PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

Title (Provisional)

Effect of Size of Capsulorhexis on the Outcome of Cataract Surgery: A Protocol for Systematic Review and Individual Participant Data Meta-analysis.

Authors

Wang, Songhong; Wu, Tiexi; Zhang, Yue; Liu, Yue; Qin, Xuejiao

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Ripa, Matteo**
Affiliation	**Sankara Eye Hospital**
Date	**16-Aug-2024**
COI	**None**

Dear Authors,

I wish to submit my review of the protocol: "Effect of Size of Capsulorhexis on the Outcome of Cataract Surgery: A Protocol for Systematic Review and Individual Participant Data Meta-analysis."

The Authors have undertaken a significant and valuable task in discussing a novel topic. Their protocol is commendable and of great importance. However, I have some comments regarding the methodology.

The Authors should clarify whether the appraisers independently performed the screening process and whether the hand-search bibliography/grey-literature evaluation was performed. The Authors should also clarify how they will conduct the meta-analyses (i.e., models, heterogeneity management, and possible subgroups meta-analysis and meta-regression).

Reviewer	**2**
Name	**Henein, Christin**
Affiliation	**University College London Institute of Ophthalmology**

Date **24-Aug-2024**

COI **None to declare**

This Protocol is well written and follows the PRISMA-P reporting guidelines well.

Notes to Authors:

Abstract

Ensure that the abstract includes explicit details on the PICO framework (Population, Intervention, Comparator, Outcomes). For instance, specify the participants (patients undergoing cataract surgery), the intervention (different capsulorrhexis sizes), and the outcomes (IOL stability, visual acuity).

Methods

Provide more detail on the types of study designs that will be included or excluded. For example, clarify if observational studies, randomised controlled trials, or both will be considered.

Include the full search strings for at least one database in the appendix or supplementary materials. This would enhance the transparency and reproducibility of the search process.

Bias

Provide more detail on how publication or data sharing bias will be assessed, particularly for smaller studies that may not be included in IPD.

Amendments to Protocol

Outline a clear plan for documenting any amendments to the protocol, including how these will be reported and justified in future publications.

Power Calculation

Estimate the statistical power of the IPD meta-analysis as it can provide useful insight into viability of the project and whether the resulting power is likely to be sufficient based on your preliminary searches.

GRADE

Include a brief explanation of how the modified GRADE framework will be applied specifically to the outcomes of interest. Consider detailing how decisions regarding downgrading or upgrading the quality of evidence will be made.

Grammar

Occasional incorrect tense is used, please check the manuscript throughout.

VERSION 1 - AUTHOR RESPONSE

Reviewer: 1

Comment 1. The Authors should clarify whether the appraisers independently performed the screening process and whether the hand-search bibliography/grey-literature evaluation was performed.

Reply: We sincerely thank the reviewer for the kind suggestion. I apologize for not expressing myself clearly. The two assessors conduct the processes of study screening, selection, data extraction and bias risk assessment independently, as indicated in lines 161-162. During the screening process, we first used software to remove duplicate references, followed by manual deletion. After removing duplicates, the two assessors independently performed manual screening, excluding case series, conference reports, grey literature, news articles, and literature reviews from the analysis.

Comment 2. The Authors should also clarify how they will conduct the meta-analyses (i.e., models, heterogeneity management, and possible subgroups meta-analysis and meta-regression).

Reply: Thank you for your valuable comments on the manuscript. We provided a more detailed description of our methodology in the 'Data synthesis and (statistical) analysis' section, presented in lines 337-372 in the revised manuscript.

Reviewer: 2

Comment 1. Abstract: Ensure that the abstract includes explicit details on the PICO framework (Population, Intervention, Comparator, Outcomes). For instance, specify the participants (patients undergoing cataract surgery), the intervention (different capsulorrhexis sizes), and the outcomes (IOL stability, visual acuity).

Reply: Thanks for your professional suggestions, we have provided a more explicit description concerning details of the PICO framework in the abstract, which is presented as follows:

Introduction In the era of functional intraocular lens implantation, it is crucial to investigate the influence of different capsulorhexis sizes (including the diameter of the capsulorhexis, area of the anterior capsule opening, anterior capsule coverage, centration, and circularity of the capsulorhexis) on the postoperative outcomes (such as visual acuity, capsule shrinkage, intraocular lens stability and intraocular pressure) in

patients undergoing cataract surgery. This is particularly important in patients with high myopia or diabetes mellitus. The proposed protocol aims to enhance the transparency of our research and offer references for future studies.

Comment 2. Methods: Provide more detail on the types of study designs that will be included or excluded. For example, clarify if observational studies, randomised controlled trials, or both will be considered.

Reply： We have provided more details on the types of study designs that will be included or excluded in lines 134-142. To enhance the data available for analysis, both randomized controlled trials and observational studies will be included.

Comment 3. Methods: Include the full search strings for at least one database in the appendix or supplementary materials. This would enhance the transparency and reproducibility of the search process.

Reply: We appreciate your suggestion and recognize the importance of transparency in research practices. The precise full search strategies for all databases has been uploaded in supplementary file S1.

Comment 4. Bias: Provide more detail on how publication or data sharing bias will be assessed, particularly for smaller studies that may not be included in IPD.

Reply: We sincerely thank you for your valuable remark. We have provided specific details regarding the strategies employed to address publication or data sharing bias in lines 313-329. The contents are also presented as follows. Thank you for highlighting this important aspect.

Publication or data sharing bias

To assess the concern regarding publication or data sharing bias, we will implement several strategies:

• Literature Review: We will undertake an extensive literature review to identify all pertinent studies, including smaller ones that might be excluded from individual participant data (IPD) analyses.

• Tool: For analyses involving ten or more trials, we assessed potential publication bias by examining asymmetry in funnel plots using Egger's test. Funnel plots will also be generated to visually inspect for potential bias in smaller studies.

• Sensitivity Analysis: We will perform sensitivity analyses to evaluate the impact of including or excluding smaller studies on the overall results.

• Meta-biases: In 2016, Smith et al. compared IPD-MA outcomes with aggregate data meta-analysis (AD-MA) outcomes and reported inconsistent results. To assess potential bias in data availability, we will perform t-tests for continuous variables and $\chi 2$ tests for categorical variables to compare characteristics across studies

that received IPD and those that did not. The effect size information obtained from the publications will be used to calculate Cohen's d effect sizes. To compare effect sizes between studies with and without IPD, the effect sizes were pooled and analysed across studies using the traditional "subgroup analysis" approach of meta-analysis.

Comment 5. Amendments to Protocol: Outline a clear plan for documenting any amendments to the protocol, including how these will be reported and justified in future publications.

Reply: To ensure transparency and maintain the integrity of our research, the following plan is implemented in case of documenting any amendments to the study protocol, which have been added in lines 374-385 in the 'Amendments to protocol' Section.

• Documentation: All amendments will be recorded in a designated section of the study protocol, detailing the nature of the change, the rationale behind it, and the date of the amendment.
• Reporting: Any amendments are to be explicitly reported in future publications. This will include a summary of the changes made, along with an explanation of their significance in relation to the study's objectives.
• Justification: For each amendment, a point-by point justification is to be provided that outlines the reasons for the changes, whether they are based on emerging evidence, feedback from peer reviewers, or unforeseen circumstances encountered during the study.

Comment 6. Power Calculation: Estimate the statistical power of the IPD meta-analysis as it can provide useful insight into viability of the project and whether the resulting power is likely to be sufficient based on follow your preliminary searches.

Reply: Thank you for your insightful suggestion regarding the estimation of statistical power for individual participant data (IPD) meta-analysis. Power calculation is often overlooked in the literature, resulting in a scarcity of references on this topic. Our brief searches indicate that the calculation methods differ slightly between randomized controlled trials and observational studies.

Our study shares similarities with that of Murphy et al., as it utilizes trial data that diverges from their original research questions [1]. Consequently, we find ourselves without a reliable method for power calculation. However, we have studied several methods to estimate power across different research types.

Whittle et al. proposed a method for examining prognostic factor effects on binary outcomes [2]. This involves a three-step approach: first, deriving the Fisher's information matrix and an approximate estimate of the variance of each study's prognostic factor effect from aggregate data. This allows for the calculation of the variance of the summary effect estimate from a two-stage IPD meta-analysis, ultimately enabling the

assessment of power for the IPD MA project.

Similarly, Ensor et al. introduced a simulation-based power calculation within a two-stage framework, illustrating a method for planned IPD meta-analyses of randomized trials with continuous outcomes [3].

While power calculations are frequently neglected in IPD meta-analysis procedures and publications, establishing a high level of statistical power in advance can enhance the credibility of the research and reassure funding bodies about the project's feasibility and value. However, this does not apply to our study. The assessment of bias risk and overall certainty of evidence can, to some extent, validate the reliability of our findings. We welcome any reliable methods the reviewer might recommend for power calculation.

The unique aspects of our protocol complicate power calculation. Nevertheless, even if the power of this study is insufficient, it is crucial to proceed with the IPD-MA. Issues such as the dichotomization of continuous factors, selective outcome reporting, and inadequate presentation of aggregate data in primary studies would limit the meta-analysis of prognostic factor studies without IPD. In contrast, IPD facilitates more complex analyses, allowing for comprehensive outcome assessment and more appropriate modeling of continuous variables.

About the issue of statistical power, we have discussed in lines 332-336 in the revised manuscript. Thanks again for your professional remarks. The added discussion is presented as follows:

High statistical power indicates a high feasibility of the project. However, due to the inclusion of various study types and the fact that some studies did not primarily focus on the outcomes of interest, there is lack of a standardized power calculation method in this study. Meanwhile, the assessment of bias risk and overall certainty of evidence can, to some extent, validate the reliability of our findings.

[1] Murphy DC, Al-Zubaidy M, Lois N, et al. The Effect of Macular Hole Duration on Surgical Outcomes: An Individual Participant Data Study of Randomized Controlled Trials. *Ophthalmology* 2023;130(2):152-63. doi: 10.1016/j.ophtha.2022.08.028 [published Online First: 2022/09/05]

[2] Whittle R, Ensor J, Hattle M, et al. Calculating the power of a planned individual participant data meta-analysis to examine prognostic factor effects for a binary outcome. Research synthesis methods 2024 doi: 10.1002/jrsm.1737 [published Online First: 2024/07/24]

[3] Ensor J, Burke DL, Snell KIE, et al. Simulation-based power calculations for planning a two-stage individual participant data meta-analysis. BMC medical research methodology 2018;18(1):41. doi: 10.1186/s12874-018-0492-z [published Online First: 2018/05/20]

Comment 7. GRADE: Include a brief explanation of how the modified GRADE framework will be applied specifically to the outcomes of interest. Consider detailing how decisions regarding downgrading or upgrading the quality of evidence will be made.

Reply: We appreciate your guidance on this matter. We provided a detailed account of the specific applications of the modified GRADE framework, outlining the criteria for downgrading or upgrading the quality of evidence, in lines 290-312. These criteria are based on key factors, including risk of bias, inconsistency, indirectness, imprecision, and publication bias. This clarification will enhance the transparency and rigor of our evaluation process, thereby ensuring that our conclusions are robustly supported by the evidence. These details are also presented as follows:

We will take the following steps to implement the modified GRADE framework:

• Determination of Study Type: We will first classify the outcomes based on the study design (e.g., randomized controlled trials, observational studies, etc.). This classification will assist us in establishing a baseline for assessing the quality of evidence.

• Assessment of Risk of Bias: We will utilize standardized tools, such as the Cochrane Bias Risk Tool, to evaluate the risk of bias for each study. Studies identified as having a high risk of bias will be considered for downgrading.

• Assessment of Consistency: We will compare the consistency of results across studies. In cases where significant differences are observed, we will consider downgrading the quality of evidence.

• Indirectness of Evidence: We will conduct an indirect assessment of whether the results apply to our study population or the intervention. Downgrading will be considered if the intervention or population in the study is deemed distant from our own.

• Precision Assessment: We will evaluate the precision of the results, including the width of the confidence intervals. If the confidence intervals are wide, indicating insufficient precision, we will consider downgrading.

• Publication Bias: We will check for signs of publication bias, for example, by employing a funnel plot. Should evidence of bias be identified, a downgrade will be considered.

• Upgrade or Downgrade: Upon completion of the assessments, we will synthesize all factors to determine whether to upgrade or downgrade the quality of evidence. For instance, if a particular study demonstrates strong performance in terms of risk of bias and consistency but exhibits issues with precision, we may opt to maintain the current quality of evidence.

• Transparent Recording: We will meticulously document each step of the evaluation process and the final grading of evidence quality to ensure transparency and reproducibility.

Comment 8. Grammar: Occasional incorrect tense is used, please check the manuscript throughout.

Reply: We appreciate your attention to details and checked the manuscript thoroughly to identify and correct any incorrect tense use.

Other changes:

Line 3: Due to the substantial contributions of Tiexi Wu in revising this article, Tiexi Wu has been designated as the second author.

We appreciate for the Editor/Reviewers' valuable work, which definitely improved our study.