PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Quality of life measured by EQ-5D at different treatment time points for coronary artery disease: Protocol for a systematic review and meta-analysis
AUTHORS	Lum, Elaine; McCreanor, Victoria; Luo, Nan; Graves, Nicholas

VERSION 1 – REVIEW

REVIEWER	Fiona Ecarnot, PhD University Hospital Besancon, and EA3920, University of Burgundy Franche-Comté, Besancon, France
REVIEW RETURNED	14-May-2020

GENERAL COMMENTS	This paper describes the protocol for a systematic review and meta-analysis of reported quality of life in patients with coronary artery disease (CAD) as assessed using the EQ-5D questionnaires, at a range of timepoints following treatment. The protocol is comprehensive and well written and complies with all the recommended guidelines for this type of work. I have just a few comments for the authors' consideration (in no particular order of importance): - Line 116. In Box 1, I think the authors should mention somewhere in the "Optimal medical therapy" section that optimal medical therapy is a combination of guidelines-recommended treatments, in line with the best evidence base. Optimal medical therapy is not just "any old combination" of therapy at the physician's discretion. There are well-established guidelines for the management of all the different presentations of CAD, issued by a number of professional societies (notably the European Society of Cardiology, American College of Cardiology and American Heart Association), based on abundant scientific evidence, with high levels of evidence and high grades of recommendation. Therefore, I believe the authors should stipulate somewhere that optimal medical therapy should be in line with guidelines. - Line 149, the track changes mode seems to have been left active on the submitted document (see correction left apparent here). - Lines 162-164, I know this is just a preliminary example, but I would advise the authors to ensure their search strategy includes the terms for all the possible clinical presentations under the umbrella term "CAD", including STEMI, NSTEMI/NSTE-ACS, as well as silent ischemia, which I don't see mentioned anywhere. Indeed, line 173, in the inclusion criteria, silent ischemia is not mentioned – what do the authors plan to do with studies of this form of CAD? - Line 190, what is the rationale for excluding specific populations, such as people with depression? Surely, QoL would be of particular interest in these groups? If there is a sound rationale for

	excluding them, e.g. so as not to skew estimates with measures from groups known to have highly impaired QoL, then this should be specified. - Line 210, for the lipid-lowering drugs, I would specify statins, ezetimibe and PCSK9 inhibitors. - Line 216, under the interventional (or non-pharmacological?) procedures, do the authors also plan to consider ICD or pacemaker implantation? If not, perhaps this could be mentioned. - Lines 247-253, regarding the assessment of bias in the included studies, perhaps the authors could mention how the results of this quality assessment will be presented (from what I understand, generally in table format, with a judgement of the level of bias, e.g. low, moderate etc?). - Line 281, EQ-5D-3L should also be specified here in the brackets. - Lines 291-292, what is the rationale for choosing the percentage of participants with diabetes mellitus or current smoking, and not, for example, other risk factors such as hypercholesterolemia, family history of CAD, or kidney disease?

REVIEWER	Supraja Sankaran Eindhoven University of Technology, Netherlands
REVIEW RETURNED	15-May-2020

GENERAL COMMENTS	The methodology described in the protocol is thorough and rigorous. I did not find any major flaws in the study plan.

REVIEWER	Leonardo De Luca AO San Camillo-Forlanini Roma
REVIEW RETURNED	28-May-2020

GENERAL COMMENTS	In this paper Lum et al present a protocol for a systematic review and meta-analysis on quality of life measurement by EQ-5D in patients with CAD (stable or unstable) at different time points (baseline, 1, 6, 12-24 and >24 months). Although the protocol is interesting, I have the following concerns: 1. The keywords used for the first search are limited. The authors should also include terms such as quality of life in order to avoid missing data or papers 2. An important subgroup analysis to consider is ACS vs stable CAD (these 2 are extremely different populations)

VERSION 1 – AUTHOR RESPONSE

Peer Reviewers' Comments		Authors' Response
Peer Reviewer 1 Fiona Ecarnot, PhD University Hospital Besancon, and EA3920, University of Burgundy Franche-Comté, Besancon, France		-
1.	The protocol is comprehensive and well written and complies with all the recommended guidelines for this type of work.	Thank you for reviewing our manuscript and providing constructive feedback to improve it.

2.	I have just a few comments for the authors' consideration (in no particular order of importance): Line 116. In Box 1, I think the authors should mention somewhere in the "Optimal medical therapy" section that optimal medical therapy is a combination of guidelines-recommended treatments, in line with the best evidence base. Optimal medical therapy is not just "any old combination" of therapy at the physician's discretion. There are well-established guidelines for the management of all the different presentations of CAD, issued by a number of professional societies (notably the European Society of Cardiology, American College of Cardiology and American Heart Association), based on abundant scientific evidence, with high levels of evidence and high grades of recommendation. Therefore, I believe the authors should stipulate somewhere that optimal medical therapy should be in line with guidelines.	The text has been amended as suggested: "Optimal medical therapy: A combination of evidence-based treatments recommended by clinical guidelines e.g. medications (pharmacological) to treat disease progression and symptoms, along with lifestyle modifications (non-pharmacological)." (page 4, Box 1).
3.	Line 149, the track changes mode seems to have been left active on the submitted document (see correction left apparent here).	Thank you, the track changes mode has been turned off in the revised manuscript.
4.	Lines 162-164, I know this is just a preliminary example, but I would advise the authors to ensure their search strategy includes the terms for all the possible clinical presentations under the umbrella term "CAD", including STEMI, NSTEMI/NSTE-ACS, as well as silent ischemia, which I don't see mentioned anywhere. Indeed, line 173, in the inclusion criteria, silent ischemia is not mentioned – what do the authors plan to do with studies of this form of CAD?	Thank you, for the search string we have included an extensive list of clinical presentations under the umbrella term "CAD"; silent ischemia has been added, and also explicitly stated in the inclusion criteria (page 5, line 168-169). The PubMed search strategy has been uploaded as a supplementary file.

5.	Line 190, what is the rationale for excluding specific populations, such as people with depression? Surely, QoL would be of particular interest in these groups? If there is a sound rationale for excluding them, e.g. so as not to skew estimates with measures from groups known to have highly impaired QoL, then this should be specified.	Thank you for pointing this out. The text has been amended: "Specific patient groups known to have highly impaired quality of life (to avoid skewing estimates) e.g. studies examining coronary artery disease in people with depression" (page 6, line 184-185).
6.	Line 210, for the lipid-lowering drugs, I would specify statins, ezetimibe and PCSK9 inhibitors.	Text amended: "...cholesterol-modifying medications (e.g. statins, ezetimibe and PCSK9 inhibitors)..." (page 6, line 204).
7.	Line 216, under the interventional (or non-pharmacological?) procedures, do the authors also plan to consider ICD or pacemaker implantation? If not, perhaps this could be mentioned.	Text clarified: "Implantable cardioverter defibrillators (ICD) will not be included." (page 7, line 212-213).
8.	Lines 247-253, regarding the assessment of bias in the included studies, perhaps the authors could mention how the results of this quality assessment will be presented (from what I understand, generally in table format, with a judgement of the level of bias, e.g. low, moderate etc?).	Text added: "The risk of bias assessment for all included studies will be reported in a table format showing the overall judgment for each study (Rob 2: low/ high/ some concerns; ROBINS-I: low/ moderate/ serious/ critical)." (page 8, line 254-256).

9.	Line 281, EQ-5D-3L should also be specified here in the brackets.	Text amended: "Survey instrument (e.g. EQ-5D, EQ-5D-3L, EQ-5D-5L)" (page 8, line 279).
10.	Lines 291-292, what is the rationale for choosing the percentage of participants with diabetes mellitus or current smoking, and not, for example, other risk factors such as hypercholesterolemia, family history of CAD, or kidney disease?	This is an arbitrary selection of two predictors for CAD. A subgroup analysis is planned for patients with diabetes.
Peer Reviewer 2 Supraja Sankaran Eindhoven University of Technology, Netherlands		-
1.	The methodology described in the protocol is thorough and rigorous. I did not find any major flaws in the study plan.	Thank you for reviewing our manuscript.
Peer Reviewer 3 Leonardo De Luca AO San Camillo-Forlanini Roma		-
1.	In this paper Lum et al present a protocol for a systematic review and meta-analysis on quality of life measurement by EQ-5D in patients with CAD (stable or unstable) at different time points (baseline, 1, 6, 12-24 and >24 months).	Thank you for reviewing our manuscript and providing constructive feedback to improve it.
2.	Although the protocol is interesting, I have the following concerns: The keywords used for the first search are limited. The authors should also include terms such as quality of life in order to avoid missing data or papers	The keywords used for the first search were simply a starting point to inform the development of the search string. The search string constructed for the systematic review included the phrase "quality of life" as a search term. We have uploaded the PubMed search string as a supplementary file.
3.	An important subgroup analysis to consider is ACS vs stable CAD (these 2 are extremely different populations)	Thank you for the suggestion. We have added ACS vs stable CAD in the subgroup analysis: "We will also conduct subgroup analysis of patients with acute coronary syndromes (ACS) vs stable CAD /stable coronary syndromes (SCS). ACS includes unstable angina, NSTEMI, STEMI, myocardial infarction with no obstructive coronary artery disease (MINOCA); and stable CAD includes obstructive CAD and ischaemia with no obstructive coronary artery disease (INOCA)" (page 9, line 319 to page10, line 322).
Editorial Requests		
1.	Please provide further detail (i.e. months) regarding the systematic search in the abstract.	Months have been added to the abstract (page 2, line 52).
2.	Please upload the precise search strategy (or strategies) for one database used in your study, including any limits and filters to be included as a supplementary file.	The PubMed search strategy has been uploaded as a supplementary file.
3.	Box citation missing: The in-text citation for 'box 1' is missing. Please provide the missing citation and ensure that all citations of boxes are in ascending order.	In-text citation for Box 1 has been added: "Definitions of terms used are in Box 1." (page 4, line 116). There are no other boxes in the manuscript.

VERSION 2 – REVIEW

REVIEWER	Fiona Ecarnot, PhD University Hospital Besancon, France
REVIEW RETURNED	30-Jun-2020

GENERAL COMMENTS	The authors have taken all my remarks into consideration. No further comments.

REVIEWER	Leonardo De Luca AO San Camillo, Italy
REVIEW RETURNED	26-Jun-2020

GENERAL COMMENTS	The authors answered to all reviewers' comments