PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy of remdesivir in patients with COVID-19: A protocol for systematic review and meta-analysis of randomized controlled trials
AUTHORS	Gebrie, Desye; Getnet, Desalegn; Manyazewal, Tsegahun

VERSION 1 – REVIEW

REVIEWER	Huseyin Naci London School of Economics and Political Science, London, UK
REVIEW RETURNED	13-Apr-2020

| GENERAL COMMENTS | In their submission, Desye and colleagues provide an overview of their planned systematic review and pair-wise meta-analysis evaluating the effectiveness of remdesivir for the treatment of COVID-19. This is an important and timely analysis, but the protocol requires substantially further detail before publication. I outline my questions and suggestions for the authors below.

I have two important concerns regarding this planned meta-analysis. The first is that it is focused on a single antiviral treatment and does not consider other treatments that are currently being investigated. Once trial results are made available, a network meta-analysis will be urgently needed to compare the efficacy of all available evidence on all potentially relevant treatment options. The second concern is that this is a fast-evolving area and the results of this meta-analysis risk being out of date by the time they are published. What is instead needed is a living meta-analysis that is continuously updated as new evidence emerges. I would encourage the authors to consider these limitations and at the very least acknowledge them in their protocol.

In the strengths and limitations section, the authors state that their focus on RCTs will increase the quality of evidence. This is potentially the case, but it remains a possibility that important methodological deficits can undermine the validity of RCTs and only RCTs at high risk of bias are identified. I would therefore suggest not listing this as one of the strengths of this study.

In the strengths and limitations section, authors mention that including only RCTs will reduce between-study heterogeneity. This is not necessarily the case. Meta-analyses including RCTs alone can still have substantial between-study heterogeneity due to differences in participants (e.g., severity), interventions (e.g., doses), comparators, outcomes, and study design issues (e.g., follow-up duration, setting, etc.). |
|---|---|

In the strengths and limitations section, the authors mention that they will use the Cochrane RoB tool (presumably RoB 2.0) to "extract and synthesize evidence based conclusions". This statement is unclear. The risk of bias tool should be used to evaluate the methodological aspects of RCTs to make a judgement about the validity of the study results.

An important limitation of this study (which should be included in the strengths and limitations section) is its singular focus on one antiviral treatment, which will preclude decision making which requires comparative information from network meta-analyses.

In the introduction section, the first 31 lines of text are well known, not necessarily relevant to this particular protocol, and thus do not need to be included. The introduction section can start with the 3rd sentence of the 2nd paragraph (line 32).

Substantially more detail is needed to describe why the authors decided to focus their systematic review and meta-analysis on remdesivir and not on other drugs that are currently under investigation.

I would encourage the authors to substantially expand the methods section of their protocol to describe their methodological choices and justify their decisions.

Data sources and searches: The search strategy can be considerably improved. It is unclear which of the search terms are MESH terms in MEDLINE (or EMTREE terms in EMBASE), which terms are used as title and abstract searches, and whether any wild cards are being used. The authors should also consider using the Cochrane randomized trial filters for MEDLINE and EMBASE. I would encourage the authors to develop and provide a more comprehensive search strategy that can be independently replicated.

Eligibility: Will the authors exclude studies that compared remdesivir to other active (investigational) drugs or treatments?

Outcomes: I would encourage the authors to discuss the primary and secondary outcomes in greater detail. Why were these outcomes selected? Do these represent the core outcome sets in trials evaluating the effectiveness of interventions in acute respiratory conditions? Have the trials that are currently ongoing adopted these as their primary endpoints?

In the data extraction, I was surprised that participant characteristics were not included (most importantly, number and types of existing conditions). More broadly, further details will need to be extracted from the eligible studies in terms of their participant characteristics, intervention characteristics, outcomes (including follow-up duration), and settings.

Risk of bias assessment correctly references the revised (2.0) version of the Cochrane tool but the domains listed on page 11 (line 30) refer to the domains covered in the older version. Please clarify.

The statistical analysis section needs further detail and clarification. Is it possible that continuous outcomes will need to

| | synthesized using standardized mean difference as the effect measure? I would recommend revising the authors' characterisation of fixed vs. random-effects models. There are several helpful sources of information about how best to choose one model vs. the other. I would strongly recommend deciding a priori which model will be used as the base case analysis (and this decision should not be driven solely by I-squared cutoffs). Please see https://www.meta-analysis.com/downloads/Intro_Models.pdf and https://www.bmj.com/content/342/bmj.d549 |
| | Similarly, the authors should decide a priori which factors will be considered in their sub-group analyses. |

REVIEWER	Lawrence Mbuagbaw McMaster University
REVIEW RETURNED	14-Apr-2020

| GENERAL COMMENTS | The investigators propose to conduct a systematic review of randomized trials comparing the use of remdesivir versus placebo to improve clinical recovery time and other outcomes in patients with COVID-19. I have the following comments.
The paper requires extensive revision for grammar.
The second strength is not accurate. Using only RCTs does not preclude substantial heterogeneity.
Using a risk of bias tool is standard practice and does not count as a strength.
A quick reminder to add the Prospero registration to the next iteration.
The background should have a description of remdesivir and the mechanism by which they authors think it might work.
Table 1: Revise the spelling of MEDLINE.
Under eligibility the comparator includes standard of care which is not mentioned in the abstract. This is an important piece, given that placebo is an unlikely treatment in this scenario, but there will always be standard of care.
Table 2 is not needed for the protocol.
Figure 1 is also not necessary.
How will continuous data not reported on the same scale be handled?
Some of your outcomes are count data e.g. adverse events. How will you pool them?
For each outcome, clarify whether you are interested in counts, proportions, or means.
Given the potential diversity in control arms and other sources of heterogeneity, a fixed effects analyses are likely unreasonable here.
What covariates will be used to inform subgroup analyses: country income? Comorbidities? Comparator?
The ethics and dissemination section could be developed a bit more.
Would you verify if the included studies have appropriate ethics approval?
Will you disseminate only in peer reviewed outlets? What about conferences and department rounds? |

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1. I have two important concerns regarding this planned meta-analysis. The first is that it is focused on a single antiviral treatment and does not consider other treatments that are currently being investigated. Once trial results are made available, a network meta-analysis will be urgently needed to compare the efficacy of all available evidence on all potentially relevant treatment options. The second concern is that this is a fast-evolving area and the results of this meta-analysis risk being out of date by the time they are published. What is instead needed is a living meta-analysis that is continuously updated as new evidence emerges. I would encourage the authors to consider these limitations and at the very least acknowledge them in their protocol.

    Re: Thank you. We focused on single antiviral treatment (remdesivir) as other similarly potential treatments are already under review and meta-analysis by some other authors elsewhere. For the 2nd comment, we initiated this review as we didn't see such study protocols registered on PROSPERO database though there are ongoing studies registered in ClinicalTrials.gov. We now included the potential limitation of the study that the reviewer tracked.

2. In the strengths and limitations section, the authors state that their focus on RCTs will increase the quality of evidence. This is potentially the case, but it remains a possibility that important methodological deficits can undermine the validity of RCTs and only RCTs at high risk of bias are identified. I would therefore suggest not listing this as one of the strengths of this study.

    Re: Thank you. We now removed the aformantioned study strength.

3. In the strengths and limitations section, authors mention that including only RCTs will reduce between-study heterogeneity. This is not necessarily the case. Meta-analyses including RCTs alone can still have substantial between-study heterogeneity due to differences in participants (e.g., severity), interventions (e.g., doses), comparators, outcomes, and study design issues (e.g., follow-up duration, setting, etc.).

    Re: Thank you. We now revised the aforementioned study strength.

4. In the strengths and limitations section, the authors mention that they will use the Cochrane RoB tool (presumably RoB 2.0) to "extract and synthesize evidence based conclusions". This statement is unclear. The risk of bias tool should be used to evaluate the methodological aspects of RCTs to make a judgement about the validity of the study results.

    Re: Thank you. We now revised the aforementioned study strength to meet the need.

5. An important limitation of this study (which should be included in the strengths and limitations section) is its singular focus on one antiviral treatment, which will preclude decision making which requires comparative information from network meta-analyses.

    Re: Thank you. We acknowledge the importance and now included the suggested limitation in the "strengths and limitations" section.

6. In the introduction section, the first 31 lines of text are well known, not necessarily relevant to this particular protocol, and thus do not need to be included. The introduction section can start with the 3rd sentence of the 2nd paragraph (line 32).

    Re: Thank you. We now omitted the first 31 lines and started the introduction section with the 3rd sentences of the 2nd paragraph as the reviewer advised.

7. Substantially more detail is needed to describe why the authors decided to focus their systematic review and meta-analysis on remdesivir and not on other drugs that are currently under investigation.

Re: Thank you. We now described the reason, which is mainly as there are many ongoing studies registered in ClinicalTrials.gov which are assessing the efficacy and/or safety of remdesivir versus placebo/ standard of care, but no registered studies in PROSPERO database regarding this.

8. I would encourage the authors to substantially expand the methods section of their protocol to describe their methodological choices and justify their decisions.

Re: Thank you. We now expanded the methods section to strengthen our evidence of choice of the methods used and the decisions.

9. Data sources and searches: The search strategy can be considerably improved. It is unclear which of the search terms are MESH terms in MEDLINE (or EMTREE terms in EMBASE), which terms are used as title and abstract searches, and whether any wild cards are being used. The authors should also consider using the Cochrane randomized trial filters for MEDLINE and EMBASE. I would encourage the authors to develop and provide a more comprehensive search strategy that can be independently replicated.

Re: We thank you. We now expanded our information regarding the search strategy, explaining more of Table 1.

10. Eligibility: Will the authors exclude studies that compared remdesivir to other active (investigational) drugs or treatments?

Re: Yes, and the reason is that as we see in the ClinicalTrials.gov registry, the comparator for most of the ongoing trials is placebo/standard of care.

11. Outcomes: I would encourage the authors to discuss the primary and secondary outcomes in greater detail. Why were these outcomes selected? Do these represent the core outcome sets in trials evaluating the effectiveness of interventions in acute respiratory conditions? Have the trials that are currently ongoing adopted these as their primary endpoints?

Re: Thank you. We have adopted both the primary and secondary endpoints from currently ongoing trials in a broader sense. We have now discussed the outcomes section in greater detail.

12. In the data extraction, I was surprised that participant characteristics were not included (most importantly, number and types of existing conditions). More broadly, further details will need to be extracted from the eligible studies in terms of their participant characteristics, intervention characteristics, outcomes (including follow-up duration), and settings.

Re: Thank you for bringing this important point. We now included participants' characteristics, intervention characteristics, outcomes, and settings sections.

13. Risk of bias assessment correctly references the revised (2.0) version of the Cochrane tool but the domains listed on page 11 (line 30) refer to the domains covered in the older version. Please clarify.

Re: Our apologies for the mistake. We now addressed the domains of the revised (2.0) version of the Cochrane tool.

14. The statistical analysis section needs further detail and clarification. Is it possible that continuous outcomes will need to synthesized using standardized mean difference as the effect measure? I would recommend revising the authors' characterisation of fixed vs. random-effects models. There are several helpful sources of information about how best to choose one model vs. the other. I would strongly recommend deciding a priori which model will be used as the base case analysis (and this decision should not be driven solely by I-squared cutoffs). Please see https://www.metaanalysis.com/downloads/Intro_Models.pdf and https://www.bmj.com/content/342/bmj.d549
Similarly, the authors should decide a priori which factors will be considered in their sub-group analyses.

Re: Thank you. We now relooked and revised the statistical analysis section, and we read and used the information in the link that the reviewer shared with us. We now opt to use a random-effect model. Mean differences (MDs) and risk ratio (RRs) with 95 confidence intervals (CIs) will be used as effect measure to summarize continuous and dichotomous data respectively. For outcome variables reported in different scales, we will use standard mean differences (SMDs) and RRs with 95% CIs. We will do a subgroup analysis between studies with different duration of follow-up, age of participants, severity of the disease, comorbidities, and settings. All these information are now addressed in the revised study protocol.

Reviewer: 2

1. The paper requires extensive revision for grammar.

   Re: We thank you. We now copyedited the whole manuscript.

2. The second strength is not accurate. Using only RCTs does not preclude substantial heterogeneity.

   Re: Thank you. We now removed the aforementioned study strength.

3. Using a risk of bias tool is standard practice and does not count as a strength.

   Re: Thank you. We accepted the comment and now addressed in the revised version.

4. A quick reminder to add the Prospero registration to the next iteration.

   Re: Thank you. The study protocol has been registered in PROSPERO database under number CRD42020177953 and now we included this information in the revised protocol.

5. The background should have a description of remdesivir and the mechanism by which the authors think it might work.

   Re: Thank you. We now included more information about remdesivir, including its mechanism of action.

6. Table 1: Revise the spelling of MEDLINE.

   Re: Thank you for catching this typing error. This is now corrected.

7. Under eligibility the comparator includes standard of care which is not mentioned in the abstract. This is an important piece, given that placebo is an unlikely treatment in this scenario, but there will always be standard of care.

   Re: Thank you. Now we included the standard of care (actual comparator) in the abstract as well.

8. Table 2 is not needed for the protocol.

   Re: We now removed table 2.

9. Figure 1 is also not necessary.

   Re: Thank you. We included figure 1 (the dummy PRISMA flow diagram) to illustrate the study search and selection processes as this would be needed by the Journal.

10. How will continuous data not reported on the same scale be handled?

    Re: Thank you. If such a condition arises, we plan to use a standard conversion formula. We now included this information to clarify the process.

11. Some of your outcomes are count data e.g. adverse events. How will you pool them?

    Re: Thank you. Our plan is to pool them using risk ratio as effect measure. For instance, the number of adverse events reported in each arm within a given sample size can be pooled using risk ratio. We now relooked the method section to clarify this.

12. For each outcome, clarify whether you are interested in counts, proportions, or means.

    Re: Thank you. We intend to use both as appropriate. For example, if the outcomes are continuous, we will be interested in using mean. E.g time to clinical recovery. We now relooked the statistics section to clarify this.

13. Given the potential diversity in control arms and other sources of heterogeneity, a fixed effects analyses are likely unreasonable here.

    Re: Comment well taken. We now revised this accordingly.

14. What covariates will be used to inform subgroup analyses: country income? Comorbidities? Comparator?

    Re: Thank you. We plan to go for subgroup between studies with different duration of follow-up, age of participants, severity of the disease, comorbidities, settings, and quality of studies interms of risk of bias. We revised the section to make sure this is clearer.

15. The ethics and dissemination section could be developed a bit more.

    Re: Thank you. We now elaborated the ethics and dissemination section.

16. Would you verify if the included studies have appropriate ethics approval?

    Re: Thank you for bringing this point. Yes, we plan to check for ethical approval of included studies, but may not go deeper as we didn't plan to do individual data analysis and as the disease under study (COVID-19) is new for science and evidence are limited.

17. Will you disseminate only in peer reviewed outlets? What about conferences and department rounds?

    Re: Thank you. We now included those in the dissemination section.

REVIEWER	Huseyin Naci
	London School of Economics and Political Science, UK
REVIEW RETURNED	03-May-2020

GENERAL COMMENTS	I thank the authors for addressing previous reviewer comments.
	A fundamental concern that remains how this and similar reviews will contribute to the growing body of literature on COVID-19 therapeutics. I would strongly encourage the authors to coordinate their efforts with other teams who are conducting similar reviews of other single potential therapeutics for COVID-19. There are also several 'living' systematic reviews and even meta-analyses and network meta-analyses (see for instance https://covid-nma.com). There is huge risk for duplication of efforts. Coordinating efforts, sharing data across teams, and iteratively updating review results will be extremely important. For example, the authors of this review are planning to end their search on May 1st, which will not capture the highly anticipated results from Gilead's phase 3 trials. Also, US NIAD's completed trial of remdesivir has not been published and will likely be missed from this review.

REVIEWER	Lawrence Mbuagbaw
	McMaster University
REVIEW RETURNED	06-May-2020

GENERAL COMMENTS	The authors have addressed the comments I raised.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

15. A fundamental concern that remains how this and similar reviews will contribute to the growing body of literature on COVID-19 therapeutics. I would strongly encourage the authors to coordinate their efforts with other teams who are conducting similar reviews of other single potential therapeutics for COVID-19. There are also several 'living' systematic reviews and even meta-analyses and network meta-analyses (see for instance https://covid-nma.com). There is huge risk for duplication of efforts. Coordinating efforts, sharing data across teams, and iteratively updating review results will be extremely important. For example, the authors of this review are planning to end their search on May 1st, which will not capture the highly anticipated results from Gilead's phase 3 trials. Also, US NIAD's completed trial of remdesivir has not been published and will likely be missed from this review.

Re: Thank you, we acknowledge the concerns. We now added some more time, essentially three months, to wait for and include additional studies as they are available. We believe that finding therapeutic options for COVID-19 is an urgent and critical issue as death is increasing globally and cases are shooting in resource-poor settings like Africa. We plan to do the systematic review and meta-analyses within the available and released studies and see if we need to conduct a clinical trial of the drug in resource-limited countries like Ethiopia. We are working to collaborate with others and publication of this protocol will escalate our efforts.

Reviewer: 2

18. The authors have addressed the comments I raised.

    Re: We thank you.

VERSION 3 – REVIEW

REVIEWER	Huseyin Naci London School of Economics and Political Science
REVIEW RETURNED	14-May-2020

GENERAL COMMENTS	The authors have addressed my previous comments.