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)

The effectiveness of biologics for patients with severe asthma: study protocol for an umbrella review of systematic reviews and meta-analyses

Authors

Xiao, Qionghua; Xue, Bingyu; Huang, Yuanming; Wang, Minghang

VERSION 1 - REVIEW

Reviewer	1
Name	K. Viswanathan , Ravi
Affiliation	
Date	30-Dec-2024
COI	**1. Novartis Pharmaceuticals - received grant support for an Investigator Initiated Research Trial**

2. Regeneron - Advisory Board Participation

The Overall stated purpose/methodology appears reasonable. The comments marked with an asterisk below may be more important considerations to revise or change or include in the protocol.

Page 2 Line 42 – consider removing the second "chronic" prior to inflammation

Page 3 Line 45 – Consider replacing sentence with "Additionally, and more importantly, patients with severe asthma have more significant symptoms...

Page 4 Line 76 – consider replacing the second occurrence of the word "evidence" with "analysis or summary"

Page 5 Line 90 - the intervention statement is unclear as currently biologic therapy is always recommended with routine background inhaler therapy (without inhaler is not approved).

**Page 5 Line 101 - Would make sure to include OCS sparing effects in the outcomes as it is clearly an important metric for many biologics and a primary outcome for many trials.

Page 5 Line 102 – consider changing to "will collect information regarding adverse events..."

Page 5 Line 107 – consider replace with "Articles for which.."

Page 6 Line 113 – Consider replacing with "The search terms used include:"

Page 6 Line 115 – consider replacing with "The search strategy used in Pubmed database is.."

Page 6 Line 116 – replace "are" with "is"

Page 7 Line 119 – consider replacing with "After removal of duplicate studies…"

Page 7 Line 123 – consider replacing "..the final studies to be included.."

**Page 7 & 8 – Consider adding information in the extractions section regarding eosinophil count, FeNO, IgE levels, atopic status (skin prick testing or sIgE) from these SRs/Mas/studies as it is an important to ascertain if these biomarkers can predict optimal efficacy or stratification for usage of a biologic over another.

Page 8 Line 139/140 – replace "have" with "has"

**Page 8 Lines 149-153 – consider adding sample size as an additional factor into the "upgrading" or "degrading" factors – would include in the discussion as well.

Page 9 Line 161 – change "P < 0.05 indicates statistical significance."

Page 9 Line 165 – consider rephrasing "many SRs/Mas have been published. However, concerns have been raised as the generalizability and validity of such analyses."

Page 9 Line 166 – consider changing "Different study populations and types of original studies included in the analyses and varying degrees of methodological defects in SRs/Mas may lead to misleading clinical decisions."

Page 9 Line 168 & 169 – Consider changing "Employing the latest evidence-based medicine analysis….based on SRs/Mas provides for a more robust and reliable evidence for clinical practice and partially compensates for some of the shortcomings of SRs/MAs."

Page 9 Line 172 – consider changing "economy" to "economic"

Page 9 Line 173 – consider adding "biologics have demonstrated good efficacy.."

Page 9 Line 174 – change "are" to "is"

Page 10 Line 179 & 180 – consider removing this last sentence.

**References - Please be sure to consider inclusion of available ITCs (indirect treatment comparison) articles that have been published recently. may use these additional keywords for searches.

Reviewer	2
Name	**Chagas, Gabriel Cavalcante Lima**
Affiliation	**Federal University of Ceara Faculty of Medicine**

Date	25-Feb-2025
COI	None

This study presents a protocol for an umbrella review aimed at synthesizing evidence from systematic reviews and meta-analyses regarding the effectiveness and safety of biologic therapies for severe asthma. The topic is both relevant and timely, and the proposed methodology is generally solid for an umbrella review. However, adding further details about the review process would strengthen and align the protocol with best-practice standards. Below are some specific comments and suggestions for improvement:

1. Clarification of Included Study Designs: Specify whether only systematic reviews and meta-analyses of randomized controlled trials will be included, or if reviews with observational studies will also be considered.

2. Language Restrictions: Clarify the reasons for imposing language restrictions.

3. Management of Duplicate Reports: Explain how duplicate publications will be addressed. For example, will the most recent publication or the study with the largest patient sample be prioritized?

4. Conference Abstracts: List the specific conference proceedings that will be searched to identify relevant abstracts for clarity.

5. Data Extraction on Certainty Assessments: It would be beneficial to extract data regarding the certainty of evidence from previously published systematic reviews and meta-analyses, as this can enhance the depth of the analysis.

6. Handling Overlapping Studies: Describe how overlapping primary studies across included systematic reviews and meta-analyses will be managed to prevent the double-counting of data.

7. Risk of Bias Assessment: Specify how the risk of bias will be assessed for the included reviews and whether the risk of bias in primary studies will also be considered.

8. Subgroup Analyses: Consider detailing planned subgroup analyses to explore potential sources of heterogeneity for transparency.

9. Publication Bias Assessment: It is advised to perform funnel plots and Egger's tests only when there are a minimum of 10 studies included to guarantee sufficient statistical power. I recommend specifying this clearly in the protocol.

10. Clarification of PRISMA Scoring Criteria: Provide explicit definitions or examples for classifying "complete," "partial," and "incomplete" reporting. This will enhance consistency and reduce subjectivity in the assessment process.

11. Reviewer Process: Indicate whether quality assessments will be conducted by independent reviewers. I recommend that at least two reviewers independently assess the

reporting quality, resolving discrepancies through discussion or consultation with a third reviewer to improve reliability.

12. PRISMA Version: Specify which version of the PRISMA statement will be used in the manuscript, as this information is currently only available in the references.

13. Justification for Cut-off Scores for PRISMA Scoring: While the proposed cut-off scores for reporting quality are reasonable, providing a rationale or referencing previous studies that employed similar thresholds would strengthen the methodology.

14. Reviewer Training and Potential Bias: Mention any training or calibration exercises conducted for reviewers before the scoring process to improve inter-rater agreement and minimize bias.

Overall, the proposed methodology is appropriate, but addressing these suggestions will enhance the rigor and transparency of the review process. I look forward to seeing these clarifications and improvements reflected in the revised protocol.

VERSION 1 - AUTHOR RESPONSE

Reviewer 1

Dr. Ravi K. Viswanathan

Thank you for carefully reading my manuscript and providing valuable suggestions.

(1) The questions you raised regarding grammar, sentence patterns, and vocabulary optimization.

Re: we have carefully reviewed and implemented the suggestions you made regarding grammar, sentence patterns, and vocabulary optimization. For example, I removed the second "chronic" prior to inflammation on line 42 of page 2, replaced the word "evidence" with "analysis or summary" on line 76 of page 4, and replaced "are" with "is" on line 116 of page 6.

(2) Page 5 Line 90-the intervention statement is unclear as currently biologic therapy is always recommended with routine background inhaler therapy (without inhaler is not approved).

Re: thanks for your helpful comment. We have clarified the intervention statement, with inhaler therapy as the routine background treatment and biologics as the add-on therapy. The corrections can be found on lines 90-94 of page 5.

(3) Page 5 Line 101-Would make sure to include OCS sparing effects in the outcomes as it is clearly an important metric for many biologics and a primary outcome for many trials.

Re: thanks for your valuable comment. We have already included the change in the dosage of OCS as an outcome. The corrections can be found on line 99 of page 5.

(4) Page 7 & 8-Consider adding information in the extractions section regarding eosinophil count, FeNO, IgE levels, atopic status (skin prick testing or sIgE) from these SRs/Mas/studies as it is an important to ascertain if these biomarkers can predict optimal efficacy or stratification for usage of a biologic over another.

Re: thanks for your precious suggestion. We have added blood eosinophil count, FeNO, IgE, and sIgE levels in the "Data extraction" section. The corrections can be found on line 141 of page 8.

(5) Page 8 Lines 149-153-consider adding sample size as an additional factor into the "upgrading" or "degrading" factors-would include in the discussion as well.

Re: thanks for your helpful suggestion. We have added sample size as an additional factor into the upgrading factors and discussed its significance in the "Discussion" section. The corrections can be found on line 178 of page 10 and lines 216-221 of pages 11-12.

(6) Page 10 Line 179 & 180-consider removing this last sentence.

Re: thanks for your valuable comment. After careful consideration, we have removed the last sentence. The corrections can be found on line 226 of page 12.

(7) References-Please be sure to consider inclusion of available ITCs (indirect treatment comparison) articles that have been published recently. may use these additional keywords for searches.

Re: thanks for your kindly question. We have already cited the recently published ITCs articles in the "References" section and used ITCs as an additional keyword for searching. The corrections can be found on lines 283-285 of pages 14-15 and line 119 of page 6.

Reviewer 2

Dr. Gabriel Cavalcante Lima Chagas

Thank you for reading my manuscript in detail and providing many professional comments.

(1) Clarification of Included Study Designs: Specify whether only systematic reviews and meta-analyses of randomized controlled trials will be included, or if reviews with observational studies will also be considered.

Re: thank you for raising this important issue. We have clarified the inclusion criteria according to your suggestion. This umbrella review will only include systematic reviews and meta-analyses of randomized controlled trials to focus on the highest level of evidence. The corrections can be found on line 107 of page 5.

(2) Language Restrictions: Clarify the reasons for imposing language restrictions.

Re: thanks for your helpful suggestion. As most databases and literature resources are in English, language restrictions ensure data accuracy and consistency, which facilitates precise data extraction and analysis. The corrections can be found on lines 223-225 of page 12.

(3) Management of Duplicate Reports: Explain how duplicate publications will be addressed. For example, will the most recent publication or the study with the largest patient sample be prioritized?

Re: thanks for your valuable question. We have already explained the approach to addressing duplicate publications in our manuscript. Duplicate publications will be resolved by prioritizing the most recent publication to capture methodological updates. If publications are within 6 months of each other, the study with the larger sample size and more comprehensive data will be selected. The corrections can be found on lines 181-188 of page 10.

(4) Conference Abstracts: List the specific conference proceedings that will be searched to identify relevant abstracts for clarity.

Re: thanks for your precious suggestion. Conference abstracts from the American Thoracic Society International Conference and the European Respiratory Society International Congress will be searched to identify relevant abstracts. The corrections can be found on lines 115-116 of page 6.

(5) Data Extraction on Certainty Assessments: It would be beneficial to extract data regarding the certainty of evidence from previously published systematic reviews and meta-analyses, as this can enhance the depth of the analysis.

Re: thanks for your valuable suggestion. To enhance the depth and robustness of our analysis, firstly, we will extract GRADE ratings (e.g., high, moderate, low, very low) for critical outcomes from SRs/MAs. Furthermore, we will also collect information on the methodological quality of these SRs/MAs using tools like AMSTAR 2, including the name and version of the assessment tool used, its core evaluation criteria or domains, assigned scores, and any conclusions drawn regarding the certainty of the evidence. The corrections can be found on lines 144-148 of page 8.

(6) Handling Overlapping Studies: Describe how overlapping primary studies across included systematic reviews and meta-analyses will be managed to prevent the double-counting of data.

Re: thanks for your valuable suggestion. To prevent the double-counting of data, we will create a comprehensive inventory of all primary studies and identify any overlaps. Then, we will exclude duplicate data to ensure that data from each primary study are included only once. Additionally, if multiple SRs/MAs include the same primary studies, the datasets may be merged. The corrections can be found on lines 130-135 of pages 7-8.

(7) Risk of Bias Assessment: Specify how the risk of bias will be assessed for the included reviews and whether the risk of bias in primary studies will also be considered.

Re: thanks for your precious question. Risk of bias of the included SRs/MAs will be assessed using AMSTAR 2 tool. Risk of bias of primary studies will be evaluated through seven aspects: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias. The corrections can be found on lines 164-174 of page 9.

(8) Subgroup Analyses: Consider detailing planned subgroup analyses to explore potential sources of heterogeneity for transparency.

Re: thanks for your valuable suggestion. We have already detailed the stratification for subgroup analyses in our manuscript. The subgroups will include population characteristics (age, baseline disease severity, and blood eosinophil count) and intervention variables (types of biologics, dosage, and treatment duration). The corrections can be found on lines 197-199 of page 11.

(9) Publication Bias Assessment: It is advised to perform funnel plots and Egger's tests only when there are a minimum of 10 studies included to guarantee sufficient statistical power. I recommend specifying this clearly in the protocol.

Re: thanks for your helpful suggestion. We have added the defining condition that the Egger's test and funnel plots will only be conducted when there are more than 10 studies. The corrections can be found on lines 200-201 of page 11.

(10) Clarification of PRISMA Scoring Criteria: Provide explicit definitions or examples for classifying "complete," "partial," and "incomplete" reporting. This will enhance consistency and reduce subjectivity in the assessment process.

Re: thanks for your valuable suggestion. We have provided explicit definitions for classifying "complete," "partial," and "incomplete" reporting. The corrections can be found on lines 157-160 of page 9.

(11) Reviewer Process: Indicate whether quality assessments will be conducted by independent reviewers. I recommend that at least two reviewers independently assess the reporting quality, resolving discrepancies through discussion or consultation with a third reviewer to improve reliability.

Re: thanks for your helpful comment. We have already incorporated this suggestion into the manuscript. All quality assessments will be conducted by two independent reviewers. Discrepancies will be resolved by consulting a third reviewer. The corrections can be found on lines 150-151 of page 8.

(12) PRISMA Version: Specify which version of the PRISMA statement will be used in the manuscript, as this information is currently only available in the references.

Re: thanks for your kindly comment. The version of the PRISMA statement used in the manuscript will be the PRISMA 2020 statement. We have already added the explanation of

the version in the main text. The corrections can be found on lines 24-25 of page 2, line 73 of page 4, and line 155 of page 9.

(13) Justification for Cut-off Scores for PRISMA Scoring: While the proposed cut-off scores for reporting quality are reasonable, providing a rationale or referencing previous studies that employed similar thresholds would strengthen the methodology.

Re: thanks for your precious comment. Regarding the cut-off scores for PRISMA scoring, we referred to the similar thresholds presented in a published publication. DOI:10.1136/bmjopen-2022-066395. It can be found on lines 293-295 of page 15.

(14) Reviewer Training and Potential Bias: Mention any training or calibration exercises conducted for reviewers before the scoring process to improve inter-rater agreement and minimize bias.

Re: thanks for your valuable suggestion. We have already added in the manuscript that specific training will be provided to all researchers before conducting quality assessments. The corrections can be found on lines 151-153 of pages 8-9.

We sincerely appreciate your invaluable time and constructive feedback, which have significantly strengthened this manuscript. Should any further clarifications or adjustments be needed, please do not hesitate to contact me.

VERSION 2 - REVIEW

Reviewer	**2**
Name	**Chagas, Gabriel Cavalcante Lima**
Affiliation	**Federal University of Ceara Faculty of Medicine**
Date	**15-Mar-2025**
COI	

The authors have addressed the suggested revisions, significantly enhancing the robustness and clarity of this umbrella review protocol. However, I recommend also searching the proceedings of the CHEST Annual Meeting (American College of Chest Physicians – ACCP) and the Asia Pacific Society of Respirology (APSR) Congress for relevant abstracts to ensure comprehensiveness.

VERSION 2 - AUTHOR RESPONSE

1.The authors have addressed the suggested revisions, significantly enhancing the robustness and clarity of this umbrella review protocol. However, I recommend also searching the proceedings of the CHEST Annual Meeting (American College of Chest

Physicians - ACCP) and the Asia Pacific Society of Respirology (APSR) Congress for relevant abstracts to ensure comprehensiveness.

Re: thank you for raising this important suggestion. We have added these two conferences to the manuscript according to your suggestion. The corrections can be found on lines 120-123 of page 6.

We sincerely appreciate your invaluable time and constructive feedback, which have significantly strengthened this manuscript. Should any further clarifications or adjustments be needed, please do not hesitate to contact me.