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)	Cardiovascular toxicity of targeted therapies for cancer: a protocol for an overview of systematic reviews
AUTHORS	van Leeuwen, Marina; Luu, Steven; Gurney, Howard; Brown, Martin; Webber, Kate; Pearson, Sallie-Anne; Hunt, Lee; Vajdic, Claire

VERSION 1 – REVIEW

REVIEWER	Husam Abdel-Qadir Women's College Hospital, Canada
REVIEW RETURNED	29-Jan-2018

GENERAL COMMENTS	This is a well-written and organized protocol. The degree of planning reflects well on the authors, and I wish them the best of luck with this ambitious and important undertaking.

REVIEWER	Folkert W. Asselbergs MD, PhD 1. Department of Cardiology, Division of Heart & Lungs, University Medical Center Utrecht, University of Utrecht, The Netherlands 2. Durrer Center for Cardiovascular Research, Netherlands Heart Institute, Utrecht, the Netherlands 3. Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, United Kingdom 4. Farr Institute of Health Informatics Research and Institute of Health Informatics, University College London, London, United Kingdom
REVIEW RETURNED	06-Mar-2018

GENERAL COMMENTS	**Peer-review: Cardiovascular toxicity of targeted therapies for cancer: a protocol for an overview of systematic reviews** Synopsis: This manuscript by van Leeuwen *et al*. describes a protocol for an umbrella review compiling evidence regarding cardiovascular toxicity of targeted therapies for cancer. Good points: • Overall the study methods have been clearly described • In the discussion section, the authors have done a good job in describing the limitations and challenges associated with umbrella reviews

	Major issues: • It is unclear whether or not this is an ongoing study. The anticipated completion date of the study is March 1st 2018 as reported on https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=80014. It is unclear whether data collection has already been completed as the dates of the study are not included in the manuscript. • The motives behind the eligibility criteria are insufficiently described. It is unclear why only studies on first-line therapeutic agents are included. This will lead to the exclusion of many agents indicated for patients with relapsed or refractory disease (such as carfilzomib in the treatment of multiple myeloma) that might be associated with considerable cardiovascular toxicity. • The authors try to prevent/limit overlap in individual primary studies by selecting the systematic review that is the highest quality review when multiple reviews have included the same studies. For reviews that show partially overlap, both reviews will be retained in case the lower-quality review consists of more than one-third new studies. This method can however, still cause considerably over representation of some studies, depending on the number of included studies in each systematic review. Furthermore, other relevant studies might be excluded by this method. It is of great importance that an overview of all excluded studies is provided. Other remarks: In case the authors have not started with the study, they should consider to change the study design. Albeit very elaborative, an in-depth analysis of all primary studies per agent and subsequent meta-analysis on the various different outcomes would be more appropriate than an umbrella review. With an in-depth analysis, the authors can take heterogeneity among studies into consideration, and pool estimates when appropriate (*e.g*. similar outcome measures and definition, similar populations etc.). Furthermore, the comprehensiveness and up to dateness of this umbrella review is limited by the absence of systematic reviews of new agents. Albeit the authors are aware of this limitation, they do not include additional primary studies on these newer agents in the absence of "an agreed method" for this inclusion, as stated in the Discussion section. Even in the absence of an agreed method, the authors are strongly encouraged to perform meta-analyses on the available studies for these newer and less established agents.

VERSION 1 – AUTHOR RESPONSE

Editor comments and requests

Please specify the names of the databases searched in the abstract and include the dates of coverage. We recommend reporting all relevant items from the PRISMA extension for abstracts (checklist): http://www.prisma-statement.org/Extensions/Abstracts.aspx

We have revised the abstract to specify the names of the databases and the search end date.

We note that this statement refers to abstracts reporting the results of systematic reviews, whereas our manuscript abstract is summarising our protocol, so we have met the criteria where relevant.

Please elaborate on the rationale for the databases selected. Should Google Scholar and Web of Science be searched too? Please see the following paper, which suggests that optimal searches in systematic reviews should search at least Embase, MEDLINE, Web of Science, and Google

Scholar: https://systematicreviewsjournal.biomedcentral.com/articles/10.1186/s136 43-017-0644-y

We aim to identify all systematic reviews of randomised clinical trials and observational studies of targeted therapies for the treatment of cancer. On the advice of our search expert we selected three trusted sources of information, Embase, Medline and the Cochrane Database of Systematic Reviews. We understand that coverage is critical, and we selected three specialised, curated medical databases with the tools and functionality we needed to create structured, optimised, search strategies.

In the preliminary work we undertook to optimise our search strategy, we considered the inclusion of other databases including Google Scholar. A 2016 manuscript comparing the coverage, recall and precision of systematic review search strategies found that the coverage of Google Scholar was high but marginally lower than Embase and Medline combined. Furthermore, "the total recall of Embase and Medline combined was 81.6% for all included references, compared to Google Scholar at 72.8%" (see Bramer WM et al Syst Rev 2016;5:39 https://www.ncbi.nlm.nih.gov/pubmed/26932789).

We sought to identify systematic reviews, not the references within systematic reviews. Nevertheless, thank you for including the link to the 2017 study that sought to identify references within systematic reviews across multiple domains. In that study the "traditional search combination" (Embase, Medline and Cochrane) retrieved 100%

of included references when the systematic reviews limited to randomized controlled trials.

We note that the literature search goes up to December 2016, so is more than 12 months old. Can the literature search be updated?

This is a substantive project that commenced in 01 May 2017, with the search strategy identifying 13,599 potentially eligible abstracts. Given the broad nature of the research question, and the number of potentially eligible and eligible studies, it is not feasible for us to update it. In our experience it is typical for the literature to lag 1-2years behind the publication of a systematic review or overview because of the complexity, scope and multi -disciplinary nature of the tasks. We will make all our search materials available online so that it can be updated periodically. This is the first time such a study has been performed in oncology.

Please add the relevant page/ line numbers to the reporting items in the PRISMA-P checklist so that the information is easy to locate in the paper.

We have added the relevant manuscript page numbers to the PRISMA-P checklist. We could not add the line numbers as the line numbering is added automatically by ManuscriptCentral to the entire combined PDF (including the PRISMA-P) after the checklist is finalised and uploaded.

Editorial office comments and requests

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.

Our draft protocol included a sub-heading entitled 'Ethics and dissemination' that addressed these issues. As a result of your request, we have changed this heading to

‘Patient and public involvement’; we are happy to take further advice on this but it did not seem appropriate to repeat this information. We modified the paragraph slightly to ensure that we met all of the relevant information needs listed above.

Reviewer 1 Dr Husam Abdel-Qadir

This is a well-written and organized protocol. The degree of planning reflects well on the authors, and I wish them the best of luck with this ambitious and important undertaking.

We thank the reviewer for this feedback.

Reviewer 2 Professor Dr Folkert W. Asselbergs

Synopsis: This manuscript by van Leeuwen et al. describes a protocol for an umbrella

review compiling evidence regarding cardiovascular toxicity of targeted therapies for

cancer.

Good points:

- Overall the study methods have been clearly described
- In the discussion section, the authors have done a good job in describing the limitations and challenges associated with umbrella reviews

We thank the reviewer for this feedback.

Major issues:

1) It is unclear whether or not this is an ongoing study. The anticipated completion date of the study is March 1st 2018 as reported on https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=80014. It is unclear

whether data collection has already been completed as the dates of the study are not included in the manuscript.

This study has commenced (01 May 2017) but data collection is not yet complete; due to the large number of potentially eligible and eligible studies, we have not met our anticipated timelines. It is not usual practice for umbrella/overview protocols to include the dates of the study, including recent BMJ Open protocols (eg. http://bmjopen.bmj.com/content/7/12/e018494.long) but we have added the study start date (page 7). The revised anticipated study end date is 30 June 2018 and we have also added that but would be happy to reposition the text as necessary.

2) The motives behind the eligibility criteria are insufficiently described. It is unclear why only studies on first-line therapeutic agents are included. This will lead to the exclusion of many agents indicated for patients with relapsed or refractory disease (such as carfilzomib in the treatment of multiple myeloma) that might be associated with considerable cardiovascular toxicity.

We thank the reviewer for this observation. We do agree that the inclusion of studies solely examining second-line therapy would add to the evidence base. However, our preliminary review of the systematic review literature identified that many of these reviews included multiple small randomised clinical trials of second-line therapy. In our judgement, such studies were at higher risk of non-random distribution of prior treatments to the trial arms, and thus potentially biased results. Nevertheless, such potential bias would be diluted in systematic reviews that included studies of first- and second-line agents. We have added this justification to the eligibility criteria text (page 6).

3) The authors try to prevent/limit overlap in individual primary studies by selecting the systematic review that is the highest quality review when multiple reviews have included the same studies. For reviews that show partially overlap, both reviews will be retained in case the lower-quality review consists of more than one-third new studies. This method can however, still cause considerably over representation of some studies, depending on the number of included studies in each systematic review. Furthermore, other relevant studies might be excluded by this method. It is of great importance that an overview of all excluded studies is provided.

We agree that it is important to be transparent about these exclusions. We confirm that the findings from these studies will be included in the overview data summary tables; they will only be excluded in the visual presentation of the evidence synthesis. Therefore, it will be possible to judge the impact of these exclusions. We will also discuss the impact when reporting the evidence synthesis. We thank the reviewer for this comment and we have revised the methods text to clarify these steps (page 10).

Other remarks:

In case the authors have not started with the study, they should consider to change the study design. Albeit very elaborative, an in-depth analysis of all primary studies per agent and subsequent meta-analysis on the various different outcomes would be more appropriate than an umbrella review. With an in-depth analysis, the authors can take heterogeneity among studies into consideration, and pool estimates when appropriate (e.g. similar outcome measures and definition, similar populations etc.). Furthermore, the comprehensiveness and up to dateness of this umbrella review is limited by the absence of systematic reviews of new agents. Albeit the authors are aware of this limitation, they do not include additional primary studies on these newer agents in the absence of “an agreed method” for this inclusion, as stated in the Discussion section. Even in the absence of an agreed method, the authors are strongly encouraged to perform meta-analyses on the available studies for these newer and less established agents.

While desirable, an in-depth analysis of all primary studies per agent, and computation of an umbrella meta -estimate, is in our judgement, not feasible given the number of primary studies and heterogeneity in study definitions. We seek to provide a single resource that captures the key findings from these studies for all agents. We agree with the limitations of the umbrella study design in terms of up-to-datedness, and we will be upfront about them when disseminating our findings. In-depth meta-analyses for individual agents are regularly conducted and published and will be incorporated into our discussion where relevant.

VERSION 2 – REVIEW

REVIEWER	Folkert W. Asselbergs MD, PhD 1. Department of Cardiology, Division of Heart and Lungs, University Medical Center Utrecht, Utrecht, the Netherlands 2. Durrer Center for Cardiovascular Research, Netherlands Heart Institute, Utrecht, the Netherlands 3. Institute of Cardiovascular Science, Faculty of Population Health Sciences, University College London, London, United Kingdom 4. Farr Institute of Health Informatics Research and Institute of Health Informatics, University College London, London, United Kingdom
REVIEW RETURNED	16-Apr-2018

GENERAL COMMENTS	The authors have done a good job in addressing the queries. I have no further questions.