PEER REVIEW HISTORY

BMJ Medicine 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)	Tocilizumab and sarilumab alone or in combination with corticosteroids for COVID-19: A systematic review and network meta-analysis
AUTHORS	Zeraatkar, Dena; Cusano, Ellen; Martínez, Juan Pablo Díaz; Qasim, Anila; Mangala, Sophia; Kum, Elena; Bartoszko, Jessica; Devji, Tahira; Agoritsas, Thomas; Guyatt, Gordon; Izcovich, Ariel; Khamis, Assem; Lamontagne, Francois; Rochwerg, Bram; Vandvik, Per; Brignardello-Petersen, Romina; Siemieniuk, Reed

VERSION 1 - REVIEW

REVIEWER	**Reviewer 1: Perera, Rafael** University of Oxford, Primary Care Health Sciences, No conflict of interest
REVIEW RETURNED	24-Nov-2021

GENERAL COMMENTS	BMJ Medicine: Tocilizumab and sarilumab alone or in combination with corticosteroids for COVID-19: A systematic review and network meta-analysis Stats Report: The authors present a systematic review with NMA of two interleukin-6 receptor blockers (tocilizumab and sarilumab) for the treatment of COVID-19. They are particularly interested in understanding the effect of these two treatments compared to regular care (placebo) and when used in combination with corticosteroids. Their findings are part of a larger living-systematic-review of interventions to treat people with COVID-19. They find that there is no evidence that IL-6 will improve survival when used as stand-alone treatment but that it improves survival when used in combination with corticosteroids. The authors have substantial experience with these reviews and have done a good job producing the manuscript. There are a few adjustments that I consider necessary before the manuscript could be recommended for publication in BMJ Medicine. Points to consider: • In the Abstract: It is important that they highlight that the beneficial effect was found only when IL-6 were used in combination with corticosteroids. This also needs to be made clear in the 'what this study adds'. • Background, Page 5, end of second paragraph, please clarify if the prospective MA found that tocilizumab reduces mortality on its own or combined with corticosteroids. This is important to set the current manuscript in the right context. • CRITICAL - The description of the inclusion of the REMAP-CAP trial for the phase where tocilizumab vs sarilumab are the

	interventions testes, suggest a critical bias as the centers would have already had been 'allocated' to one of the interventions, turning this into an observational study, not an RCT. If this is the case, I suggest this evidence is excluded from the current manuscript. • The description of the Sarilumab-COVID-19 trial phases needs improving. Please provide more information regarding what these phases are or at least signpost to where this information can be found. • In the Discussion, please be explicit that the evidence you are reporting from comes from 36 trials, not 45. This also needs to be made clear in your Flow-chart which should include the number of studies that provided data and were actually included in their NMA. • Final conclusion, make it explicit that the strong recommendation of using IL-6 is 'in combination with corticosteroids' ONLY. Typos: - 'WE' at the end of page 7. - I am unsure if the word be 'Supplement' instead of 'Supplementary' for the last two paragraphs in the Results section. Please just revise.

VERSION 1 – AUTHOR RESPONSE

Dear Dr. Rourke, Dr. Perera, Dr. Cook, and BMJ Medicine Editorial Team;

Thank you for the opportunity to revise our manuscript. We extend a sincere thank you to the statistical editor for the thorough review thoughtful and valuable input. We have taken into account the issues raised and have implemented changes, which we hope has improved the quality and clarity of our manuscript.

It is our pleasure to resubmit our manuscript for consideration for publication in *BMJ Medicine*.

Sincerely,

Dena Zeraatkar, PhD

Formatting Amendments (where applicable):

- We note that the corresponding author in the system and in the title page of your submission do not match

> **Our response:** The corresponding author is Dr. Reed Siemieniuk. I, Dena Zeraatkar, am, however, handling the submission process.

- Please remove all your figures in your main document and upload each of them separately under file designation 'image'(except tables). NOTE: They can be in TIFF, JPG or PDF format and make sure

that they have a resolution of at least 300 dpi. I have attached here your guide for figure resolution. Figures in DOCUMENT, EXCEL and POWER POINT format are not acceptable.

For more information about formatting figures, please refer to:

https://authors.bmj.com/writing-and-formatting/formatting-your-paper/

https://s16086.pcdn.co/wp-content/uploads/2017/01/Further-information-on-figure-preparation.pdf

- Please update the end of your manuscript to include figure legends for each figure

> **Our response:** We have revised as suggested. We have uploaded each of the two figures as JPG with resolution of 300 dpi. Figure legends are presented at the end of the manuscript.

** We agreed that your manuscript adds detail to what is already known in this area and appreciated the time taken in providing a comprehensive response to the previous reviewer comments.

** Our statistician raised a query about the REMAP CAP trial, which we would like authors to respond to as a priority.

> **Our response:** We have revised to clarify that we took into account the issue raised by the statistician in the analysis and queried the investigators of REMAP-CAP for data on patients who were directly randomized between tocilizumab and sarilumab.

** There were some queries about presentation and reporting, detailed below.

** We found that the presentation of results in terms of deaths in the abstract was quite difficult to follow. We would suggest including the NMA results and CIs are they are presented in Table 2, either alongside or instead of the deaths per 1000.

> **Our response:** We have revised as suggested.

Revision	**Page**	**Line**
Results: We identified 45 eligible trials (20,650 patients), 36 (19,350 patients) of which could be included in the network meta-analysis. Of 36 trials, 27 were at high risk of bias, primarily due to lack of blinding. Tocilizumab, in combination with corticosteroids, probably reduces the risk of death compared to corticosteroids alone (OR: 0.79, 0.95% credible interval 0.70 to 0.88; 35 fewer per 1000, 52 fewer to 18 fewer; moderate certainty) and sarilumab, in combination with corticosteroids, may reduce the risk of death compared to corticosteroids alone (OR: 0.73; 0.95% CI 0.58 to 0.92; 43 fewer, 73 fewer to 12 fewer; low certainty). Tocilizumab and sarilumab, each in combination with corticosteroids, may have similar effects on mortality when compared to each other (OR: 1.07, 95% CI 0.86 to 1.34; 8 more per 1000, 20 fewer to 35 more; low certainty). The effects of tocilizumab (OR: 1.12, 95% CI 0.91 to 1.38; 20 more per 1000, 16 fewer to 59 more;	3	89-99

low certainty) and sarilumab (OR: 1.07,0.95% CI 0.81 to 1.40; 11 more per 1000, 38 fewer to 55 more; low certainty), when used alone, may not be beneficial.		

** At times, we found that the data was buried in the tables. This information is important for readers to see and, as an online journal with greater flexibility, we would invite you to bring key data into the main body of the text to allow for easier viewing. Please at a minimum include the key findings from Table 2 in the text as well.

Our response: We have revised as suggested.

Revision	**Page**	**Line**
Compared to corticosteroids alone, tocilizumab, in combination with corticosteroids, probably reduces mortality and sarilumab, in combination with corticosteroids, may reduce mortality (OR 0.79, 95% credible interval 0.70 to 0.88; 34.54 fewer per 1,000, 51.80 to -18.23; moderate certainty). In combination with corticosteroids, tocilizumab may have similar effects to sarilumab in reducing mortality (OR 1.07, 95% CI 0.86 to 1.34; 8.19 more per 1,000, -20.49 to 34.96; low certainty). The effects of tocilizumab and sarilumab, when used alone, are unclear and may increase or reduce mortality compared to standard care (Tocilizumab OR: 1.12, 95% CI 0.91 to 1.38; 19.73 more per 1,000,-15.78 to 58.52; low certainty. Sarilumab OR: 1.07 95% CI 0.81 to 0.40; 10.60 more per 1,000, -38.37 to 55.17; low certainty). Supplement 2 presents all direct and indirect comparisons and their certainty of evidence.	10-11	296-304

** In the Mortality section under Results, it is stated that: 'Tocilizumab and sarilumab alone may not reduce mortality compared to standard care…'. However, the NMA CIs cross 1, and in the Table 2 it says that tocilizumab and sarilumab alone 'may increase mortality compared to standard care'. We would suggest the message might be clearer if expressed simply that the effects of tocilizumab and sarilumab alone remain unknown, and may increase or decrease mortality according to the findings of this NMA. The expression of the results must be consistent throughout the text and the tables.

Our response: We have revised as suggested.

Revision	**Page**	**Line**
The effects of tocilizumab and sarilumab, when used alone, are unclear and may increase or reduce mortality compared to standard care (Tocilizumab OR: 1.12, 95% CI 0.91 to 1.38; 19.73 more per 1,000,-15.78 to 58.52; low certainty. Sarilumab OR: 1.07 95% CI 0.81 to 0.40; 10.60 more per 1,000, -38.37 to 55.17; low certainty).	10	300-302
Tocilizumab may increase or reduce mortality compared to standard care.	23	Table 2

Sarilumab may increase or reduce mortality compared to standard care.		

** Editors noted some possible typos, for example, in Table 2. The OR for sarilumab vs standard care is stated as 1.07, with a 95% CI 0.81 - 0.40.

Our response: We have revised.

Revision	**Page**	**Line**
1.07 (95% CI: 0.81 – 1.40)	23	Table 2

* Please provide strong justification why this is a separate publication from other existing and ongoing reviews including the BMJ living review.

Our response: We have revised to provide additional justification.

Revision	**Page**	**Line**
To inform recommendations for the World Health Organization (WHO) Living Guidelines on drugs for treatment of COVID-19, we conducted a systematic review and network meta-analysis addressing the effectiveness of IL-6 receptor blockers, alone or in combination with corticosteroids, for patients with COVID-19 (13). This review capitalizes on the methods and data of our living systematic review and network meta-analysis (SRNMA) of drug therapies for COVID-19 and represents the most comprehensive and rigorous assessment of the evidence addressing IL-6 receptor blockers (2). This SRNMA is distinct from our living SRNMA of drug therapies in two ways. First, in this review, we consider tocilizumab and sarilumab separately to assess their comparative effectiveness whereas our living review combines classes of the same drug within the same node. Second, in this review, we separate tocilizumab and sarilumab based on concomitant use of corticosteroids into different nodes to assess possible interactions with corticosteroids.	5-6	143-153

Reviewer: 1

Prof. Rafael Perera, University of Oxford

Comments to the Author

BMJ Medicine: Tocilizumab and sarilumab alone or in combination with corticosteroids for COVID-19: A systematic review and network meta-analysis

Stats Report:

The authors present a systematic review with NMA of two interleukin-6 receptor blockers (tocilizumab and sarilumab) for the treatment of COVID-19. They are particularly interested in understanding the effect of these two treatments compared to regular care (placebo) and when used in combination with corticosteroids. Their findings are part of a larger living-systematic-review of interventions to treat people with COVID-19. They find that there is no evidence that IL-6 will improve survival when used as stand-alone treatment but that it improves survival when used in combination with corticosteroids.

The authors have substantial experience with these reviews and have done a good job producing the manuscript. There are a few adjustments that I consider necessary before the manuscript could be recommended for publication in BMJ Medicine.

Points to consider:

- In the Abstract: It is important that they highlight that the beneficial effect was found only when IL-6 were used in combination with corticosteroids. This also needs to be made clear in the 'what this study adds'.

Our response: We have revised as suggested.

Revision	**Page**	**Line**
• In patients with severe or critical COVID-19, tocilizumab, in combination with corticosteroids, probably reduces mortality, and sarilumab, in combination with corticosteroids, may reduce mortality. Tocilizumab and sarilumab, when used without corticosteroids, may not be beneficial.	4	115-117

- Background, Page 5, end of second paragraph, please clarify if the prospective MA found that tocilizumab reduces mortality on its own or combined with corticosteroids. This is important to set the current manuscript in the right context.

Our response: We have revised as suggested.

Revision	**Page**	**Line**
Further, corticosteroids are now recommended for patients with severe or critical COVID-19 and, like corticosteroids, IL-6 receptor blockers target inflammation (13). Whether IL-6 receptor blockers offer any incremental benefits above corticosteroids is unknown (13). A prospective pairwise meta-analysis reported that tocilizumab reduces mortality when used alone or with corticosteroids but with greater effects when combined with corticosteroids (11).	5	138-142
Our findings are consistent with a prospective pairwise meta-analysis (11), and the largest trials on IL-6 receptor blockers, RECOVERY and REMAP-CAP (6, 7).	11	319-320

- CRITICAL - The description of the inclusion of the REMAP-CAP trial for the phase where tocilizumab vs sarilumab are the interventions testes, suggest a critical bias as the centers would have already had been 'allocated' to one of the interventions, turning this into an observational study, not an RCT. If this is the case, I suggest this evidence is excluded from the current manuscript.

Our response: REMAP-CAP randomized patients to tocilizumab or standard care (among centres with access to tocilizumab) or to sarilumab or standard care (among centres with access to sarilumab). Randomization to standard care was halted when an interim analysis showed efficacy of tocilizumab and sarilumab after which patients were randomized to either tocilizumab or sarilumab, with both groups receiving corticosteroids. As such, we treated REMAP-CAP as three separate trials in our analyses (i.e., tocilizumab versus standard care; sarilumab versus standard care; tocilizumab versus sarilumab). We received data on patients that were eligible for randomization to both tocilizumab and sarilumab in the latter phase of REMAP-CAP and restricted the comparison of tocilizumab with sarilumab from REMAP-CAP to this group of patients, thus avoiding this bias. We have revised to clarify.

Revision	**Page**	**Line**
One trial, REMAP-CAP (7), randomized patients to tocilizumab or standard care (among centres with access to tocilizumab) or to sarilumab or standard care (among centres with access to sarilumab). Randomization to standard care was halted when an interim analysis showed efficacy of tocilizumab and sarilumab after which patients were randomized to either tocilizumab or sarilumab, with both groups receiving corticosteroids. As such, we treated REMAP-CAP as three separate trials in our analyses (i.e., tocilizumab versus standard care; sarilumab versus standard care; tocilizumab versus sarilumab). We used 90-day mortality for the comparisons of tocilizumab and sarilumab with standard care and obtained data on in-hospital mortality from the investigators for the comparison of tocilizumab and sarilumab. The comparison between tocilizumab and sarilumab was restricted to patients who were eligible for randomization to either of the two drugs in the latter phase of the trial.	9	256-265

- The description of the Sarilumab-COVID-19 trial phases needs improving. Please provide more information regarding what these phases are or at least signpost to where this information can be found.

Our response: We have revised to provide additional information.

Revision	**Page**	**Line**
Another trial, Sarilumab-COVID-19, was conducted in two phases (35). The first phase randomized patients to sarilumab 400 mg, sarilumab 200 mg, or placebo (phase 1). A prespecified interim analysis of the first phase showed benefit of sarilumab 400 mg in patients in the critical stratum (high-flow supplemental oxygen and/or mechanical ventilation) and potential harm of sarilumab 400 mg in patients in the severe (low-flow supplemental oxygen) and multi-system organ dysfunction strata. Subsequently, enrollment into the severe and multisystem organ	9-10	266-278

dysfunction strata and the 200-mg dose were discontinued. Thereafter, the second phase was amended to restrict enrollment to critical patients receiving mechanical ventilation with further randomization to sarilumab 400 mg and placebo and to add a new cohort of critical patients receiving mechanical ventilation randomized to sarilumab 800 mg or placebo (phase 3 modification 1) and a new cohort of critical patients not receiving mechanical ventilation, but requiring high-flow oxygen or non-invasive ventilation, randomized to sarilumab 800 mg or placebo (phase 2 modification 2). The trial was thus treated as four separate trials (phase 1, phase 2 amendment 0, phase 2 amendment 1, phase 2 amendment 2).		

- In the Discussion, please be explicit that the evidence you are reporting from comes from 36 trials, not 45. This also needs to be made clear in your Flow-chart which should include the number of studies that provided data and were actually included in their NMA.

Our response: We have revised as suggested.

Revision	**Page**	**Line**
Figure 1.	NA	NA
This systematic review and network meta-analysis, which includes data from 45 randomized trials and 20,650 patients (36 trials with 19,350 patients eligible for network meta-analysis), provides a comprehensive overview of the evidence for IL-6 receptor blockers, alone and in combination with corticosteroids	11	310-313

- Final conclusion, make it explicit that the strong recommendation of using IL-6 is 'in combination with corticosteroids' ONLY.

Our response:

Revision	**Page**	**Line**
Evidence from this systematic review and network meta-analysis demonstates that in patients with severe or critical COVID-19, IL-6 receptor blockers, when administered with corticosteroids, probably reduce mortality. The available evidence suggests that tocilizumab and sarilumab may be similarly effective. Our findings support linked WHO guidelines on IL-6 receptor blockers, which provides a strong recommendation for using either tocilizumab or sarilumab in combination with corticosteroids for patients with severe or critical COVID-19 (13).	13	368-1373

Typos:

- 'WE' at the end of page 7.

Our response: We have revised.

Revision	Page	Line
We classified trials that compared corticosteroids with standard care or placebo into corticosteroids and standard care nodes.	8	214-216

- I am unsure if the word be 'Supplement' instead of 'Supplementary' for the last two paragraphs in the Results section. Please just revise.

Our response: We have revised.

Revision	Page	Line
Supplement 1 presents data for the network meta-analysis. Table 2 presents results from the network meta-analysis.	10	294-295
Supplement 2 presents all direct and indirect comparisons and their certainty of evidence.	11	303-304
Supplement 3 presents results from the random-effects model, which were consistent with results from the fixed-effects model—though the random-effects model produced effect estimates that were more imprecise due to the incorporation of an additional heterogeneity parameter in the model.	11	305-307