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)	Automatic brain lesion segmentation on standard magnetic resonance images of the human head: a scoping review protocol.
AUTHORS	Gryska, Emilia; Schneiderman, Justin; Heckemann, Rolf

VERSION 1 – REVIEW

REVIEWER	Sarah Munce Toronto Rehabilitation Institute-University Health Network, Toronto, Ontario, Canada
REVIEW RETURNED	16-Jul-2018

GENERAL COMMENTS	Thank you for the opportunity to review "Automatic lesion segmentation on standard magnetic resonance images of the human brain: a scoping review protocol". Abstract The abstract lacks a research objective and this should be added. Furthermore, with respect to the section on "strengths and limitations" section, as outlined in the instructions for authors, this section should refer to strengths and weaknesses of the methods only. Thus, the first two and last points should be eliminated. Introduction The Introduction section would benefit from some references. In particular, the text from line 48-54 needs some references. The authors also need to introduce the acronym MR. The study aims and objectives listed in the Introduction section are, in fact, part of the methods e.g., perform a comprehensive search and gather available evidence. It is suggested that this section is eliminated and that the authors use the questions that are listed under "identifying research questions". It is suggested that the research questions objectives are included in the Introduction section for flow. Methods and Design The authors should clarify what they mean by "The resulting draft protocol will be refined throughout the process of conducting the study". Initial search The authors have indicated that they will include review papers – will they limit this to systematic review and/or scoping reviews only? Please clarify. The study design types included is not clear.

	The clause, "…we presume that any other research publication types than stated in the protocol contain duplicated information or ineligible evidence" is unclear. Similarly, the sentence, "Therefore, the publication type limitation should neither substantially increase the risk of bias of the review nor limit the number of records retrieved during the screening and selection phase" is unclear. The sentence, "We will not impose any date of publication limitations in the initial search" reads awkwardly and should be revised to "We will not impose any limitations with respect to year of publication". It is recommended that the authors have their search strategy peer reviewed and include this detail as part of their protocol. Page 6, line 34-37: "An artificial limit of the number of papers included…" is unclear and needs further justification. Will the authors use any online software to facilitate the screening and abstraction phases? The authors should ensure that their data charting is consistent with their research objectives e.g., it is unclear from the data charting process described whether data on mathematical and computational theories, efficacy, and limitations will be collected. The sentence, "We are aware that the proposed classification may turn out to be impractical and that modifications may be necessary for a well-structured and thorough analysis" is also unclear/requires justification e.g., the protocol should not be adjusted because it "may turn out to be impractical". It is also suggested that the author abstract data on study design and main findings (i.e., efficacy). The authors should include a list of anticipated limitations.

REVIEWER	Habibollah Haron Universiti Teknologi Malaysia
REVIEW RETURNED	19-Sep-2018

GENERAL COMMENTS	Not suitable for journal publication

REVIEWER	Mohammed A. Al-masni Kyung Hee University, Korea
REVIEW RETURNED	18-Oct-2018

GENERAL COMMENTS	The subject of this review is very important and will provide good details for further researchers in the field of brain lesion identification. There are some comments should be taken care of by authors: 1. Segmentation is a key prerequisite step for brain lesion diagnosis. This review should be clarified that it will be only on brain lesion segmentation (it is fine) or also it will cover lesion classification methods (it is better). Authors mentioned the classification in the body of this scoping review but they did not mention it in the title. I recommend to modify the title to "Automatic lesion segmentation and classification on …".

	2. It is better to present examples of the outcome that will result from this scoping review. Authors could utilize table including methods with brief description and the used MR datasets. 3. The five stages of the Arksey and O'Malley framework should be stated. For example, use “Stage 1: Identifying research questions” instead of “Identifying research questions”, “Stage 2: Identifying relevant studies” instead of “Identifying relevant studies”, and so on. 4. In stage 1: Identifying research questions, add the question of what are the most common utilized MR datasets which have ground truth for both lesion segmentation and classification. 5. It is preferred to use more than two online searched databases. In addition to PubMed and IEEE Xplore, Scopus and Google scholar should also be utilized in order to include all feasible studies. 6. I recommend to present inclusive comparison of the methods’ performance that utilized same MR datasets.

REVIEWER	M.Lavanya Saveetha School of Engineering, Saveetha Institute of Medical and Technical Sciences, India
REVIEW RETURNED	20-Oct-2018

GENERAL COMMENTS	Your paper was written well. But Everywhere the conditions that are considered for reviewing is mentioned but the brief analysis and comparing of methods are nowhere mentioned.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Sarah Munce
Institution and Country: Toronto Rehabilitation Institute-University Health Network, Toronto, Ontario, Canada.
Please state any competing interests or state ‘None declared’: None.

Thank you for the opportunity to review “Automatic lesion segmentation on standard magnetic resonance images of the human brain: a scoping review protocol”.

*Abstract
The abstract lacks a research objective and this should be added.

Our response: The introduction in the abstract was rephrased to include a clear statement of aims of this scoping review (lines 4-5).

*Furthermore, with respect to the section on “strengths and limitations” section, as outlined in the instructions for authors, this section should refer to strengths and weaknesses of the methods only. Thus, the first two and last points should be eliminated.

Our response: We apologise for misreading the guidelines. We followed the reviewer’s suggestions and removed irrelevant points.

*Introduction
The Introduction section would benefit from some references. In particular, the text from line 48-54 needs some references. The authors also need to introduce the acronym MR.

Our response: Appropriate references have been added according to the reviewer’s suggestion. We

also ensured that all abbreviations and acronyms are properly introduced.

*The study aims and objectives listed in the Introduction section are, in fact, part of the methods e.g., perform a comprehensive search and gather available evidence. It is suggested that this section is eliminated and that the authors use the questions that are listed under “identifying research questions”. It is suggested that the research questions objectives are included in the Introduction section for flow.

Our response: We agree with the reviewer that the aims we listed represent methodological steps. We prefer, however, to retain this section to comply with the checklist developed for PRISMA Extension for Scoping Reviews [Tricco AC et al. 2018]. We carefully rephrased the aims and objectives to ensure that they are accurate and that the section does not disrupt the flow of the article. Similarly, the section “Identifying research questions” section is a component of the methodological framework for scoping reviews as proposed by Arksey and O’Malley (2005), and we therefore prefer to leave it in Section Methods and Design. The correspondence between recommended scoping review stages and our implementation plan is now clearer – cf. Reviewer 3 Comment 3.

Tricco, Andrea C., et al. "PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation." Annals of internal medicine 169.7 (2018): 467-473.

*Methods and Design
The authors should clarify what they mean by “The resulting draft protocol will be refined throughout the process of conducting the study”.

Our response: We agree that this statement lacked clarity. We deleted this part from the protocol and we justify doing so with the following reasoning. At the time of submission, we anticipated that we would have to refine minor aspects of the study design, such as inclusion criteria and the search strategy, to strike a balance between inclusivity and feasibility. While the manuscript was under review, we explored the range and breadth of the available evidence and made adjustments to the protocol that will, to our mind, be beneficial to this study.

*Initial search
The authors have indicated that they will include review papers – will they limit this to systematic review and/or scoping reviews only? Please clarify.

Our response: This is a fair question which also has been addressed by the progress we made since the manuscript submission. We realised that literature review and survey papers that do not propose any new brain lesion segmentation method do not meet the inclusion criterion “proposing a method” and thus should not be included in our study. The revised manuscript reflects this (p. 5, lines 4-5).

*The study design types included is not clear.

Our response: All articles that match the inclusion criteria will be included, irrespective of the study design chosen by the authors. This will ensure that our scoping review will reveal which designs are favoured by authors. It will also ensure that we will include studies whose design does not fit any premeditated category. We also described our reasoning briefly in the “Eligibility criteria” section for the sake of clarity (p. 4, lines 6-9).

*The clause, “…we presume that any other research publication types than stated in the protocol contain duplicated information or ineligible evidence” is unclear. Similarly, the sentence, “Therefore, the publication type limitation should neither substantially increase the risk of
bias of the review nor limit the number of records retrieved during the screening and selection phase”

is unclear.

Our response: We apologise for the lack of clarity. We revised the paragraph in question and it now reads: “Eligible studies will be retrieved from peer-reviewed journal articles and conference papers.” (p. 4, line 14). We provide a detailed reasoning for the criterion in the Study limitaitons section (p. 6, lines 30-33).

*The sentence, “We will not impose any date of publication limitations in the initial search” reads awkwardly and should be revised to “We will not impose any limitations with respect to year of publication”.

Our response: We agree with the reviewer and implemented the suggestion (p. 4, lines 14-15).

*It is recommended that the authors have their search strategy peer reviewed and include this detail as part of their protocol.

Our response: We are grateful for this recommendation. The search strategy was peer-reviewed internally among the paper authors. Additionally we consulted with a librarian from the University of Gothenburg at this stage. We now provide the information in the “Initial search” section (p. 4, lines 12-13).

*Page 6, line 34-37: “An artificial limit of the number of papers included…” is unclear and needs further justification.

Our response: We agree with the reviewer’s point. We decided to completely omit this section as a result of the development of the review protocol since the date of submission. While we do not exclude the possibility of limiting the number of papers we will include in the scoping study (based e.g. on publication date), we decided to refrain from making any assumptions in that regard at this stage of the project.

*Will the authors use any online software to facilitate the screening and abstraction phases?

Our response: We will use locally installed reference management software as well as a web-based application for systematic reviews – Rayyan QCRI. We provided the information in the protocol (p. 4, lines 44-46).

*The authors should ensure that their data charting is consistent with their research objectives e.g., it is unclear from the data charting process described whether data on mathematical and computational theories, efficacy, and limitations will be collected.

Our response: We thank the reviewer for the valuable comment as it made us revisit our data charting strategy. We also provide further explanation regarding the procedure in the paper (pp. 5-6, lines 35-1).

*The sentence, “We are aware that the proposed classification may turn out to be impractical and that modifications may be necessary for a well-structured and thorough analysis” is also unclear/requires justification e.g., the protocol should not be adjusted because it “may turn out to be impractical”.

Our response: We apologise for the poor choice of phrasing of our intent. We intended to point out that our preliminary framework may not be able to capture the information we want to extract from the studies. Following the suggestions by Levac et al. (2010), we will modify the data charting framework to ensure that we capture all the information in a structured way to be able to answer the posed

research questions. We revised the paragraph accordingly (p. 6, lines 2-7).

*It is also suggested that the author abstract data on study design and main findings (i.e., efficacy).

Our response: We thank the reviewer for the suggestion. We will now include the items in the data charting framework (p.5, lines 35-47).

*The authors should include a list of anticipated limitations.

Our response: We have now added a section “Study limitations” (p. 6, lines 28-47).

Reviewer: 2
Reviewer Name: Habibollah Haron
Institution and Country: Universiti Teknologi Malaysia
Please state any competing interests or state ‘None declared’: no

*Not suitable for journal publication

Our response: We regret that we could not convince the reviewer about the merit of publishing this study protocol. We are ready to address any specific concerns that Professor Haron has regarding our manuscript and invite him to share these with us.

Reviewer: 3
Reviewer Name: Mohammed A. Al-masni
Institution and Country: Kyung Hee University, Korea
Please state any competing interests or state ‘None declared’: None declared

*The subject of this review is very important and will provide good details for further researchers in the field of brain lesion identification.

Our response: We thank the reviewer for the positive assessment.

*There are some comments should be taken care of by authors:
1. Segmentation is a key prerequisite step for brain lesion diagnosis. This review should be clarified that it will be only on brain lesion segmentation (it is fine) or also it will cover lesion classification methods (it is better). Authors mentioned the classification in the body of this scoping review but they did not mention it in the title. I recommend to modify the title to “Automatic lesion segmentation and classification on …”.

Our response: We thank the reviewer for this comment. While we agree with the reviewer that lesion segmentation and subsequent clinical diagnostic classification would provide an excellent and even more comprehensive overview of computer-aided methods for diagnosis support, the scope of such a review would exceed the resources available to us. In the current design, we mention classification as a synonym of segmentation, as many segmentation methods are, in fact, equivalent to image feature classification. We will, however, make note of methods that, on top of brain lesion segmentation, include differential lesion classification.

*2. It is better to present examples of the outcome that will result from this scoping review. Authors could utilize table including methods with brief description and the used MR datasets.

Our response: We will extract the method description and the MR databases used in the data charting stage from the included articles (p. 5, line 38). In the comprehensive analysis, we will capture

recurring themes regarding the used methods and databases. The result presentation will be conditioned on our findings. However, detailed planning at this stage is counterproductive to the aimed objective of the scoping review.

*3. The five stages of the Arksey and O'Malley framework should be stated. For example, use “Stage 1: Identifying research questions” instead of “Identifying research questions”,
“Stage 2: Identifying relevant studies” instead of “Identifying relevant studies”, and so on.

Our response: We thank the reviewer for this valuable suggestion. We edited the “Methods” section accordingly.

*4. In stage 1: Identifying research questions, add the question of what are the most common utilized MR datasets which have ground truth for both lesion segmentation and classification.

Our response: Following the reviewer’s suggestion, we added this point to our research questions (p. 3, lines 39-40).

*5. It is preferred to use more than two online searched databases. In addition to PubMed and IEEE Xplore, Scopus and Google scholar should also be utilized in order to include all feasible studies.

Our response: Following the reviewer’s suggestion, we now conduct the search for eligible studies in Scopus as well as PubMed and IEEE Xplore (p. 4, line 17). We decided not to use Google Scholar (GS) for the following reasons. GS does not feature an export function for search results. Considering the large number of matches for our search phrases, manually saving search results would be impractical. Another concern we have regarding GS is data quality. While there are many important use cases for GS, we contend that it is not suitable for conducting a systematic and unbiased scoping study. Our decision was in part based on the fact that it is relatively easy to manipulate the citation count and ranking of a publication, or to make a publication match search terms that it does not actually contain, by uploading falsified papers.

López-Cózar ED, Robinson-Garcia N, Torres-Salinas D. Manipulating Google Scholar citations and Google Scholar metrics: Simple, easy and tempting. arXiv preprint arXiv:1212.0638. 2012 Dec 4.

Beel J, Gipp B. On the robustness of Google Scholar against spam. InProceedings of the 21st ACM conference on Hypertext and hypermedia 2010 Jun 13 (pp. 297-298). ACM.

*6. I recommend to present inclusive comparison of the methods’ performance that utilized same MR datasets.

Our response: We appreciate the suggestion and have now included the proposed comparison in the data that will be reported in this study (p. 6, lines 13-15).

Reviewer: 4
Reviewer Name: M.Lavanya
Institution and Country: Saveetha School of Engineering, Saveetha Institute of Medical and Technical Sciences, India
Please state any competing interests or state ‘None declared’: None declared

*Your paper was written well. But Everywhere the conditions that are considered for reviewing is mentioned but the brief analysis and comparing of methods are nowhere mentioned.

Our response: We thank the reviewer for the favourable assessment and the constructive suggestion.

We updated the “Data charting” section to include information that will help compare and analyse brain lesion segmentation methods (pp. 5-6, lines 35-7).

VERSION 2 – REVIEW

REVIEWER	Sarah Munce Toronto Rehabilitation Institute-University Health Network
REVIEW RETURNED	12-Dec-2018

GENERAL COMMENTS	The sub-heading "General" in the Methods and Design section should be removed and replaced with "Overview".

REVIEWER	Mohammed A. Al-masni Kyung Hee University
REVIEW RETURNED	02-Dec-2018

GENERAL COMMENTS	The paper has possibility to be published in this version.