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# Efficacy of remdesivir versus placebo for the treatment of COVID-19: A protocol for systematic review and meta-analysis of randomized controlled trials



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# Efficacy of remdesivir versus placebo for the treatment of COVID-19: A protocol for systematic review and meta-analysis of randomized controlled trials

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# Abstract

**Background:** In spite of the global containment on prevention efforts, the spread of coronavirus disease 2019 (COVID-19) is continuing to rise, with 1.1 million confirmed cases and 60,124 deaths recorded worldwide since 04 April 2020. The outbreak has a significant threat to international health and economy. At present, there is no approved vaccine or treatment for the disease, while efforts are underway. Remdesivir, a nucleotide-analogue antiviral drug developed for Ebola, is determined to prevent and stop infections with COVID-19, while results are yet controversial. Here, we aim to conduct a systematic review and meta-analysis of randomized controlled trials to compare the effectiveness of remdesivir and placebo in patients with COVID-19.

**Method and analysis:** We will search MEDLINE-PubMed, Embase, Cochrane Library, ClinicalTrials.gov, and Google scholar databases without restriction in year of publication. We will include randomized controlled trials that assessed the effectiveness of remdesivir versus placebo for patients confirmed with COVID-19. We will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA 2015) guidelines for the design and reporting of the results. The primary endpoint will be time to clinical recovery. The secondary endpoints will be all cause mortality, discharged date, frequency of respiratory progression, and treatment-emergent adverse events. Two independent authors will perform study selection, data extraction, and methodology quality assessment. RevMan 5.3 software will be used for statistical analysis. Random/fixed effect model will be carried out to calculate mean differences for continuous outcomes and risk ratio for dichotomous outcomes between remdesivir and placebo.

**Ethics and dissemination**: This study does not require ethical approval, because no participant's data will be involved in this systematic review and meta-analysis. The findings of this study will be published in reputable and peer-reviewed journal.

**Registration**: This review protocol is submitted in PROSPERO database for registration and we will include the registration number in the revised version of the manuscript.


**Keywords**: 2019 novel coronavirus, 2019-nCoV, Coronavirus diseases 2019, COVID-19, SARS-cov-2, Remdesivir, Randomized Controlled Trials. Systematic review, Meta-analysis, protocol

## Strengths and limitations of this study

- This systematic review and meta-analysis will be derived from only randomized controlled trials which will increase the quality of evidences.
- This systematic review and meta-analysis will be derived from only randomized controlled trials which will reduce between study heterogeneity.
- Subgroup and sensitivity analysis will be carried out to identify possible reasons that may cause significant heterogeneity between studies.
- The use of Cochrane risk of bias tool to assess risk of bias for each included studies to extract and synthesize evidence based conclusions.
- One of the limitation of this study might be the restriction of trials published in English language.

# Introduction

Over the course of December 2019, the health authority of Wuhan City, Hubei province, China reported a cluster of pneumonia cases of unknown etiology [1]. The Chinese researcher rapidly isolated Sever Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) from a patient on 7 January 2020 and came out to genome sequencing of the SARS-CoV-2 [2]. On 9 January 2020, China's communicable diseases control authority announced that 2019 novel coronavirus (2019-nCoV) had been detected as the causative agent for the epidemics [3]. On 11 February 2020 World Health Organization officially named the disease as coronavirus disease 2019 (COVID-19). COVID-19 is caused by a novel β-coronavirus which is named as SARS-CoV-2. SARS-CoV-2 shares 79% sequence identity with Sever Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) which caused a major outbreak since 2002 and 2012 in China and Saud Arabia respectively [4-6].

In spite of the global containment on prevention efforts, the spread of COVID-19 is continuing to rise with 1.1 million confirmed cases and 60,124 deaths recorded worldwide since 04 April 2020. [7-8]. The outbreak of COVID-19 infection has a significant threat to international health and economy [9]. At present, there is no approved vaccine or treatment for COVID-19, so that identifying the drug treatment options as soon as possible is critical agenda to overcome the outbreak [10-11].

Despite the lack of approved drugs and vaccine for COVID-19, many scientists are endeavoring to find medicines specific to the virus and they have been looking into repurposing the already approved drugs. As of 29 March 2020, there has been 209 clinical trials registered in clinicaltrials.gov and estimated to be over 500 [12]. Currently, several drugs such as remdesivir, hydroxychloroquine, chloroquine, Ritonavir+Lopinavir, Arbidol and interferon are undergoing randomized controlled trials (RCTs) to test their efficacy and safety for the treatment of COVID-19 in many countries [13-18]. Among these investigating drugs remdesivir showed promising results [18-19]. Remdesivir is nucleotide analog prodrug and shows broad spectrum antiviral activity against many RNA viruses including SARS-CoV-2 [20-21]. Remdesivir has been reported as a treatment of COVID-19 in United States, China and Italy [13,15, 22]. while results are yet controversial [9]. To bridge this gap, here we aim to conduct a systematic review and meta-analysis of RCTs to compare the effectiveness of remdesivir and placebo in patients with COVID-19.

# Methods

## Study registration

The protocol for this systematic review and meta-analysis is submitted in PROSPERO database for registration and we will include the registration number in the revised version of the manuscript.

## Data sources and searches

We will search MEDLINE/PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Embase (http://www.embase.com/), The Cochrane Library (http://www.cochranelibrary.com/), ClinicaTtrials.gov (https://www.clinicaltrials.gov/), and google scholar (https://scholar.google.com/) databases for completed studies that reported the efficacy of remdesivir versus placebo for patients with COVID-19. We will include randomized controlled trials that assessed the effectiveness of remdesivir versus placebo for patients with COIVID-19 without restriction on year of publication, but published in English language. The Medical Subject Headings (MeSH) and keywords we will used in different combinations using balloon operators will be 2019 novel coronavirus, 2019-nCov, coronavirus disease 2019, COVID-19, SARS-cov-2, remdesivir, nucleotide-analogue, antiviral drug and randomized controlled trials. All potentially eligible studies will be considered for this review, irrespective of the primary outcomes. Manual searching will be performed to find out additional eligible trials from the reference lists of key articles.

**Table 1**: Search strategy for the MEDILINE-PubMed database

| | | | | | |
|---|---|---|---|---|---|
| "Antiviral drug" OR "Nucleotide-analogue" OR "Remdesivir" | AND | ''Coronavirus disease 2019'' OR "COVID-19'' OR "SARS-CoV-2" OR "2019 novel coronavirus" OR "2019-nCoV" | AND | "Randomized controlled trials" OR "RCTs" | |

## Eligibility

Study eligibility criteria for this systematic review and meta-analysis will be in accordance with Participants, Intervention, Comparison, Outcomes and Study designs (PICOS) descriptions [23].

**Population:** The population will be patients confirmed with COVID-19 and with or without other co-morbid conditions in all age groups.

**Intervention:** The intervention/ experimental group will be any dose of remdesivir

**Comparator:** The comparator group will be placebo/ standard of care

**Outcomes:** The primary endpoints will be time to clinical recovery and proportion of participants relieved from clinical symptoms defined at the time (in hours) from initiation of the study treatment. The secondary endpoints will be all cause mortality, discharged date, frequency of respiratory progression, oxygen saturation and treatment-emergent adverse events in each groups.

**Study design**: Only RCTs evaluating effectiveness of remdesivir versus placebo for patients with COVID-19 will be included.

## Study selection

The title and abstract of all searched studies will be examined by two independent review authors. From the title and abstract of all studies identified by the database search, those studies duplicated and not meet the eligibility criteria will be excluded. The full texts of the remaining studies will be further reviewed. Disagreements will be resolved by consensus and if persisted, we will be arbitrated through discussion with a third review author. We will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA 2015) guidelines [24] for the design and reporting of the results.

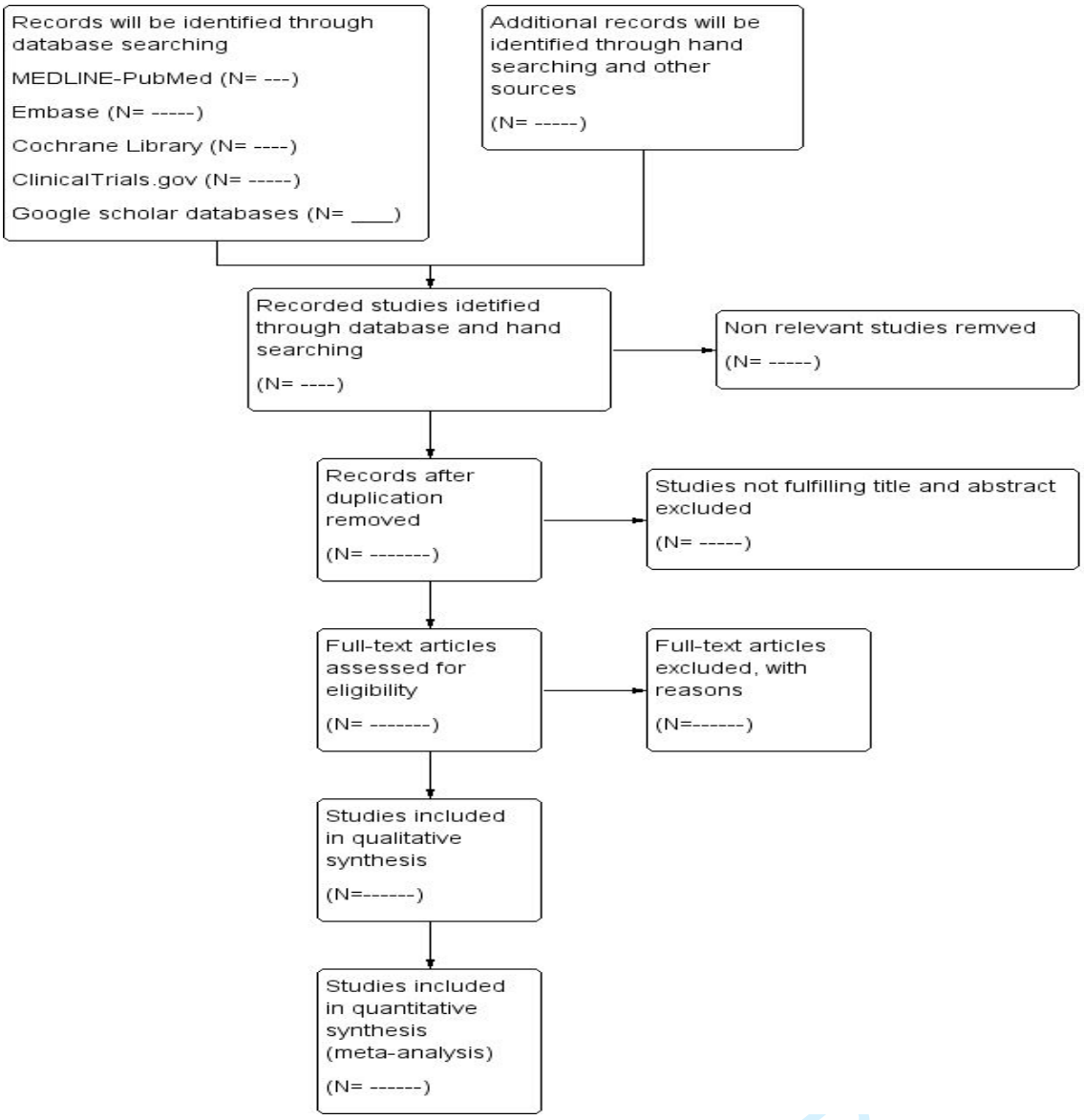


**Figure 1:** Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the study selection process and search results

## Data extraction

Two authors will independently extract data according to the pre-designed data extraction tool. The following data will be extracted from each included RCTs: first author, year of publication, funding information, setting, mean age of the participant, interventions, comparators, doses, number of participants randomized, duration of treatment, all primary, secondary and other outcome measurements. If any disagreement regarding the data extraction between the two review authors exist, the third author will be consulted and consensus will be made through discussion.

**Table 2**: characteristics of RCTs included in the systematic review and/or meta-analysis

| 1st author (year) | Country | Age (year) | No. of pts | Intervention | Comparator | Follow –up (days) | Outcomes | Results | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Remdesivir | Placebo |
| | | | | Remdesivir (n=) | Placebo (n=) | | Time to clinical recovery<br>No. of patients relieved from symptoms<br>Frequency of respiratory progression<br>Oxygen saturation<br>Adverse events<br>DeatH events | | |



## Assessment of risk of bias

The Cochrane risk of bias tool [25] will be used to assess the risk of bias for each included study. The risk of bias of each trial will be judged by two independent review authors as "Low", "Unclear", or "High" based on the critical domains, including random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other source of biases. Disagreements will be resolved by discussion among all authors. If the disagreements cannot be resolved through discussion, an arbiter will make the final decision.

## Statistical analysis

Meta-analysis will be carried out using the computer software packages RevMan 5.3 [26]. Continuous outcome data will be reported using a mean difference (MD) and a 95% confidence interval (CI). Binary outcome data will be summarized using risk ratio (RR) and 95% CI. Mantel-Haenszel method [27] will be used to pool effect estimates of dichotomous outcomes and inverse variance for continuous outcomes. Cochrane Q test [28] will be used to assess heterogeneity between studies, and $I^2$ testing [29] will be done to quantify heterogeneity between studies, with values > 50% representing moderate-to-high heterogeneity. If heterogeneity between study is acceptable, a fixed-effect model will be used to pool the data. On the other hand, if unacceptable heterogeneity detected or if the number of studies are small, a random-effect model will be used to pool the data [30]. Subgroup analysis will be carried out to identify possible reasons that may

cause significant heterogeneity between studies. If we get acceptable heterogeneity after the subgroup analysis, we will perform meta-analysis. Otherwise, we will do a narrative description. Sensitivity analysis will be conducted to see the robustness of pooled data by removing low quality studies. Statistical analysis with a p-value < 0.05 will be considered statistically significant.

### Addressing missing data

When individual participant's data are initially unavailable, we will review the original source, and/or published trial reports and we will contact the authors to obtain clarification for these data.

### Reporting bias

We will conduct funnel plot and Egger test to check any possible reporting bias if a sufficient number of included studies (at least 10 trials) are available in this study [31].

## Ethics and dissemination

This study does not require ethical approval, because no participant's data will be involved in this systematic review and meta-analysis. The findings of this study will be published in reputable and peer-reviewed journal.

## Abbreviations

2019-nCoV = 2019 novel Coronavirus, COVID-19 = Coronavirus Disease-2019, SARS = Sever Acute Respiratory Syndrome, RCTs = Randomized Controlled Trials, SARS-CoV-2 = Sever Acute Respiratory Syndrome Coronavirus-2, MERS = Middle East Respiratory Syndrome

## Declarations

### Competing interests

All review authors declare that they have no competing interests. The funder has not any role in the design, syntheses and report of the study.

### Funding

This study is supported by Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University.

**Authors' contributions**

DG (first author) conceived the study, developed the study criteria, searched the literature, wrote the protocol and drafting the manuscript. DG (second author) conducted the preliminary search and TM revised the manuscript. All authors have read and approved the manuscript.

**Acknowledgement**

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# Efficacy of remdesivir in patients with COVID-19: A protocol for systematic review and meta-analysis of randomized controlled trials

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# Abstract

**Background:** Despite global containment measures to fight the coronavirus disease 2019 (COVID-19), the pandemic continued to rise, resulting in 2.6 million confirmed cases and 185,061 deaths worldwide as of 23 April 2020. Yet, there are no approved vaccines or drugs to make the disease less deadly, while efforts are underway. Remdesivir, a nucleotide-analogue antiviral drug developed for Ebola, is determined to prevent and stop infections with COVID-19, while results are yet controversial. Here, we aim to conduct a systematic review and meta-analysis of randomized controlled trials to evaluate the efficacy of remdesivir in patients with COVID-19.

**Method and analysis:** We will search MEDLINE-PubMed, Embase, Cochrane Library, ClinicalTrials.gov, and Google scholar databases for articles published as of 01 May 2020 and we will complete the study on 01 July 2020. We will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA-P) 2015 guidelines for the design and reporting of the results. We will include randomized controlled trials that assessed the efficacy of remdesivir versus placebo or standard of care. The primary endpoint will be time to clinical recovery. The secondary endpoints will be all-cause mortality, discharged date, frequency of respiratory progression, and treatment-emergent adverse events. RevMan 5.3 software will be used for statistical analysis. Random effect model will be carried out to calculate mean differences for continuous outcome data and risk ratio for dichotomous outcome data between remdesivir and placebo or standard of care.

**Ethics and dissemination**: There are no ethical considerations associated with this study as we will use publicly available data from previously published studies. We plan to publish results in open-access peer-reviewed journals and present at international and national conferences.

**PROSPERO registration number**: CRD42020177953.


**Keywords**: coronavirus disease 2019; COVID-19; 2019 novel coronavirus; 2019-nCoV; remdesivir; treatment; randomized controlled trials; systematic review; meta-analysis; protocol.

## Strengths and limitations of this study

- This will be the first systematic review and meta-analysis to evaluate the efficacy of remdesivir for COVID-19, which is a newly originated deadly disease.
- Its compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) will ensure the quality of reporting.
- The use of a combination of multiple electronic databases will include all eligible articles and provide accurate conclusions.
- The use of rigorous subgroup and sensitivity analysis will identify possible reasons that may cause significant heterogeneity between studies.
- Its singular focus on one antiviral treatment may preclude decision making and calls for network meta-analyses once trial results are made available.

# Introduction

Coronavirus diseases 2019 (COVID-19) is caused by a novel β-coronavirus which is named as SARS-CoV-2. SARS-CoV-2 shares 79% sequence identity with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) which caused a major outbreak since 2002 and 2012 in China and Saud Arabia respectively [1-3]. Despite global containment measures to fight the disease, the pandemic continued to rise, resulting in 2.6 million confirmed cases and 185,061 deaths worldwide as of 23 April 2020 [4,5]. The outbreak of COVID-19 infection has a significant threat to international health and the economy [6]. Yet, there are no approved vaccines or drugs to make the disease less deadly; implying that therapeutic options are critical issues to overcome the outbreak [7-8].

Studies are strongly underway to discover rapidly drug candidates for COVID-19, and studies are looking into repurposing drugs that have been used for the treatment of other diseases. As of 29 March 2020, there were 209 clinical trials registered in ClinicalTrials.gov for COVID-19 therapeutic studies and this number is estimated to go over 500 [9]. Currently, several drugs including remdesivir, hydroxychloroquine, chloroquine, Ritonavir+Lopinavir, Arbidol, and interferon are under randomized controlled trials (RCTs) for efficacy and/or safety evaluations in patients with COVID-19 in different countries [10-15]. Remdesivir is among these investigational drugs and some studies reported promising results [15-16]. Remdesivir is a nucleotide analogue intravenous prodrug developed by Gilead Sciences, Inc., an American biopharmaceutical company, for treatment of Ebola virus during the 2014 Ebola outbreak in Western Africa. Remdesivir shows broad-spectrum antiviral activity against many RNA viruses including SARS-CoV-2 through blocking RNA polymerase thereby terminating RNA transcription. A recent study led by the US National Institutes of Health (NIH) that involved two groups of six rhesus macaque experiment monkeys, with one group treated with remdesivir, revealed a significantly lowered COVID-19 disease progression due to remdesivir [17]. According to a recent report of the U.S Centers for Disease Control and Prevention (CDC), in vitro and cell culture studies demonstrated broad-spectrum activity of remedesivir against coronavirus [18]. Nucleoside analogues such as remedesivir can have multiple mechanisms of action, including lethal mutagenesis, obligate or nonobligate chain termination, and perturbation of natural nucleotide triphosphate pools via inhibition of nucleotide biosynthesis [19-20]. Remdesivir was among the first treatments used in

China as the outbreak emerges and it has been reported as potential treatment options for COVID-19 in the United States, China, and Italy [10, 12, 21]. Some completed trials have evaluated remdesivir as a treatment option for COVID-19, while their results are controversial [6]. Thus, the proposed systematic review and meta-analysis of RCTs aims to synthesize existing evidence on the efficacy of remdesivir in patients with COVID-19.

# Methods

We will conduct a systematic review and meta-analysis that will comply with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA-P) 2015 guidelines for the design and reporting of the results [22] (see checklist in Additional file 1). The protocol has been registered at PROSPERO database, ID: CRD42020177953 [23].

### Data sources and searches

We will search MEDLINE/PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Embase (http://www.embase.com/), The Cochrane Library (http://www.cochranelibrary.com/), ClinicaTtrials.gov (https://www.clinicaltrials.gov/), and google scholar (https://scholar.google.com/) databases for primary articles published as of 01 May 2020 and we will complete the study by 01 July 2020. We will perform hand search from the reference lists of a key articles to identify eligible RCTs and supplement the searching. We will include all potential RCTs that evaluated the efficacy of remdesivir versus placebo or standard of care in patients with COIVID-19 with no limitations on the geographical location of studies but published in English-language. We will do a rigorous search strategy using the key words including 2019 novel coronavirus, 2019-nCov, coronavirus disease 2019, COVID-19, SARS-cov-2, severe acute respiratory syndrome-coronavirus-2, remdesivir, nucleotide-analogue, antiviral agents, randomized controlled trials and RCTs. Table 1 summarizes the search strategy that we will applied in PubMed, while details of this strategy that we will also adapt for other databases' searches is described in Additional file 2 (Table 1).

**Table 1**: Search strategy for the MEDLINE-PubMed database

| | | | | |
|---|---|---|---|---|
| "Antiviral agents" OR "Nucleotide-analogue" OR "Remdesivir" | AND | ''Coronavirus disease 2019'' OR "COVID-19'' OR "Severe acute respiratory syndrome-coronavirus-2" OR "SARS-Cov-2" OR "2019 novel coronavirus" OR "2019-nCoV" | AND | "Randomized controlled trials" OR "RCTs" |



## Eligibility criteria

We will formulate our participant's eligibility criteria using PICOS (participants, interventions, comparison, outcomes, and study designs) model [24].

- Participants
  - Patients with confirmed COVID-19
  - Men and/or women of any age
  - At any clinical stage of the disease, thus mild, moderate or severe/critical case
  - With or without other co-morbid conditions
- Intervention
  - Remdesivir of any dose.
- Comparator
  - Placebo or standard of care.
- Outcomes/endpoints
  - Primary endpoints
    - Time to clinical recovery
    - Proportion of participants relieved from clinical symptoms defined at the time (in hours) from initiation of the study treatment

- Secondary endpoints
    - All-cause mortality
    - Discharged date
    - Frequency of respiratory progression
    - Oxygen saturation
    - Treatment-emergent adverse events

- Study design
    - Only RCTs evaluating the efficacy of remdesivir versus placebo and/or standard of care in patients with COVID-19

**Study selection**

All the retrieved papers will be transferred to EnDnote 7 and duplicates will be removed. Two investigators will independently assess the title and abstract of all the retrieved papers based on the eligibility criteria. The two investigators will independently evaluate the full texts. Disagreements between the two investigators will settle through discussion and if persisted, the third investigator will involve as arbitrator. Figure 1 summarizes the design that we will use to report the study result in line with the PRISMA -P 2015 guidelines (Figure 1).

**Figure 1:** PRISMA-P flow diagram of the study

**Data extraction**

Two authors will independently extract data according to the pre-designed data extraction tool. The following data will be extracted from each included RCTs

- First author,
- Year of publication,
- Study country
- Funding information
- Patient characteristics (mean age of the participant, sex, co-morbid conditions, number of comorbidities, symptom severity),
- Interventions (remdsivir, dose of remdesivir and route of administration)
- Comparators (placebo, standard of care),

- Number of participants randomized in each group,
- Treatment follow-up period,
- Outcomes (primary, secondary and other outcomes)

**Assessment of risk of bias**

The Cochrane risk of bias tool [25] will be used to assess the risk of bias for each included study. The risk of bias of each trial will be judged by two independent investigators as "Low", "Some concerns", or "High" based on the critical domains, including bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result. Disagreements will be resolved by discussion among the two investigators. If the disagreements persist, the third investigator will chip in as an arbitrator.

**Statistical analysis**

All statistical analyses will be carried out using the computer software packages RevMan 5.3 [26]. Mean differences (MDs) with 95% confidence intervals (CIs) will be used to measure the effects of treatment for continuous outcome data. We will convert other forms of data into MDs using standard conversion formula. For outcome variables reported in different scales, we will use standard mean differences (SMDs) with 95% CIs. The treatment effect of binary outcome data will be summarized using risk ratios (RRs) with 95% CIs. Other binary outcome data will be converted into RRs. Mantel-Haenszel method [27] will be used to pool effect estimates of dichotomous outcomes and inverse variance for continuous outcomes. Cochrane Q test [28] will be used to assess heterogeneity between studies, and $I^2$ testing [29] will be done to quantify heterogeneity between studies, with values > 50% representing moderate-to-high heterogeneity. A random-effect model will be used to pool the data [30]. Subgroup analysis will be carried out between studies with different duration of follow-up, age of participants, severity of the disease, comorbidities, settings, and quality of studies for risk of bias. Following the subgroup analysis, we will look at the data for heterogeneity, and if acceptable, we will perform a meta-analysis. If the data is heterogeneous, we will do a narrative description of findings. To see the robustness of pooled data, sensitivity analysis will be conducted between low and high risk of bias, and with or without biased studies.. We will use the GRADEprofiler software from Cochrane Systematic Reviews to assess the quality of evidence per outcome and ultimately to create a summary of findings table and

evidence profile. All statistical analysis with a p-value < 0.05 will be considered statistically significant.

**Addressing missing data**

When individual participant's data are initially unavailable, we will review the original source, and/or published trial reports, and we will contact the authors to obtain clarification for these data.

**Reporting bias**

We will conduct funnel plot and Egger test to check any possible reporting bias if a sufficient number of included studies (at least 10 trials) are available in this study [31].

**Patient and public involvement**

Patients and public will not be involved in this systematic review and meta-analysis. However, once our findings are disseminated, it will be shared through social networks.

## Ethics and dissemination

There are no ethical considerations associated with this study as we will use publicly available data from previously published studies. We plan to publish results in open-access peer-reviewed journals and present at international and national conferences.

## Amendments

The protocol for this study will be amended as necessary.

## Abbreviations

2019-nCoV = 2019 novel Coronavirus, COVID-19 = Coronavirus Disease-2019, SARS = Severe Acute Respiratory Syndrome, RCTs = Randomized Controlled Trials, SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus-2, MERS = Middle East Respiratory Syndrome

# Declarations

## Competing interests

All review authors declare that they have no competing interests. The funder has not any role in the design, syntheses, and report of the study.

## Funding

This study is supported by Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University.

## Authors' contributions

DG (first author) conceived the study, developed the study criteria, searched the literature, wrote the protocol and drafting the manuscript. DG (second author) conducted the preliminary search and TM revised the manuscript. All authors have read and approved the manuscript.

## Acknowledgment

The authors would like to acknowledge the Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University which funds this study.

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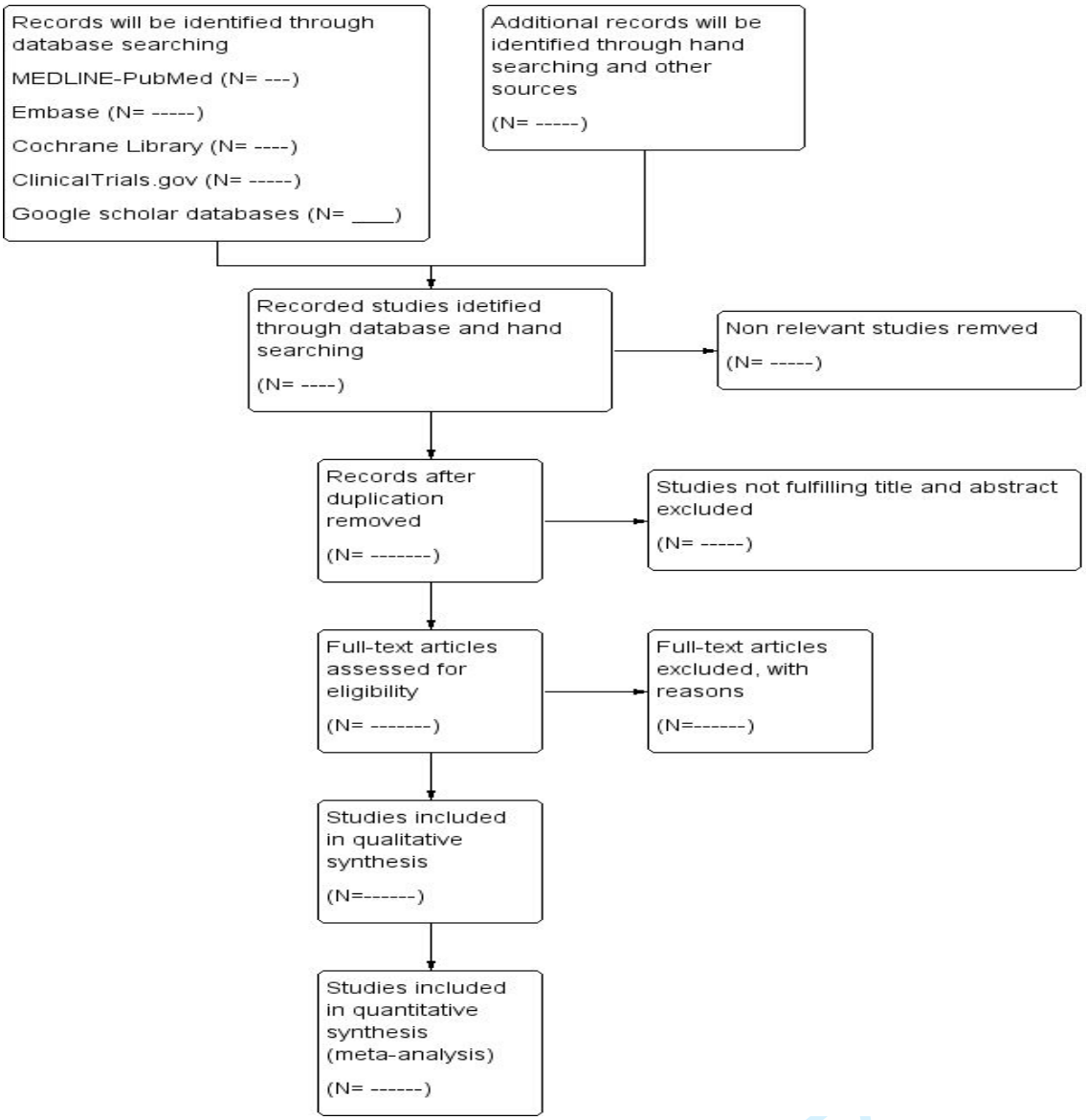
Records will be identified through database searching
MEDLINE-PubMed (N= ---)
Embase (N= -----)
Cochrane Library (N= ----)
ClinicalTrials.gov (N= -----)
Google scholar databases (N= ____)
Additional records will be identified through hand searching and other sources
(N= -----)
Recorded studies idetified through database and hand searching
(N= ----)
Non relevant studies remved
(N= -----)
Records after duplication removed
(N= -------)
Studies not fulfilling title and abstract excluded
(N= -----)
Full-text articles assessed for eligibility
(N= -------)
Full-text articles excluded, with reasons
(N=------)
Studies included in qualitative synthesis
(N=------)
Studies included in quantitative synthesis (meta-analysis)
(N= ------)

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item | Page |
|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | |
| Title: | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | 1 |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | 2 |
| Authors: | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | 9 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | 8 |
| Support: | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | 9 |
| **INTRODUCTION** | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | 4 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 4 |
| **METHODS** | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 6 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 5 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | 5 |

| | | | |
|---|---|---|---|
| Study records: | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 6 |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | 6 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | 6 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | 6,7 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 6 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | 7 |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | 7 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | 7 |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 7 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | 7 |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | 8 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 8 |

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

**PubMed search strategy**

This search strategy does not include any limit and this will be updated because there are ongoing trials which should be included in this study.

| # | Searches | Results |
|---|---|---|
| 1 | "remdesivir"[Supplementary Concept] OR "remdesivir"[All Fields] | 81 |
| 2 | "viruses/drug effects"[MeSH Terms] | 59,974 |
| 3 | (("antiviral agents"[Pharmacological Action] OR "antiviral agents"[MeSH Terms]) OR ("antiviral"[All Fields] AND "agents"[All Fields])) OR "antiviral agents"[All Fields] | 383,998 |
| 4 | "Nucleotide-analogue"[All Fields] | 797 |
| 5 | ((((("antiviral agents"[Pharmacological Action] OR "antiviral agents"[MeSH Terms]) OR ("antiviral"[All Fields] AND "agents"[All Fields])) OR "antiviral agents"[All Fields]) OR ("antiviral"[All Fields] AND "drug"[All Fields])) OR "antiviral drug"[All Fields] | 392,120 |
| 6 | (((((("antiviral agents"[Pharmacological Action] OR "antiviral agents"[MeSH Terms]) OR ("antiviral"[All Fields] AND "agents"[All Fields])) OR "antiviral agents"[All Fields]) OR ("antiviral"[All Fields] AND "drug"[All Fields])) OR "antiviral drug"[All Fields]) AND "antiviral agents/therapeutic use"[MeSH Terms] | 98,451 |
| 7 | 1 OR 2 OR 3 OR 4 OR 5 OR 6 | 407,526 |
| 8 | "coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields] | 18,508 |
| 9 | (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) OR "coronaviruses"[All Fields]) AND "coronavirus infections/virology"[MeSH Major Topic] | 1,050 |
| 10 | "covid 19"[Supplementary Concept] OR "covid 19"[All Fields] OR "coronavirus disease 2019"[All Fields] | 4,227 |
| 11 | ((((((("covid 19"[All Fields] OR "covid 2019"[All Fields]) OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]) OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR "2019 ncov"[All Fields]) OR "sars cov 2"[All Fields]) OR "2019ncov"[All Fields]) OR (("wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12/1:2019/12/31[Date - Publication] OR 2020/1/1:2020/12/31[Date - Publication])) | 4,656 |
| 12 | "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019 novel coronavirus"[All Fields] | 1,429 |

| | | |
|---|---|---|
| 13 | "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019 ncov"[All Fields] | 1,465 |
| 14 | "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars cov 2"[All Fields] | 1,931 |
| 15 | "spike glycoprotein sars cov"[Supplementary Concept] | 452 |
| 16 | (((((((("sever"[All Fields] OR "severe"[All Fields]) OR "severed"[All Fields]) OR "severely"[All Fields]) OR "severer"[All Fields]) OR "severes"[All Fields]) OR "severing"[All Fields]) OR "severities"[All Fields]) OR "severity"[All Fields]) OR "severs"[All Fields]) AND (("acute"[All Fields] OR "acutely"[All Fields]) OR "acutes"[All Fields]) AND "respiratory"[All Fields] AND (((((((("syndrom"[All Fields] OR "syndromal"[All Fields]) OR "syndromally"[All Fields]) OR "syndrome"[MeSH Terms]) OR "syndrome"[All Fields]) OR "syndromes"[All Fields]) OR "syndrome s"[All Fields]) OR "syndromic"[All Fields]) OR "syndroms"[All Fields]) AND (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) OR "coronaviruses"[All Fields]) | 4,936 |
| 17 | 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 | 20,471 |
| 18 | "randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trials"[All Fields] OR "randomised controlled trials"[All Fields] | 676,631 |
| 19 | "randomized controlled trials as topic/methods"[MeSH Terms] | 9,652 |
| 20 | "RCTs"[All Fields] | 32,846 |
| 21 | 18 OR 19 OR 20 | 681,739 |
| 22 | 7 AND 17 AND 21 | 18 |

BMJ Open

# Efficacy of remdesivir in patients with COVID-19: A protocol for systematic review and meta-analysis of randomized controlled trials



| | |
|---|---|
| Journal: | *BMJ Open* |
| Manuscript ID | bmjopen-2020-039159.R2 |
| Article Type: | Protocol |
| Date Submitted by the Author: | 13-May-2020 |
| Complete List of Authors: | Gebrie, Desye; Center for Innovative Drug Development and Therapeutic Trials for Africa, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia, ; School of Pharmacy, College of Health Sciences, Mekelle University, Mekelle, Ethiopia,<br>Getnet, Desalegn; Pharmacology and Toxicology Course and Research Team, Department of Pharmacy, College of Health Sciences, Adigrat University, Adigrat, Ethiopia<br>Manyazewal, Tsegahun; Center for Innovative Drug Development and Therapeutic Trials for Africa , ; Ethiopian Public Health Association, |
| Primary Subject Heading: | Respiratory medicine |
| Secondary Subject Heading: | Respiratory medicine, Infectious diseases |
| Keywords: | Clinical trials < THERAPEUTICS, VIROLOGY, Respiratory infections < THORACIC MEDICINE, Infection control < INFECTIOUS DISEASES |
| | |

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# Efficacy of remdesivir in patients with COVID-19: A protocol for systematic review and meta-analysis of randomized controlled trials

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# Abstract

**Background:** Despite global containment measures to fight the coronavirus disease 2019 (COVID-19), the pandemic continued to rise, rapidly spread across the world, and resulting in 2.6 million confirmed cases and 185,061 deaths worldwide as of 23 April 2020. Yet, there are no approved vaccines or drugs to make the disease less deadly, while efforts are underway. Remdesivir, a nucleotide-analogue antiviral drug developed for Ebola, is determined to prevent and stop infections with COVID-19, while results are yet controversial. Here, we aim to conduct a systematic review and meta-analysis of randomized controlled trials to evaluate the efficacy of remdesivir in patients with COVID-19.

**Method and analysis:** We will search MEDLINE-PubMed, Embase, Cochrane Library, ClinicalTrials.gov, and Google scholar databases for articles published as of 30 June 2020 and we will complete the study on 30 August 2020. We will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA-P) 2015 guidelines for the design and reporting of the results. We will include randomized controlled trials that assessed the efficacy of remdesivir versus placebo or standard of care. The primary endpoint will be time to clinical recovery (TTCR). The secondary endpoints will be proportion of participants relieved from clinical symptoms defined at the time (in hours) from initiation of the study treatment, all-cause mortality, discharged date, frequency of respiratory progression, and treatment-emergent adverse events. RevMan 5.3 software will be used for statistical analysis. Random effect model will be carried out to calculate mean differences for continuous outcome data and risk ratio for dichotomous outcome data between remdesivir and placebo or standard of care.

**Ethics and dissemination**: There are no ethical considerations associated with this study as we will use publicly available data from previously published studies. We plan to publish results in open-access peer-reviewed journals and present at international and national conferences.

**PROSPERO registration number**: CRD42020177953.


**Keywords**: coronavirus disease 2019; COVID-19; 2019 novel coronavirus; 2019-nCoV; remdesivir; treatment; randomized controlled trials; systematic review; meta-analysis; protocol.

## Strengths and limitations of this study

- This will be the first systematic review and meta-analysis to evaluate the efficacy of remdesivir for COVID-19, which is a newly originated deadly disease.
- Its compliance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses for Protocols 2015 (PRISMA-P 2015) will ensure the quality of reporting.
- The use of a combination of multiple electronic databases will include all eligible articles and provide accurate conclusions.
- The use of rigorous subgroup and sensitivity analysis will identify possible reasons that may cause significant heterogeneity between studies.
- Its singular focus on one antiviral treatment may preclude decision making and calls for network meta-analyses once trial results are made available.

# Introduction

Coronavirus diseases 2019 (COVID-19) is caused by a novel β-coronavirus which is named as SARS-CoV-2. SARS-CoV-2 shares 79% RNA sequence identity with Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and 50% genomic sequence identity with Middle East Respiratory Syndrome Coronavirus (MERS-CoV) which caused a major outbreak since 2002 and 2012 in China and Saud Arabia respectively [1-4]. Despite global containment measures to fight the disease, the pandemic continued to rise, rapidly spread across the world, and resulting in 2.6 million confirmed cases and 185,061 deaths worldwide as of 23 April 2020 [5,6]. The outbreak of COVID-19 infection has a significant threat to international health, the economy, psychological stress and mental health worldwide, [7-10]. Yet, there are no approved vaccines or drugs to make the disease less deadly; implying that searching therapeutic options are critical issues to overcome the outbreak [11-12].

Studies are strongly underway to discover rapidly drug candidates for COVID-19, and studies are looking into repurposing drugs that have been used for the treatment of other diseases. As of 29 March 2020, there were 209 clinical trials registered in ClinicalTrials.gov for COVID-19 therapeutic studies and this number is estimated to go over 500 [13]. Currently, several drugs including remdesivir, hydroxychloroquine, chloroquine, Ritonavir+Lopinavir, Arbidol, and interferon are under randomized controlled trials (RCTs) for efficacy and/or safety evaluations in patients with COVID-19 in different countries [14-19]. Remdesivir (GS-5734) is among these investigational drugs and some studies reported promising results [19-20]. Remdesivir is a nucleotide analogue intravenous prodrug developed by Gilead Sciences, Inc., an American biopharmaceutical company, for treatment of Ebola virus during the 2014 Ebola outbreak in Western Africa. Remdesivir shows broad-spectrum antiviral activity against many RNA viruses including SARS-CoV-2 through blocking RNA polymerase thereby terminating RNA transcription. A recent study led by the US National Institutes of Health (NIH) that involved two groups of six rhesus macaque experiment monkeys, with one group treated with remdesivir, revealed a significantly lowered COVID-19 disease progression due to remdesivir [21]. According to a recent report of the U.S Centers for Disease Control and Prevention (CDC), in vitro and cell culture studies demonstrated broad-spectrum activity of remedesivir against coronavirus [22]. Nucleoside analogues such as remedesivir can have multiple mechanisms of action, including

lethal mutagenesis, obligate or nonobligate chain termination, and perturbation of natural nucleotide triphosphate pools via inhibition of nucleotide biosynthesis [23-24]. In vitro, remdesivir inhibits all human and animal coronaviruses including SARS-CoV-2, and has shown antiviral and clinical effects in animal models of SARS-CoV-1 and MERS-CoV infections [25-29]. Remdesivir was among the first treatments used in China as the outbreak emerges and it has been reported as potential treatment options for COVID-19 in the United States, China, and Italy [14, 16, 30]. Following the topline data from the randomized, double-blinded, placebo-controlled trial conducted by National Institute of Allergy and Infectious Diseases (NIAID) [31], the US Food and Drug Administration (FDA) has issued an emergency use authorization (EUA) of the antiviral drug remdesivir for the trestment of patients with COVID-19 [32]. Though clinical trials [31,33] have showed remdesivir as a treatment option for COVID-19, while results are controversial. Thus, the proposed systematic review and meta-analysis of RCTs aims to synthesize existing evidence on the efficacy and safety of remdesivir in patients with COVID-19.

# Methods

We will conduct a systematic review and meta-analysis that will comply with the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA-P) 2015 guidelines for the design and reporting of the results [34] (see checklist in Additional file 1). The protocol has been registered at PROSPERO database, ID: CRD42020177953 [35].

### Data sources and searches

We will search MEDLINE/PubMed (http://www.ncbi.nlm.nih.gov/pubmed/), Embase (http://www.embase.com/), The Cochrane Library (http://www.cochranelibrary.com/), ClinicaTtrials.gov (https://www.clinicaltrials.gov/), and google scholar (https://scholar.google.com/) databases for primary articles published as of 30 June 2020 and we will complete the study by 30 August 2020. We will perform hand search from the reference lists of a key articles to identify eligible RCTs and supplement the searching. We will include all potential RCTs that evaluated the efficacy of remdesivir versus placebo or standard of care in patients with COIVID-19 with no limitations on the geographical location of studies but published in English-language. We will do a rigorous search strategy using the key words including 2019 novel coronavirus, 2019-nCov, coronavirus disease 2019, COVID-19, SARS-cov-2, severe acute

respiratory syndrome-coronavirus-2, remdesivir, GS-5734, nucleotide-analogue, antiviral agents, randomized controlled trials, clinical trials and RCTs. Table 1 summarizes the search strategy that we will applied in PubMed database, while details of this strategy that we will also adapt for other databases' searches is described in Additional file 2 (Table 1).

**Table 1**: Search strategy for the MEDLINE-PubMed database

| | | | | |
|---|---|---|---|---|
| "Antiviral agents"<br>OR<br>"Nucleotide-analogue"<br>OR<br>"Remdesivir"<br>OR<br>"GS-5734" | AND | ''Coronavirus disease 2019''<br>OR<br>"COVID-19''<br>OR<br>"Severe acute respiratory syndrome-coronavirus-2"<br>OR<br>"SARS-Cov-2"<br>OR<br>"2019 novel coronavirus"<br>OR<br>"2019-nCoV" | AND | "Randomized controlled trials"<br>OR<br>"RCTs"<br>OR<br>"Clinical trials" |

## Eligibility criteria

We will formulate our participant's eligibility criteria using PICOS (participants, interventions, comparison, outcomes, and study designs) description model [36].

- Participants
  - Patients with confirmed COVID-19
  - Men and/or women of any age
  - At any clinical stage of the disease, thus mild, moderate or severe/critical case
  - With or without other co-morbid conditions
- Intervention
  - Remdesivir of any dose.
- Comparator
  - Remdesivir placebo or standard of care.
- Outcomes/endpoints

- Primary endpoints
    - Time to clinical recovery (TTCR)
- Secondary endpoints
    - Proportion of participants relieved from clinical symptoms defined at the time (in hours) from initiation of the study treatment
    - All-cause mortality
    - Discharged date
    - Frequency of respiratory progression
    - Oxygen saturation
    - Treatment-emergent adverse events

- Study design
    - Only RCTs evaluating the efficacy of remdesivir versus placebo or standard of care in patients with COVID-19

**Study selection**

All the retrieved papers will be transferred to EnDnote 7 and duplicates will be removed. Two investigators will independently assess the title and abstract of all the retrieved papers based on the eligibility criteria. The two investigators will independently evaluate the full texts. Disagreements between the two investigators will settle through discussion and if persisted, the third investigator will involve as arbitrator. Figure 1 summarizes the design that we will use to report the study result in line with the PRISMA -P 2015 guidelines (Figure 1).

**Data extraction**

Two authors will independently extract data according to the pre-designed data extraction tool. The following data will be extracted from each included RCTs

- First author
- Year of publication
- Study country
- Funding information
- Patient characteristics (mean age of the participant, sex, co-morbid conditions, number of comorbidities, symptom severity)

- Interventions (remdsivir, dose of remdesivir and route of administration)
- Comparators (remdesivir placebo, standard of care)
- Number of participants randomized in each group
- Treatment follow-up period
- Outcomes (primary, secondary and other outcomes)

**Assessment of risk of bias**

The Cochrane risk of bias tool [37] will be used to assess the risk of bias for each included study. The risk of bias of each trial will be judged by two independent investigators as "Low", "Some concerns", or "High" based on the critical domains, including bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result. Disagreements will be resolved by discussion among the two investigators. If the disagreements persist, the third investigator will chip in as an arbitrator.

**Statistical analysis**

All statistical analyses will be carried out using the computer software packages RevMan 5.3 [38]. Mean differences (MDs) with 95% confidence intervals (CIs) will be used to measure the effects of treatment for continuous outcome data. We will convert other forms of data into MDs using standard conversion formula. For outcome variables reported in different scales, we will use standard mean differences (SMDs) with 95% CIs. The treatment effect of binary outcome data will be summarized using risk ratios (RRs) with 95% CIs. Other binary outcome data will be converted into RRs. Mantel-Haenszel method [39] will be used to pool effect estimates of dichotomous outcomes and inverse variance for continuous outcomes. Cochrane Q test [40] will be used to assess heterogeneity between studies, and $I^2$ testing [41] will be done to quantify heterogeneity between studies, with values > 50% representing moderate-to-high heterogeneity. A random-effect model will be used to pool the data [42]. Subgroup analysis will be carried out between studies with different duration of follow-up, age of participants, severity of the disease, comorbidities, settings, and quality of studies for risk of bias. Following the subgroup analysis, we will look at the data for heterogeneity, and if acceptable, we will perform a meta-analysis. If the data is heterogeneous, we will do a narrative description of findings. To see the robustness of pooled data, sensitivity analysis will be conducted between low and high risk of bias, and with or without biased

studies.. We will use the GRADEprofiler software from Cochrane Systematic Reviews to assess the quality of evidence per outcome and ultimately to create a summary of findings table and evidence profile. All statistical analysis with a p-value < 0.05 will be considered statistically significant.

**Addressing missing data**

When individual participant's data are initially unavailable, we will review the original source, and/or published trial reports, and we will contact the authors to obtain clarification for these data.

**Reporting bias**

We will conduct funnel plot and Egger test to check any possible reporting bias if a sufficient number of included studies (at least 10 trials) are available in this study [43].

**Patient and public involvement**

Patients and public will not be involved in this systematic review and meta-analysis. However, once our findings are disseminated, it will be shared through social networks.

## Ethics and dissemination

There are no ethical considerations associated with this study as we will use publicly available data from previously published studies. We plan to publish results in open-access peer-reviewed journals and present at international and national conferences.

## Amendments

The protocol for this study will be amended as necessary.

## Abbreviations

2019-nCoV = 2019 novel Coronavirus, COVID-19 = Coronavirus Disease-2019, SARS = Severe Acute Respiratory Syndrome, RCTs = Randomized Controlled Trials, SARS-CoV-2 = Severe Acute Respiratory Syndrome Coronavirus-2, MERS-CoV = Middle East Respiratory Syndrome Coronavirus

# Declarations

## Competing interests

All review authors declare that they have no competing interests. The funder has not any role in the design, syntheses, and report of the study.

## Funding

This study is supported by Center for Innovative Drug Development and Therapeutic Trials for Africa (CDT-Africa), College of Health Sciences, Addis Ababa University.

## Authors' contributions

DG (first author) conceived the study, developed the study criteria, searched the literature, wrote the protocol and drafting the manuscript. DG (second author) conducted the preliminary search and TM copyediting and revised the manuscript. All authors have read and approved the manuscript.

## Acknowledgment

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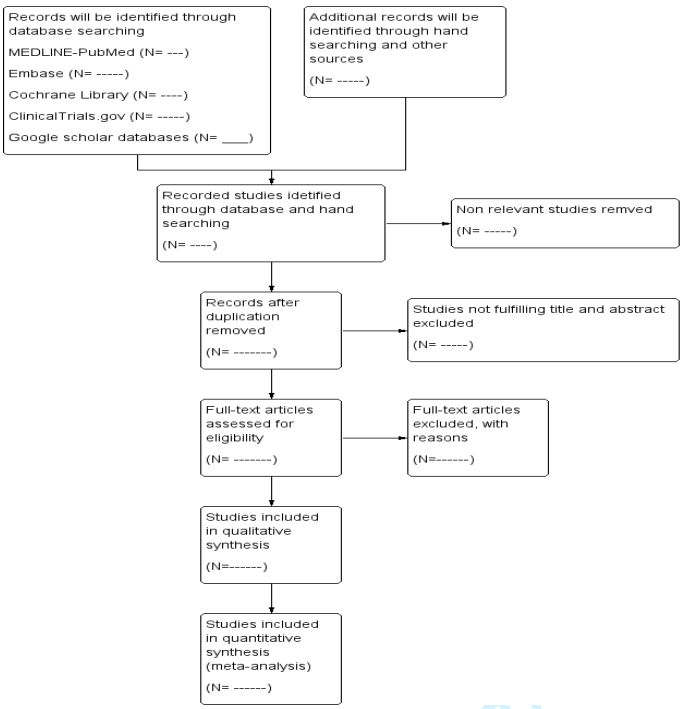
# Figure legend/caption

**Figure 1:** PRISMA-P flow diagram of the study



**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item | Page |
|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | |
| Title: | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | 1 |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | 2 and 5 |
| Authors: | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | 10 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | 9 |
| Support: | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | 10 |
| **INTRODUCTION** | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | 4-5 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 5 |
| **METHODS** | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | 6-7 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | 5-6 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | 5-6 |

| | | | |
|---|---|---|---|
| Study records: | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 7 |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | 7 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | 7 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | 7-8 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 6-7 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | 8 |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | 8 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | 8 |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 8 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | 8 |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | 9 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 9 |

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

**PubMed search strategy**

This search strategy does not include any limit and this will be updated because there are ongoing trials which should be included in this study.

| # | Searches | Results |
|---|---|---|
| 1 | "remdesivir"[Supplementary Concept] OR "remdesivir"[All Fields] | 81 |
| 2 | "viruses/drug effects"[MeSH Terms] | 59,974 |
| 3 | (("antiviral agents"[Pharmacological Action] OR "antiviral agents"[MeSH Terms]) OR ("antiviral"[All Fields] AND "agents"[All Fields])) OR "antiviral agents"[All Fields] | 383,998 |
| 4 | "Nucleotide-analogue"[All Fields] | 797 |
| 5 | ((((("antiviral agents"[Pharmacological Action] OR "antiviral agents"[MeSH Terms]) OR ("antiviral"[All Fields] AND "agents"[All Fields])) OR "antiviral agents"[All Fields]) OR ("antiviral"[All Fields] AND "drug"[All Fields])) OR "antiviral drug"[All Fields] | 392,120 |
| 6 | (((((("antiviral agents"[Pharmacological Action] OR "antiviral agents"[MeSH Terms]) OR ("antiviral"[All Fields] AND "agents"[All Fields])) OR "antiviral agents"[All Fields]) OR ("antiviral"[All Fields] AND "drug"[All Fields])) OR "antiviral drug"[All Fields]) AND "antiviral agents/therapeutic use"[MeSH Terms] | 98,451 |
| 7 | 1 OR 2 OR 3 OR 4 OR 5 OR 6 | 407,526 |
| 8 | "coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields] | 18,508 |
| 9 | (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) OR "coronaviruses"[All Fields]) AND "coronavirus infections/virology"[MeSH Major Topic] | 1,050 |
| 10 | "covid 19"[Supplementary Concept] OR "covid 19"[All Fields] OR "coronavirus disease 2019"[All Fields] | 4,227 |
| 11 | ((((((("covid 19"[All Fields] OR "covid 2019"[All Fields]) OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]) OR "severe acute respiratory syndrome coronavirus 2"[All Fields]) OR "2019 ncov"[All Fields]) OR "sars cov 2"[All Fields]) OR "2019ncov"[All Fields]) OR (("wuhan"[All Fields] AND ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields])) AND (2019/12/1:2019/12/31[Date - Publication] OR 2020/1/1:2020/12/31[Date - Publication])) | 4,656 |
| 12 | "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019 novel coronavirus"[All Fields] | 1,429 |

| | | |
|---|---|---|
| 13 | "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "2019 ncov"[All Fields] | 1,465 |
| 14 | "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "sars cov 2"[All Fields] | 1,931 |
| 15 | "spike glycoprotein sars cov"[Supplementary Concept] | 452 |
| 16 | (((((((("sever"[All Fields] OR "severe"[All Fields]) OR "severed"[All Fields]) OR "severely"[All Fields]) OR "severer"[All Fields]) OR "severes"[All Fields]) OR "severing"[All Fields]) OR "severities"[All Fields]) OR "severity"[All Fields]) OR "severs"[All Fields]) AND (("acute"[All Fields] OR "acutely"[All Fields]) OR "acutes"[All Fields]) AND "respiratory"[All Fields] AND ((((((("syndrom"[All Fields] OR "syndromal"[All Fields]) OR "syndromally"[All Fields]) OR "syndrome"[MeSH Terms]) OR "syndrome"[All Fields]) OR "syndromes"[All Fields]) OR "syndrome s"[All Fields]) OR "syndromic"[All Fields]) OR "syndroms"[All Fields]) AND (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields]) OR "coronaviruses"[All Fields]) | 4,936 |
| 17 | 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 | 20,471 |
| 18 | "randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trials"[All Fields] OR "randomised controlled trials"[All Fields] | 676,631 |
| 19 | "randomized controlled trials as topic/methods"[MeSH Terms] | 9,652 |
| 20 | "RCTs"[All Fields] | 32,846 |
| 21 | 18 OR 19 OR 20 | 681,739 |
| 22 | 7 AND 17 AND 21 | 18 |