemental file."

Ability to "continue or maintain paid employment". If "continue" and "maintain" are different concepts here, they need to be further distinguished. If they are not, only one of those words is needed.

Response: This phrase has been revised as suggested by removing the words "or maintain" (p5);

"...and reduced household income from a diminished ability to continue paid employment..."

Authors suggest out-of-pocket expenses are "irrespective of universal health coverage status" which seems like an overstatement. Certainly, individuals with insurance may still experience high out-of-pocket costs, but the extent of financial burden and the nature of financial burden definitely vary by insurance status – as described in one of the studies cited in this point. I think the authors can make a point that insurance is not fully protective against financial burden, but it is wrong to suggest (as the word "irrespective" does) that burden is similar for the insured/uninsured (or for individuals living in universal coverage settings vs. non-universal settings). Certainly the authors will explore the role that study setting has in the primary categories and overall extent of financial burden.

Response: The paragraph on out-of-pocket expenses in the introduction has been simplified by removing the phrase "irrespective of universal health coverage status" to avoid misinterpretation (p5):

"People affected by cancer can experience substantial out-of-pocket expenses associated with treatment costs, travel expenses, and reduced household income from a diminished ability to continue paid employment 8 9.

Methods:

"studies before 2010 were considered less relevant due to changes in HNC management" – This wording makes it sound as though you did consider these studies but just down-weighted their importance. I think it needs to be said here that they were excluded for this reason rather than "considered less relevant".

Response: The text has been revised as follows (p7):

"Studies published before 2010 were excluded due to more recent advances in HNC management which will affect the relative level of financial burden experienced by people by HNC."

Risk of bias: Again, for a study proposal it feels adequate to say "critical appraisal checklists such as..." but when publishing a protocol study, it feels that the uncertainty on which checklists will be used should be resolved.

Response: The wording has been revised to reflect which checklists will be used (p9):

"The methodological quality of the included studies will be evaluated independently by two reviewers (NM, LE) using Larg & Moss's guide to critical evaluation of cost-of-illness studies³⁴ and the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for observational studies critical appraisal checklists."

Otherwise, the methods are sound. In particular, I am enthusiastic about the authors categorizing the expenses into formal healthcare sector, informal healthcare sector, and non-healthcare sector. I think this format will provide really useful insight.

Response: Thank you for the positive feedback about the value of the systematic review.

Reviewer: 2

I have little to comment on this protocol, since its authors have fulfilled the checklist for PRISMA-P, the reporting guidelines for protocols of systematic reviews. I find that the manuscript is covering substantially all the relevant parts demanded for this kind of protocols, with the necessary detail and rigor, although there are a couple of points they should address.

Response: Thank you for the positive feedback on the quality of the protocol.

Search strategy, page 7/18, lines 54-56. I was not able to find a clear justification for this precise threshold (year 2010) in these studies (Refs 29-31), perhaps because I'm not an expert in the field.

Just in case, I would recommend the authors to relax a little their constraints, and be open to consider research made before 2010. Specially if they expected to find a low number of studies.

Response: Thank you for this suggestion. The text has been revised to provide clearer justification for considering research published only since 2010. Given the management of HNC has rapidly evolved over recent years, the financial burden reported in costing studies published earlier than 2010 has less value for estimating current out-of-pocket costs, reduced or lost income and informal care costs (p7).

“Studies published before 2010 were excluded due to more recent advances in HNC management which will affect the relative level of financial burden experienced by people by HNC.”

Selection process, pages 8,9/18. Please clarify and rewrite the section. Several sentences appear repeated, maybe by mistake, or perhaps referring to similar steps. Make the flow clearer, and differentiate better between the lone researcher and the others.

Response: The selection process has been rewritten and restructured to aid clarity, including the removal of duplicated sentences (pp8-9):

“Step 1: The titles and abstracts of the studies identified by the search will be screened independently by one researcher (SK) to determine eligibility for inclusion in the review. Full text articles will be retrieved when there is insufficient information to judge relevance. Corresponding authors will be contacted to ascertain whether studies meet inclusion criteria if necessary. Three researchers (NM, LE, SA) will independently screen a subset of 30% citations, i.e. 10% each. Agreement between the reviewers will be assessed using the Kappa statistic to determine if further duplicate title and abstract reviewing is required (Kappa <0.4, i.e. fair agreement)³³. If required, an additional 25% of citations will be screened (NM, LE, SA).

Step 2: The full text articles of potentially eligible studies will be retrieved and independently assessed by three reviewers (NM, LE, SK). Backwards and forwards citation tracing of included articles will be conducted for additional literature unidentified by the search.

Any disagreement will be resolved by consensus amongst the team.”

Data collection, page 9/18. This section made me wonder what about the studies involving two or more groups (possibly, different interventions). It seems that this case was not anticipated. Consider adding the group descriptor to the list of variables.

Response: Thank you for spotting this omission. Two group descriptors have been added to capture studies involving two or more groups: subgroups and intervention (p9):

“... study characteristics (first author’s name, publication date, country of origin, design, intervention), study population (age, gender, primary tumour site, sample size, subgroup), timeframe, and costs...”

Data synthesis, page 9/18. The authors renounce to make a meta-analysis because they anticipate high heterogeneity in the data. This is a respectable position for a scientific work like this, but most systematic reviews find heterogeneity and face it properly, which means that those authors try to estimate the amount of heterogeneity present between the studies, so they can differentiate between.

Response: There are multiple sources of heterogeneity across different economic and costing studies such as resource use and unit cost inputs, different perspectives for costs, resources provided across different health systems, different price years and different currencies meaning a meta-analysis is “rarely feasible or robust” and will not provide “meaningful results” as highlighted recently by Shield and Elvidge (2020)¹. Rather, heterogeneity between the studies and subgroups will be explored in the narrative synthesis and discussion.

Reviewer: 3

This is a well written protocol to perform a systematic review of patient costs and lost income for head and neck cancer since January 2010. This is an area in need of further study. Most of my comments are minor in nature. They include a few suggestions and some minor grammar advise.

Response: Thank you for the positive feedback on the quality of the protocol.

Pg 5 of 26 lines 39-41. Each of three researchers reviewed 30% of citations. Do you mean 33%, hence all citations are covered?

Response: In the first instance, a total of 30% of citations will be independently screened by three reviewers (NM, LE, SA), i.e. 10% each. If required, further duplicate screening will be conducted (see below). The selection process section been rewritten and restructured to aid clarity (pp8-9):

“Step 1: The titles and abstracts of the studies identified by the search will be screened independently by one researcher (SK) to determine eligibility for inclusion in the review. Full text articles will be retrieved when there is insufficient information to judge relevance. Corresponding authors will be contacted to ascertain whether studies meet inclusion criteria if necessary. Three researchers (NM, LE, SA) will independently screen a subset of 30% citations, i.e. 10% each. Agreement between the reviewers will be assessed using the Kappa statistic to determine if further duplicate title and abstract reviewing is required (Kappa <0.4, i.e. fair agreement)³³. If required, an additional 25% of citations will be screened (NM, LE, SA).

Step 2: The full text articles of potentially eligible studies will be retrieved and independently assessed by three reviewers (NM, LE, SK). Backwards and forwards citation tracing of included articles will be conducted for additional literature unidentified by the search.

Any disagreement will be resolved by consensus amongst the team.”

Pg 7 of 26 line 34 Should read " ...fatigue and depression"

Response: Thank you for spotting this grammatical error which we have now corrected (p5).

“...dry mouth, fatigue and depression...”

Pg 10 of 26 line 27 Should read "...used to manage records..."

Response: Again, thank you for spotting this grammatical error which we have now corrected (p8).

“...will be used to manage records...”

line 42-43 as above 30% or 33%?

Response: In the first instance, a total of 30% of citations will be independently screened by three reviewers (NM, LE, SA), i.e. 10% each (p8).

“Three researchers (NM, LE, SA) will independently screen a subset of 30% citations, i.e. 10% each.”

Pg 11 of 26 line 44-45 I would advise having separate categories for lost patient income and lost caregiver income as this is not covered in the second panel.

Response: Thank you for this valuable suggestion. We have included lost patient income and lost informal carer income in the variable list as follows (p9):

“...second panel on cost-effectiveness in health and medicine (formal health care sector, informal health care sector and non-health care sectors)³⁶, and lost patient income and lost informal carer income.”

Pg 12 of 26 line 8-9 I wonder if you have considered the OECD purchase price parity dataset rather than CCEMG-EPPI centre cost converter.

Response: Thank you for this suggestion. The CCEMG-EPPI centre cost converter uses the OECD ‘Purchasing Power Parities for GDP’ dataset and the IMF World Economic Outlook Database (see <https://epi.ioe.ac.uk/costconversion/>).

I look forward to reading the published outcome of this work.

References

1. Shields GE, Elvidge J. Challenges in synthesising cost-effectiveness estimates. *Systematic Reviews* 2020;9(1):289. doi: 10.1186/s13643-020-01536-x

VERSION 2 – REVIEW

REVIEWER	Spencer, Jennifer University of North Carolina at Chapel Hill, Health Policy and Management
REVIEW RETURNED	21-Dec-2021
GENERAL COMMENTS	I appreciate the author's attentions to my concerns. In its present state I think this protocol paper will be a valuable resource and I look forward to reading the review produced from this work.

REVIEWER	González, José Antonio Barcelona-Tech, Statistics and Operations Research Department
REVIEW RETURNED	10-Dec-2021
GENERAL COMMENTS	No further comments after the changes