Author’s response to reviews

Title: Instrument-based Tests for Measuring Anterior Chamber Cells in Uveitis: A Systematic Review Protocol

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Author’s response to reviews:

We'd like to thank the associate editor and the reviewer for taking the time to consider our manuscript and giving their very helpful and constructive comments. We have considered each of these carefully and made the appropriate revisions in our manuscript. For each point, I have commented on our thoughts and actions below. I hope our changes are satisfactory and thank you again for taking the time to review our work.

Reviewer reports:

Reviewer #1: Many thanks for sending me this paper, which seeks to investigate the available instrument-based technologies for measuring anterior chamber cells in uveitis.

I will start with some general comments and methodological and more minor issues will follow.

The study is likely to make an original contribution, by pulling available evidence on ophthalmic imaging techniques that could provide more reliable measures of ocular inflammation compared to the SUN grading scheme. The study protocol has also been registered in the PROSPERO database.

There are a number of methodological issues identified:

P8, lines 2-3: Although authors mention the word 'Appendix' in the manuscript, MEDLINE search strategy is presented in P19 in a table. Authors could submit the search strategy as 'Appendix 1' in a supplementary file, instead.
Thank you, we have attached the search strategy as appendix in a supplementary file instead.

P9, 'Selection criteria': In order to maintain transparency of the review process, the key components of the review question should be set out using the rule PICOT, as described in PRISMA-P checklist and preferably with the following order: 'population', 'index test', 'comparator/reference standard', 'outcome/target condition', 'type of study'. Authors should also specify whether they plan to prioritise their outcomes, i.e. by defining primary or secondary outcomes.

Thank you, we have restructured the selection criteria section as per PICOT and defined our primary and secondary outcomes.

P9, 'Study designs': The authors state that they will analyse cross-sectional studies. What do they plan to do with relevant case-control studies, particularly when the control group is part of the suspected population?

We thank the reviewers for raising this point. To clarify, we require clinical grading and instrument-based grading of AC cells to be done in a cross-sectional manner (i.e. within 24 hours of each other), but not necessarily the study design. For example, if a longitudinal study took multiple measurements of AC cells, we would only include this study if we can extract matched clinical grading and instrument based measurements for each time point.

As for case-control studies, we will include patients as per the selection criteria ('those with evidence of anterior chamber cells and/or a diagnosis of uveitis' (Pg 10 line 193-197). This means we will not include healthy controls, but we will include quiescent uveitis patients (i.e. clinically grade 0). During the analysis, we will consider the distribution in severity of disease in each study.

P10, 'Selection process' & 'Data extraction': The software should be added.

Thank you. EndNote is used for selection, this is mentioned on page 8, Excel is used for data extraction and this is now included on page 10.

P12, lines 17-20: If the authors plan to include longitudinal studies, this should be stated under the 'Study design' section, instead.

Apologies that this was not clear. We have clarified in 'study design' section now that there will be no restriction on study design. The cross sectional measurement of index test and comparator can be found in both cross sectional studies and longitudinal studies. However, studies will only be included if the measurements are matched to same point-in-time.

P14, 'Minimising Bias': It is unusual for a protocol to have a subsection entitled 'minimising bias'. Authors should preferably specify that two independent reviewers will perform each step under the relevant sections, and remove this paragraph.
We have removed the minimising bias section and clarified in each section regarding two independent reviewers.

P15, lines 35-37, 58/P16, lines 1-3: Authors state that they will not perform subgroup analyses based on age, gender etc. Notwithstanding, they also report that subgroup analyses may be considered if permitted by data. It should be specified whether they plan to perform a subgroup analysis or not, and one of the two sentences should be removed, accordingly.

Thank you. We will perform subgroup analysis if the data permits, however we are anticipating this is unlikely. I have removed the first statement (now Pg17) and kept the second statement.

P18: The following listed abbreviations 'CINAHL', 'NEI-FDA-', 'ROBINS-I' are found nowhere in the manuscript.

Thank you, these are now removed from the abbreviations list.

P19, MEDLINE search strategy: Preferably submit search strategy as 'Appendix 1'.

We have now attached the search strategy as appendix in a supplementary file instead.

PRISMA-P checklist: Authors do not mention whether they plan to perform quality assessment of the body of evidence, i.e. using GRADE.

Thank you for raising this important point. After much consideration, we have decided not to use GRADE and instead give a narrative summary of the quality of evidence, with supporting risk of bias assessment using QUADAS2. The main reason for this is because there is currently no clear guidance on how to assess correlation studies for a diagnostic/monitoring test using GRADE, therefore we are unsure of how to upgrade and downgrade studies appropriately. We anticipate a small number of 'proof of concept' studies with likely small, heterogenous populations, which inevitably will be graded as poor quality. The most relevant guidance from the GRADE working group is assessment of diagnostic test accuracy which focuses on sensitivity and specificity performance metrics, and this is not applicable to our review. We will be very happy to take guidance from the editor/reviewers if they have further insight on how to apply GRADE in these types of studies, however our perspective was that there is inadequate guidance to carry out meaningful quality assessment using GRADE.

Minor comments:

We thank the reviewer for pointing out these following points, we have gone through each one and amended all of the following changes.

P2, Abstract: Please add grey literature in your searches.

P7, 'Design': please replace 'design', which is often used for 'study design' under PICOT format, with 'protocol'.
P14, line 45: Please use 'data synthesis' instead.

P16, 'Reporting': This sentence should preferably be incorporated under 'Protocol' section in P8.

P16, 'Discussion and potential impact': Preferably change to 'Discussion'.

P22, line 39: Reference 7 needs to be more fully cited.

P22, lines 45-52: References 8-9 represent the same study cited twice.

Associate Editor Comments:

Thank you for submitting this paper. Overall it is very well written but there are few sentences to re-write and more detail needed for some of the methodology. Please see my additional comments below. I look forward to receiving a re-submission.

1. P4 line 47. 'in as per the SUN grading' doesn’t make sense. Perhaps replace with ‘in the SUN grading’

Thank you, we have reworded this sentence.

2. P7 line 2. Your aim implies you are only looking to see what instrument-based technologies are available, but you are also evaluating them against SUN and describing reliability and repeatability. Please consider re-wording to reflect this e.g. ‘To investigate the nature of instrument..’ or ‘To investigate the accuracy of instrument.’

Thank you. We have added ‘…and assess their level of validation’ (P8 line 138)

3. P8 Bibliographic databases. The Cochrane Library no longer contains the Database of Abstracts of Review of Effects, or the HTA database). HTA can be access via http://www.crd.york.ac.uk/PanHTA/ and an archive version of DARE is also available from York CRD databases website. Please consider re-wording to just ‘The Cochrane Library’ as you may want to look at all of its content now, and consider adding the CRD HTA database.

Thank you. We have amended this to HTA (via York CRD), DARE (archive in York CRD) and Cochrane library.

4. For each database add planned dates of coverage (as per PRISMA-P item 9). E.g. Medline (Ovid) 1946 – present. Different institutions subscribe to different date coverages of databases such as Medline and Embase so it’s helpful to know if it’s the 1996+ version or another. If the
start date of the database is not indicated on the database website e.g Cochrane, then say 'database inception to present'

We have now added the database dates.

5. P10 Selection process. Please indicate how many reviewers will be independently screening titles and abstracts, and how you plan to resolve different screening decisions.

Thank you, we have added 'Two independent reviewers will carry out quality assessment and reach consensus by discussion or referral to a third reviewer' (P11 line 225)

6. P10 - 12. State how many reviewers will be data extracting and assessing articles independently in these sections rather than having a minimising bias section.

We have added a statement in this section saying 'The extraction process will be carried out by will be undertaken by two reviewers independently with referral to a third reviewer if necessary' and removed the minimising bias section. (P12 line 232)

7. P15 line 5-10. Suggest moving the position of commas so the sentence reads ‘For each type of technology we are expecting small numbers of studies, therefore we will analyses different platforms, generations…’

Thank you, this is done.

8. P22 reference 5 requires editing – it has the title listed twice. Also remove the work [Internet] unless this sources is only available on the Internet in which case please add the URL and the last date it was accessed.

We have made this correction. Thank you.

9. PRISMA-P Checklist. Three columns are missing from the checklist where you tick 'yes' or 'no' to indicate if you have included the item in your protocol, and the final column where you list the location of the relevant text (a line number/page number). Please submit a completed checklist to indicate the items you've included in your protocol and where they can be found in the text.

Thank you, we have updated the PRISMA-P checklist with the missing columns and marked where each point can be found in the manuscript.

In addition to the above points, we would like to suggest an additional amendment. We would like to include all slit-lamp based clinical grading systems for measuring AC cells as the
comparator. Previously we described only the SUN grading system, which has been the standard for counting AC cells since 2005. However, previous to the SUN there were a number of alternatives (P5 line 94-96). During full text screening, we have come across an older clinical system being used as a comparator which otherwise fits the inclusion criteria. These older systems are structured in a similar way to the SUN system, however there are small variations in the number of grades and the cell range for each grade and therefore in the context of calculating correlation, we will need to consider them separately. We would like to change the 'comparator' from SUN grading system to any 'slit-lamp based clinical grading system'. During data synthesis, studies will be split by clinical grading system (P15 line 354).