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[Intervention Review]

Remdesivir for the treatment of COVID-19

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ABSTRACT

Background

Remdesivir is an antiviral medicine approved for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19). This led to widespread implementation, although the available evidence remains inconsistent. This update aims to fill current knowledge gaps by identifying, describing, evaluating, and synthesising all evidence from randomised controlled trials (RCTs) on the effects of remdesivir on clinical outcomes in COVID-19.

Objectives

To assess the effects of remdesivir and standard care compared to standard care plus/minus placebo on clinical outcomes in patients treated for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Search methods

We searched the Cochrane COVID-19 Study Register (which comprises the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, ClinicalTrials.gov, World Health Organization (WHO) International Clinical Trials Registry Platform, and medRxiv) as well as Web of Science (Science Citation Index Expanded and Emerging Sources Citation Index) and WHO COVID-19 Global literature on coronavirus disease to identify completed and ongoing studies, without language restrictions. We conducted the searches on 31 May 2022.

Selection criteria

We followed standard Cochrane methodology.

We included RCTs evaluating remdesivir and standard care for the treatment of SARS-CoV-2 infection compared to standard care plus/minus placebo irrespective of disease severity, gender, ethnicity, or setting.

We excluded studies that evaluated remdesivir for the treatment of other coronavirus diseases.

Data collection and analysis

We followed standard Cochrane methodology.

To assess risk of bias in included studies, we used the Cochrane RoB 2 tool for RCTs. We rated the certainty of evidence using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach for outcomes that were reported according to our prioritised categories: all-cause mortality, in-hospital mortality, clinical improvement (being alive and ready for discharge up to day 28) or worsening (new need for invasive mechanical ventilation or death up to day 28), quality of life, serious adverse events, and adverse events (any grade).

We differentiated between non-hospitalised individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19 and hospitalised individuals with moderate to severe COVID-19.

Main results

We included nine RCTs with 11,218 participants diagnosed with SARS-CoV-2 infection and a mean age of 53.6 years, of whom 5982 participants were randomised to receive remdesivir. Most participants required low-flow oxygen at baseline. Studies were mainly conducted in high- and upper-middle-income countries. We identified two studies that are awaiting classification and five ongoing studies.

Effects of remdesivir in hospitalised individuals with moderate to severe COVID-19

With moderate-certainty evidence, remdesivir probably makes little or no difference to all-cause mortality at up to day 28 (risk ratio (RR) 0.93, 95% confidence interval (CI) 0.81 to 1.06; risk difference (RD) 8 fewer per 1000, 95% CI 21 fewer to 6 more; 4 studies, 7142 participants), day 60 (RR 0.85, 95% CI 0.69 to 1.05; RD 35 fewer per 1000, 95% CI 73 fewer to 12 more; 1 study, 1281 participants), or in-hospital mortality at up to day 150 (RR 0.93, 95% CI 0.84 to 1.03; RD 11 fewer per 1000, 95% CI 25 fewer to 5 more; 1 study, 8275 participants).

Remdesivir probably increases the chance of clinical improvement at up to day 28 slightly (RR 1.11, 95% CI 1.06 to 1.17; RD 68 more per 1000, 95% CI 37 more to 105 more; 4 studies, 2514 participants; moderate-certainty evidence). It probably decreases the risk of clinical worsening within 28 days (hazard ratio (HR) 0.67, 95% CI 0.54 to 0.82; RD 135 fewer per 1000, 95% CI 198 fewer to 69 fewer; 2 studies, 1734 participants, moderate-certainty evidence).

Remdesivir may make little or no difference to the rate of adverse events of any grade (RR 1.04, 95% CI 0.92 to 1.18; RD 23 more per 1000, 95% CI 46 fewer to 104 more; 4 studies, 2498 participants; low-certainty evidence), or serious adverse events (RR 0.84, 95% CI 0.65 to 1.07; RD 44 fewer per 1000, 95% CI 96 fewer to 19 more; 4 studies, 2498 participants; low-certainty evidence).

We considered risk of bias to be low, with some concerns for mortality and clinical course. We had some concerns for safety outcomes because participants who had died did not contribute information. Without adjustment, this leads to an uncertain amount of missing values and the potential for bias due to missing data.

Effects of remdesivir in non-hospitalised individuals with mild COVID-19

One of the nine RCTs was conducted in the outpatient setting and included symptomatic people with a risk of progression. No deaths occurred within the 28 days observation period.

We are uncertain about clinical improvement due to very low-certainty evidence. Remdesivir probably decreases the risk of clinical worsening (hospitalisation) at up to day 28 (RR 0.28, 95% CI 0.11 to 0.75; RD 46 fewer per 1000, 95% CI 57 fewer to 16 fewer; 562 participants; moderate-certainty evidence). We did not find any data for quality of life.

Remdesivir may decrease the rate of serious adverse events at up to 28 days (RR 0.27, 95% CI 0.10 to 0.70; RD 49 fewer per 1000, 95% CI 60 fewer to 20 fewer; 562 participants; low-certainty evidence), but it probably makes little or no difference to the risk of adverse events of any grade (RR 0.91, 95% CI 0.76 to 1.10; RD 42 fewer per 1000, 95% CI 111 fewer to 46 more; 562 participants; moderate-certainty evidence).

We considered risk of bias to be low for mortality, clinical improvement, and safety outcomes. We identified a high risk of bias for clinical worsening.

Authors' conclusions

Based on the available evidence up to 31 May 2022, remdesivir probably has little or no effect on all-cause mortality or in-hospital mortality of individuals with moderate to severe COVID-19. The hospitalisation rate was reduced with remdesivir in one study including participants with mild to moderate COVID-19. It may be beneficial in the clinical course for both hospitalised and non-hospitalised patients, but certainty remains limited. The applicability of the evidence to current practice may be limited by the recruitment of participants from mostly unvaccinated populations exposed to early variants of the SARS-CoV-2 virus at the time the studies were undertaken.

Future studies should provide additional data on the efficacy and safety of remdesivir for defined core outcomes in COVID-19 research, especially for different population subgroups.

PLAIN LANGUAGE SUMMARY

Remdesivir to treat people with COVID-19

Is remdesivir (an antiviral medicine) an effective treatment for COVID-19?

Key messages

• For adults hospitalised with COVID-19, remdesivir probably has little or no effect on deaths up to 150 days after treatment compared with placebo (sham treatment) or usual care.

• Remdesivir probably slightly raises the chance for hospitalised patients to improve and get discharged (leave the hospital or go home). It may also decrease the risk of becoming worse (invasive ventilation through a breathing tube or death).

• Usually patients who have mild symptoms and are not hospitalised are less likely to die. Remdesivir probably reduces the risk of getting worse and being hospitalised, but we cannot say if it affects recovery (e.g. relief in symptoms).

• Future studies should investigate the impact of remdesivir on the course of COVID-19 in different subgroups (e.g. less or more severely ill people).

What is remdesivir?

Remdesivir is a medicine that fights viruses. It has been shown to prevent the virus that causes COVID-19 (SARS-CoV-2) from reproducing. Medical regulators have approved remdesivir to treat people with COVID-19. Common reported side effects are nausea, vomiting, and headaches, as well as changes in blood tests.

What did we want to find out?

We wanted to know if remdesivir is an effective treatment for people with COVID-19 and if it causes unwanted effects compared to placebo or usual care. Its effect could depend on how advanced the illness is when treatment begins. We therefore distinguished between hospitalised patients with moderate to severe disease (e.g. having ventilation) and non-hospitalised people who have tested positive for COVID-19 but have no or mild symptoms.

We were interested in the following outcomes for hospitalised patients:

• deaths in the 28 days after treatment or after more than 28 days, if available;

• deaths that occurred during hospitalisation;

• whether patients got better after treatment and were ready to be discharged;

• whether patients' condition worsened so that they needed mechanical ventilation through a breathing tube or died;

• any unwanted effects; and

• serious unwanted effects.

We were interested in the following outcomes for non-hospitalised patients:

• deaths in the 28 days after treatment or after more than 28 days, if available;

• whether patients got better after treatment so that they were free of symptoms;

• whether patients' condition worsened so that they needed to be hospitalised or that they died;

• quality of life;

• any unwanted effects; and

• serious unwanted effects.

What did we do?

We searched for studies that investigated remdesivir to treat adults with COVID-19 compared to placebo or standard care. Patients could be of any gender or ethnicity.

We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found eight studies with 10,656 people hospitalised with moderate to severe COVID-19 and one study with 562 people with mild COVID-19. Of these, 5982 people were given remdesivir. No studies evaluated people without symptoms of COVID-19. The average age of patients was 59 years.

Main results

The included studies compared remdesivir and usual care to usual care (plus/minus placebo) in people with COVID-19.

Hospitalised people with moderate to severe COVID-19

Remdesivir probably makes little or no difference to deaths after 28 days, after 60 days, or to deaths in hospital during 150 days. It probably raises the chance for patients to get better slightly, and it probably lowers the risk of getting worse. The rates of unwanted effects of any severity were similar between the compared groups.

Non-hospitalised people with mild COVID-19

In the study with outpatients no one died during the investigation (28 days). After treatment with remdesivir, people were less likely to get worse and be hospitalised. We do not know whether remdesivir leads to more or less chance for patients to improve. Patients may suffer fewer serious unwanted effects with remdesivir than with placebo or standard care. The rates of unwanted effects of any severity were similar between the compared groups.

What are the limitations of the evidence?

We are moderately confident in the evidence for deaths and course of disease in hospitalised people. Our confidence in the evidence of all other results in this group is limited because of differences between studies and a possible influence of their methods. For non-hospitalised people with mild COVID-19, we are moderately confident in the evidence for worsening of patients' condition and unwanted effects. Our confidence in the evidence of all other results is limited, especially for improvement of patients' condition, for methodological reasons (e.g. measurements were carried out inadequately or are not comparable, or both) and different results between studies. The studies were conducted at a time when vaccine programmes had not been started and the virus differed from subsequent strains. Most of the people in the studies also live in high- and middle-income countries. This might limit the applicability of the findings to people who are vaccinated and in low-income countries with less access to medical care.

How up-to-date is this evidence?

This is an update of the initial review and the evidence is current to 31 May 2022.

SUMMARY OF FINDINGS

Summary of findings 1. Remdesivir and standard care versus standard care (plus/minus placebo) for individuals with moderate to severe COVID-19

Remdesivir and standard care versus standard care (plus/minus placebo) for individuals with moderate to severe COVID-19

Patient or population: hospitalised adults with moderate to severe COVID-19
Settings: in-hospital
Intervention: remdesivir (10 days)
Comparator: placebo or standard care alone

Outcomes	Anticipated absolute effects		Relative effect 95% CI	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Placebo or standard care alone	Remdesivir				
All-cause mortality at up to day 28[1]	108 per 1000	100 per 1000 (21 fewer to 6 more)	RR 0.93 (0.81 to 1.06)	7142 (4 RCTs)	⊕⊕⊕⊖ MODERATE [a]	Remdesivir probably makes little or no difference to all-cause mortality up to 28 days.
All-cause mortality at up to day 60	235 per 1000	200 per 1000 (73 fewer to 12 more)	RR 0.85 (0.69 to 1.05)	1281 (1 RCT)	⊕⊕⊕⊖ MODERATE [b]	Remdesivir probably makes little or no difference to all-cause mortality up to 60 days.
In-hospital mortality at up to day 150	156 per 1000	145 per 1000 (25 fewer to 5 more)	RR 0.93 (0.84 to 1.03)	8275 (1 RCT)	⊕⊕⊕⊖ MODERATE [c]	Remdesivir probably makes little or no difference to in-hospital mortality up to 150 days.
Clinical improvement: participants alive and ready to be discharged at up to day 28[2]	617 per 1000	685 per 1000 (37 more to 105 more)	RR 1.11 (1.06 to 1.17)	2514 (4 RCTs)	⊕⊕⊕⊖ MODERATE [d]	Remdesivir probably increases the chance of clinical improvement slightly.
Clinical worsening: time to new need for invasive mechanical ventilation or death within 28 days[3]	544 per 1000	409 per 1000 (198 fewer to 69 fewer)	HR 0.67 (0.54 to 0.82)	1734 (2 RCTs)	⊕⊕⊕⊖ MODERATE [d]	Remdesivir probably decreases the risk of clinical worsening up to day 28.
Adverse events (any grade) at up to day 28	579 per 1000	602 per 1000 (46 fewer to 104 more)	RR 1.04 (0.92 to 1.18)	2498 (4 RCTs)	⊕⊕⊖⊖ LOW [a,e]	Remdesivir may make little or no difference to the risk of adverse events (any grade).

Serious adverse events at up to day 28	273 per 1000	229 per 1000 (96 fewer to 19 more)	RR 0.84 (0.65 to 1.07)	2498 (4 RCTs)	⊕⊕⊖⊖ LOW [a,e]	Remdesivir may make little or no difference to the risk of serious adverse events.

CI: confidence interval; **HR:** hazard ratio; **RCT:** randomised controlled trial; **RD:** risk difference; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

1. Time to all-cause mortality (time-to-event): HR 0.88, 95% CI 0.67 to 1.16; 2 studies, 6513 participants; I^2 = 57%.
2. Time to clinical improvement (time-to-event): alive and ready to discharge: HR 1.06, 95% CI 0.93 to 1.20; 2 studies, 1225 participants; I^2 = 0%.
3. Clinical worsening: new need for invasive mechanical ventilation or death: RR 0.70, 95% CI 0.52 to 0.94; RD 76 fewer per 1000, 95% CI 121 fewer to 15 fewer; 1 study, 683 participants; I^2 = not applicable; low-certainty evidence.

[a]Downgraded one level due to serious imprecision because of wide confidence intervals in the studies and/or the 95% confidence interval includes both benefits and harms.
[b]Downgraded one level due to serious imprecision because optimal information size not reached.
[c]Downgraded one level due to serious risk of bias because of selective reporting.
[d]Downgraded one level due to serious risk of bias because of lack of blinding.
[e]Downgraded one level due to serious risk of bias because of lack of blinding and one study was stopped earlier than scheduled.

Summary of findings 2. Remdesivir and standard care versus standard care (plus/minus placebo) for individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19

Remdesivir and standard care versus standard care (plus/minus placebo) for individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19

Patient or population: non-hospitalised adults with mild COVID-19
Settings: outpatient
Intervention: remdesivir
Comparator: placebo or standard care alone

Outcomes	Anticipated absolute effects		Relative effect 95% CI	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Placebo or standard care alone	Risk with remdesivir				
All-cause mortality at up to day 28	—	—	Not estimable	562 (1 RCT)	—	There were no events observed, thus it was not possible to determine whether remdesivir makes a difference to 28-day mortality.

Clinical improvement: participants with symptom alleviation at up to day 14	250 per 1000	333 per 1000 (61 fewer to 289 more)	HR 1.41 (0.73 to 2.71)	126 (1 RCT)	⊕⊖⊖⊖ Very low[b,c]	We are uncertain whether remdesivir increases or decreases the chance of symptom alleviation by day 14.
Clinical worsening: participants admitted to hospital or deceased at up to day 28	64 per 1000	18 per 1000 (57 fewer to 16 fewer)	RR 0.28 (0.11 to 0.75)	562 (1 RCT)	⊕⊕⊕⊖ Moderate[c]	Remdesivir probably decreases the rate of hospitalisation or death by day 28.
Quality of life	—	—	—	—	—	Not reported.
Serious adverse events at up to day 28	67 per 1000	18 per 1000 (60 fewer to 20 fewer)	RR 0.27 (0.10 to 0.70)	562 (1 RCT)	⊕⊕⊖⊖ Low [c,d]	Remdesivir may decrease the rate of serious adverse events by day 28.
Adverse events (any grade) at up to day 28	463 per 1000	421 per 1000 (111 fewer to 46 more)	RR 0.91 (0.76 to 1.10)	562 (1 RCT)	⊕⊕⊕⊖ Moderate[c]	Remdesivir probably makes little or no difference to the risk of adverse events (any grade).

CI: confidence interval; **HR:** hazard ratio; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded one level due to serious imprecision because there was only one study.
[b]Downgraded two levels due to serious risk of bias and serious indirectness because of differences in pre-defined outcome and measurement.
[c]Downgraded one level due to serious imprecision because of wide confidence interval and optimal information size not reached.
[d]Downgraded one level due to serious indirectness (due to huge overlap with COVID-19 symptoms, already considered in hospitalisation or death).

BACKGROUND

This work is part of a series of Cochrane Reviews investigating treatments and therapies for coronavirus disease 2019 (COVID-19). Reviews of this series share information in the background section and methodology based on the first published reviews about monoclonal antibodies and convalescent plasma (Kreuzberger 2021; Piechotta 2021), as well as recently published or updated reviews on Janus-kinase inhibitors or systemic corticosteroids (Griesel 2022; Kramer 2022). They are part of the German research project "CEOsys" (COVID-19 Evidence-Ecosystem; CEOsys 2021).

Description of the condition

COVID-19 is a rapidly spreading infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). On 11 March 2020, the WHO declared the current COVID-19 outbreak as a pandemic (WHO 2020a). COVID-19 is unprecedented compared to previous coronavirus outbreaks, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS, Table 1), with 813 and 858 deaths, respectively (WHO 2003; WHO 2019). Despite intensive international efforts to contain its spread, SARS-CoV-2 has resulted in an ongoing increase of new weekly cases and deaths in several regions around the globe (WHO 2022a). In the meantime, the emergence of SARS-CoV-2 variants with the potential for altered transmission or disease characteristics, or to impact the effectiveness of vaccines, therapeutics, diagnostics, or public health and social measures, challenges strategies to control disease spread (WHO 2022b).

The risk for severe disease mainly depends on underlying medical conditions, in addition to the serological status of the infected person and the causative virus variant. In patients without effective immunisation, such as unvaccinated or incompletely vaccinated individuals, or individuals who fail to develop an immunological response despite being fully vaccinated, the risk for severe disease is higher among individuals aged 65 years or older, smokers, and those with certain underlying medical conditions such as cancer, chronic kidney disease, chronic obstructive pulmonary disease (COPD), heart conditions, immunocompromised state, obesity, sickle cell disease, or type 2 diabetes mellitus (Huang 2020; Liang 2020; Williamson 2020a). COVID-19 case fatality ratios vary widely between countries and reporting periods, from 0.0% to more than 18% (Johns Hopkins 2022). However, these numbers may be misleading as they tend to overestimate the infection fatality ratio due to varying testing frequency, a lack of reporting dates, and variations in case definitions, especially in the beginning of the pandemic when the main focus was on severe cases (WHO 2020b).

The median incubation time and time to symptom onset depends on the virus variant and is estimated to be three days (range zero to eight days) in the case of an infection with the Omicron SARS-CoV-2 variant, which is shorter compared with previous reports for the Delta SARS-CoV-2 variant and other previously circulating non-Delta SARS-CoV-2 variants (five to six days) (Brandal 2021; Lauer 2020). Sore throat, cough, fever, headache, fatigue, and myalgia or arthralgia are the most commonly reported symptoms (Brandal 2021; Struyf 2021). Other symptoms include dyspnoea, chills, nausea or vomiting, diarrhoea, and nasal congestion (CDC 2022). The reported frequency of asymptomatic infections varies greatly, depending on the time of the investigation, the cohort investigated, and the virus variant, and ranges between approximately 14% and 50% (Buitrago-Garcia 2022).

A smaller proportion of infected individuals are affected by severe (approximately 11% to 20%) or critical (approximately 1% to 5%) disease with hospitalisation and intensive care unit (ICU) admittance due to respiratory failure, septic shock, or multiple organ dysfunction syndrome (Funk 2021; Lewnard 2022; Nyberg 2022; Wolter 2022; Wu 2020). In a case series from 12 New York hospitals, 14% of patients hospitalised due to COVID-19 were treated in ICU (Richardson 2020). In an observational study of 10,021 hospitalised adult patients in Germany with a confirmed COVID-19 diagnosis, 17% received mechanical ventilation (non-invasive and invasive). Mortality in patients not receiving mechanical ventilation was 16%, and up to 53% in ventilated patients. Mortality in patients receiving mechanical ventilation (non-invasive and invasive) and dialysis was 73% (Karagiannidis 2020). In one systematic review and meta-analysis of international studies, the proportion of patients who died was estimated at 34% amongst those treated in ICU, and 83% amongst those receiving invasive mechanical ventilation (Potere 2020). However, the hospitalisation and ICU treatment rates seem to depend on the virus variant.

Analyses from the United Kingdom show a significant reduction in the relative risk of hospitalisation for adult Omicron cases compared to Delta (Nyberg 2022). There may also have been a different threshold for admission to hospital or ICU during the course of the pandemic. Depending on the local pressure on ICU resources, some normal wards will have learned to provide continuous positive airway pressure (CPAP) therapy equivalent to ICU support in other healthcare systems. It is unclear whether triage criteria in some healthcare systems may have influenced admission to hospital or ICU (or both).

As the evidence for the treatment options for COVID-19 that were investigated in the course of the pandemic increased, national and international guidelines emerged to support daily clinical decisions (NICE guideline 2021; NIH guideline 2022; WHO living guideline 2022). However, so far there are only a few substances with clearly proven benefits and clear recommendations as well as approval by national and international authorities for the treatment of COVID-19 (EMA 2022; FDA 2022a; WHO living guideline 2022). In light of the extent of the COVID-19 pandemic and the scarcity of effective treatments, there is an urgent need for effective therapies to save lives and to reduce the high burden on healthcare systems (either with a high workload caused by COVID-19 or staff shortages due to infected health care providers), especially in the face of evolving variants of the virus with the potential for increased transmissibility and the limited global availability of vaccines.

Description of the intervention

Remdesivir (GS-5734) is an antiviral agent derived from a small-molecule library and designed to target the replication of pathogenic ribonucleic acid (RNA) viruses (Siegel 2017). It showed a broad-spectrum in vitro efficacy against various emerging viruses, such as *Filoviridae* (e.g. *Ebolavirus* and *Marburgvirus*), *Pneumoviridae* (respiratory syncytial virus), and *Coronaviridae* (MERS-CoV, SARS-CoV)) (Choy 2020; Sheahan 2017). Initially developed for the treatment of Ebola virus disease, studies on animals showed effective reduction in virus replication and clinical improvement for MERS as well as SARS infection (Sheahan 2020; Williamson 2020a; de Wit 2020).

During the course of the COVID-19 pandemic, the antiviral agent was initially administered to hospitalised patients with COVID-19 in a compassionate-use attempt. The Adaptive COVID-19 Treatment Trial (ACTT-1) was one of the first multicentre RCTs to report a shortened time to recovery in hospitalised COVID-19 patients compared to standard care (Beigel 2020). Shortly after its publication, the US Food and Drug Administration (FDA) released an Emergency Use Authorisation on 1 May 2020 (EUA 2021). Based on the recommendation of the European Medicines Agency, the European Union Commission followed in July 2020 with the authorisation of remdesivir as the first treatment option in patients at least 12 years of age with COVID-19 pneumonia and the need for supplementary oxygen (EUA 2020). Later that year, the Committee for Medicinal Products for Human Use narrowed the indication to patients with low- or high-flow oxygen or other non-invasive ventilation (EMA 2020). Recently, the FDA expanded approval to paediatric patients of at least 28 days of age with a minimal weight of three kilograms who are hospitalised, or not hospitalised with mild-to-moderate COVID-19 and a high risk for progression to severe COVID-19, including hospitalisation or death (FDA 2022b). However, supporting data have not been published to date and the paediatric trial by the manufacturer, Gilead Science, is still ongoing (NCT04431453). The recommended regimen has been changed to an intravenous route of three days instead of 10. Proposed dosing is 200 mg intravenously (loading dose), followed by 100 mg for adults and 5 mg/kg followed by 2.5 mg/kg for children of 3.5 kg to less than 40 kg (EUA 2022). To date, the available data revealed good tolerability and safety of intravenous administration of remdesivir in healthy individuals. Reported common side effects include nausea, headache, rash, as well as transient increase in transaminases, prothrombin time, and blood glucose in laboratory findings (NIH guideline 2022).

Meanwhile, further RCTs have added to the evidence of the efficacy and safety of remdesivir application in adolescent and adult COVID-19 patients. Amongst them were the interim results of the WHO Solidarity trial, which could not find a benefit for time to clinical improvement, need for mechanical ventilation, or mortality (WHO Solidarity Trial Consortium 2022). Based on a meta-analysis of four RCTs, including the preprint data from the aforementioned trial, the WHO COVID-19 treatment guideline recommended against the use of remdesivir in hospitalised patients in November 2020 (WHO 2022c). As the first RCT evaluating remdesivir usage in an outpatient setting, the PINETREE trial showed a reduction in hospitalisation in ambulatory patients with symptomatic COVID-19 (Gottlieb 2021). This led the guideline development group to an update in April 2022, suggesting treatment with remdesivir for patients with non-severe illness at highest risk of hospitalisation (WHO 2022c).

How the intervention might work

Remdesivir (GS-5734) is a mono phosphoramidate nucleoside prodrug, which inhibits the synthesis of viral RNA. By competing with its natural analogue adenosine triphosphate, it blocks the RNA-polymerase and leads to delayed chain termination, hence inhibiting the virus replication (Siegel 2017). The addition of the monophosphate prodrug improves the intracellular uptake, where phosphorylation turns it into its active metabolite (Lo 2017; McGuigan 2006).

In the early stage of a SARS-CoV-2-associated pneumonia, the reduction of the viral load is postulated to prevent a systemic inflammatory reaction and, in particular, alveolar damage. The clinical presentation of COVID-19 in the late pulmonary phase as well as in the hyper inflammatory phase is dominated by immunological processes, so that antiviral therapy strategies are no longer likely to be effective (Gautret 2020).

In summary, the broad-spectrum nucleoside analogue remdesivir could be beneficial in the early stages of SARS-CoV-2-infection by inhibiting virus replication. This hypothesis is supported by promising in vitro and animal experiments (Choy 2020; Wang 2020; Williamson 2020b), and could be the rationale for the current recommendation of early application to prevent disease progression. However, a new laboratory study shows that mutations in the viral polymerase can lead to partial resistance to remdesivir (Stevens 2022). This highlights the importance of targeted use in patients with the highest expected benefit as well as re-evaluation of its effect in virus variants.

Why it is important to do this review

There is a clear and urgent need for more evidence-based information to guide clinical decision-making for COVID-19 patients. Current standard care consists of supportive care with oxygen supply in moderately severe cases, and non-invasive ventilation or invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO) in severe cases. Systematic corticosteroids were the first formulation to show a reduction in mortality as well as risk for disease progression and became recommended standard care, however solely for severe or critical COVID-19 (Wagner 2021; WHO 2022c). To date, there have been applications for emergency use authorisation for several drugs. Few of them have been approved for the treatment of COVID-19 in the European Union (such as monoclonal antibodies) and international guidelines on their clinical implementation are constantly updated (EMA 2022). Remdesivir remains the only fully FDA-approved drug for usage in COVID-19, in particular for early-stage disease, with widespread implementation.

The first version of this review represents the difficulty in comparing available data due to inconsistent endpoint definitions (Ansems 2021). We included five RCTs with 7452 participants and concluded with moderate certainty that remdesivir probably has little or no effect on all-cause mortality at up to 28 days in hospitalised adults with SARS-CoV-2 infection. However, when it comes to analysis of patient subgroups by disease severity at baseline, as well as reduction of symptom severity and disease progression, the evidence left us uncertain about its efficacy. The publication of further trials, assessing this lack of evidence, led to a change from recommendation against its application to conditional recommendation for certain patients. Additionally, the reduced susceptibility to monoclonal antibodies of the Omicron variant of concern calls for a re-evaluation, considering that remdesivir is believed to remain active against variants in cell cultures (Vangeel 2022).

This first update of this systematic review aims to fill current gaps by identifying, describing, evaluating, and synthesising all evidence for remdesivir on clinical outcomes in COVID-19. There is a need for a thorough understanding and an extensive review of the current body of evidence regarding the use of remdesivir for the treatment of COVID-19. The primary goal of this update is to provide practising clinicians, healthcare providers, and interested

laypersons with reliable and evidence-based information that will lead to improvement in the treatment of COVID-19.

OBJECTIVES

To assess the effects of remdesivir and standard care compared to standard care plus/minus placebo on clinical outcomes in patients treated for SARS-CoV-2 infection.

METHODS

Criteria for considering studies for this review

Types of studies

The main description of methods is based on a template from the Cochrane Haematology working group in line with the series of Cochrane Reviews investigating treatments and therapies for COVID-19. We made specific adaptations related to the research question where necessary. The protocol for this review was registered with PROSPERO on 26 February 2021 (CRD42021238065).

To assess the effects of remdesivir for treatment in COVID-19, we included randomised controlled trials (RCTs), as this study design, if performed appropriately, provides the best evidence for experimental therapies in highly controlled therapeutic settings. We used the methods recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022a). We had planned to also accept non-standard RCT designs, such as cluster-randomised trials (methods as recommended in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions*) and cross-over trials (Higgins 2022b). We would only have considered results from the first period for cross-over trials, because COVID-19 is not a chronic condition, and its exact course and long-term effects have yet to be defined.

We excluded controlled non-randomised studies of the intervention and observational studies. We also excluded animal studies, pharmacokinetic studies, and in vitro studies.

We included the following formats, if sufficient information was available on study design, characteristics of participants, interventions, and outcomes.

- Full-text publications
- Preprint articles
- Abstract publications
- Results published in trials registries
- Personal communication with investigators

We included preprints and conference abstracts to have a complete overview of the ongoing research activity, especially for tracking newly emerging studies about remdesivir in COVID-19. We did not apply any limitation with respect to length of follow-up.

Types of participants

We included adults with a confirmed diagnosis of SARS-CoV-2 infection (as described in the study) and did not exclude any studies based on gender, ethnicity, disease severity, or setting.

We excluded studies that evaluated remdesivir for the treatment of other coronavirus diseases such as SARS or MERS, or other viral diseases, such as Ebola. We planned that if studies enrolled populations with or who were exposed to mixed viral diseases, we would only include these if the trial authors provided subgroup data for SARS-CoV-2 infection.

Types of interventions

We included the following interventions, independent of dose, frequency, and duration:

- Remdesivir and standard care for the treatment of SARS-CoV-2 infection.

We included the following control groups:

- Standard care (plus/minus placebo).

Types of outcome measures

We evaluated core outcomes based on the Core Outcome Measures in Effectiveness Trials (COMET) initiative for people with COVID-19 (COMET 2020), and additional outcomes that have been prioritised by consumer representatives and the German guideline panel for therapy of people with SARS-CoV-2 infection.

We defined outcome sets with primary and secondary outcomes for two populations:

- **hospitalised individuals with moderate to severe COVID-19** (defined as participants with SARS-CoV-2 detection and need for inpatient medical care plus/minus need for respiratory support with low-flow oxygen, high-flow oxygen, non-invasive mechanical ventilation, invasive mechanical ventilation (plus/minus ECMO) due to COVID-19); and
- **non-hospitalised individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19** (defined as participants with SARS-CoV-2 detection plus/minus symptoms of COVID-19 without need for inpatient medical care or respiratory support).

Primary outcomes were used to inform the summary of findings tables.

Hospitalised individuals with moderate to severe COVID-19

Primary outcomes

- All-cause mortality at day 28.
- All-cause mortality at day 60 and up to longest follow-up.
- In-hospital mortality at up to longest follow-up.
- Clinical improvement: proportion of participants alive and ready to be discharged at up to day 28, up to longest follow-up, and time-to-event. Participants should be discharged without clinical deterioration or death.
- Clinical worsening: proportion of participants with new need for invasive mechanical ventilation or deceased within 28 days, up to longest follow-up, and time-to-event.
- Adverse events (any grade) during the study period, defined as number of participants with any event.
- Serious adverse events during the study period, defined as number of participants with any event.

Secondary outcomes

- All-cause mortality, time-to-event.
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO Quality of Life 100-

question patient-reported questionnaire (WHOQOL-100)) at up to seven days, up to 28 days, and longest follow-up available.
- Adverse events grades 3 and 4.
- Ventilator-free days (defined as days alive and free from mechanical ventilation).

Non-hospitalised individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19

- All-cause mortality at day 28, up to longest follow-up, and time-to-event.
- Clinical improvement: proportion of participants with symptom resolution (all symptoms resolved) at up to day 14, day 28, up to longest follow-up, and time-to-event.
- Clinical worsening: proportion of participants admitted to the hospital or deceased within 14 days, 28 days, up to longest follow-up, and time-to-event.
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days, up to 28 days, and longest follow-up available.
- Serious adverse events during the study period, defined as number of participants with any event.
- Adverse events (any grade) during the study period, defined as number of participants with any event.

Timing of outcome measurement

In the case of time-to-event analysis (e.g. for time to discharge from hospital and time to mortality), we included the outcome measure based on the longest follow-up time. We also collected information on outcomes from all other time points reported in the publications.

Search methods for identification of studies

Electronic searches

Our Information Specialist (MIM) conducted systematic searches in the following sources from the inception of each database to 31 May 2022 (date of last search for all databases), placing no restrictions on the language of publication.

- Cochrane COVID-19 Study Register (CCSR) (covid-19.cochrane.org/) comprising:
  - Cochrane Central Register of Controlled Trials (CENTRAL), monthly updates;
  - PubMed, weekly updates;
  - Embase.com, weekly updates;
  - ClinicalTrials.gov (www.clinicaltrials.gov), daily updates;
  - World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (trialsearch.who.int), weekly updates;
  - medRxiv (www.medrxiv.org), weekly updates.
- Web of Science Clarivate:
  - Science Citation Index Expanded (1945 to 31 May 2022);
  - Emerging Sources Citation Index (2015 to 31 May 2022).
- WHO COVID-19 Global literature on coronavirus disease (search.bvsalud.org/global-literature-on-novel-coronavirus-2019-ncov/).

We did not conduct separate searches of the databases as required by the MECIR standards (Higgins 2022a), since these databases are regularly searched in the production of the CCSR.

For detailed search strategies, see Appendix 1.

Searching other resources

We identified other potentially eligible studies or ancillary publications by searching the reference lists of included studies, systematic reviews, and meta-analyses. In addition, we contacted investigators of the included studies to obtain additional information on the retrieved studies.

Data collection and analysis

Selection of studies

Four review authors (FG, KA, KD, VT) independently screened the results of the search strategies for eligibility by reading the titles and abstracts using Covidence software (Covidence 2021). We coded the abstracts as either 'include' or 'exclude'. In the case of disagreement, or if it was unclear whether the abstract should be retrieved, we obtained the full-text publication for further discussion. Several review authors (FG, KA, KD, VT) assessed the full-text articles of the selected studies. If two review authors were unable to reach a consensus, they consulted a third review author to reach a final decision.

As recommended in the PRISMA statement (Moher 2009), we documented the study selection process in a flow chart showing the total numbers of retrieved references and the numbers of included and excluded studies. We listed all studies excluded after full-text assessment and the reasons for their exclusion in the Excluded studies section.

Data extraction and management

We conducted data extraction according to the guidelines proposed by Cochrane (Li 2020). Several review authors (FG, KA, KD, VT, AM, NS) extracted data independently and in duplicate, using a customised data extraction form developed in Microsoft Excel (Microsoft 2018). Any disagreements were resolved by discussion or by consulting a third review author if necessary.

Two out of several review authors (FG, KA, KD, AM, VT, MG, NS) independently assessed the included studies for methodological quality and risk of bias. If the review authors were unable to reach a consensus, a third review author was consulted.

We extracted the following information, where reported.

- General information: author, title, source, publication date, country, language, duplicate publications.
- Study characteristics: trial design, setting, and dates, source of participants, inclusion/exclusion criteria, comparability of groups, treatment cross-overs, compliance with assigned treatment, length of follow-up.
- Participant characteristics: age, gender, ethnicity, number of participants recruited/allocated/evaluated, additional diagnoses, severity of disease, previous treatments, concurrent treatments, comorbidities (e.g. diabetes, respiratory disease, hypertension, immunosuppression, obesity, heart failure).
- Interventions: dosage, frequency, timing, duration and route of administration, setting, duration of follow-up.

- Control interventions (placebo or standard care alone): dosage, frequency, timing, duration and route of administration, setting, duration of follow-up.
- Outcomes: as specified in Types of outcome measures section.
- Risk of bias assessment: randomisation process, deviations from the intended interventions, missing outcome data, measurement of the outcome, selection of the reported result.

Assessment of risk of bias in included studies

We used the RoB 2 tool (beta version 7) to analyse the risk of bias of the included studies (Sterne 2019). Of interest in this review was the effect of the assignment to the intervention (the intention-to-treat effect), thus we performed all assessments with RoB 2 on this effect. The outcomes that we assessed are those specified for inclusion as described in the Methods section.

Two out of several review authors (FG, KA, KD, AM, VT, MG, NS) independently assessed the risk of bias for each outcome using the RoB 2 Excel tool to manage and record assessments. In case of discrepancies amongst judgements and inability to reach consensus, a third review author was consulted reach a final decision. We assessed the following types of bias as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022c).

- Bias arising from the randomisation process
- Bias due to deviations from the intended interventions
- Bias due to missing outcome data
- Bias in measurement of the outcome
- Bias in selection of the reported result

For cluster-RCTs, we had planned to add a domain to assess bias arising from the timing of identification and recruitment of participants in relation to timing of randomisation, as recommended in the archived RoB 2 guidance for cluster-randomised trials and in Chapter 23 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Eldridge 2016; Higgins 2022b).

To address these types of bias, we used the signalling questions recommended in RoB 2 and made a judgement according to the following options.

- 'Yes': if there is firm evidence that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'Probably yes': a judgement has been made that the question is fulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'No': if there is firm evidence that the question is unfulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'Probably no': a judgement has been made that the question is unfulfilled in the study (i.e. the study is at low or high risk of bias given the direction of the question).
- 'No information': if the study report does not provide sufficient information to permit a judgement.

We used the algorithms proposed by RoB 2 to assign each domain one of the following levels of bias.

- Low risk of bias
- Some concerns
- High risk of bias

We subsequently derived an overall risk of bias rating for each prespecified outcome in each study in accordance with the following suggestions.

- 'Low risk of bias': we judge the trial to be at low risk of bias for all domains for the result.
- 'Some concerns': we judge the trial to raise some concerns in at least one domain for the result, but not to be at high risk of bias for any domain.
- 'High risk of bias': we judge the trial to be at high risk of bias in at least one domain for the result, or we judge the trial to have some concerns for multiple domains in a way that substantially lowers our confidence in the results.

We used the RoB 2 Excel tool to implement RoB 2 (beta version 7, available from riskofbias.info), and stored and presented our detailed RoB 2 assessments in the analyses section and as supplementary online material.

For domain three of the tool ('bias due to missing outcome data'), we considered death as a competing risk factor, especially for dichotomous clinical progression outcomes. We judged improvement to be at high risk of bias due to missing data because it is likely that death during follow-up impeded liberation from respiratory support, and hence missing data on improvement depends on its true value.

Measures of treatment effect

For continuous outcomes, we recorded the mean, standard deviation, and total number of participants in both the treatment and control groups. Where continuous outcomes used the same scale, we performed analyses using the mean difference (MD) with 95% confidence intervals (CIs). For continuous outcomes measured with different scales, we performed analyses using the standardised mean difference (SMD). In our interpretation of SMDs, we re-expressed SMDs in the original units of a particular scale with the most clinical relevance and impact (e.g. clinical symptoms with the WHO Clinical Progression Scale) (WHO 2020c).

For dichotomous outcomes, we recorded the number of events and the total number of participants in both the treatment and control groups. We reported the pooled risk ratio (RR) with its associated 95% CI, and risk difference (RD) with its associated 95% CI (Deeks 2020).

If sufficient information was available, we extracted and reported hazard ratios (HRs) for time-to-event outcomes (e.g. time to mortality). If HRs were not available, we made every effort to estimate the HR as accurately as possible from available data using the methods proposed by Parmar and Tierney (Parmar 1998; Tierney 2007). If a sufficient number of studies provided HRs, we used HRs rather than RRs or MDs in a meta-analysis, as they provide more information.

Unit of analysis issues

The aim of this review was to summarise trials that analyse data at the level of the individual. We would also have accepted cluster-randomised trials for inclusion had any been identified. We collated

multiple reports of a given study so that each study, rather than each report, was the unit of analysis.

Studies with multiple treatment groups

As recommended in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022d), for studies with multiple treatment groups of the same intervention (i.e. dose, route of administration), we planned to evaluate if study arms were sufficiently homogeneous to be combined. We planned that if study arms could not be pooled, we would compare each arm with the common comparator separately. For pair-wise meta-analysis, we planned to split the 'shared' group into two or more groups with a smaller sample size, and include two or more (reasonably independent) comparisons. For this purpose, both the number of events and the total number of participants would have been divided for dichotomous outcomes, and the total number of participants would have been divided with unchanged means and standard deviations for continuous outcomes.

One study included in the review had multiple treatment arms of the same intervention (5-day course of remdesivir versus 10-day course of remdesivir) (Spinner 2020). Given the small number of participants in this study, we did not perform meta-analysis, but have reported the results for each treatment arm narratively in our subgroup analysis (see Effects of interventions, Duration of remdesivir application).

Dealing with missing data

In Chapter 10 of the *Cochrane Handbook for Systematic Reviews of Interventions*, a number of potential sources for missing data are suggested, which we took into account: at study level, at outcome level, and at summary data level (Deeks 2020). At all levels, it is important to differentiate between data 'missing at random', which may often be unbiased, and 'not missing at random', which may bias the study and in turn the review results.

In the case of missing data, we requested this information from the principal investigators; details are provided in the Included studies section. Beigel 2020 and Spinner 2020 provided additional data on all-cause mortality at up to day 28 for subgroups of respiratory support, and Spinner 2020 provided data on clinical course.

If, after this, data were still missing, we consulted with content experts to judge whether data were missing at random (e.g. if missing outcomes were balanced across study arms, reasons for loss to follow-up were common and reasonable). If we judged data to be missing at random, we performed a complete case analysis. When we judged data to be not missing at random, and we identified no supporting evidence that the results were not biased by missing outcome data, we did not make any assumptions about the missing outcome data. We had planned to conduct sensitivity analyses to assess the impact of missing data on the overall effect (excluding studies with more than 10% missing outcome data), however none of the included studies had more than 10% of missing outcome data. In future updates, we will discuss the potential impact of missing data on results.

Assessment of heterogeneity

We assessed heterogeneity of treatment effects between trials using a Chi^2 test with a significance level of $P < 0.1$. We used the I^2 statistic, Higgins 2003, and visual examination of the forest plot, to assess possible heterogeneity ($I^2 > 30\%$ to signify moderate heterogeneity, $I^2 > 75\%$ to signify considerable heterogeneity) (Deeks 2020). We planned that if the I^2 was above 80%, we would explore possible causes of heterogeneity through sensitivity analyses. If we could not find a reason for heterogeneity, we would not perform a meta-analysis, but instead would comment on the results from all studies and present these in tables.

Assessment of reporting biases

As mentioned above, we searched the trials registries to identify completed trials that have not been published elsewhere, to minimise publication bias or determine publication bias. We intended to explore potential publication bias by generating a funnel plot and statistically testing this by conducting a linear regression test for meta-analyses involving at least 10 trials (Sterne 2019). We would consider $P < 0.1$ as significant for this test.

Data synthesis

If the clinical and methodological characteristics of individual studies were sufficiently homogeneous, we pooled the data in meta-analysis. We performed analyses according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020). We planned to treat placebo and no treatment as the same intervention, as well as standard care at different institutions and time points.

We used the Review Manager Web (RevMan Web) software for analyses (RevMan Web 2021). One review author entered the data into the software, and a second review author checked the data for accuracy. We used the random-effects model for all analyses, as we anticipated that true effects would be related but not the same for included studies. We planned that if meta-analysis was not possible, we would comment on the results narratively with the results from all studies, and present these in tables. If meta-analysis was possible, we would assess the effects of potential biases in sensitivity analyses (see Sensitivity analysis). For binary outcomes, we based the estimation of the between-study variance using the Mantel-Haenszel method. We used the inverse-variance method for continuous outcomes, outcomes that included data from cluster-RCTs, or outcomes where HRs were available.

Subgroup analysis and investigation of heterogeneity

In the first version of this review we conducted subgroup analyses for all-cause mortality at up to day 28 exclusively. Additional analyses were performed where longer follow-up data on mortality were available.

In the case of sufficient data, we performed subgroup analyses of the following characteristics for remdesivir and standard care versus standard care plus/minus placebo.

- Age of participants (divided into applicable age groups, e.g. 18 to 65 years, 65 to 79 years, 80 years and older).
- Pre-existing conditions (e.g. diabetes, respiratory disease, hypertension, immunosuppression, obesity, cardiac injury).
- Timing of first dose administration with illness onset.
- Severity of condition, based on respiratory support at baseline:
  - No oxygen versus low-flow oxygen versus low-flow or high-flow oxygen versus mechanical ventilation (including high-

flow oxygen, non-invasive ventilation, invasive mechanical ventilation, and extracorporeal membrane oxygenation).
- Duration of remdesivir application:
  - 5-day course of remdesivir versus 10-day course of remdesivir.

We used the tests for interaction to test for differences between subgroup results.

Sensitivity analysis

We performed sensitivity analysis of the following study characteristics for our prioritised outcomes, as described in the Types of outcome measures section.

- Risk of bias assessment components (studies with a low risk of bias or some concerns versus studies with a high risk of bias).
- Comparison of preprints versus peer-reviewed articles.
- Comparison of premature termination of studies with completed studies.

Summary of findings and assessment of the certainty of the evidence

We created Summary of findings 1 and Summary of findings 2 and evaluated the certainty of the evidence using the GRADE approach for interventions evaluated in RCTs.

Summary of findings

We used MAGICapp software to create summary of findings tables (MAGICapp). For time-to-event outcomes, we calculated absolute effects at specific time points, as recommended in the GRADE guidance 27 (Skoetz 2020).

Chapter 14 of the updated *Cochrane Handbook for Systematic Reviews of Interventions* specifies that the "most critical and/or important health outcomes, both desirable and undesirable, limited to seven or fewer outcomes" should be included in the summary of findings table(s) (Schünemann 2021). We included our primary outcomes prioritised according to the Core Outcome Set for intervention studies, COMET 2020, and patient relevance; these are listed below.

Hospitalised individuals with moderate to severe COVID-19

- **All-cause mortality**: all-cause mortality at up to day 28 and longest follow-up available.
- **In-hospital mortality:** in-hospital mortality at up to longest follow-up available.
- **Clinical improvement**: proportion of participants alive and ready to be discharged at up to day 28, up to longest follow-up, and time-to-event. Participants should be discharged without clinical deterioration or death.
- **Clinical worsening**: proportion of participants with new need for invasive mechanical ventilation or deceased within 28 days, up to longest follow-up, and time-to-event.
- **Adverse events** (any grade).
- **Serious adverse events**.

Non-hospitalised individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19

- **All-cause mortality**: all-cause mortality at up to day 28 and longest follow-up available.
- **Clinical improvement**: proportion of participants with symptom resolution (all symptoms resolved) at up to day 14, day 28, up to longest follow-up, and time-to-event.
- **Clinical worsening**: proportion of participants admitted to the hospital or deceased within 14 days, 28 days, up to longest follow-up, and time-to-event.
- **Quality of life**: quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days, up to 28 days, and longest follow-up available.
- **Adverse events** (any grade).
- **Serious adverse events**.

Assessment of the certainty of the evidence

We used the GRADE approach to assess the certainty of the evidence for the outcomes listed above.

The GRADE approach uses five domains (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of the body of evidence for each prioritised outcome.

We downgraded the certainty of the evidence for:

- serious (−1) or very serious (−2) risk of bias;
- serious (−1) or very serious (−2) inconsistency;
- serious (−1) or very serious (−2) uncertainty about directness;
- serious (−1) or very serious (−2) imprecise or sparse data;
- serious (−1) or very serious (−2) probability of reporting bias.

The GRADE system uses the following criteria for assigning grades of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

We followed the current GRADE guidance for these assessments in its entirety as recommended in Chapter 14 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2021).

We used the overall risk of bias judgement, derived from the RoB 2 Excel tool, to inform our decision on downgrading the certainty of the evidence for risk of bias. We phrased the findings and certainty of the evidence as suggested in the informative statement guidance (Santesso 2020).

RESULTS

Description of studies

See Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies tables.

Results of the search

In the primary review (Ansems 2021) we included 42 records (five studies: Beigel 2020; Mahajan 2021; Spinner 2020; Wang 2020; WHO Solidarity Trial Consortium 2022) in our narrative analysis and 41 records (four studies: Beigel 2020; Spinner 2020; Wang 2020; WHO Solidarity Trial Consortium 2022) in our meta-analyses. Two studies were listed as ongoing (NCT04252664; NCT04596839).

We performed update searches on 31 May 2022 and identified 1119 records. After removing duplicates, we screened 302 records based on title and abstract, of which 255 studies did not meet the prespecified inclusion criteria and were excluded. We screened the full texts or, if these were not available, the trial register entries, of the remaining 47 references. Reasons for exclusion at full-text stage are listed in Characteristics of excluded studies. One ongoing study moved to awaiting classification because, although it was registered as completed, there are no data available yet (NCT04596839).

We identified six additional ongoing records (five studies: IRCT20210709051824N1; NCT04351724; NCT04843761; NCT04978259; REDPINE 2022; Characteristics of ongoing studies; Table 2). Overall, we included 60 records (nine studies) in our narrative analyses and 55 records (seven studies) in our meta-analyses. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram (Figure 1).

Figure 1.

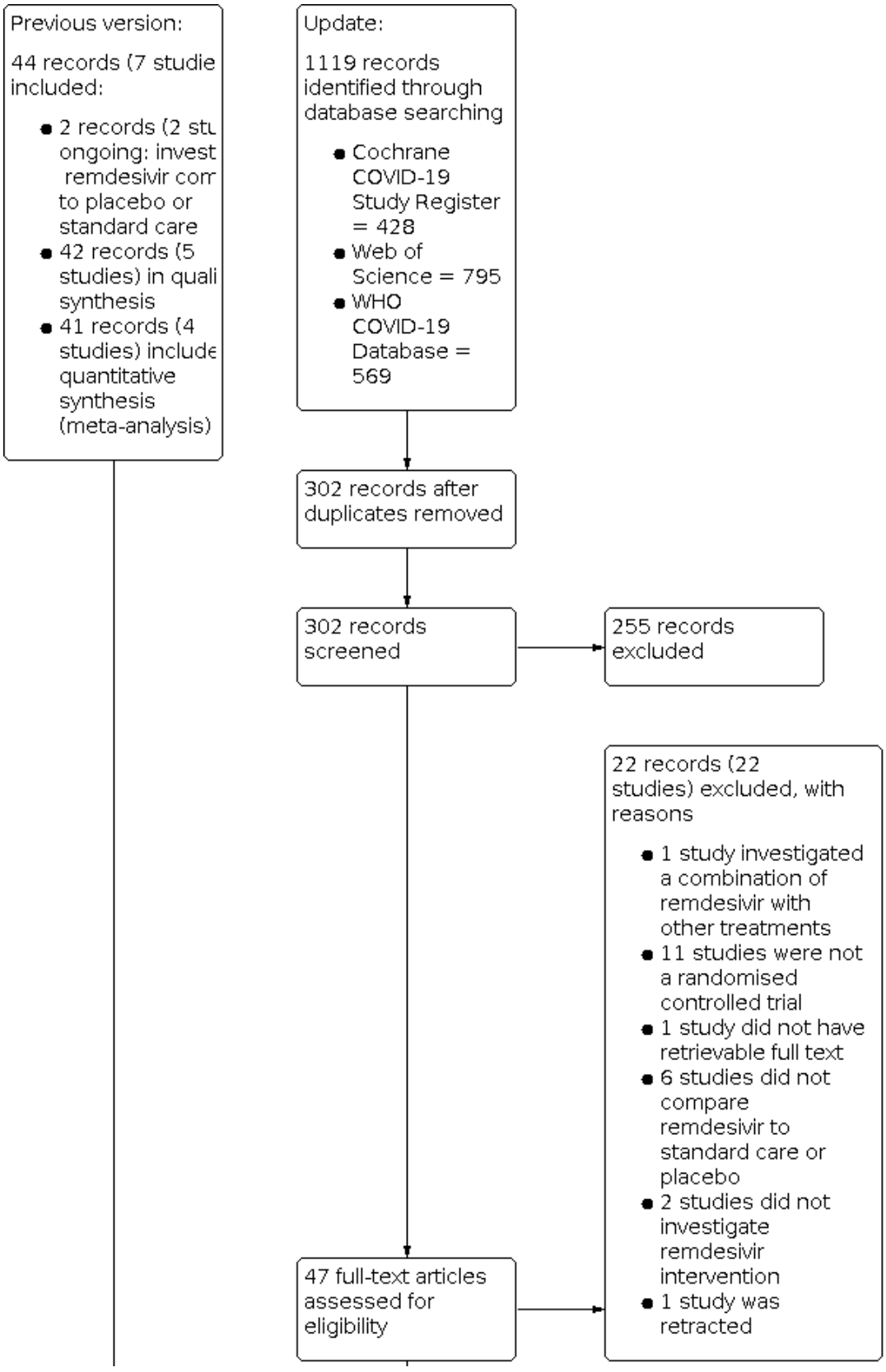
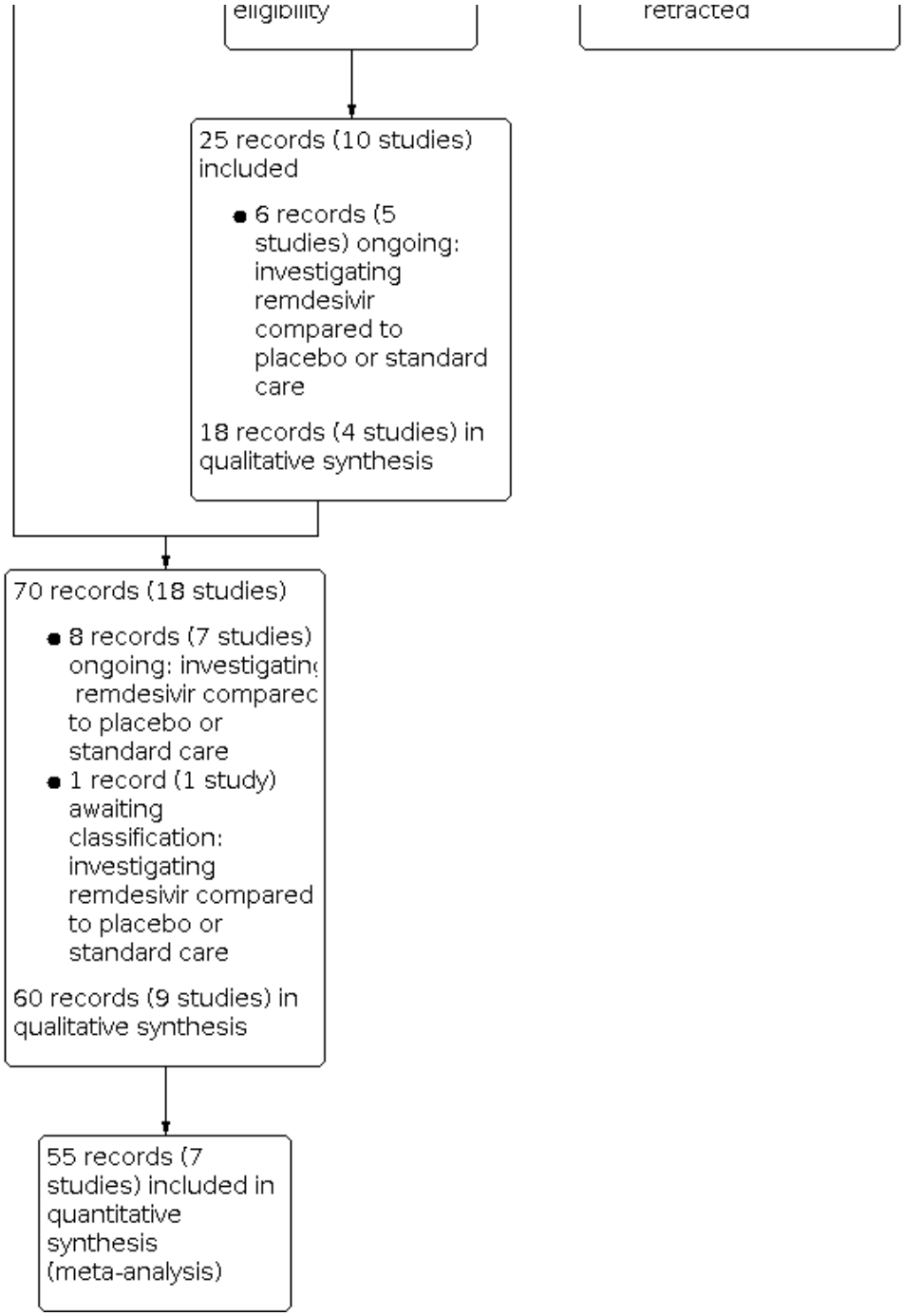


Figure 1. (Continued)



Included studies

We included nine RCTs with 11,218 participants with symptomatic SARS-CoV-2 infection (Beigel 2020; Gottlieb 2021; Mahajan 2021; Spinner 2020; Wang 2020; WHO Solidarity Canada 2022; WHO Solidarity France 2021; WHO Solidarity Norway 2021; WHO Solidarity Trial Consortium 2022). Three studies were national add-on trials to the WHO Solidarity Trial Consortium 2022, of which two recruited additional participants, not reported in the WHO Solidarity trial (WHO Solidarity Canada 2022; WHO Solidarity France 2021). In our meta-analyses we only included participants of the WHO Solidarity Trial Consortium 2022, and its add-on trials, if there was no overlap between participants.

One study was performed in an outpatient setting, including participants with mild SARS-CoV-2 infection (Gottlieb 2021). The other eight studies included hospitalised patients with COVID-19. The included participants in the outpatient setting (mean age 50 years, 52.10% male), as well as the included participants in the hospitalised setting (mean age 60.9 years, 65.0% male) presented with symptomatic SARS-CoV-2 infection and were randomly assigned to receive either remdesivir or placebo in addition to local

standard care. The majority of included studies were conducted in high- and upper-middle-income countries; the only reported lower-middle-income countries were Egypt, Honduras, India, and the Philippines. A detailed overview of the characteristics of included studies is provided in Characteristics of included studies and Table 3.

Study design and control

All included RCTs used a parallel-group design. Six studies had an open-label design with comparison of remdesivir to standard care alone (Mahajan 2021; Spinner 2020; WHO Solidarity Canada 2022; WHO Solidarity France 2021; WHO Solidarity Norway 2021; WHO Solidarity Trial Consortium 2022), whereas three studies were double-blinded and placebo-controlled (Beigel 2020; Gottlieb 2021; Wang 2020).

In one study (Beigel 2020), participants in the control arm received a lyophilised placebo identical in physical appearance to the active lyophilised formulation and containing the same inactive ingredients; alternatively, a normal saline of equal volume was given if there were limitations on matching placebo supplies. Gottlieb 2021 and Wang 2020 were provided with a placebo drug by Gilead Science. Notably, three studies did not provide details on standard care (Gottlieb 2021; Mahajan 2021; Wang 2020). The other studies performed non-specified standard care according to local guidelines (Beigel 2020; Spinner 2020; WHO Solidarity Canada 2022; WHO Solidarity France 2021; WHO Solidarity Norway 2021; WHO Solidarity Trial Consortium 2022).

The WHO Solidarity Trial Consortium 2022 evaluated several possible COVID-19 treatment options. If a participant was allocated to one control group in a study site with more than one study drug available, he or she could have also been allocated to another control arm, creating a partial overlap between control groups.

Intervention

A total of 5982 participants of the included RCTs were randomised to receive remdesivir. The treatment regimen in the interventional arm consisted of standard care plus 200 mg remdesivir intravenously as a loading dose on day 1, followed by 100 mg daily. The majority of included studies applied a 10-day course of remdesivir (Beigel 2020; Spinner 2020; Wang 2020; WHO Solidarity Canada 2022; WHO Solidarity France 2021; WHO Solidarity Norway 2021; WHO Solidarity Trial Consortium 2022). Spinner 2020 (additionally) and Mahajan 2021 (solely) reported outcomes also for a five-day treatment course. The participants in the outpatient study received remdesivir for three days (Gottlieb 2021). Participants in the WHO Solidarity Trial Consortium 2022 were randomly assigned to receive either remdesivir (n = 4169), hydroxychloroquine (n = 956), lopinavir (n = 1414), or interferon beta-1a (n = 2154).

Setting

Five studies were multicentre studies performed in several countries (Beigel 2020 in 73 sites in Denmark, Germany, Greece, Japan, Korea, Mexico, Singapore, Spain, the UK, and the USA; Gottlieb 2021 in 64 centres in the United States, Spain, Denmark, and the United Kingdom; Spinner 2020 in 105 hospitals in Asia, Europe, and the USA; WHO Solidarity Trial Consortium 2022 in 454 hospitals in Albania, Argentina, Austria, Belgium, Brazil, Canada, Colombia, Egypt, Ethiopia, Finland, France, Georgia, Germany, Honduras, India, Indonesia, Iran, Ireland, Israel, Italy, Kuwait, Kenya, Lebanon, Malaysia, Mali, North Macedonia, Norway, Oman, Pakistan, Peru, the Philippines, Portugal, Qatar, Saudi Arabia, South Africa, Spain, Switzerland, and Thailand; WHO Solidarity France 2021 in 48 centres in France, Belgium, Austria, Portugal, and Luxembourg). Three studies were multicentre studies performed in one country (Wang 2020 in 10 centres in China; WHO Solidarity Canada 2022 in 52 Canadian hospitals; WHO Solidarity Norway 2021 in 23 sites in Norway). Mahajan 2021 performed a single-centre study in India.

One study was performed in an outpatient setting (Gottlieb 2021), and eight studies included hospitalised patients with COVID-19 (Beigel 2020; Mahajan 2021; Spinner 2020; Wang 2020; WHO Solidarity Canada 2022; WHO Solidarity France 2021; WHO Solidarity Norway 2021; WHO Solidarity Trial Consortium 2022).

Participants

All studies included individuals with symptomatic SARS-CoV-2 infection. The majority of included participants in the outpatient as well as inpatient setting were middle-aged and male (mean age 50 years, 52.10% male; mean age 60.9 years, 65.0% male). Notably, two studies included adolescents younger than 18 years: Gottlieb 2021 with eight (1.423%) and Spinner 2020 with one (0.171%) of the recruited participants. Frequent comorbidities reported by some RCTs involved obesity, diabetes, and hypertension. Full details on comorbidities are provided in Table 3.

Diagnosis of SARS-CoV-2 infection

Whereas most studies required a positive polymerase chain reaction (PCR) test prior to inclusion, WHO Solidarity Trial Consortium 2022 stated that diagnosis of COVID-19 was made "in the view of the responsible physician; PCR confirmation was not required". Four studies additionally instructed clinical or radiological signs of pneumonia (Beigel 2020; Mahajan 2021; Spinner 2020; Wang 2020). In Gottlieb 2021 and WHO Solidarity France 2021 a SARS-CoV-2 antigen rapid test was considered equal to PCR, as well as other commercial or public health assay in any specimen in WHO Solidarity Canada 2022. Gottlieb 2021 provided details about the proportion of PCR-confirmed SARS-CoV-2 patients at baseline: 215 of 279 participants (77.1%) in the remdesivir group and 213 of 283 participants (75.3%) in the placebo group. Wang 2020 reported "viral positive population" in their supplements: 131 of 158 participants in the remdesivir group (83%) and 65 of 78 participants in the placebo group (83%).

Severity of illness

Severity of disease, interpreted by extent of respiratory support, was reported in different terms and definitions throughout all studies. The PINETREE trial included ambulatory patients without need for oxygen and at least one pre-existing risk factor for progression to severe COVID-19 (Gottlieb 2021). In Beigel 2020, participants were considered to have severe disease if they required mechanical ventilation; if the oxygen saturation as measured by pulse oximetry (SpO2) was 94% or lower whilst they were breathing ambient air; or if they had tachypnoea (respiratory rate ≥ 24 breaths per minute). The majority of participants in this study met the aforementioned criteria and needed supplemental oxygen (intervention 42.9%, control 39.0%), non-invasive ventilation or high-flow oxygen (intervention 17.6%, control 18.8%), or invasive mechanical ventilation or extracorporeal membrane

oxygenation (ECMO) (intervention 24.2%, control 29.6%). Only 13.9% of participants in the intervention arm and 12.1% of participants in the control arm were hospitalised without requiring supplemental oxygen. Mahajan 2021 classified participants in both groups as “highest disease severity”. However, participants were excluded if receiving invasive mechanical ventilation or if having multi-organ failure. The majority (79.4%) of participants in the intervention group versus 72.2% of participants in the control group received low-flow supplemental oxygen, and 20.6% versus 27.8% received non-invasive ventilation or high-flow oxygen, respectively. In Spinner 2020, the majority (84%) of participants in the intervention group versus 80% of participants in the control group did not require supplemental oxygen. Although measured SpO2 at screening was above 94% whilst breathing room air, 13% of participants in the intervention group and 19% in the control group used supplemental oxygen because of deteriorating clinical status or for breathing comfort. Wang 2020 defined severe COVID-19 as SpO2 of 94% or lower on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mmHg or less. The majority of participants in this study needed oxygen supplementation (intervention 82%, control 83%), whilst non-invasive ventilation or high-flow oxygen was necessary in 18% and 12% of participants, respectively. Invasive mechanical ventilation or ECMO was only required in 1% of the control group and none in the intervention group.

Protocol for recruitment was identical for all studies contributing to the WHO Solidarity trial (WHO Solidarity Canada 2022; WHO Solidarity France 2021; WHO Solidarity Norway 2021; WHO Solidarity Trial Consortium 2022). Disease severity was not protocol-defined, and baseline respiratory support was broadly divided into “no supplemental oxygen”, “supplemental oxygen”, and “mechanical ventilation” (including non-invasive and invasive mechanical ventilation). After the Solidarity interim analysis was published in February 2021, recruitment preferentially focused on patients who were not mechanically ventilated. The majority of participants in WHO Solidarity Trial Consortium 2022 received supplemental oxygen (70.4% of the intervention group, 70.7% of the control group), whilst no supplemental oxygen was needed in 21% and 20.9%. The minority of participants received mechanical ventilation at entry: 8.7% and 8.4%, respectively. WHO Solidarity Canada 2022 and WHO Solidarity France 2021 further divided baseline respiratory support. In WHO Solidarity Canada 2022, the majority of participants in the intervention group (52.7%) and the control group (56.2%) received low-flow oxygen at entry, whereas no supplemental oxygen was needed in 11.2% and 8.4% of participants; high-flow oxygen via nasal cannula in 23.5% and 23.7%; non-invasive ventilation in 3.5% and 3.6%; and invasive ventilation in 9.1% and 8.3%, respectively. In WHO Solidarity France 2021, the majority of participants in the intervention group (60%) and the control group (59%) received supplemental oxygen at entry, whereas no supplemental oxygen was needed in 1% and 1%; high-flow nasal cannula in 17% and 18%; non-invasive ventilation in 4% and 4%; invasive mechanical ventilation in 18% and 17%; and ECMO in 0% and < 1%, respectively. In WHO Solidarity Norway 2021, severity of condition at baseline was divided into "admitted to ward" or "admitted to ICU". The majority of participants in the intervention group (92.9%) and control group (98.2%) were admitted to ward compared to participants admitted to ICU: 7.1% and 1.8%, respectively.

Concomitant medications

For an overview of concomitant medications and their distribution between groups, see Table 3.

Gottlieb 2021 did not report concomitant medication, but stated in the protocol the prohibition of combination of "investigational agents for COVID-19 including approved HIV protease inhibitors such as lopinavir/RTV, chloroquine, interferon, etc.; use of hydroxychloroquine or chloroquine within 7 days of randomization; strong inducers of P-glycoprotein (e.g., rifampin or herbal medications)" with remdesivir. Concomitant medication was restricted to heparin and corticosteroids in one study (Mahajan 2021). Wang 2020 reported baseline receipt of lopinavir–ritonavir, interferon, antibiotics, and corticosteroids. Considering that Beigel 2020 was one of the early trials in the pandemic, they solely prohibited "other experimental treatment or off-label use of marketed medications intended as specific treatment for Covid-19". They listed antibiotics, vasopressors, corticosteroids, other anti-inflammatory medications, monoclonal antibodies targeting cytokines, other biological therapies, hydroxychloroquine, and other putative SARS-CoV-2 and antiviral medication, with antibiotics being the most frequently used. In WHO Solidarity Trial Consortium 2022, non-study drugs (corticosteroids, convalescent plasma, anti-interleukin-6 medication, non-trial-interferon, non-trial antiviral) were balanced between groups. Additional therapy with traditional herbs including sho-saiko-to (or Xiao-Shai-Hu-Tang) or investigational agents with putative antiviral activity against COVID-19 was prohibited by protocol for participants receiving remdesivir in one study (Spinner 2020). However, concomitant use of lopinavir-ritonavir, hydroxychloroquine/chloroquine, interferon, steroids, tocilizumab, and azithromycin was reported for all participants, predominantly in the control arm. In WHO Solidarity Canada 2022, the decisions for all other care were left to the treating clinicians, including co-medication, such as dexamethasone or tocilizumab or both for eligible patients, depending on time period, hospital setting, and participation in other RCTs. In WHO Solidarity France 2021, patients received dexamethasone (added to the standard care on 1 October 2020), other immunomodulatory agents (at investigator's discretion), and prophylactic or therapeutic anticoagulation. In WHO Solidarity Norway 2021, the concomitant medication included in addition to systemic steroids (given as standard care for severe and critical COVID-19 from 4 September 2020) and other immunomodulatory drugs, angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers.

Outcomes

Primary outcomes differed between included RCTs. Studies contributing to the WHO Solidarity trial all reported in-hospital mortality up to day 28, as pre-defined by the core protocol. As the time point of measurement was not pre-defined, some additionally reported mortality up to day 60 (WHO Solidarity Canada 2022; WHO Solidarity Norway 2021) and day 150 (WHO Solidarity Trial Consortium 2022). WHO Solidarity France 2021 selected clinical status at day 15 as primary outcome. Within aforementioned studies are cross-references and synonymous use of the term all-cause mortality. WHO Solidarity Trial Consortium 2022 used direct comparison through meta-analyses with other RCTs reporting all-cause mortality, like the ACTT-1 trial (Beigel 2020). The latter prioritised time to recovery, defined as first day on which a

participant was ready to be discharged. Further primary outcomes were: improvement in clinical outcomes (Mahajan 2021); clinical status on day 11 (Spinner 2020); and time to clinical improvement within 28 days (Wang 2020). As the only outpatient trial, Gottlieb 2021 provided a composite of hospitalisation related to COVID-19 (as determined by site investigators, who were unaware of trial-group assignments, and defined as ≥ 24 hours of acute care) or death from any cause by day 28.

Common safety end points included incidence of any adverse event, treatment-emergent adverse events, adverse events grade three or four, and serious adverse events. Specific safety analyses regarded discontinuation of infusion (Beigel 2020; Wang 2020), changes in laboratory values (Beigel 2020; Mahajan 2021; Spinner 2020; Spinner 2020), grade changes in the biological and inflammatory patterns of participants over time (WHO Solidarity France 2021), new hepatic dysfunction, and renal replacement therapy (WHO Solidarity Canada 2022).

Awaiting classification

We classified two randomised controlled trials as 'awaiting classification': one open-label trial, comparing the effects of remdesivir to standard care alone (NCT04596839), and one double-blinded trial, comparing the effects of remdesivir to placebo (REDPINE 2022). Both of them are multicentre studies, performed in hospitalised patients with severe COVID-19 in Bangladesh (NCT04596839), or in 63 study centres in the United States, in the United Kingdom, in Portugal, Brazil, South Africa, and Spain (REDPINE 2022). NCT04596839 is already completed (completion data: 30 April 2021) and recruited 60 participants, according to the information in the study register. Recruitment in REDPINE 2022 was currently terminated after enrolment of 249 from 1116 estimated participants due to "study enrollment feasibility".

Ongoing studies

An overview of the characteristics of ongoing studies is provided in Characteristics of ongoing studies and Table 2. We identified five records of ongoing studies comparing the effects of remdesivir with placebo (IRCT20210709051824N1; NCT04252664; NCT04843761) or standard care alone (NCT04351724; NCT04978259). The majority performed intervention with remdesivir for 10 days. IRCT20210709051824N1 performed an intervention with remdesivir for five days and NCT04351724 for either five or 10 days. All studies were performed among hospitalised patients with COVID-19 and aimed to enrol a total of 1750 participants (IRCT20210709051824N1 n = 100, NCT04252664 n = 308, NCT04351724 n = 500, NCT04843761 n = 640, NCT04978259 n = 202). IRCT20210709051824N1 was expected to be completed on 20 February 2022; the last update of the registry was performed on 11 January 2022. NCT04252664 was discontinued: “The epidemic of COVID-19 has been controlled well at present, no eligible patients can be recruited”. NCT04351724 is a platform trial investigating different interventions with an estimated enrolment of 500 participants in all study arms, without specifying the planned number of enrolments in the remdesivir arm and was expected to be completed in 2022. The last registry update was posted on 2 March 2021. NCT04843761 is active, not recruiting, and was expected to be completed in 2023. NCT04978259 is recruiting, and was expected to be completed in 2023.

Excluded studies

In the primary review (Ansems 2021) we excluded 57 references (57 studies) that did not match our inclusion criteria. In this update we excluded 22 records (22 studies).

- One reference investigated a combination of remdesivir with other treatments.
- 11 studies were not randomised controlled trials.
- One study did not have retrievable full text.
- Six studies did not compare remdesivir to standard care or placebo.
- Two studies did not investigate remdesivir intervention.
- One study, included in the first version of this review, was retracted.

Risk of bias in included studies

We assessed risk of bias for the results within the nine included RCTs (Beigel 2020; Gottlieb 2021; Mahajan 2021; Spinner 2020; Wang 2020; WHO Solidarity Canada 2022; WHO Solidarity France 2021; WHO Solidarity Norway 2021; WHO Solidarity Trial Consortium 2022), using the RoB 2 tool, as recommended in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2022c; Sterne 2019). Outlined below are outcomes according to our updated set (Table 4). The completed RoB 2 tool with responses to all assessed signalling questions is available online at https://doi.org/10.5281/zenodo.5101320.

Remdesivir plus standard care versus standard care (plus/minus placebo)

Individuals with moderate to severe COVID-19

All-cause mortality

Four studies reported this outcome (see Risk of bias table for Analysis 1.1). Overall, we rated the risk of bias for mortality to be low for three studies (Beigel 2020; Spinner 2020; WHO Solidarity Trial Consortium 2022), and as 'some concerns' for one study (Wang 2020). We assessed this outcome on a study level at up to day 28 and as time-to-event, if provided (see Risk of bias table for Analysis 1.4), as well as for our subgroup analyses (see Risk of bias table for Analysis 2.1; Risk of bias table for Analysis 3.1; Risk of bias table for Analysis 4.1; Risk of bias table for Analysis 5.1). For one study, there were some concerns arising from baseline differences in gender distribution, respiratory status, comorbidities, and time from symptom onset, suggesting a possible problem with the block wise and stratified randomisation process (Wang 2020). We did not identify any concerns that could have biased the reported outcome in three studies, and therefore judged the risk of bias to be low (Beigel 2020; Spinner 2020; WHO Solidarity Trial Consortium 2022).

In-hospital mortality

One study reported this outcome for the longest follow-up available, 150 days (see Risk of bias table for Analysis 1.3). We rated the risk of bias for in-hospital mortality as 'some concerns', because outcome measurement and analyses were appropriate but not pre-defined with a risk of selective reporting. This could not be clarified after contacting the authors.

Improvement of clinical status

Four studies reported this outcome (see Risk of bias table for Analysis 1.5). We assessed this outcome by survival of participants, who are ready to be discharged from the hospital at up to day 28 and as time-to-event, if provided (see Risk of bias table for Analysis 1.6). Overall, we rated the risk of bias for clinical improvement to be low for two studies (Spinner 2020; Beigel 2020), and as 'some concerns' for two studies (Wang 2020; WHO Solidarity France 2021). Concerns arose because of baseline differences between groups (Wang 2020), and lack of blinding of participants and assessors, which could have influenced the assessment and caused the small amount of deviations from intended interventions (WHO Solidarity France 2021).

Worsening of clinical status

One study reported this outcome (see Risk of bias table for Analysis 1.7), and two studies reported this outcome as time-to-event (see Risk of bias table for Analysis 1.8). Overall, we rated the risk of bias for clinical worsening as 'some concerns' in one study, providing data for both analyses (WHO Solidarity France 2021). Concerns arose due to lack of blinding of participants and assessors, which could have influenced the assessment and caused the small amount of deviations from intended interventions. One study, providing a hazard ratio over time, was a post hoc analysis of the ACTT-1 trial (Beigel 2020). It therefore had a high risk for selective reporting.

Adverse events (any grade)

Four studies reported this outcome (see Risk of bias table for Analysis 1.9). We identified concerns for risk of bias in all of the contributing studies. Reasons were inappropriate analysis and population selection (Beigel 2020), differences in baseline characteristics (Wang 2020), and the open-label study design in Spinner 2020 and WHO Solidarity France 2021, particularly in the reporting of lower-grade adverse events in participants who were aware of the intervention. We judged missing outcome data as 'some concerns' in all studies due to competing risk of death without evidence, that missing outcome data does not depend on its true value.

Serious adverse events

Four studies reported this outcome (see Risk of bias table for Analysis 1.11) and we judged these as 'some concerns'. The judgement in Beigel 2020 was based on inappropriate analyses and selection of participants, which did not comply with the appropriate safety population. We assessed Wang 2020 as 'some concerns' due to baseline differences between the intervention and control group. For Spinner 2020 and WHO Solidarity France 2021, there was a low risk arising from the awareness of the assigned intervention (open-label), which is unlikely to have affected the outcome measurement. However, we judged missing outcome data as 'some concerns' of bias in all studies due to competing risk of death without evidence, that missing outcome data does depend on its true value.

Individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19

Data solely arose from one trial in the ambulatory setting (Gottlieb 2021). All judgements refer to this study.

All-cause mortality

We judged risk of bias for all-cause mortality to be low (see Risk of bias table for Analysis 6.1). We did not identify any concerns that could have biased the reported outcome.

Improvement of clinical status

We judged risk of bias for clinical improvement to be high (see Risk of bias table for Analysis 6.2). There were a large number of missing values and analyses were not performed as pre-defined by protocol, with a high risk of selective reporting. Additionally, measurement of the outcome had limited validity.

Worsening of clinical status

We judged risk of bias for clinical worsening to be low (see Risk of bias table for Analysis 6.3). We did not identify any concerns that could have biased the reported outcome.

Quality of life

There were no data available for this outcome, thus risk of bias could not be judged.

Adverse events (any grade)

We judged risk of bias for any adverse events to be low (see Risk of bias table for Analysis 6.5). We did not identify any concerns that could have biased the reported outcome.

Serious adverse events

We judged risk of bias for serious adverse events to be low (see Risk of bias table for Analysis 6.4). We did not identify any concerns that could have biased the reported outcome.

Effects of interventions

See: **Summary of findings 1** Remdesivir and standard care versus standard care (plus/minus placebo) for individuals with moderate to severe COVID-19; **Summary of findings 2** Remdesivir and standard care versus standard care (plus/minus placebo) for individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19

See: Summary of findings 1: Remdesivir and standard care versus standard care (plus/minus placebo) for individuals with moderate to severe COVID-19; Summary of findings 2 Remdesivir and standard care versus standard care (plus/minus placebo) for individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19. Adaptions made in our outcome set compared to the first version of this review are outlined in Differences between protocol and review and Table 4.

Remdesivir plus standard care versus standard care (plus/minus placebo)

Individuals with moderate to severe COVID-19

We have presented the summary of findings and the certainty of the evidence for adult in-hospital participants with moderate to severe COVID-19, comparing a 10-day course of remdesivir to placebo or standard care alone.

Primary outcomes

All-cause mortality

We assessed all-cause mortality at up to day 28, day 60 (longest follow-up available), and as time-to-event (secondary outcome).

All-cause mortality at up to day 28

Four studies reported this outcome for 7142 participants (see Analysis 1.1). In the control group an estimated 108 of 1000 participants died up to day 28. Remdesivir probably makes little or no difference to all-cause mortality at up to day 28 (estimated 100 per 1000 participants; 95% confidence interval (CI) 21 fewer to 6 more per 1000) compared to placebo or standard care alone (risk ratio (RR) 0.93, 95% confidence interval (CI) 0.81 to 1.06; 4 studies, 7142 participants; I^2 = 0%; moderate-certainty evidence). Our main reasons for downgrading the certainty of the evidence were serious imprecision because of wide confidence intervals in the studies, and the 95% confidence interval includes both benefits and harms.

All-cause mortality at up to day 60

One study reported this outcome for 1281 participants (see Analysis 1.2). In the control group an estimated 236 of 1000 participants died up to day 60. Remdesivir probably makes little or no difference to all-cause mortality at up to day 60 (estimated 200 per 1000 participants; 95% CI 73 fewer to 12 more per 1000) compared to placebo or standard care alone (RR 0.85, 95% CI 0.69 to 1.05; 1 study, 1281 participants; I^2 = not applicable; moderate-certainty evidence). Our main reasons for downgrading the certainty of the evidence were serious imprecision because the optimal information size was not reached. WHO Solidarity Norway 2021 solely provided the 60-day mortality rate as a percentage: 7.1% (95% CI 1.8 to 17.5) versus 5.3% (95% CI 1.3 to 13.1) for remdesivir and standard care alone; estimated marginal risk difference in percentage points: 1.9 (95% CI -7.8 to 11.6).

In-hospital mortality

We assessed in-hospital mortality at the longest follow-up available, which was 150 days.

In-hospital mortality at up to day 150

One study reported this outcome for 8275 participants (see Analysis 1.3). In the control group an estimated 156 of 1000 participants died in hospital at up to day 150. Remdesivir probably makes little or no difference to in-hospital mortality up to 150 days (estimated 145 per 1000 participants; 95% CI 25 fewer to 5 more per 1000) compared to placebo or standard care alone (RR 0.93, 95% CI 0.84 to 1.03; 1 study, 8275 participants; I^2 = not applicable; moderate-certainty evidence). We downgraded the certainty of the evidence because of serious risk of bias due to selective reporting.

Clinical status

We assessed clinical status at day 28 by improvement of clinical status (participants alive and ready to be discharged) and worsening of clinical status (composite of participants with new need for invasive mechanical ventilation or death). Where available, we assessed time-to-event data for this endpoint. We did not find data for clinical improvement or worsening beyond day 28.

Improvement of clinical status (alive and ready to discharge at up to day 28)

Four studies reported this outcome for 2514 participants (see Analysis 1.5). When treated without remdesivir, 617 per 1000 participants experienced clinical status improvement within 28 days. Remdesivir probably increases the chance of clinical improvement slightly (estimated 685 per 1000 participants; 95% CI 37 more to 105 more per 1000) compared to placebo or standard care alone (RR 1.11, 95% CI 1.06 to 1.17; 4 studies, 2514 participants; I^2 = 0%; moderate-certainty evidence). Our main reasons for downgrading the certainty of the evidence were risk of bias because of lack of blinding and one study was stopped earlier than scheduled.

Two studies reported time-to-event data for this outcome for 1225 participants (see Analysis 1.6). Treatment with remdesivir probably makes little or no difference to the chance of clinical improvement compared to placebo or standard care alone when measured over time (hazard ratio (HR) 1.06, 95% CI 0.93 to 1.20; 2 studies, 1225 participants; I^2 = 0%).

Worsening of clinical status (new need for invasive mechanical ventilation or death at up to day 28)

Two studies reported time-to-event data for this outcome for 1734 participants (see Analysis 1.8). When treated without remdesivir, 544 per 1000 participants experienced clinical status worsening within 28 days. Remdesivir probably decreases the risk of clinical worsening (estimated 409 per 1000 participants; 95% CI 198 fewer to 69 fewer per 1000) compared to placebo or standard care over time (HR 0.67, 95% CI 0.54 to 0.82; 2 studies, 1734 participants; I^2 = 0%; moderate-certainty evidence). Our main reason for downgrading the certainty of the evidence was very serious risk of bias because of lack of blinding and retrospective analyses of RCT data with a high risk for selective reporting. One study reported this composite outcome for 683 participants (see Analysis 1.7): RR 0.70, 95% CI 0.52 to 0.94; risk difference (RD) 76 fewer per 1000, 95% CI 121 fewer to 15 fewer; 1 study, 683 participants; I^2 = not applicable; low-certainty evidence. Our main reasons for downgrading the certainty of the evidence were serious imprecision because the optimal information size was not reached, and serious risk of bias because of lack of blinding. One study reported a composite of progression to mechanical ventilation or death for 7569 participants, but did not differ between non-invasive and invasive ventilation (WHO Solidarity Trial Consortium 2022). Therefore, we could not include these data in the meta-analysis. Progression or death occurred in 744 of 3787 cases (19.6%) in the remdesivir group and 851 of 3782 cases (22.5%) in the control group (rate ratio 0.84, 95% CI 0.75 to 0.93; P value = 0.001; 1 study, 7569 participants; I^2 = not applicable).

Adverse events (any grade at up to day 28)

Four studies reported this outcome for 2498 participants (see Analysis 1.9). In the control group, adverse events of any grade occurred in an estimated 579 per 1000 people. Remdesivir may make little or no difference to the risk of adverse events within 28 days (estimated 602 per 1000 participants; 95% CI 46 fewer to 104 more per 1000) when compared to placebo or standard care alone (RR 1.04, 95% CI 0.92 to 1.18; 4 studies, 2498 participants; I^2 = 68%; low-certainty evidence). Our main reasons for downgrading the certainty of the evidence were serious imprecision because of wide confidence intervals in the studies and/or the 95% confidence

interval includes both benefits and harms and serious risk of bias because of lack of blinding, and one study was stopped earlier than scheduled.

Serious adverse events (at up to day 28)

Four studies reported this outcome for 2498 participants (see Analysis 1.11). In the control group, serious adverse events occurred in an estimated 273 per 1000 people. Remdesivir may make little or no difference to the risk of serious adverse events within 28 days (estimated 229 per 1000 participants; 95% CI 96 fewer to 19 more per 1000) when compared to placebo or standard care alone (RR 0.84, 95% CI 0.65 to 1.07; 4 studies, 2498 participants; I^2 = 59%; low-certainty evidence). Our main reasons for downgrading the certainty of the evidence were serious imprecision because of wide confidence intervals in the studies and/or the 95% confidence interval includes both benefits and harm. We also downgraded for serious risk of bias because of lack of blinding, and one study was stopped earlier than scheduled.

Secondary outcomes

All-cause mortality at up to day 28 (time-to-event)

Two studies reported this outcome for 6513 participants (see Analysis 1.4). Treatment with remdesivir resulted in no difference in mortality when measured over time (HR 0.88, 95% CI 0.67 to 1.16; 2 studies, 6513 participants; I^2 = 57%). One study reported median number of days and interquartile range (IQR) from randomisation to death for 236 participants (Wang 2020): 9.5 days (IQR 6.0 to 18.5) for 158 participants in the remdesivir group and 11.0 days (IQR 7.0 to 18.0) for 78 participants in the control group. A Kaplan-Meier curve was not provided, and a hazard ratio could not be estimated.

Quality of life

We did not find any data for this outcome.

Adverse events, grade 3 to 4

Four studies reported this outcome for 2498 participants (see Analysis 1.10). Considering the reported event rates across studies, we estimated that remdesivir results in 39 fewer participants sustaining at least one adverse event grade 3 to 4 compared to placebo or standard care alone amongst 1000 participants. Treatment with remdesivir probably results in little or no difference in the occurrence of adverse events grade 3 to 4 within 28 days when compared to placebo or standard care alone (RR 0.92, 95% CI 0.84 to 1.01; 4 studies, 2498 participants; I^2 = 0%).

Ventilator-free days

One study reported this outcome for 1281 participants (see Analysis 1.12). We found that remdesivir may increase the number of ventilator-free days compared to placebo or standard care alone (mean difference 1.90, 95% CI 0.61 to 3.19; P value = 0.004; 1 study, 1281 participants; I^2 = not applicable). One study provided median ventilator- or oxygenation-free days at up to day 29 for 832 participants (WHO Solidarity France 2021): 29 days (IQR 20 to 29) versus 29 days (IQR 16 to 29) for remdesivir or standard care alone.

Individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19

We have presented the summary of findings and the certainty of the evidence for adult non-hospitalised participants with mild COVID-19 and at least one risk factor for clinical progression, comparing a three-day course of remdesivir to placebo or standard care alone. We did not identify any studies in individuals with asymptomatic SARS-CoV-2 infection, therefore we have no data on this subgroup to include in the analysis.

Primary outcomes

All-cause mortality

We assessed all-cause mortality at up to day 28. We did not find data for all-cause mortality beyond day 28.

All-cause mortality at up to day 28

One study reported this outcome for 562 participants (see Analysis 6.1). There were no events observed, thus it was not possible to determine whether remdesivir makes a difference to 28-day mortality.

Improvement of clinical status (symptom alleviation up to day 14)

One study reported symptom alleviation (regression or resolution) for 126 participants at up to day 14 (see Analysis 6.2). When treated without remdesivir, an estimated 250 per 1000 participants experience improvement of clinical status within 14 days. We are uncertain whether remdesivir increases or decreases the chance of symptom alleviation by day 14 (estimated 333 per 1000, 95% CI 61 fewer to 289 more) compared to placebo (hazard ratio 1.41, 95% CI 0.73 to 2.69; 1 study, 126 participants; I^2 = not applicable; very low-certainty evidence). Reasons for downgrading were serious risk of bias because of a large amount of missing data and differences between pre-definition and reporting of the outcome, leading to selective reporting and indirectness. Additionally, the outcome measurement was performed with the FLU-PRO plus questionnaire, initially validated for influenza and adapted to SARS-CoV-2 infection. Although performance seems to be good for the evaluation of COVID-19 symptoms (Richard 2021), those seem to differ even between variants of the virus. We downgraded the certainty of the evidence another level because of imprecision due to the wide confidence interval and because the optimal information size was not reached.

Worsening of clinical status (admission to hospital or death within 28 days)

One study reported this outcome for 562 participants (see Analysis 6.3). When treated without remdesivir, an estimated 64 per 1000 participants had to be hospitalised within 28 days. Remdesivir probably decreases clinical worsening by day 28 (estimated 18 per 1000, 95% CI 57 fewer to 16 fewer) compared to placebo (RR 0.28, 95% CI 0.11 to 0.75; 1 study, 562 participants; I^2 = not applicable; moderate-certainty evidence). Our main reasons for downgrading the certainty of the evidence were serious imprecision because of the wide confidence interval and because the optimal information size was not reached.

Quality of life

We did not find any data for this outcome.

Serious adverse events

One study reported this outcome for 562 participants (see Analysis 6.4). In the control group, serious adverse events occurred in an estimated 67 per 1000 people. Remdesivir may decrease the rate of serious adverse events by day 28 (estimated 18 per 1000, 95%

CI 60 fewer to 20 fewer) compared to placebo (RR 0.27, 95% CI 0.10 to 0.70; 1 study, 562 participants; I^2 = not applicable; low-certainty evidence). Our main reasons for downgrading the certainty of the evidence were serious imprecision because of the wide confidence interval and because the optimal information size was not reached, and serious indirectness due to huge overlap with COVID-19 symptoms, already considered in hospitalisation or death.

Adverse events (any grade)

One study reported this outcome for 562 participants (see Analysis 6.5). In the control group, adverse events of any grade occurred in an estimated 463 per 1000 people. Remdesivir probably makes little or no difference to the risk of adverse events by day 29 (estimated 421 per 1000, 95% CI 111 fewer to 46 more) compared to placebo (RR 0.91, 95% CI 0.76 to 1.10; 1 study, 562 participants; I^2 = not applicable; moderate-certainty evidence). Our main reasons for downgrading the certainty of the evidence were serious imprecision because of the wide confidence interval and because the optimal information size was not reached.

Subgroup analyses

We conducted subgroup analyses for prioritised effectiveness outcomes to explore heterogeneity between predefined subgroups. In the first version of this review, we performed analyses solely for 28-day mortality in individuals with moderate to severe disease. With the publication of in-hospital mortality at up to day 150 in the WHO Solidarity trial, additional data for subgroups with different disease severity, based on respiratory support at baseline, became available. The only RCT in non-hospitalised individuals with mild disease available to date did not report any deaths and therefore subgroups depending on severity at baseline could not be determined.

Age of participants

One study reported all-cause mortality at up to day 28 divided by age groups (< 50 years, 50 to 69 years, > 69 years) for 5451 participants (see Analysis 2.1). There were no subgroup differences (Chi^2= 0.10, df = 2, P = 0.95, I^2 not applicable).

Pre-existing conditions

Protocol-specified comorbidities included diabetes, respiratory disease, hypertension, immunosuppression, obesity, and cardiac injury. One study reported all-cause mortality at up to day 28 subdivided by pre-existing conditions of interest (WHO Solidarity Trial Consortium 2022, interim results). They compared the effect of remdesivir in one specific subgroup (e.g. with asthma) to a control without that condition (e.g. without asthma). However, since there is a partial overlap of comorbidities between subgroups, control groups might therefore involve participants with other pre-existing conditions of interest.

Timing of first dose administration with illness onset

One study reported all-cause mortality at up to day 28 divided by timing of first dose administration with illness onset for 233 participants (see Analysis 3.1). There were no relevant subgroup differences (Chi^2= 0.74, df = 1, P = 0.39, I^2 not applicable).

Severity of condition

Three studies reported all-cause mortality by day 28 subdivided by respiratory support at baseline for 3194 participants (see Analysis 4.1). The evidence suggests a benefit for remdesivir compared to placebo or standard care alone only in the subgroup with low-flow oxygen at baseline (RR 0.32, 95% CI 0.15 to 0.66; 1 study, 435 participants; I^2 not applicable). The test for subgroup differences suggests relevant subgroup differences and reveals high heterogeneity: Chi^2 = 8.32, df = 2, P = 0.02, I^2 = 75.7%.

One study reported in-hospital mortality within 150 days subdivided by respiratory support at baseline for 8275 participants (see Analysis 4.2). The evidence does not show a relevant subgroup difference: Chi^2 = 4.02, df = 2, P = 0.13, I^2 = 50%. Compared to 28-day mortality, there are no data reported for the subgroup with low-flow oxygen only.

Duration of remdesivir application

We compared a five-day course of remdesivir to a 10-day course for this subgroup. One study reported all-cause mortality at up to day 28 subdivided by duration of remdesivir application for 584 participants (see Analysis 5.1). There were no subgroup differences (Chi^2= 0.09, df = 1, P = 0.09, I^2 not applicable).

Sensitivity analysis

None of the analyses had an I^2 above 80%, therefore we did not perform sensitivity analyses. Highest detected heterogeneity was 68% and 59% for adverse events of any grades and serious adverse events in the hospitalised population, respectively. For the analysis of any adverse events, heterogeneity might be caused by the divergent effects in Beigel 2020 and Spinner 2020. Whereas Beigel 2020 (placebo-controlled, double-blinded) reported fewer events in the control group, Spinner 2020 (open-label) reported fewer events in the remdesivir group. For the analysis of serious adverse events, heterogeneity might be caused by the opposing effect of WHO Solidarity France 2021 (open-label), which reported fewer events in the control group, whereas the other studies included reported fewer events in the remdesivir group.

DISCUSSION

Summary of main results

The aim of this review was to assess the effects of remdesivir and standard care compared to standard care plus/minus placebo on clinical outcomes in patients treated for SARS-CoV-2 infection. This is the first update of the initial systematic review (Ansems 2021). We included nine RCTs with 11,218 participants diagnosed with SARS-CoV-2 infection, of whom 5982 were randomised to receive remdesivir. We classified two studies as "awaiting classification": one completed study with 60 participants and one study that was terminated early after enrolment of 249 from 1116 planed participants due to study enrolment feasibility. Furthermore, we identified five ongoing studies, one of which was suspended (recruitment was not possible due to infection incidences).

Remdesivir plus standard care versus standard care (plus/minus placebo)

Hospitalised individuals with moderate to severe COVID-19

Remdesivir probably makes little or no difference to all-cause mortality at up to day 28 (RR 0.93, 95% CI 0.81 to 1.06; moderate-

certainty evidence). This assertion remains unchanged since the first version of the review: no additional data could be included. However, the Canadian WHO Solidarity add-on trial provided follow-up data at up to day 60, which supports the assumption that remdesivir probably makes little to no difference to all-cause mortality (RR 0.85, 95% CI 0.69 to 1.05; moderate-certainty evidence). With the publication of the final results from the WHO Solidarity trial, data on in-hospital mortality at up to day 150 for 8257 participants became available: RR 0.93, 95% CI 0.84 to 1.03; moderate-certainty evidence. Overall, having evaluated five RCTs with 11,247 participants, we assume, with moderate certainty, that remdesivir has no beneficial effect on survival.

In the first version of this review we had difficulties assessing the effect of remdesivir on clinical improvement or deterioration due to differing endpoint definitions and competing risk of death. After deciding on more comprehensive surrogate parameters for the clinical course of COVID-19, we evaluated data from four RCTs and 2514 participants. We found that remdesivir probably increases the chance of clinical improvement slightly with an estimated 685 per 1000 participants compared to 617 per 1000 treated with placebo or standard care alone (RR 1.11, 95% CI 1.06 to 1.17; moderate-certainty evidence). Data on improvement over time were limited and less conclusive (HR 1.06, 95% CI 0.93 to 1.20). Only one study reported data for the composite of new invasive mechanical ventilation or death, with a reduced risk of clinical worsening after remdesivir application (RR 0.70, 95% CI 0.52 to 0.94; low-certainty evidence). Time-to-event data in more than double the population (1734 versus 683 participants) supports the favouring direction towards remdesivir with an estimated 409 versus 544 per 1000 participants experiencing clinical worsening (HR 0.67, 95% CI 0.54 to 0.82, low-certainty evidence). However, the certainty of the evidence was only low due to imprecision and risk of bias. Overall, remdesivir may be beneficial in the clinical course of COVID-19, but certainty of the evidence remains low to moderate.

In the first version of this review we identified subgroup differences for all-cause mortality at up to day 28 in the subgroup analysis for severity of condition, although with high heterogeneity ($Chi^2 = 8.32$, df = 2, P = 0.02, $I^2 = 75.7\%$). The evidence suggested a benefit for remdesivir compared to placebo or standard care alone only in the subgroup with low-flow oxygen at baseline (RR 0.32, 95% CI 0.15 to 0.66; 1 study, 435 participants). However, these findings were based on data from one study only that reported the outcome based on differentiated respiratory support at baseline (Beigel 2020). Data for this subgroup and outcome were not provided by any other matching study. However, WHO Solidarity Trial Consortium 2022 reported in-hospital mortality at up to day 150 subdivided by respiratory support at baseline. Although each cohort was relevantly larger than the available groups for 28-day mortality, longer-term data could not reproduce the finding of Beigel 2020 in the subgroup with low-flow or high-flow oxygen at baseline (RR 0.9, 95% CI 0.79 to 1.01; 1 study, 5839 participants). Comparison however is impeded, because the subgroups are less differentiated than preferable. The tendency towards a favouring effect for remdesivir in the subgroup with less severe respiratory impairment can still not be safely interpreted due to missing evidence. We detected no differences for mortality at up to day 28 in further participant subgroups relevant for daily clinical routine, namely age, timing of first remdesivir dose, and duration of remdesivir application.

We included results from one additional RCT to assess the adverse effects profile of remdesivir compared to placebo or standard care alone (2498 participants, four studies). Remdesivir may make little or no difference to the incidence of serious adverse events (RR 0.84, 95% CI 0.65 to 1.07, low-certainty evidence), or any adverse events (RR 1.04, 95% CI 0.92 to 1.18; low-certainty evidence). The assumption that remdesivir does not appear to cause more adverse events than standard care alone remains the same as in the first version of this review, but the certainty of the evidence had to be adapted due to risk of bias.

Non-hospitalised individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19

Since the first version of this review, the PINETREE trial published data on the outpatient use of remdesivir in non-hospitalised patients with mild COVID-19 (Gottlieb 2021). Since in terms of baseline disease severity, clinical course, and duration of the treatment (3 days versus 10 days) this population differs relevantly from the hospitalised population, we analysed the data separately. To date, this is the only RCT in the outpatient setting of our knowledge. All data analysed derived from this one study with 562 participants. All the participants were symptomatic and had at least one risk factor for disease progression. None of the participants died within the study period of 28 days, but remdesivir probably decreased the rate of hospitalisation by an estimated 18 versus 64 per 1000 participants (RR 0.28, 95% CI 0.11 to 0.75, moderate-certainty evidence). Clinical improvement in terms of symptom resolution remains uncertain due to lack of data. Remdesivir may decrease the incidence of serious adverse events by an estimated 18 versus 67 per 1000 participants (RR 0.27, 95% CI 0.10 to 0.70; low-certainty evidence) and makes little to no difference to the risk of adverse events of any grade (RR 0.91, 95% CI 0.76 to 1.10; moderate-certainty evidence) by day 28. Quality of life was not assessed.

Overall completeness and applicability of evidence

We identified nine RCTs, mainly from high- and upper-middle-income countries, investigating the therapeutic effects of remdesivir compared to placebo or standard care alone in a total of 11,218 hospitalised and non-hospitalised adults with SARS-CoV-2 infection. The diagnosis of SARS-CoV-2 infection was confirmed by polymerase chain reaction (PCR) or antigen test and, in some studies, radiological signs of COVID-19 pneumonia. The largest of the included studies stated that diagnosis of COVID-19 was made "in the view of the responsible physician"; PCR confirmation was not required (WHO Solidarity Trial Consortium 2022). The proportion of PCR-negative participants at baseline was reported in two studies (Gottlieb 2021; Wang 2020). The majority of participants received other experimental or standardised COVID-19 treatment options, such as corticosteroids, antimicrobials, hydroxychloroquine, convalescent plasma, or combinations of these treatments. All trials were conducted between February 2020 and April 2021, before the emergence of the B.1.617.2 (Delta) and B.1.1.529 (Omicron) variant. They also preceded widespread vaccination or vaccinated participants were specifically excluded (Gottlieb 2021; WHO Solidarity France 2021). There is a general underrepresentation of female participants in COVID-related treatment studies. As suggested by the investigation of de Vries 2022 this is due to the higher proportion of men affected by severe illness in the early stage of the pandemic than structural underrepresentation.

Eight of the included studies involved hospitalised, moderately, or severely ill people with SARS-CoV-2 infection, or both, and compared the effect of a 10-day course of remdesivir additional to standard care (10,876 evaluated participants) to placebo (1198 evaluated participants) or standard care alone (9678 evaluated participants). To evaluate the effects of remdesivir through meta-analysis, we included data from seven RCTs (10,706 evaluated participants). One of the participants was adolescent between 12 and 18 years old. The analysis of safety outcomes (serious adverse events, adverse events) was affected by a relevant lack of data. Since the largest study did not report safety data (WHO Solidarity Trial Consortium 2022), we could only include data for 2498 participants from four RCTs in our analysis. One study involved non-hospitalised symptomatic participants with SARS-CoV-2 infection and at least one risk factor for disease progression. They compared a three-day course of remdesivir to placebo (both in addition to standard care) in 562 participants. Eight of the participants were adolescents between 12 and 18 years old. Different scales and definitions for disease severity and progression were used amongst studies. For hospitalised patients with moderate to severe COVID-19, the need for respiratory support essentially determines their course within the hospital (e.g. ICU admission). We therefore analysed respiratory support at baseline and during the observational period as a surrogate for COVID-19 disease severity. The combination of low- and high-flow oxygen as well as non-invasive and invasive mechanical ventilation in the WHO Solidarity trial unfortunately impeded pairing with data from other studies.

Since the first version of this review no additional data on 28-day mortality became available through randomised controlled studies. Add-on trials, published by participating sites of the multinational WHO Solidarity trial, provided further information but meta-analysis was partially limited due to overlap in the participant cohort with the main investigation. With the publication of their final results, WHO Solidarity Trial Consortium 2022 provided the largest analysed collective (8275 evaluated participants) with a follow-up of 150 days. It supports our former conclusion, that remdesivir may not have an effect on mortality in hospitalised patients with COVID-19. In addition, analyses of mortality in subgroups with respect to disease severity display a tendency towards a beneficial effect of remdesivir in patients with less extensive oxygen support. However, the decreased mortality in patients with low-flow oxygen support shown by Beigel 2020 has yet not been replicated.

For non-hospitalised individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19, mortality appears to be insufficient to evaluate the efficacy of remdesivir treatment, because it is expected to be very low in a subgroup of less severely ill patients. We rate the composite endpoint of admission to hospital or death as quite crucial for this specific subgroup, since clinical deterioration essentially determines the person's health-related quality of life, functional independence, and autonomy. The according data, published by Gottlieb 2021, suggest a beneficial effect of remdesivir in addition to standard care. This finding is supported indirectly by our analyses of clinical course in the hospitalised setting with moderate to severe illness. However, it is to be noted that both collectives (non-hospitalised and hospitalised) differ significantly in the extent of additional standard care, remdesivir treatment length (three versus 10 days), and prognosis. Since we did not identify any studies on individuals with asymptomatic SARS-CoV-2 infection, we have no data on this subgroup. Therefore, further investigations, especially in patients with asymptomatic SARS-CoV-2 infection or mild COVID-19 in the non-hospitalised setting, are needed.

Although we contacted all study authors, especially with regard to detailed description of the extent of respiratory support (e.g. low- versus high-flow oxygen, non-invasive versus invasive mechanical ventilation), there remained differences in reporting severity of illness and incomplete data sets, resulting in a relevant obstacle to the planned subgroup analysis. Hence, due to incompleteness of the data, uncertainty remains regarding a possible benefit of remdesivir treatment for COVID-19 patients receiving low-flow oxygen support only.

The applicability of our results to the current medical care for COVID-19 patients is limited by the large proportion of unvaccinated participants exposed to early variants of SARS-CoV-2 in the RCTs contributing to this version of the review. The a priori risk for progression to severe disease (e.g. hospitalisation and respiratory support) has markedly decreased since the early stages of the pandemic and risk factors have changed, now essentially including insufficient immune responses to vaccination. It is difficult to establish how our findings apply to current practice due to these features of the evidence base. Hence, our conclusions account for the outlined population that has been studied in available previous RCTs and this must be carefully considered when translated into current clinical practice for treating COVID-19 patients. Future RCTs in selected populations bearing a high risk of a severe course of COVID-19 (e.g. immunodeficient patients with insufficient vaccination responses) infected with current variants of SARS-CoV-2 could provide further insight into the question of how virus variants and vaccination response status affect our conclusions.

Certainty of the evidence

We included data from seven RCTs in our meta-analyses to assess the effects of remdesivir for hospitalised individuals with moderate to severe COVID-19 and one RCT for non-hospitalised individuals with mild disease. We evaluated the certainty of the evidence using the GRADE approach, with any downgrading substantiated (see Summary of findings 1; Summary of findings 2). The evidence for efficacy and safety outcomes was of moderate to very low certainty.

Individuals with moderate to severe COVID-19

All-cause mortality (at up to day 28 and 60)

We downgraded to moderate certainty of evidence for serious imprecision due to wide 95% confidence intervals that include both benefits and harms and for serious imprecision because data for 60-day mortality did not reach the optimal information size, respectively.

In-hospital mortality (at up to day 150)

We downgraded to moderate certainty of evidence for serious risk of bias because of selective reporting.

Clinical improvement: alive and ready for discharge (at up to day 28)

We downgraded to moderate certainty of evidence due to serious risk of bias because of inadequate blinding of participants, personnel, and outcome assessors.

Clinical worsening: time to new need for invasive mechanical ventilation or death (at up to day 28)

We downgraded to moderate certainty of evidence for serious risk of bias because of lack of blinding of participants, personnel, and outcome assessors.

Serious adverse events

We downgraded to low certainty of evidence for serious imprecision due to wide 95% confidence intervals that include both benefits and harms, and for risk of bias because of lack of blinding and because one study was stopped earlier than scheduled.

Adverse events (any grade)

We downgraded to low certainty of evidence because of serious imprecision due to wide 95% confidence intervals that included both benefits and harms, and risk of bias because of lack of blinding and because one study was stopped earlier than scheduled.

Individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19

All-cause mortality

There were no deaths reported within 28 days of the study period.

Clinical improvement: symptom alleviation (at up to day 14)

We downgraded to very low certainty of evidence because of serious risk of bias due to missing values and selective reporting, and serious imprecision due to the wide confidence interval, including both benefit and harm. Additionally, we downgraded for serious indirectness due to differences in pre-defined outcome and measurement, as well as use of an adapted questionnaire.

Clinical worsening: admission to hospital or death (at up to day 28)

We downgraded to moderate certainty of evidence for serious imprecision because of the wide confidence interval and because the optimal information size was not reached.

Serious adverse events

We downgraded to low certainty of evidence for serious imprecision because of the wide confidence interval, and because the optimal information size was not met. We also downgraded for indirectness because there was a relevant overlap of COVID-19 symptoms, which were already considered in hospitalisation or death.

Adverse events (any grade)

We downgraded to moderate certainty of evidence because of serious imprecision due to the wide confidence interval, and because the optimal information size was not met.

Potential biases in the review process

Experienced medical information specialists of the CEOsys consortium developed an all-encompassing search strategy to identify the available evidence to answer our research question. We aimed to identify all completed, but also ongoing, studies for inclusion in this review. The sensitive search included relevant electronic databases as well as clinical trial registries. As a supplementary search, we screened reference lists of included studies. Where data were missing, we contacted study authors; for details, see Characteristics of included studies. An overview of included studies is provided in Table 3. We are confident that we have identified all relevant studies, and we will monitor ongoing studies as well as full publication of preprints closely after the publication of this review.

Differences to review protocol and first version

For a detailed description of differences see the Differences between protocol and review section. A prespecified protocol is available at an international prospective register of systematic reviews (CRD42021238065). As a major difference to the protocol, we initially planned a living approach for this review in the light of the uncertainties that came with the early phase of the pandemic. With emerging knowledge of treatment options on the one side and fast development of virus variants with altering demands on the other side, we regard a re-evaluation of future updates based on necessity as more fitting. In contrast to our predefined inclusion criteria (adult participants), we did not exclude the studies Spinner 2020 and Gottlieb 2021, which involved adolescent participants between 12 and 18 years. Since only 0.18% and 1.42% of participants were under the age of 18, respectively, we presumed them to have a non-relevant impact on our results.

We adapted our main outcome set in the first version and in the update according to current knowledge and patient-oriented relevance (see Table 4). In this update this mainly concerns the modification of clinical course parameters. Since the initial review we agreed on condensed surrogates for either improvement or worsening in clinical status. This allows for a more precise conclusion but also bears the risk of underestimating other aspects of clinical course. Definition of disease severity is no longer linked to classification by the WHO but remains coupled with impairment and respiratory support. As a major difference between the first version and the update, we now include non-hospitalised individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19. This was based on newly published data on a possible benefit for early (ambulatory) admission of remdesivir. Any change of methodology was done before analysis. We identified no other potential sources of bias in our review process.

Agreements and disagreements with other studies or reviews

The results we found do not decisively differ from those of other systematic reviews (Al-Abdouh 2021; Angamo 2022; Tanni 2022; Vegivinti 2022) or living guidelines (Kaka 2022). Kaka 2022 published the fifth and final update of its living review in May 2022, with almost identical inclusion of RCTs and methodology (Beigel 2020; Spinner 2020; Wang 2020; WHO Solidarity France 2021; WHO Solidarity Norway 2021; WHO Solidarity Trial Consortium 2022 (interim results)). Comparable to our finding, they identified no relevant effect on mortality, but a moderate increase in improvement parameters and a small reduction in serious adverse events. Whereas they reported a small reduction in the proportion of participants receiving ventilation or ECMO from day 11 to 15, there was little to no difference in the need for new need for

ventilation or ECMO from 28 days to six months. They found no benefit of a 10-day course of remdesivir treatment, when compared to a five-day course. Lee 2022 also solely included RCTs that evaluated the efficacy and safety of remdesivir compared to placebo or standard care alone. They used an approach of a priori probability with restricted maximum likelihood estimates and highlighted the increased probability that remdesivir reduces mortality by ≥ 1% in the subgroups without supplemental oxygen and non-ventilated participants requiring oxygen. Analogically, the latest review with RCT meta-analysis published in June 2022 by Beckermann 2022 emphasises the benefit of remdesivir for clinical outcomes in the subgroup of low-flow oxygen support. It is noteworthy that the review used a targeted literature search and was funded by Gilead Science. One systematic review focused on the safety analysis and reported no or little difference in acute kidney injury and cognitive dysfunction by analysis of Beigel 2020 and Wang 2020 (Izcovich 2022).

In contrast to our review, some cited reviews did not exclusively include RCTs with a placebo or standard care control arm, but also observational cohort studies and case studies (Angamo 2022; Tanni 2022; Thiruchelvam 2022). One of them judged the current data to be insufficient for recommended usage due to high heterogeneity (Thiruchelvam 2022). None of the other reviews included the final results of the WHO Solidarity Trial Consortium 2022, due to its publication in May 2022. Our review excluded the publication Goldman 2020, which compared clinically used dosing schemes of remdesivir, but had no placebo or standard of care arm. The synthetic interpretation of the results of the aforementioned reviews and guidelines is difficult due to different methodological approaches, the type of subgroup formation, and the partial inclusion of non-RCTs. However, we found no major differences from our conclusions in the cited reviews.

AUTHORS' CONCLUSIONS

Implications for practice

Individuals with moderate to severe COVID-19

The finding of the first version of this review, that remdesivir probably has little or no effect on all-cause mortality at up to 28 days, remains unaltered due to lack of supplementary data. Additional data on longer-term mortality up to 150 days supports this finding. Subgroup analyses by initial disease severity (characterised by the level of respiratory support at the start of treatment) led to contradictory results. Hence, the important clinical question, whether the effect of remdesivir treatment on mortality varies according to disease severity, remains unanswered. In contrast to the lack of effectiveness in terms of mortality, there is low- to moderate-certainty evidence that remdesivir treatment has a beneficial effect on clinical course in terms of a reduction in the necessity for invasive ventilation, while slightly increasing the chance of the patient reaching a clinical state of being ready for discharge. In terms of safety, including the new data set, we conclude that remdesivir may not make a relevant difference to the incidence of serious adverse events or any adverse events. However, clinicians have to keep in mind that for the majority of participants included in this review, there were insufficient high-quality data on safety available due to the specific characteristics of the platform trial included.

Individuals with mild COVID-19

Only one study provided data for non-hospitalised, symptomatic individuals at risk for progression at an observational period of 28 days. There were no deaths reported, but remdesivir probably decreases the rate of hospitalisation. Due to incompleteness of data on symptom alleviation we are uncertain whether remdesivir increases or decreases the chance of clinical improvement. Safety analyses show a decreased rate of serious adverse events and no relevant difference in the incidence of any adverse events.

Considering that all previous RCTs did not include vaccinated people and were conducted before the emergence of the Delta and Omicron variants of SARS-CoV-2, the applicability of their results to current clinical practice is limited and needs to be re-evaluated if commensurate evidence becomes available.

Implications for research

In this update of a systematic review on remdesivir in individuals with SARS-CoV-2 infection of varying degrees of severity - from asymptomatic infection through mild to severe disease - we included data from nine randomised controlled trials. Only one of them was performed in non-hospitalised individuals with mild COVID-19, hence the application of remdesivir in the earliest stage of disease. However, there are no data on the treatment of asymptomatic patients with SARS-CoV-2 infection and the risk of clinical deterioration. Treatment duration was three days in the outpatient setting versus five or 10 days in the hospitalised setting. Furthermore, different scales of disease severity were applied to characterise subgroups, and safety data reporting was incomplete. These aspects lower the certainty of the evidence and make it difficult to draw valid conclusions for important clinical questions during an ongoing pandemic. In particular, differences in the potential benefits or harms of remdesivir for the treatment of COVID-19 depending on disease severity could not be analysed sufficiently.

Additional data on the efficacy and safety of remdesivir for different population subgroups (e.g. depending on age, severity of disease, vaccination or immunological status, or treatment duration), for current virus variants, for the timing of application of remdesivir in the course of the infection, and for the establishment of core outcomes for COVID-19 research, may allow us to reduce the uncertainty around the potentially beneficial or harmful effects of remdesivir in future updates of this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Beigel 2020

Study characteristics

Methods

- Trial design: parallel assigned, RCT, double-blind, placebo-controlled
- Type of publication: journal publication
- Setting: inpatient
- Recruitment dates: from 21 February 2020 to 19 April 2020
- Country: the USA (45 sites), Denmark (8 sites), the UK (5 sites), Greece (4 sites), Germany (3 sites), Korea (2 sites), Mexico (2 sites), Spain (2 sites), Japan (1 site), and Singapore (1 site)
- Language: English
- Number of centres: 60 trial sites and 13 sub-sites
- Trial registration number: NCT04280705 (ClinicalTrials.gov)
- Date of trial registration: 21 February 2020

Participants

Baseline characteristics

- Age (years, mean (SD)): intervention group 58.6 (14.6), control group 59.2 (15.4)
- Gender (male, n (%)): intervention group 352 (65.1), control group 332 (63.7)
- Race or ethnic group, intervention group vs control group (n (%)): American Indian or Alaska Native 4 (0.7) vs 3 (0.6); Asian 79 (14.6) vs 56 (10.7); black or African-American 109 (20.1) vs 117 (22.5); white 279 (51.6) vs 287 (55.1); Hispanic or Latino 134 (24.8) vs 116 (22.3)
- Number of participants (recruited/allocated/evaluated): 1114/1062/1062:
  - Remdesivir: intention-to-treat population 541; as-treated population 532
  - Control: intention-to-treat population 521; as-treated population 516
- Severity of condition according to the level of respiratory support (intervention group vs control group, (n (%))):
  - hospitalised not requiring supplemental oxygen: 75 (13.9) vs 63 (12.1)
  - hospitalised requiring supplemental oxygen: 232 (42.9) vs 203 (39.0)
  - hospitalised requiring high-flow nasal cannula or non-invasive mechanical ventilation: 95 (17.6) vs 98 (18.8)
  - hospitalised requiring extracorporeal membrane oxygenation or invasive mechanical ventilation: 131 (24.2) vs 154 (29.6)
  - baseline score missing: 8 (1.5) vs 3 (0.6)
- Comorbidities (intervention group vs control group (n/N (%))):
  - Type 2 diabetes 164/532 (30.8) vs 158/519 (30.4)
  - Hypertension 269/532 (50.6) vs 264/519 (50.9)
  - Obesity 242/531 (45.6) vs 234/518 (45.2)

Inclusion criteria:

- Admitted to a hospital with symptoms suggestive of COVID-19 infection

Beigel 2020 *(Continued)*

- Participant (or legally authorised representative) provides informed consent prior to initiation of any study procedures
- Participant (or legally authorised representative) understands and agrees to comply with planned study procedures
- Male or non-pregnant female adult ≥ 18 years of age at time of enrolment
- Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR or other commercial or public health assay in any specimen, as documented by either or the following:
  - PCR positive in sample collected < 72 hours prior to randomisation;
  - PCR positive in sample collected ≥ 72 hours prior to randomisation, documented inability to obtain a repeat sample (e.g. due to lack of testing supplies, limited testing capacity, results taking > 24 hours, etc.) and progressive disease suggestive of ongoing SARS-CoV-2 infection.

Illness of any duration, and at least 1 of the following:

- radiographic infiltrates by imaging (chest x-ray, CT scan, etc.);
- SpO_2 ≤ 94% on room air;
- requiring supplemental oxygen;
- requiring mechanical ventilation;
- women of childbearing potential must agree to either abstinence or use at least 1 primary form of contraception not including hormonal contraception from the time of screening through day 29;
- agrees to not participate in another clinical trial for the treatment of COVID-19 or SARS-CoV-2 through day 29.

Exclusion criteria:

- ALT or AST > 5 times the upper limit of normal
- eGFR < 30 mL/min (including individuals receiving haemodialysis or haemofiltration)
- Pregnancy or breastfeeding
- Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours
- Allergy to any study medication

Previous treatments: lopinavir/ritonavir (Kaletra)

Interventions

- Treatment details of intervention group:
  - Remdesivir 200 mg intravenously as a loading dose on day 1, followed by a 100 mg maintenance dose administered daily on days 2 through 10 or until hospital discharge or death
- Treatment details of control group:
  - The supplied placebo lyophilised formulation is identical in physical appearance to the active lyophilised formulation and contains the same inactive ingredients. Alternatively, a placebo of normal saline of equal volume may be given if there are limitations on matching placebo supplies.
- Concomitant therapy:
  - Supportive care according to the standard care for the trial site hospital
  - If a hospital had a written policy or guideline for use of other treatments for COVID-19, participants could receive those treatments
- Treatment cross-overs: yes. After the data and safety monitoring board recommended that the preliminary primary analysis report be provided to the sponsor, data on a total of 51 participants (4.8% of the total study enrolment; 16 (3.0%) in the remdesivir group and 35 (6.7%) in the placebo group) were unblinded; 26 (74.3%) of those in the placebo group whose data were unblinded were given remdesivir. Sensitivity analyses evaluating the unblinding (participants whose treatment assignments were unblinded had their data censored at the time of unblinding) and cross-over (participants in the placebo group treated with remdesivir had their data censored at the initiation of remdesivir treatment) produced results similar to those of the primary analysis.
- Duration of follow-up: day 29
- Compliance with assigned treatment: yes

Beigel 2020 *(Continued)*

Outcomes	**Primary study outcome:** time to recovery: the day of recovery was defined as the first day on which the participant satisfies 1 of the following 3 categories from the ordinal scale:
	1. hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care;
	2. not hospitalised, limitation on activities and/or requiring home oxygen;
	3. not hospitalised, no limitations on activities.
	Review outcomes
	Primary outcomes
	• All-cause mortality at day 28, day 60, and at hospital discharge: reported
	• Clinical status at day 28, day 60, and up to longest follow-up, including:
	  ○ improvement of clinical status; i.e. participants discharged alive. Participants should be discharged without clinical deterioration or death: NR
	  ○ worsening of clinical status; i.e. participants with clinical deterioration, defined as new need for invasive mechanical ventilation or death: reported
	• Adverse events (any grade) during the study period, defined as number of participants with any event: reported
	• Serious adverse events during the study period, defined as number of participants with any event: reported
	Secondary outcomes
	• All-cause mortality, time-to-event: reported
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO Quality of Life 100-question patient-reported questionnaire (WHOQOL-100)) at up to 7 days, up to 28 days, and longest follow-up available: NR
	• Adverse events grades 3 and 4: reported
	• Ventilator-free days (defined as days alive and free from mechanical ventilation): NR

Identification	

Notes	• Date of publication: 5 November 2020
	• Sponsor/funding:
	  ○ National Institute of Allergy and Infectious Diseases (NIAID, main sponsor)
	  ○ National Cancer Institute
	  ○ Department of Defence, Defence Health Program
	  ○ In part funded by the governments of Denmark, Japan, Mexico, and Singapore
	  ○ Gilead Sciences provided remdesivir for use in this trial but did not provide any financial support
	• Authors were contacted for additional data on all-cause mortality at up to day 28 for subgroups of respiratory support; they kindly responded and provided the requested data.

Gottlieb 2021

Study characteristics	
Methods	• Trial design: double-blind, placebo-controlled, multicentre, RCT • Type of publication: journal publication

Gottlieb 2021 *(Continued)*

- Setting: outpatient
- Recruitment dates: from 18 September 2020 to 8 April 2021
- Country: international (United States, Spain, Denmark, and the United Kingdom)
- Language: English
- Number of centres: 64 sites
- Trial registration number: EudraCT number 2020-003510-12, NCT04501952 (ClinicalTrials.gov)
- Date of trial registration: 6 August 2020

Participants

Baseline characteristics

- Age (years, mean (SD)): intervention group 50 (15), control group 51 (15)
- Gender (male, n (%)): intervention group 148 (53), control group 145 (51.2)
- Race or ethnic group, intervention group vs control group (n (%)): White 228 (81.7) vs 224 (79.2); Black 20 (7.2) vs 22 (7.8); American Indian or Alaska Native 15 (5.4) vs 21 (7.4); Asian, Native Hawaiian, or Pacific Islander 7 (2.5) vs 7 (2.5); Hispanic or Latinx 123 (44.1) vs 112 (39.6); Other 3 (1.1) vs 2 (0.7)
- Number of participants (recruited/allocated/evaluated): 584/584/562:
  - Remdesivir: efficacy and safety analyses: 279 patients in the remdesivir group
  - Control: efficacy and safety analyses: 283 patients in the placebo group
- Severity of condition according to the level of respiratory support (intervention group vs control group, (n (%)):
  - non-hospitalised participants without respiratory support: 279 (100) vs 283 (100)
- Comorbidities (intervention group vs control group (n(%)):
  - Diabetes mellitus 173 (62.0) vs 173 (61.1)
  - Obesity 154 (55.2) vs 156 (55.1)
  - Hypertension 138 (49.5) vs 130 (45.9)
  - Chronic lung disease 67 (24) vs 68 (24)

Key Inclusion criteria:

- Willing and able to provide written informed consent (individuals ≥ 18 years of age) or assent (individuals ≥ 12 and < 18 years of age) prior to performing study procedures. Individuals age ≥ 18 years may be enrolled with the consent of a legal representative where permitted according to local law and approved nationally and by the relevant institutional review board (IRB) or independent ethics committee (IEC). For individuals ≥ 12 and < 18 years of age, a parent or legal guardian must be willing and able to provide written informed consent prior to performing study procedures

Either:

- Age ≥ 18 years (at all sites) or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg (where permitted according to local law and approved nationally and by the relevant IRB or IEC with at least 1 pre-existing risk factor for progression to hospitalisation (chronic lung disease, hypertension, cardiovascular or cerebrovascular disease, diabetes, obesity (body mass index ≥ 30), immunocompromised, chronic mild or moderate kidney disease, chronic liver disease, current cancer, or sickle cell disease)
- Or aged ≥ 60 years
- Severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2 infection confirmed by molecular diagnosis (nucleic acid (polymerase chain reaction (PCR) or antigen testing) ≤ 4 days prior to screening
- Presence of ≥ 1 symptom(s) consistent with COVID-19 for ≤ 7 days prior to randomisation
- Not currently requiring hospitalisation (hospitalisation defined as ≥ 24 hours of acute care)

Exclusion criteria:

- Participation in any other clinical trial of an experimental treatment and prevention for COVID-19
- Prior hospitalisation for COVID-19
- Treatment with other agents with actual or possible direct antiviral activity against SARS-CoV-2 or administration of any SARS-CoV-2 (or COVID-19) vaccine

Gottlieb 2021 *(Continued)*

	• Requiring oxygen supplementation **Previous treatments:** NR
Interventions	• Treatment details of intervention group: intravenous remdesivir (200 mg on day 1 followed by 100 mg on days 2 and 3) • Treatment details of control group: placebo • Concomitant therapy: NR • Duration of follow-up: ○ 28 days • Treatment cross-overs: no • Compliance with assigned treatment: partly (intervention group: 13 patients not treated; control group: 9 patients not treated)
Outcomes	**Primary study outcomes:** • Percentage of participants with coronavirus disease 2019 (COVID-19) related hospitalisation (defined as at least 24 hours of acute care) or all-cause death by day 28 • Percentage of participants who experienced treatment-emergent adverse events (TEAEs) **Review outcomes:** *Primary outcomes* • All-cause mortality at day 28, day 60, time-to-event, and up to longest follow-up: reported • Admission to hospital or death within 28 days: reported • Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 28 days, and longest follow-up available: NR • Serious adverse events during the study period, defined as number of participants with any event: reported • Adverse events (any grade) during the study period, defined as number of participants with any event: reported
Identification	
Notes	• Date of publication: 27 January 2022 • Sponsor/funding: Gilead Sciences

Mahajan 2021

Study characteristics	
Methods	• Trial design: RCT, open-label • Type of publication: journal publication • Setting: inpatient • Recruitment dates: from June 2020 to December 2020 • Country: India • Language: English • Number of centres: 1 • Trial registration number: NR • Date of trial registration: NR
Participants	**Baseline characteristics** • Age (years, mean (SD)): intervention group 58.08 (12.1); control group 57.41 (14.1)

Mahajan 2021 *(Continued)*

- Gender (male, n (%)): intervention group 21 (61.7); control group 27 (75.0)
- Ethnicity: NR
- Number of participants (recruited/allocated/evaluated): 82/82/70
- Severity of condition according to the level of respiratory support (intervention group vs control group, (n (%))):
  - hospitalised requiring supplemental oxygen: 27 (79.4) vs 26 (72.2)
  - hospitalised requiring high-flow nasal cannula or non-invasive mechanical ventilation: 7 (20.6) vs 10 (27.8)
- Comorbidities (intervention group vs control group (n/N (%))):
  - Diabetes 21/34 (61.8) vs 21/36 (58.3)
  - Hypothyroidism 4/34 (11.8) vs 3/36 (8.3)
  - Hypertension 15/34 (44.1) vs 17/36 (47.2)
  - Hyperlipidaemia 4/34 (11.8) vs 3/36 (8.3)
  - CAD 4/34 (11.8) vs 5/36 (13.9)
  - CKD 2/34 (5.9) vs 1/36 (2.8)
  - Asthma 1/34 (2.9) vs 0/36 (0.0)

Inclusion criteria

- Adults (18 to 60 years)
- Admitted to a hospital with moderate to severe COVID-19 with:
  - respiratory rate > 24 per minute;
  - radiographic evidence of pneumonia;
  - oxygen saturation of 94% or less.
- Has laboratory-confirmed SARS-CoV-2 infection by PCR within the last 4 days
- Participant (or a close relative) provides written informed consent before taking part in the study

Exclusion criteria

- AST or ALT levels greater than 3 times the upper limit of the normal range
- Creatinine clearance ≤ 40 mL per minute
- Invasive mechanical ventilation
- Multi-organ failure

Previous treatments: NR

Interventions	• Treatment details of intervention group: 200 mg remdesivir intravenously as loading dose on day 1, followed by 100 mg remdesivir intravenously once daily for subsequent 4 days
	• Treatment details of control group: standard of care
	• Concomitant therapy: standard of care including heparin and corticosteroids; other drugs for COVID-19 treatment not allowed
	• Duration of follow-up:
	  ◦ At least 12 days, 24 days, or until discharge or death
	  ◦ For `time-to-recovery` and `time-to-`improvement analyses, data for participants who did not recover and data for participants who died were collected at day 24
	• Treatment cross-overs: yes; 1 participant in the control group requested remdesivir after enrolment
	• Compliance with assigned treatment: partly

Outcomes	**Primary study outcome:** clinical status from day 12 to 24 on 6-point ordinal scale **Review outcomes** *Primary outcomes* • All-cause mortality at day 28, day 60, and at hospital discharge: NR • Clinical status at day 28, day 60, and up to longest follow-up, including:

Mahajan 2021 *(Continued)*

- improvement of clinical status; i.e. participants discharged alive. Participants should be discharged without clinical deterioration or death: NR
- worsening of clinical status; i.e. participants with clinical deterioration, defined as new need for invasive mechanical ventilation or death: NR

- Adverse events (any grade) during the study period, defined as number of participants with any event: NR
- Serious adverse events during the study period, defined as number of participants with any event: NR

Secondary outcomes

- All-cause mortality, time-to-event: NR
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO Quality of Life 100-question patient-reported questionnaire (WHOQOL-100)) at up to 7 days, up to 28 days, and longest follow-up available: NR
- Adverse events grades 3 and 4: NR
- Ventilator-free days (defined as days alive and free from mechanical ventilation): NR

Identification	
Notes	• There is no protocol publicly available • Date of publication: 20 March 2020 • Sponsor/funding: no information • Authors were contacted for additional data on all-cause mortality at up to day 28 for subgroups of respiratory support; we received no response

Spinner 2020

Study characteristics

Methods

- Trial design: parallel assigned, randomised, controlled, open-label
- Type of publication: journal publication
- Setting: inpatient
- Recruitment dates: from 15 March 2020 to 18 April 2020
- Countries: the USA, Europe, and Asia
- Language: English
- Number of centres: 105
- Trial registration number: NCT04292730 (ClinicalTrials.gov)
- Date of trial registration: 3 March 2020

Participants

Baseline characteristics

- Age (years; median (IQR)): 10-day intervention group 56 (45 to 66); 5-day intervention group 58 (48 to 66); control group 57 (45 to 66)
- Gender (male n (%)/female n (%)): 10-day intervention group 118 (61)/75 (39); 5-day intervention group 114 (60)/77 (40); control group 125 (63)/75 (38)
- Race or ethnic group (10-day intervention group/5-day intervention group/control group, n (%)): white 107 (57)/109 (59)/112 (58); black 37 (20)/35 (19)/27 (14); Asian 31 (16)/34 (18)/37 (19); other 13 (7)/8 (4)/17 (9); Hispanic or Latino ethnicity 42 (23)/25 (13)/34 (18)
- Number of participants (recruited/allocated/evaluated): 612/596/584
  - 5-day remdesivir group 199/191

Spinner 2020 *(Continued)*

- 10-day remdesivir group 197/193
- control group 200/200

- Severity of condition according to the level of respiratory support (intervention group vs control group, (n (%))):
  - hospitalised not requiring supplemental oxygen or ongoing medical care: 169 (87) vs 162 (81)
  - hospitalised requiring low-flow supplemental oxygen: 23 (12) vs 36 (18)
  - hospitalised requiring high-flow oxygen or non-invasive mechanical ventilation: 1 (1) vs 2 (1)
- Comorbidities (10-day intervention group/5-day intervention group/control group (n (%))):
  - Cardiovascular disease 111 (58)/111 (58)/107 (54)
  - Hypertension 85 (44)/82 (43)/81 (41)
  - Diabetes 85 (44)/71 (37)/76 (38)
  - Asthma 31 (16)/22 (12)/28 (14)

Inclusion criteria:

- Willing and able to provide written informed consent prior to performing study procedures (participants ≥ 18 years of age) or assent (participants ≥ 12 and < 18 years of age) prior to performing study procedures. For participants ≥ 12 and < 18 years of age, a parent or legal guardian willing and able to provide written informed consent prior to performing study procedures
- Aged ≥ 18 years (at all sites), or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg (where permitted according to local law and approved nationally and by the relevant institutional review board or independent ethics committee)
- SARS-CoV-2 infection confirmed by PCR test ≤ 4 days before randomisation
- Currently hospitalised and requiring medical care for COVID-19
- SpO_2 > 94% on room air at screening
- Radiographic evidence of pulmonary infiltrates
- Men and women of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception.

Exclusion criteria

- Participation in any other clinical trial of an experimental treatment for COVID-19
- Concurrent treatment or planned concurrent treatment with other agents with actual or possible direct-acting antiviral activity against SARS-CoV-2
- Requiring mechanical ventilation at screening
- ALT or AST > 5x upper limit of normal. If per local practice only ALT is routinely measured, exclusion criteria were evaluated on ALT alone.
- Creatinine clearance < 50 mL/min using Cockcroft-Gault formula for participants ≥ 18 years of age, and Schwartz formula for participants < 18 years of age
- Positive pregnancy test
- Breastfeeding women
- Known hypersensitivity to the study drug, the metabolites, or formulation excipient

Previous treatments: not reported

Interventions

- Treatment details of intervention group:
  - 5-day intervention group: continued standard care therapy together with intravenous remdesivir 200 mg on day 1, followed by intravenous remdesivir 100 mg daily on days 2 to 5
  - 10-day intervention group: continued standard care therapy together with intravenous remdesivir 200 mg on day 1, followed by intravenous remdesivir 100 mg daily on days 2 to 10
- Treatment details of control group:
  - Standard care (according to local guidelines)
- Concomitant therapy:
  - Concomitant use of the following is prohibited in participants receiving remdesivir:
    - Traditional herbal treatments including herb sho-saiko-to (or Xiao-Shai-Hu-Tang)

Spinner 2020 *(Continued)*

- Investigational agents with putative antiviral activity for COVID-19 including approved HIV protease inhibitors such as lopinavir/ritonavir, chloroquine, interferon, steroid, tocilizumab, azithromycin
- Duration of follow-up: day 28 (± 5 days)
- Treatment cross-overs: no
- Compliance with assigned treatment: yes

Outcomes

Primary study outcome: clinical status assessed by a 7-point ordinal scale on day 11

- Clinical status was derived from death, hospital discharge, and ordinal scale as follows: score of 1 was used for all days on or after the date of death; score of 7 was used for all days on or after discharged-alive date; last available assessment for missing value
  - The scale is as follows:
    a. death;
    b. hospitalised, on invasive mechanical ventilation or ECMO;
    c. hospitalised, on non-invasive ventilation or high-flow oxygen devices;
    d. hospitalised, requiring low-flow supplemental oxygen;
    e. hospitalised, not requiring supplemental oxygen - requiring ongoing medical care (COVID-19 related or otherwise);
    f. hospitalised, not requiring supplemental oxygen - no longer required ongoing medical care (other than per-protocol remdesivir administration);
    g. not hospitalised.

Review outcomes

Primary outcomes

- All-cause mortality at day 28, day 60 and at hospital discharge: reported
- Clinical status at day 28, day 60, and up to longest follow-up, including:
  - improvement of clinical status; i.e. participants discharged alive. Participants should be discharged without clinical deterioration or death: reported
  - worsening of clinical status; i.e. participants with clinical deterioration, defined as new need for invasive mechanical ventilation or death: reported
- Adverse events (any grade) during the study period, defined as number of participants with any event: reported
- Serious adverse events during the study period, defined as number of participants with any event: reported

Secondary outcomes

- All-cause mortality, time-to-event: NR
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO Quality of Life 100-question patient-reported questionnaire (WHOQOL-100)) at up to 7 days, up to 28 days, and longest follow-up available: NR
- Adverse events grades 3 and 4: reported
- Ventilator-free days (defined as days alive and free from mechanical ventilation): NR

Identification

Notes

- Date of publication: 21 August 2020
- Sponsor/funding: this study was sponsored by Gilead Sciences
- Authors were contacted for additional data on all-cause mortality at up to day 28 for subgroups of respiratory support; they kindly responded and provided the requested data

Spinner 2020 *(Continued)*

Wang 2020

Study characteristics

Methods

- Trial design: parallel assigned, randomised, placebo-controlled, double-blind
- Type of publication: journal publication
- Setting: inpatient
- Recruitment dates: 6 February 2020 to 12 March 2020
- Country: China
- Language: English
- Number of centres: 10
- Trial registration number: NCT04257656 (ClinicalTrials.gov)
- Date of trial registration: 31 January 2020

Participants

Baseline characteristics

- Age (years, median (IQR)): intervention group: 66.0 (57.0 to 73.0), control group: 64.0 (53.0 to 70.0)
- Gender (male/female, n (%)): intervention group: 89 (56)/69 (44), control group: 51 (65)/27 (35)
- Ethnicity: not reported
- Number of participants (recruited/allocated/evaluated): 236/intervention group: 158, control group: 78
- Severity of condition according to the level of respiratory support (intervention group vs control group, (n (%))):
  - hospitalised not requiring supplemental oxygen: 0 vs 3 (4)
  - hospitalised requiring supplemental oxygen: 129 (82) vs 65 (83)
  - hospitalised requiring high-flow nasal cannula or non-invasive mechanical ventilation: 28 (18) vs 9 (12)
  - hospitalised requiring extracorporeal membrane oxygenation or invasive mechanical ventilation: 0 vs 1 (1)
  - dead 1 (1) vs 0
- Comorbidities (intervention group vs control group, (n (%))):
  - Hypertension 72 (46) vs 30 (38)
  - Diabetes 40 (25) vs 16 (21)
  - Coronary heart disease 15 (9) vs 2 (3)

Inclusion criteria

- Age ≥ 18 years at time of signing of informed consent form
- Laboratory (RT-PCR)-confirmed COVID-19
- Pneumonia confirmed by chest imaging
- Oxygen saturation (SaO_2/SpO_2) ≤ 94% on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) ratio < 300 mmHg
- ≤ 12 days of symptom onset
- Willingness of study participant to accept randomisation to any assigned treatment arm
- Eligible participants of child-bearing age (men and women) agreed to take effective contraceptive measures (including hormonal contraception, barrier methods, or abstinence) during the study period and for at least 7 days after the last study drug administration

Wang 2020 *(Continued)*

- Participants must agree not to enrol in any other study of an antiviral agent prior to completing the 28-day follow-up.

Exclusion criteria:

- Physician decides that trial involvement is not in the patient's best interest, or any condition that does not allow the protocol to be followed safely
- Severe liver disease (e.g. Child-Pugh score ≥ C, AST > 5 times upper limit)
- Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
- Patients with known severe renal impairment (eGFR ≤ 30 mL/min/1.73 m^2) or receiving continuous renal replacement therapy, haemodialysis, peritoneal dialysis
- Will be transferred to another hospital which is not the study site within 72 hours
- Receipt of any experimental treatment for COVID-19 within the 30 days prior to the time of the screening evaluation

Previous treatments (received before and after enrolment): injection of interferon alfa-2b; lopinavir–ritonavir; vasopressors; renal replacement therapy; antibiotics; corticosteroids

Interventions

- Treatment details of intervention group: remdesivir
  - Loading dose: 200 mg in 350 mL normal saline (0.9% sodium chloride) intravenous on day 1
  - Maintenance doses: 100 mg in 250 mL normal saline (0.9% sodium chloride) intravenous once daily on days 2 to 10
- Treatment details of control group: placebo infusions
  - Loading dose: in 350 mL normal saline (0.9% sodium chloride) intravenous on day 1
  - Maintenance doses: 250 mL normal saline (0.9% sodium chloride) intravenous once daily on days 2 to 10
- Concomitant therapy: concomitant use of the following:
  - Lopinavir–ritonavir
  - Interferon alfa-2b
  - Antibiotics
  - Corticosteroids
  - No information about standard of care
- Treatment cross-overs: no
- Duration of follow-up: day 28
- Compliance with assigned treatment: yes

Outcomes

Primary study outcome: time to clinical improvement at up to day 28. Clinical improvement was defined as a 2-point reduction in participant's admission status on a 6-point ordinal scale, or live discharge from the hospital, whichever came first. The scale is as follows: 6. death; 5. hospital admission for ECMO or mechanical ventilation; 4. hospital admission for non-invasive ventilation or high-flow oxygen therapy; 3. hospital admission for oxygen therapy (but not requiring high-flow or non-invasive ventilation); 2. hospital admission but not requiring oxygen therapy; 1. discharged or having reached discharge criteria (defined as clinical recovery, i.e. normalisation of pyrexia, respiratory rate < 24 breaths per minute, saturation of peripheral oxygen > 94% on room air, and relief of cough, all maintained for at least 72 hours).

Review outcomes

Primary outcomes

- All-cause mortality at day 28, day 60, and at hospital discharge: reported
- Clinical status at day 28, day 60, and up to longest follow-up, including:
  - improvement of clinical status; i.e. participants discharged alive. Participants should be discharged without clinical deterioration or death: reported

Wang 2020 *(Continued)*

- worsening of clinical status; i.e. participants with clinical deterioration, defined as new need for invasive mechanical ventilation or death: NR

- Adverse events (any grade) during the study period, defined as number of participants with any event: reported
- Serious adverse events during the study period, defined as number of participants with any event: reported

Secondary outcomes

- All-cause mortality, time-to-event: NR
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO Quality of Life 100-question patient-reported questionnaire (WHOQOL-100)) at up to 7 days, up to 28 days, and longest follow-up available: NR
- Adverse events grades 3 and 4: NR
- Ventilator-free days (defined as days alive and free from mechanical ventilation): NR

Identification	

Notes

- Date of publication: 29 April 2020
- Sponsor/funding:
  - This study was funded by Chinese Academy of Medical Sciences Emergency Project of COVID-19, National Key Research and Development Program of China, the Beijing science and technology project
  - Remdesivir or placebo infusions for a total of 10 days were both provided by Gilead Sciences, Foster City, CA, USA
- Authors were contacted for additional data on all-cause mortality at up to day 28 for subgroups of respiratory support; we did not receive a response

WHO Solidarity Canada 2022

Study characteristics

Methods

- Trial design: parallel assigned, RCT, open-label
- Type of publication: journal publication
- Setting: inpatient
- Recruitment dates: from 18 March 2020 to 1 April 2021
- Country: Canada
- Language: English
- Multicentre, number of centres: 52
- Trial registration number: NCT04330690 (ClinicalTrials.gov)
- Date of trial registration: 23 March 2020

Participants

Baseline characteristics (Canadian cohort of the WHO Solidarity Trial Consortium, unless otherwise noted)

- Age (years, median (IQR)): intervention group 65 (53 to 77) vs control group 66 (54 to 77)
- Gender (male, n (%)): intervention group 374 (59); control group 392 (60,6)

WHO Solidarity Canada 2022 *(Continued)*

- Race or ethnic group, intervention group vs control group (n (%)): white 269 (42.4) vs 255 (39.4); South Asian 90 (14.2) vs 110 (17.0); East Asian 40 (6.3) vs 42 (6.5); Indigenous or First Nations 40 (6.3) vs 28 (4.3); Black 20 (3.2) vs 25 (3.9); Arab 22 (3.5) vs 24 (3.7); Latin American 23 (3.6) vs 21 (3.2); West Asian 8 (1.3) vs 12 (1.9); Other 9 (1.4) vs 14 (2.2); Not available 119 (18.8) vs 126 (19.5)
- Number of participants (recruited/allocated/evaluated):
  - Patients included in WHO Solidarity Trial: 1282/1282/1281
  - Patients enrolled separate from WHO Solidarity Trial and evaluated: 323
- Severity of condition according to the level of respiratory support:
  - Inclusive patients included in the WHO Solidarity Trial; intervention group vs control group, (n (%)):
    - hospitalised not requiring supplemental oxygen: 71 (11.2) vs 54 (8.4)
    - hospitalised requiring supplemental low-flow oxygen: 334 (52.7) vs 363 (56.2)
    - hospitalised requiring high-flow nasal cannula: 149 (23.5) vs 153 (23.7)
    - hospitalised requiring non-invasive ventilation: 22 (3.5) vs 23 (3.6)
    - hospitalised requiring invasive ventilation: 58 (9.1) vs 54 (8.3)
  - Patients enrolled separate from WHO Solidarity Trial; intervention group vs control group, (n (%)):
    - hospitalised not requiring supplemental oxygen: 11 (6.5) vs 10 (6.5)
    - hospitalised requiring supplemental low-flow oxygen: 96 (56.5) vs 89 (58.2)
    - hospitalised requiring high-flow nasal cannula: 44 (25.9) vs 43 (28.1)
    - hospitalised requiring non-invasive ventilation: 5 (2.9) vs 4 (2.6)
    - hospitalised requiring invasive ventilation: 14 (8.2) vs 7 (4.5)
- Comorbidities (intervention group vs control group (n (%)):
  - Diabetes 155 (33.6) vs 188 (38.4)
  - Chronic cardiovascular disease 120 (26.0) vs 135 (27.6)
  - Chronic respiratory disease 67 (14.5) vs 65 (13.3)
  - Asthma 49 (10.6) vs 55 (11.2)
  - Chronic liver disease 8 (1.7) vs 19 (3.9)

Inclusion criteria:

1. ≥ 18 years of age
2. Has laboratory-confirmed SARS-CoV-2 infection as determined by PCR, or other commercial or public health assay in any specimen prior to randomisation
3. Hospitalised at a participating centre

Exclusion criteria:

1. Anticipated transfer to another hospital, within 72 hours, which is not a study site
2. Expected to not survive beyond 24 hours
3. Known allergy to study medication or its components (non-medicinal ingredients)
4. Receiving one of the study drugs at time of enrolment

Previous treatments: NR

Interventions

- Treatment details of intervention group: 200 mg remdesivir intravenously as loading dose on day 1, followed by 100 mg remdesivir intravenously once daily for subsequent 9 days plus standard care (study intervention was stopped if discharge occurred before completion of a full course of treatment)
- Treatment details of control group: standard care
- Concomitant therapy: all other care decisions were left to the treating clinicians, including co-interventions, such as dexamethasone or tocilizumab or both for eligible patients, according to time period, hospital setting and participation in other RCTs
- Duration of follow-up:
  - 60 days

WHO Solidarity Canada 2022 *(Continued)*

- Treatment cross-overs: no
- Compliance with assigned treatment: partly (8 participants in the intervention group did not receive at least one dose of intervention)

Outcomes	**Primary study outcome:** in-hospital mortality
	
	Review outcomes (new outcomes, not reported in the WHO Solidarity Trial Consortium and used for the analyses in this review, are marked)
	
	Primary outcomes
	
	• All-cause mortality at day 28, day 60, and at hospital discharge: reported
	• Clinical status at day 28, day 60, and up to longest follow-up, including:
	  ◦ improvement of clinical status; i.e. participants discharged alive. Participants should be discharged without clinical deterioration or death: NR
	  ◦ worsening of clinical status; i.e. participants with clinical deterioration, defined as new need for invasive mechanical ventilation or death: reported (new)
	• Adverse events (any grade) during the study period, defined as number of participants with any event: NR
	• Serious adverse events during the study period, defined as number of participants with any event: NR
	
	Secondary outcomes
	
	• All-cause mortality, time-to-event: reported
	• Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO Quality of Life 100-question patient-reported questionnaire (WHOQOL-100)) at up to 7 days, up to 28 days, and longest follow-up available: NR
	• Adverse events grades 3 and 4: NR
	• Ventilator-free days (defined as days alive and free from mechanical ventilation): NR

Identification	
Notes	• Date of publication: 19 January 2022 • Sponsor/funding: ◦ Sunnybrook Health Sciences Centre

WHO Solidarity France 2021

Study characteristics	
Methods	• Trial design: open-label, adaptive, multicentre, RCT • Type of publication: journal publication • Setting: inpatient • Recruitment dates: from 22 March 2020 to 21 January 2021 • Country: international (France, Belgium, Austria, Portugal, Luxembourg) • Language: English • Number of centres: 48 sites: in France (39), Belgium (3), Austria (3), Portugal (2), and Luxembourg (1)

WHO Solidarity France 2021 *(Continued)*

- Trial registration number: EudraCT2020-000936-23, NCT04315948 (ClinicalTrials.gov)
- Date of trial registration: 20 March 2020

Participants	**Baseline characteristics (French cohort of the WHO Solidarity Trial Consortium and additional participants, not evaluated in the WHO Solidarity Trial Consortium)**
	• Age (years, median (range)): intervention group 63 (55 to 73), control group 64 (54 to 72)
	• Gender (male, n (%)): intervention group 291 (70), control group 288 (69)
	• Race or ethnic group, intervention group vs control group (n (%)): White 244 (68) vs 255 (70); North African 49 (14) vs 61 (17); Sub-Saharan African 30 (8) vs 17 (5); Other 37 (10) vs 31 (9)
	• Number of participants (recruited/allocated/evaluated): 1308/857/832:
	  ○ Remdesivir: intention-to-treat population 414; modified intention-to-treat population 406
	  ○ Control: intention-to-treat population 418; modified intention-to-treat population 418
	• Severity of condition according to the level of respiratory support (intervention group vs control group, (n (%))):
	  ○ hospitalised not requiring supplemental oxygen: 6 (1) vs 6 (1)
	  ○ hospitalised requiring supplemental oxygen: 247 (60) vs 245 (59)
	  ○ hospitalised requiring high-flow nasal cannula: 71 (17) vs 77 (18)
	  ○ hospitalised requiring non-invasive mechanical ventilation: 15 (4) vs 16 (4)
	  ○ hospitalised requiring invasive mechanical ventilation: 75 (18) vs 72 (17)
	  ○ hospitalised requiring extracorporeal membrane oxygenation: 0 vs 2 (< 1)
	• Comorbidities (intervention group vs control group (n/N (%)):
	  ○ Obesity 138/414 (45.6) vs 140/418 (34)
	  ○ Chronic cardiac disease 111/414 (27) vs 118/418 (28)
	  ○ Diabetes 104/414 (26) vs 113/418 (27)
	  ○ Chronic pulmonary disease 71/414 (17) vs 75/418 (18)
	
	Inclusion criteria:
	• Adult ≥ 18 years of age at the time of enrolment
	• Hospitalised patients with any of the following criteria:
	  ○ the presence of pulmonary rales/crackles on clinical exam OR SpO2 ≤ 94% on room air; OR
	  ○ requirement for supplementary oxygen including high-flow oxygen devices or non-invasive ventilation
	• A time between onset of symptoms and randomisation of less than 11 days
	• A positive SARS-CoV-2 PCR performed on a nasopharyngeal swab within the 5 days preceding randomisation
	• The result of a rapid antigen test performed on a nasopharyngeal swab within the 6 hours preceding randomisation
	• Contraceptive use by men or women. Male participants: contraception for male participants is required; to avoid the transfer of any fluids, all male participants must use a condom from Day 1 and agree to continue for 90 days following administration of IMP. Female participants: women of child-bearing potential must agree to use contraception for 365 days following administration of IMP.
	
	Exclusion criteria:
	• Refusal to participate expressed by patient or legally authorised representative
	• Need for invasive mechanical ventilation and/or ECMO at the time of enrolment
	• Spontaneous blood ALT/AST levels > 5 times the upper limit of normal
	• Glomerular filtration rate (GFR) < 15 mL/min or requiring maintenance dialysis
	• Pregnancy or breast-feeding
	• Anticipated transfer to another hospital, which is not a study site within 72 hours following randomisation
	• Known history of allergy or reaction to any component of the study drug formulation

WHO Solidarity France 2021 *(Continued)*

- Previous hypersensitivity, infusion-related reaction, or severe adverse reaction following administration of monoclonal or polyclonal antibodies.
- Any prior receipt of investigational or licenced other mAb/biologic indicated for the prevention of SARS-CoV-2 infection or COVID-19, and for those not vaccinated, expected receipt of vaccine in the 30 days following hospital discharge, according to current recommendation in each country.
- Any medical condition which, in the judgement of the investigator, could interfere with the interpretation of the trial results or that preludes to protocol adherence

Interventions

- Treatment details of intervention group: 200 mg remdesivir intravenously as loading dose on day 1, followed by 100 mg remdesivir intravenously once daily for subsequent 9 days (its cessation was allowed after 5 days if the participant was discharged from the hospital)
- Treatment details of control group: standard care
- Concomitant therapy: standard of care including dexamethasone (added to the standard care on 1 October 2020) 6 mg once daily for 10 days or until discharge or in case of ARDS 20 mg once daily for 5 days, followed by 10 mg once daily for 5 days, other immunomodulatory agents (investigator's discretion), prophylactic or therapeutic anticoagulation
- Duration of follow-up:
  - 29 days, or until death (daily assessment while hospitalised and at days 3, 5, 8, 11, 15 (plus or minus 2) and 29 (plus or minus 3) if discharged)
- Treatment cross-overs: no
- Compliance with assigned treatment: partly (8 participants in the intervention group did not receive at least one dose of intervention)

Outcomes

Primary study outcome: clinical status at day 15 as measured on the 7-point ordinal scale of the WHO Master Protocol (version 3.0, 3 March 2020)

- The scale is as follows:

(1) not hospitalised, no limitation on activities; (2) not hospitalised, limitation on activities; (3) hospitalised, not requiring supplemental oxygen; (4) hospitalised, requiring supplemental oxygen; (5) hospitalised, on non-invasive ventilation or high-flow oxygen devices; (6) hospitalised, on invasive mechanical ventilation or ECMO; and (7) dead

Review outcomes (new outcomes, not reported in the WHO Solidarity Trial Consortium and used for the analyses in this review, are marked)

Primary outcomes

- All-cause mortality at day 28, day 60, and at hospital discharge: reported
- Clinical status at day 28, day 60, and up to longest follow-up, including:
  - improvement of clinical status; i.e. participants discharged alive. Participants should be discharged without clinical deterioration or death: reported (new)
  - worsening of clinical status; i.e. participants with clinical deterioration, defined as new need for invasive mechanical ventilation or death: reported (new)
- Adverse events (any grade) during the study period, defined as number of participants with any event: reported (new)
- Serious adverse events during the study period, defined as number of participants with any event: reported (new)

Secondary outcomes

- All-cause mortality, time-to-event: NR
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO Quality of Life 100-question patient-reported questionnaire (WHOQOL-100)) at up to 7 days, up to 28 days, and longest follow-up available: NR
- Adverse events grades 3 and 4: reported (new)

WHO Solidarity France 2021 *(Continued)*

- Ventilator-free days (defined as days alive and free from mechanical ventilation): NR

Identification	

Notes	• Date of publication: 14 September 2021
	• Sponsor/funding:
	  ○ European Union Commission
	  ○ French Ministry of Health
	  ○ Domaine d'intérêt majeur One Health Île-de-France
	  ○ REACTing
	  ○ Fonds Erasme-COVID-Université Libre de Bruxelles
	  ○ Belgian Health Care Knowledge Centre
	  ○ Austrian Group Medical Tumor
	  ○ European Regional Development Fund
	  ○ Portugal Ministry of Health
	  ○ Portugal Agency for Clinical Research and Biomedical Innovation

WHO Solidarity Norway 2021

Study characteristics	
Methods	• Trial design: open-label, adaptive, multicentre, RCT • Type of publication: journal publication • Setting: inpatient • Recruitment dates: from 7 April to 5 October 2020 • Country: Norway • Language: English • Number of centres: 23 • Trial registration number: NCT04321616 (ClinicalTrials.gov) • Date of trial registration: 25 March 2020

Participants	**Baseline characteristics**
	• Age (years, mean (SD), intervention group vs control group): 59.7 (16.5) vs 58.1 (15.7)
	• Gender (male, n (%)): intervention group 29 (69); control group 43 (75.4)
	• Ethnicity (geographic region, n (%) intervention group vs n (%) control group): NR
	• Number of participants (recruited/allocated/evaluated): 101/101/83
	• Severity of condition according to the level of respiratory support (intervention group vs control group, (n (%))):
	  ○ hospitalised not requiring supplemental oxygen: NR
	  ○ hospitalised requiring supplemental oxygen: NR
	  ○ hospitalised requiring extracorporeal membrane oxygenation or invasive mechanical ventilation: NR
	• Severity of condition according to the level of medical care (intervention group vs control group, (n (%)):
	  ○ admitted to ward: 39 (92.9) vs 56 (98.2)
	  ○ admitted to ICU: 3 (7.1) vs 1 (1.8)
	• Comorbidities (intervention group vs control group (n (%)):
	  ○ Diabetes: 9 (22) vs 9 (15.8)

WHO Solidarity Norway 2021 *(Continued)*

- Chronic cardiac disease: 6 (14.6) vs 12 (21.1)
- Chronic pulmonary disease: 4 (9.8) vs 3 (5.3)
- Hypertension: 15 (36.6) vs 14 (24.6)
- Obesity: 11 (28.9) vs 9 (18.4)

Inclusion criteria:

- Adult patients, 18 years and above
- Confirmed SARS-2-CoV-2 infection by PCR
- Admitted to the hospital ward or the ICU
- Patient (or legally authorised representative) provides written informed consent prior to initiation of the study

Exclusion criteria:

1. Severe co-morbidity with life expectancy < 3 months according to investigators' assessment
2. (Aspartate transaminase/alanine aminotransferase) ASAT/ALAT > 5 times the upper limit of normal
3. Acute co-morbidity within 7 days before inclusion such as myocardial infarction
4. Known intolerance to the available study drugs
5. Pregnancy, possible pregnancy, or breastfeeding
6. Any reason why, in the opinion of the investigators, the patient should not participate
7. Patient participates in a potentially confounding drug or device trial during the course of the study
8. Prolonged QT interval (> 450 ms)

Previous treatments: NR

Interventions	• Treatment details of intervention group: 200 mg of intravenous remdesivir on day 1, then 100 mg daily up to 9 days in addition to standard care • Treatment details of control group: standard care • Concomitant therapy (intervention group vs control group, n (%)): systemic steroids 1 (2.4) vs 2 (3.6), other immunomodulatory drugs 1 (2.4) vs 1 (1.8), ACE inhibitors 2 (4.9) vs 4 (7.1), angiotensin II receptor blockers 11 (26.8) vs 7 (12.5). Systemic steroids as standard care for severe and critical COVID-19 from 4 September 2020 • Duration of follow-up: ◦ 3 months • Treatment cross-overs: no • Compliance with assigned treatment: partly (9 participants in the intervention group excluded after randomisation)

Outcomes	**Primary study outcome:** all-cause, in- hospital mortality
	
	Review outcomes (new outcomes, not reported for those patients in the WHO Solidarity Trial Consortium and used for the analyses in this review, are marked)
	
	Primary outcomes
	
	• All-cause mortality at day 28, day 60, and at hospital discharge: reported (new)
	• Clinical status at day 28, day 60, and up to longest follow-up, including:
	  ◦ improvement of clinical status; i.e. participants discharged alive. Participants should be discharged without clinical deterioration or death: NR
	  ◦ worsening of clinical status; i.e. participants with clinical deterioration, defined as new need for invasive mechanical ventilation or death: NR
	• Adverse events (any grade) during the study period, defined as number of participants with any event: reported (new)
	• Serious adverse events during the study period, defined as number of participants with any event: reported (new)

WHO Solidarity Norway 2021 *(Continued)*

	Secondary outcomes • All-cause mortality, time-to-event: NR • Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO Quality of Life 100-question patient-reported questionnaire (WHOQOL-100)) at up to 7 days, up to 28 days, and longest follow-up available: NR • Adverse events grades 3 and 4: NR • Ventilator-free days (defined as days alive and free from mechanical ventilation): NR
Identification	
Notes	• Date of publication: 13 July 2021 • Sponsor/funding: National Clinical Therapy Research in the Specialist Health Services, Norway

WHO Solidarity Trial Consortium 2022

Study characteristics	
Methods	• Trial design: RCT, open-label • Type of publication: journal publication • Setting: inpatient • Recruitment dates: 22 March 2020 to 29 January 2021 • Country: Albania, Austria, Belgium, Finland, France, Ireland, Italy, Lithuania, Luxembourg, North Macedonia, Norway, Spain, Switzerland, Canada, Argentina, Brazil, Colombia, Honduras, Peru, Egypt, India, Indonesia, Iran, Kuwait, Lebanon, Malaysia, Pakistan, the Philippines, Saudi Arabia, South Africa • Language: English • Number of centres: 454 • Trial registration number: NCT04315948 (ClinicalTrials.gov); ISRCTN83971151 (ISRCTN registry) • Date of trial registration: 20 March 2020

Participants	**Baseline characteristics**
	• Age (years, n intervention group vs n control group) < 50 years, 1310 vs 1326; 50 to 69 years, 1920 vs 1908; ≥ 70 years, 916 vs 895
	• Gender (male, n (%)): intervention group 2601 (62.709%); control group 2639 (63.90%)
	• Ethnicity (geographic region, n intervention group vs n control group): Europe and Canada 1649 vs 1594; Latin America 558 vs 53; Asia and Africa 1939 vs 1942
	• Number of participants (recruited/allocated/evaluated): 8320 (remdesivir: 4169, control: 4151)/8275 (remdesivir: 4146, control: 4129)
	• Severity of condition according to the level of respiratory support (intervention group vs control group, (n (%)):
	  ◦ hospitalised not requiring supplemental oxygen: 869 (20.9) vs 861 (20.8)
	  ◦ hospitalised requiring supplemental oxygen (not differentiated into low- and high-flow): 2918 (70.4) vs 2921 (70.7)
	  ◦ hospitalised requiring extracorporeal membrane oxygenation or invasive mechanical ventilation: 359 (8.6) vs 347 (8.4)
	• Comorbidities (intervention group vs control group (n (%)):
	  ◦ Diabetes 1129 (27.2) vs 1120 (27.1)
	  ◦ Heart disease 929 (22.4) vs 935 (22.5)
	  ◦ Chronic lung disease 284(6.8) vs 281 (6.8)
	  ◦ Asthma 247 (5.9) vs 242 (5.8)
	  ◦ Chronic liver disease 57 (1.4) vs 72(1.7)

WHO Solidarity Trial Consortium 2022 *(Continued)*

Inclusion criteria:

- Adults (aged ≥ 18 years) hospitalised with definite COVID-19
- Not already receiving any of the study drugs
- Without known allergy or contraindications to any of the study drugs (in the view of the physician responsible for their care)
- Without anticipated transfer within 72 h to a non-study hospital

Exclusion criteria:

- Refusal to participate expressed by patient or legally authorised representative if they are present
- Spontaneous blood ALT/AST levels > 5 times the upper limit of normal
- Stage 4 severe chronic kidney disease or requiring dialysis (i.e. eGFR < 30 mL/min)
- Pregnancy or breastfeeding
- Anticipated transfer to another hospital which is not a study site within 72 hours
- Patients previously treated with 1 of the antivirals evaluated in the trial (i.e. remdesivir, interferon beta-1a, lopinavir/ritonavir, hydroxychloroquine) in the past 29 days
- Contraindication to any study medication including allergy

Previous treatments: NR

Interventions

- Treatment details of intervention group:
  - Remdesivir was administered as a 200 mg intravenous loading dose on day 1, followed by a 100 mg once-daily intravenous maintenance dose for the duration of the hospitalisation up to a 10-day total course, plus local standard care
- Treatment details of control group:
  - The controls were patients assigned to the standard care at a time and place in which drug was locally available
- Concomitant therapy: local SoC
- Treatment cross-overs: no
- Duration of follow-up: day 28
- Compliance with assigned treatment: yes

Outcomes

Primary study outcome: all-cause mortality, subdivided by the severity of disease at the time of randomisation, measured using patient records throughout the study

Review outcomes

Primary outcomes

- All-cause mortality at day 28, day 60, and at hospital discharge: reported
- Clinical status at day 28, day 60, and up to longest follow-up, including:
  - improvement of clinical status; i.e. participants discharged alive. Participants should be discharged without clinical deterioration or death: reported
  - worsening of clinical status; i.e. participants with clinical deterioration, defined as new need for invasive mechanical ventilation or death: NR
- Adverse events (any grade) during the study period, defined as number of participants with any event: NR
- Serious adverse events during the study period, defined as number of participants with any event: NR

Secondary outcomes

- All-cause mortality, time-to-event: reported
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO Quality of Life 100-question patient-reported questionnaire (WHOQOL-100)) at up to 7 days, up to 28 days, and longest follow-up available: NR
- Adverse events grades 3 and 4: NR

WHO Solidarity Trial Consortium 2022 *(Continued)*

	• Ventilator-free days (defined as days alive and free from mechanical ventilation): NR
Identification	
Notes	• Date of publication: 2 May 2022 • Sponsor/funding: in each country the co-sponsors of this study are the National Ministry of Health and the WHO • Authors were contacted for additional data on all-cause mortality at up to day 28 for subgroups of respiratory support; they kindly responded that there were no additional data to provide

Abbreviations:
ALT = alanine transaminase
ARDS = acute respiratory distress syndrome
AST = aspartate transaminase
CAD = coronary artery disease
CKD = chronic kidney disease
CT = computed tomography
ECMO = extracorporeal membrane oxygenation
eGFR = estimated glomerular filtration rate
HR = hazard ratio
ICU = intensive care unit
IMP = investigational medicinal product
IQR = interquartile range
IWRS = interactive web response system
N = total number of participants
n = number of participants
NA = not applicable
NR = not reported
NEWS = National Early Warning Score
NIAID = National Institute of Allergy and Infectious Diseases
OR = odd ratio
PaO_2/FiO_2 = ratio of arterial oxygen partial pressure to fractional inspired oxygen
PCR = polymerase chain reaction
RCT = randomised controlled trial
RT-PCR = reverse transcription polymerase chain reaction
SaO_2 = arterial oxygen saturation
SD = standard deviation
SoC = standard of care
SpO_2 = peripheral oxygen saturation
ULN = upper limit of normal
WHO = World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abd-Elsalam 2021	The study was retracted
Ader 2020	Duplicate
Ader 2021	No data about the remdesivir intervention
Alpern 2020	Not a randomised controlled trial
Anderson 2021	Not a randomised controlled trial

Study	Reason for exclusion
Antinori 2020	Not a randomised controlled trial
Banerjee 2020	Not a randomised controlled trial
CTRI/2020/12/029613	No intervention with remdesivir
CTRI/2020/12/029615	Combination of remdesivir with other treatments
CTRI/2021/01/030830	Intervention with remdesivir not compared to standard care or placebo
CTRI/2021/12/038637	Not a randomised controlled trial
CTRI/2021/12/039011	Not a randomised controlled trial
CTRI/2022/03/041252	Not a randomised controlled trial
Deresinski 2020	Not a randomised controlled trial
Elliott 2020	Not a randomised controlled trial
Elliott 2021	Combination of remdesivir with other treatments
EUCTR2020-000841-15-ES	Intervention with remdesivir not compared to standard care or placebo
EUCTR2020-000936-23	Duplicate
Euctr2020-003510-12-dk	Wrong patient population
EUCTR2020-004928-42-HU	Wrong patient population
Goldberg 2021	Not a randomised controlled trial
Goldman 2020	Combination of remdesivir with other treatments
Goldman 2020a	Intervention with remdesivir not compared to standard care or placebo
Grein 2020	Not a randomised controlled trial
Grundmann 2022	Full text not retrievable
IRCT20151227025726N28	Intervention with remdesivir not compared to standard care or placebo
IRCT20210324050760N1	Not a randomised controlled trial
ISRCTN15874265	Combination of remdesivir with other treatments
ISRCTN85762140	Wrong patient population
Jang 2021	Combination of remdesivir with other treatments
Kalil 2021	Combination of remdesivir with other treatments
Lapadula 2020	Not a randomised controlled trial
LBCTR2020043495	Duplicate

Study	Reason for exclusion
Medical Brief	Full-text not retrievable
NCT04252664a	Duplicate
NCT04256395	Not a randomised controlled trial
NCT04280705	Duplicate
NCT04292899	Combination of remdesivir with other treatments
NCT04302766	Wrong patient population
NCT04321928	No intervention with remdesivir
NCT04323761	Intervention with remdesivir not compared to standard care or placebo
NCT04353596	No intervetion with remdesivir
NCT04401579	Combination of remdesivir with other treatments
NCT04410354	Combination of remdesivir with other treatments
NCT04480333	Wrong patient population
NCT04488081	Combination of remdesivir with other treatments
NCT04492475	Combination of remdesivir with other treatments
NCT04501978	Intervention with remdesivir not compared to standard care or placebo
NCT04518410	No intervention with remdesivir
NCT04539262	Wrong patient population
NCT04583956	Combination of remdesivir with other treatments
NCT04583969	Combination of remdesivir with other treatments
NCT04610541	Intervention with remdesivir not compared to standard care or placebo
NCT04640168	Combination of remdesivir with other treatments
NCT04647695	Combination of remdesivir with other treatments
NCT04678739	Combination of remdesivir with other treatments
NCT04693026	Combination of remdesivir with other treatments
NCT04713176	Combination of remdesivir with other treatments
NCT04728880	Not a randomised controlled trial
NCT04746183	No intervention with remdesivir
NCT04832880	Combination of remdesivir with other treatments

Study	Reason for exclusion
NCT04847622	Not a randomised controlled trial
Olender 2020	Intervention with remdesivir not compared to standard care or placebo
Olender 2021	Not a randomised controlled trial
Padilla 2022	Not a randomised controlled trial
Pan 2020	Duplicate
Pan 2021	Duplicate
PER-101-20	Intervention with remdesivir not compared to standard care or placebo
Rosas 2021	Combination of remdesivir with other treatments
Saito 2020	Not a randomised controlled trial
Shakir 2022	Not a randomised controlled trial
Shih 2020	Not a randomised controlled trial
Soto 2020	Not a randomised controlled trial
Sun 2020	Not a randomised contolled trial
Tran 2020	Not a randomised controlled trial
Winstead 2021	Not a randomised controlled trial

Characteristics of studies awaiting classification *[ordered by study ID]*

NCT04596839

Methods	Trial design: RCT • Allocation: randomised • Intervention model: parallel assignment • Masking: none (open-label) • Primary purpose: treatment Sample size: • Actual enrolment: 60 participants Setting: inpatient Language: Bengali Number of centres: multicentre Type of intervention: drug
Participants	**Inclusion criteria:** • Age ≥ 18 years at time of signing informed consent form

NCT04596839 *(Continued)*

- Hospitalised with diagnosed COVID-19 confirmed by RT-PCR test ≤ 7 days before randomisation with any 1 following criteria:
  - Respiratory distress (≥ 30 breaths/min)
  - Finger oxygen saturation ≤ 93% at rest
  - Arterial partial pressure of oxygen (PaO_2)/fraction of inspired oxygen (FiO_2) ≤ 300 mmHg
- Willingness of study participant to accept randomisation to any assigned treatment arm
- Must agree not to enrol in another study of an investigational agent prior to completion of day 28 of study

Exclusion criteria:

- Physician decides that trial involvement is not in patient's best interest, or any condition that does not allow the protocol to be followed safely
- Severe liver disease (ALT or AST > 5 times the upper limit of normal)
- Estimated glomerular filtration rate (eGFR) < 30 mL/min (including patients receiving haemodialysis or haemofiltration)
- Mechanically ventilated (including venovenous ECMO) ≥ 5 days, or any duration of venoarterial ECMO
- Known hypersensitivity to the remdesivir, the metabolites, or formulation excipient
- Pregnancy or breastfeeding
- Anticipated discharge from the hospital or transfer to another hospital which is not a study site within 72 hours

Interventions

- Details of intervention:
  - SoC + RDV 200 mg (day 1)/RDV 100 mg (days 2, 3, 4, and 5)
  - Remdesivir 100 mg lyophilised powder for infusion
- Treatment details of control group (e.g. dose, route of administration):
  - SoC
  - Standard care treatment for COVID-19 Infection
- Concomitant therapy: NR

Outcomes

Primary study outcome:

- Duration of hospital stay (days) (time frame: 28 days)

Secondary study outcomes:

- Time to clinical improvement (time frame: 28 days). Time to clinical improvement (censored at day 28), defined as the time (in days) from randomisation of study treatment until a decline of 2 categories on a 6-category ordinal scale of clinical status (1 = discharged; 6 = death) or live discharge from hospital. 6-category ordinal scale:
  - Hospital discharge or meets discharge criteria
  - Hospitalisation, not requiring supplemental oxygen
  - Hospitalisation, requiring supplemental oxygen (but not non-invasive ventilation/high-flow nasal cannula)
  - ICU/hospitalisation, requiring non-invasive ventilation/high-flow nasal cannula therapy
  - ICU, requiring ECMO and/or invasive mechanical ventilation
  - Death
- All causes mortality (time frame: 28 days)
- Duration (days) of mechanical ventilation (time frame: 28 days)
- Duration (days) of supplemental oxygenation (time frame: 28 days)
- Time to 2019-nCoV RT-PCR negativity in nasopharyngeal swab (time frame: 28 days)
- Frequency of serious adverse drug events (time frame: 28 days)

NCT04596839 *(Continued)*

Review outcomes

Inpatient setting:

- All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge: planned
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020c), WHO Ordinal Scale for Clinical Improvement (WHO 2020c)) at day 28, day 60, and up to longest follow-up), including:
  - improvement of clinical status: planned:
    - weaning or liberation from invasive mechanical ventilation in surviving participants;
    - ventilator-free days;
    - duration to liberation from invasive mechanical ventilation;
    - liberation from supplemental oxygen in surviving participants;
    - duration to liberation from supplemental oxygen.
  - Worsening of clinical status: not planned:
    - new need for mechanical ventilation;
    - new need for invasive mechanical ventilation;
    - new need for non-invasive mechanical ventilation or high-flow oxygen;
    - new need for oxygen by mask or nasal prongs.
- Need for dialysis (at up to 28 days): not planned
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available: not planned
- Admission to ICU: planned
- Duration of hospitalisation: planned
- Time to discharge from hospital: planned
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline and up to 3, 7, and 15 days: planned
- Vitamin D serum levels: not planned
- Serious adverse events, defined as number of participants with event: planned
- Adverse events (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with event: not planned

Notes

- Recruitment status: completed
- Primary completion date: 30 April 2021
- Date last update was posted: 9 August 2021
- Sponsor/funding: Dr Md. Alimur Reza, Beximco Pharmaceuticals Ltd.

REDPINE 2022

Methods

Trial design: RCT

- Allocation: randomised
- Intervention model: parallel assignment
- Masking: double-blinded
- Primary purpose: treatment

Sample size: 249

- Estimated enrolment: 1116 participants
- Actual enrolment: 249 participants

REDPINE 2022 *(Continued)*

	Setting: inpatient Language: English Number of centres: 63 Type of intervention: drug

Participants	**Key Inclusion criteria**
	• Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positive as determined by polymerase chain reaction (PCR) or other commercially available or public health assay (e.g. nucleic acid amplification test (NAAT) and antigen tests) in any respiratory specimen
	• Hospitalised for COVID-19
	• 12 years and older
	• Weighing at least 40 kilograms (kg)
	• Oxygen (O2) saturation ≤ 94% on room air or requiring O2 supplement or radiographic evidence of pulmonary infiltrates for COVID-19
	• Have either:
	  ○ a) Severely reduced kidney function (estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2), including people with end-stage kidney disease (ESKD) requiring chronic dialysis
	  ○ b) Ongoing acute kidney injury (AKI): defined as a 50% increase in serum creatinine (SCr) within a 48-hour period that is sustained (i.e. requires confirmatory SCr) for ≥ 6 hours despite supportive care
	• The interval between COVID-19 symptoms onset and randomisation is no more than 10 days
	Key exclusion criteria
	• Received any investigational drug, RDV, or other antiviral treatment for COVID-19
	• Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 times the upper limit of normal
	• Invasive mechanical ventilation, non-invasive mechanical ventilation, ECMO, or RRT for acute kidney injury (AKI)
	• Positive serum pregnancy test at screening for women of childbearing potential or currently breastfeeding
	• Known hypersensitivity to the study drug, metabolites, or formulation sulfobutylether-beta-cyclodextrin (SBECD)

Interventions	**Intervention details** • Drug: remdesivir ○ Administered as intravenous (IV) infusion once daily **Treatment details of the control group:** • Placebo administered as IV saline once daily + standard of care

Outcomes	**Primary outcomes**
	• Composite of all-cause mortality or invasive mechanical ventilation (IMV) through day 29 (time frame: first dose date up to day 29)
	  ○ The composite of all-cause mortality or IMV is the combined endpoint of the percentage of participants who die or initiate on IMV through day 29
	Secondary outcomes
	• All-cause mortality through day 29 (time frame: first dose date up to day 29)
	  ○ The percentage of participants who die through day 29 will be assessed
	• Invasive mechanical ventilation through day 29 (time frame: first dose date up to day 29)
	  ○ The percentage of participants who initiate on IMV through day 29 will be assessed
	• Time to Recovery (time frame: first dose date up to day 29)
	  ○ Time to recovery is the time from first dose to recovery. Recovery is defined as the first day on which the participant satisfies one of the following three categories from the 8-point ordinal

REDPINE 2022 *(Continued)*

scale: 1) Not hospitalised, no limitations on activities; 2) Not hospitalised, limitation on activities and/or requiring home oxygen; 3) Hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per-protocol RDV/saline as placebo administration).

- Clinical status assessed by an 8-point ordinal scale on day 15 (time frame: day 15)
  - Clinical status is derived from death, hospital discharge, and the ordinal scale. Each day, the worst (highest) score from the previous day will be recorded. The ordinal scale is as follows:
    - 1. Not hospitalised, no limitations on activities
    - 2. Not hospitalised, limitation on activities and/or requiring home oxygen
    - 3. Hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per-protocol RDV/saline as placebo administration)
    - 4. Hospitalised, not requiring supplemental oxygen - requiring ongoing medical care for COVID-19-specific medical care (other than per-protocol RDV administration)
    - 5. Hospitalised, supplemental oxygen
    - 6. Hospitalised, on non-invasive ventilation or high-flow oxygen devices
    - 7. Hospitalised, on invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
    - 8. Death. Higher scores indicate worst clinical status.
- Clinical status assessed by an 8-point ordinal scale on day 29 (time frame: day 29)
  - Clinical status is derived from death, hospital discharge, and the ordinal scale. Each day, the worst (highest) score from the previous day will be recorded. The ordinal scale is as follows:
    - 1. Not hospitalised, no limitations on activities
    - 2. Not hospitalised, limitation on activities and/or requiring home oxygen
    - 3. Hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per-protocol RDV/saline as placebo administration)
    - 4. Hospitalised, not requiring supplemental oxygen - requiring ongoing medical care for COVID-19-specific medical care (other than per-protocol RDV administration)
    - 5. Hospitalised, supplemental oxygen
    - 6. Hospitalised, on non-invasive ventilation or high-flow oxygen devices
    - 7. Hospitalised, on invasive mechanical ventilation or ECMO
    - 8. Death. Higher scores indicate worst clinical status.
- Renal replacement therapy (RRT)-free days (among those without end-stage kidney disease (ESKD) at randomisation) through day 29 (time frame: first dose date up to day 29)
- Recovery through day 29 (time frame: first dose date up to day 29)
  - Recovery is defined as the participant satisfying one of the following 3 categories from the 8-point ordinal scale:
    - 1. Not hospitalised, no limitations on activities
    - 2. Not hospitalised, limitation on activities and/or requiring home oxygen
    - 3. Hospitalised, not requiring supplemental oxygen - no longer requires ongoing medical care (other than per-protocol RDV/saline as placebo administration)
- Percentage of participants experiencing serious adverse events (SAEs) (time frame: first dose date up to last dose date (maximum: day 5) plus 30 days)
- Percentage of participants who permanently discontinue investigational drug due to adverse events (AEs) (time frame: first dose date up to last dose date (maximum: day 5) plus 30 days)

Notes

- Recruitment status: terminated. The study was terminated due to study enrolment feasibility. This decision is not based on efficacy or safety concerns.
- Actual completion date: 24 May 2022
- Date last update was posted: 3 June 2022
- Sponsor/funding: Gilead Sciences

ALT = alanine transaminase
AST = aspartate transaminase
ECMO = extracorporeal membrane oxygenation
eGFR = estimated glomerular filtration rate
ICU = intensive care unit
IMV = invasive mechanical ventilation
NR = not reported
RCT = randomised controlled trial
RDV = remdesivir
RRT = renal replacement therapy
RT-PCR = reverse transcription polymerase chain reaction
SoC = standard of care

Characteristics of ongoing studies *[ordered by study ID]*

IRCT20210709051824N1

Study name	'Assessment of utility of remdesivir in patients with acute kidney injury or cronic kidney disease in admitted COVID-19 patients'
Methods	Trial design: RCT • Allocation: randomised • Intervention model: parallel assignment • Masking: single-blinded (participants), placebo-controlled • Primary purpose: treatment Sample size: NR • Estimated enrolment: 100 participants Setting: NR (probable inpatient, since inclusion criterion: lung involvement above 20% or hypoxia) Language: English Number of centres: NR Type of intervention: drug
Participants	**Inclusion criteria:** • Age ≥ 18 years • Acute or chronic renal failure • Definitive diagnosis of COVID-19 • Pulmonary involvement caused by COVID-19 • Lung involvement above 20% or hypoxia (oxygen saturation less than or equal to 93%) **Exclusion criteria:** • Previous history of COVID-19 infection and heart disease and receiving remdesivir • History of lung disease • History of liver disease (such as hepatitis, cirrhosis) • History of underlying diseases other than renal impairment that contribute to poor prognosis and increased mortality following coronary heart disease (e.g. heart failure, active cancer, advanced diabetes with severe macrovascular and microvascular complications, previous stroke) • Immunosuppressive use except in the field of kidney transplantation • Prohibition of remdesivir (except low GFR)
Interventions	**Details of intervention:** • Drug: remdesivir (RDV)

IRCT20210709051824N1 *(Continued)*

	○ Dose: RDV 200 mg loading dose (day 1) followed by 100 mg once daily, up to 5 doses ○ Route of administration: intravenous **Treatment details of control group**: • Drug: placebo ○ Dose: 200 mg loading dose (day 1), followed by 100 mg once daily, up to 5 doses ○ Route of administration: intravenous Concomitant therapy: NR
Outcomes	**Primary study outcomes:** • Changes of laboratory parameters (time point: the beginning of the visit, while receiving remdesivir, after received remdesivir): ○ ALT ○ AST ○ Lymphocyte count ○ Alkaline phosphatase ○ Bilirubin ○ CRP ○ Creatinine ○ Red blood cell count ○ White blood cell count ○ Neutrophil count ○ Erythrocyte sedimentation rate ○ INR ○ Medium platelet volume ○ Platelet count • Result of hospitalisation (death or discharge). Time point: end of hospitalisation • Duration of hospitalisation. Time point: end of hospitalisation • O2 saturation. Time point: the beginning of the visit, while receiving remdesivir, after received remdesivir **Secondary study outcomes:** NR
Starting date	Date of registration: 8 December 2021
Contact information	Mahboobeh Freidoon Shahid Beheshti University of Medical Sciences, Tehran Iran (Islamic Republic of)
Notes	• Recruitment status: recruiting • Prospective completion date: NR • Date last update was posted: 11 January 2022 • Sponsor/funding: Men's Health and Reproductive Health Research Center (MHRHRC)

NCT04252664

Study name	'A trial of remdesivir in adults with mild and moderate COVID-19'
Methods	Trial design: RCT • Allocation: randomised • Intervention model: parallel assignment

NCT04252664 *(Continued)*

- Masking: quadruple (participant, care provider, investigator, outcomes assessor)
- Primary purpose: treatment

Sample size: NR

- Estimated enrolment: 308 participants

Setting: inpatient

Language: Chinese

Number of centres: 1 (Jin Yin-tan Hospital Wuhan, Hubei, China, 100013)

Type of intervention: drug

Participants	**Inclusion criteria:**
	• Age ≥ 18 years at time of signing informed consent form
	• Laboratory (RT-PCR)-confirmed COVID-19
	• Lung involvement confirmed with chest imaging
	• Hospitalised with:
	  ○ fever ≥ 36.7 °C axilla or oral temperature ≥ 38.0 °C or ≥ 38.6 °C tympanic or rectal and
	  ○ at least 1 of respiratory rate > 24/min or cough
	• ≤ 8 days since illness onset
	• Willingness of study participant to accept randomisation to any assigned treatment arm
	• Must agree not to enrol in another study of an investigational agent prior to completion of day 28 of study
	Exclusion criteria:
	• Physician decides that trial involvement is not in patient's best interest, or any condition that does not allow the protocol to be followed safely
	• Severe liver disease (e.g. Child-Pugh score ≥ C, AST > 5 times upper limit)
	• SaO_2/SPO_2 ≤ 94% in room air condition, or PaO_2/FiO_2 ratio < 300 mmHg
	• Known allergic reaction to remdesivir
	• Patients with known severe renal impairment (eGFR ≤ 30 mL/min/1.73 m^2) or receiving continuous renal replacement therapy, haemodialysis, peritoneal dialysis
	• Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
	• Will be transferred to another hospital which is not the study site within 72 hours
	• Receipt of any experimental treatment for COVID-19 within the 30 days prior to the time of the screening evaluation

Interventions	**Details of intervention:**
	• Drug: remdesivir (other name: GS-5734)
	  ○ Dose: RDV 200 mg loading dose (day 1), 100 mg (once daily, 9 days) maintenance doses
	  ○ Route of administration: intravenous
	Treatment details of control group:
	• Drug: remdesivir placebo
	  ○ Dose: RDV placebo 200 mg loading dose (day 1), 100 mg (once daily, 9 days) maintenance dose
	  ○ Route of administration: intravenous
	Concomitant therapy: NR

Outcomes	**Primary study outcome:** Time to clinical recovery (TTCR) (time frame: up to 28 days)

NCT04252664 *(Continued)*

TTCR is defined as the time (in hours) from initiation of study treatment (active or placebo) until normalisation of fever, respiratory rate, and oxygen saturation, and alleviation of cough, sustained for at least 72 hours, or live hospital discharge, whichever comes first.

Normalisation and alleviation criteria:

- Fever: < 37 °C
- Respiratory rate: ≤ 24/min on room air
- Oxygen saturation: > 94% on room air
- Cough: mild or absent on a patient-reported scale of severe, moderate, mild, absent

Secondary outcome measures:

- All-cause mortality (time frame: up to 28 days)
  - Baseline SpO_2 during screening, PaO_2/FiO_2 < 300 mmHg or a respiratory rate ≥ 24 breaths per minute without supplemental oxygen
- Frequency of respiratory progression (time frame: up to 28 days)
  - Defined as SpO_2 ≤ 94% on room air or PaO_2/FiO_2 < 300 mmHg and requirement for supplemental oxygen or more advanced ventilator support
- Time to defervescence (in those with fever at enrolment) (time frame: up to 28 days)
- Time to cough reported as mild or absent (in those with cough at enrolment rated severe or moderate) (time frame: up to 28 days)
- Time to dyspnoea reported as mild or absent (on a scale of severe, moderate, mild absent, in those with dyspnoea at enrolment rated as severe or moderate) (time frame: up to 28 days)
- Frequency of requirement for supplemental oxygen or non-invasive ventilation (time frame: up to 28 days)
- Time to 2019-nCoV RT-PCR negative in upper respiratory tract specimen (time frame: up to 28 days)
- Change (reduction) in 2019-nCoV viral load in upper respiratory tract specimen as assessed by area under viral load curve (time frame: up to 28 days)
- Frequency of requirement for mechanical ventilation (time frame: up to 28 days)
- Frequency of serious adverse events (time frame: up to 28 days)

Review outcomes:

Inpatient setting:

- All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge: planned
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020c), WHO Ordinal Scale for Clinical Improvement (WHO 2020c)) at day 28, day 60, and up to longest follow-up), including:
  - improvement of clinical status: planned:
    - weaning or liberation from invasive mechanical ventilation in surviving participants, i.e. WHO ≤ 6, if ≥ 7 at baseline;
    - ventilator-free days; ventilator-free defined as WHO ≤ 6;
    - duration to liberation from invasive mechanical ventilation;
    - liberation from supplemental oxygen in surviving participants, i.e. WHO ≤ 4, if ≥ 5 at baseline;
    - duration to liberation from supplemental oxygen.
  - worsening of clinical status: planned:
    - new need for mechanical ventilation;
    - new need for invasive mechanical ventilation;
    - new need for non-invasive mechanical ventilation or high-flow oxygen;
    - new need for oxygen by mask or nasal prongs.
- Need for dialysis (at up to 28 days): not planned
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to 7 days, up to 30 days, and longest follow-up available: not planned
- Admission to ICU: not planned

NCT04252664 *(Continued)*

- Duration of hospitalisation: planned
- Time to discharge from hospital: planned
- Viral clearance, assessed with RT-PCR test for SARS-CoV-2 at baseline and up to 3, 7, and 15 days: planned
- Vitamin D serum levels: not planned
- Serious adverse events, defined as number of participants with event: planned
- Adverse events (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with event: not planned

Starting date	12 February 2020
Contact information	Bin Cao, China-Japan Friendship Hospital
Notes	• Recruitment status: suspended, "The epidemic of COVID-19 has been controlled well at present, no eligible patients can be recruited." • Prospective completion date: 10 April 2020 • Date last update was posted: 15 April 2020 • Sponsor/funding: Capital Medical University

NCT04351724

Study name	'A multicenter, randomized, active controlled, open label, platform trial on the efficacy and safety of experimental therapeutics for patients with COVID-19 (caused by infection with severe acute respiratory syndrome coronavirus-2)'
Methods	Trial design: RCT • Allocation: randomised • Intervention model: parallel assignment; 3 main study arms (antiviral treatments) and 3 substudies (A, B, C) are planned. The main study arms are exclusive, while patients from the main study arms may participate in one or more substudies. • Masking: open-label • Primary purpose: treatment Sample size: NR • Estimated enrolment: 500 participants Setting: inpatient, except for sub-study B, which may also include outpatients with COVID-19 Language: English Number of centres: 9 ((Austria)
Participants	**Inclusion criteria** • Laboratory confirmed (i.e. PCR-based assay) infection with SARS-CoV-2 (ideally but not necessarily) • ≤ 72 hours before randomisation for "antiviral" treatments) OR radiological signs of COVID-19 in chest X-ray or computed tomography • Hospitalisation due to SARS-CoV-2 infection, except for sub-study B, which may also include outpatients with COVID-19

NCT04351724 *(Continued)*

- Requirement of oxygen support (due to oxygen saturation < 94% on ambient air or > 3% drop in case of chronic obstructive lung disease)
- Informed consent obtained, the patient understands and agrees to comply with the planned study procedures, except for sub-study C: obtaining informed consent may be impossible due to the severe condition of the patient and may be waived
- ≥ 18 years of age
- Sub-study A: not on chronic anticoagulation
- Sub-study B: blood pressure ≥ 130/85 mmHg in 2 consecutive measurements OR patients with established and treated hypertension
- Sub-study B: Control group 1: Patients with suspicion of but negative tests for COVID-19. This group may consist of hospitalised and non-hospitalised patients.
- Sub-study B: healthy volunteers
- Sub-study C: signs of respiratory deterioration and progressing inflammation: need for oxygen supplementation, non-invasive ventilation, high-flow oxygen devices or mechanical ventilation AND CRP levels > 5 mg/dL (for pentaglobin only) and ICU admission (for pentaglobin only)
- For female patients with childbearing potential: willingness to perform effective measures of contraception during the study

Exclusion criteria

- Moribund, or estimated life expectancy < 1 month (e.g. terminal cancer, etc.)
- Patient does not qualify for intensive care, based on local triage criteria
- Pregnancy or breastfeeding
- Severe liver dysfunction (e.g. ALT/AST > 5 times upper limit of normal)
- Stage 4 chronic kidney disease or requiring dialysis for direct anticoagulant treatment
- Allergy or intolerances to experimental substance (ineligibility for treatment arm), for asunercept known hereditary fructose intolerance
- Anticipated discharge from hospital within 48 hours (for any given reason)
- Contraindications for treatment arm 2 (lopinavir/ritonavir): severe hepatic impairment, CYP3A4/5 metabolised drugs, as deemed relevant by treating physicians
- Contraindications for treatment arm 3 (remdesivir): < 40 kg bodyweight
- Known active HIV or viral hepatitis
- Substudy A contraindications for rivaroxaban: active bleeding or bleeding diathesis, lesion or condition considered as major risk factor for bleeding, recent brain or spinal injury, recent brain or spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms, major intraspinal or intracerebral vascular abnormalities, ongoing therapeutic anticoagulation, which will be continued, according to clinical practice
- Sub-study B contraindications for nitrendipine: chronic heart failure, allergies, hypersensitivities and intolerances, severe hepatic impairment and/or cholestasis, concomitant therapy with aliskiren containing medications (for patients with diabetes mellitus or a GFR < 60 mL/min/1.73 m^2), known significant bilateral renal artery stenosis or renal artery stenosis of a solitary kidney
- Sub-study C contraindications for IL-6 blockade: contraindications: allergies and intolerances, active untreated diverticulitis, inflammatory bowel disease, any treatment with an IL-6 or IL-6R blocking drug (e.g. tocilizumab, sarilumab, siltuximab) < 30 days before study inclusion
- Sub-study C: known active tuberculosis
- Asunercept: females of childbearing potential
- Sub-study C with pentaglobin: contraindications to pentaglobin

Interventions	**Details of intervention:** different antivirals, depending on intervention arm (lopinavir/ritonavir; chloroquine or hydroxychloroquine; remdesivir) and other substances (sub-studies A-C: rivaroxaban, thromboprophylaxis, candesartan, non-RAS blocking antihypertensives, asunercept, pentaglobin) Drug: remdesivir

NCT04351724 *(Continued)*

- 200 mg on day 1, thereafter 100 mg for a total of 5 to 10 treatment days, according to local standards

Treatment details of control group:

- Best standard of care

Concomitant therapy: NR

Outcomes

Primary outcomes

- Sustained improvement (> 48 h) of 1 point on the WHO Scale (time frame: inclusion to day 29, daily evaluation)
- The primary endpoint is time to clinical improvement, which is defined as time from randomisation to a (sustained) improvement of at least 1 category on 2 consecutive days compared to the status at randomisation measured on a 7-category ordinal scale (proposed by WHO). The 7 categories of the World Health Organization proposed scale, as follows:

1. Not hospitalised, no limitations on activities
2. Not hospitalised, limitation on activities
3. Hospitalised, not requiring supplemental oxygen
4. Hospitalised, requiring supplemental oxygen
5. Hospitalised, on non-invasive ventilation or high-flow oxygen devices
6. Hospitalised, on invasive mechanical ventilation or ECMO
7. Death

Secondary outcomes

- Time to improvement on WHO Scale (time frame: inclusion to day 29, daily evaluation)
- Mean change in the ranking on an ordinal scale from baseline (time frame: inclusion to day 29, daily evaluation)
- Time to discharge or a National Early Warning Score (NEWS) ≤ 2 (maintained for 24 h), whichever occurs first (time frame: inclusion to day 29, daily evaluation)
  - The National Early Warning Score includes respiratory rate, oxygen saturation, use of supplemental oxygen, temperature, systolic blood pressure, heart rate and levels of consciousness (AVPU Scale)
- Change from baseline in National Early Warning Score (NEWS) (time frame: inclusion to day 29, daily evaluation)
- Oxygenation-free days (time frame: inclusion to day 29, daily evaluation)
- Incidence of new oxygen use during the trial (time frame: inclusion to day 29, daily evaluation)
  - New oxygen may include insufflation or oxygen mask, high-flow oxygen devices, non-invasive ventilation devices or mechanical ventilation
- Duration of oxygen use during the trial (time frame: inclusion to day 29, daily evaluation)
- Ventilator-free days until day 29 (time frame: inclusion to day 29, daily evaluation)
  - Number of days with requirement of mechanical ventilation
- Incidence of new mechanical ventilation use during the trial (time frame: inclusion to day 29, daily evaluation)
- Duration of mechanical ventilation use during the trial (time frame: inclusion to day 29, daily evaluation)
- Viral load/viral clearance (time frame: inclusion to day 29, daily evaluation)
  - Obtained by polymerase chain reaction in nasal/oropharyngeal swabs, performed at baseline and then 3 times a week, if possible
- Duration of hospitalisation (time frame: inclusion to day 29, daily evaluation)
- Mortality (time frame: 15-day, 29-day, 60-day, 90-day mortality)
- Obesity - mortality (time frame: BMI at admission, mortality until day 29)
  - BMI (kg/m2), within all participants the impact of obesity on overall mortality will be investigated
- Obesity - duration of hospitalisation (time frame: BMI at admission, duration of hospitalisation until day 29 or discharge)

NCT04351724 *(Continued)*

- BMI (kg/m2), within all participants the impact of obesity on the duration of hospitalisation will be investigated
- Obesity - ICU admission (time frame: BMI at admission, ICU admission until day 29 or discharge)
  - BMI (kg/m2), within all participants the impact of obesity on ICU admission will be investigated
- Obesity - new oxygen use (time frame: BMI at admission, new oxygen use until day 29 or discharge)
  - BMI (kg/m2) new oxygen may include insufflation or oxygen mask, high-flow oxygen devices, non-invasive ventilation devices or mechanical ventilation
- Drug-drug interactions with lopinavir/ritonavir (time frame: inclusion to day 29, daily evaluation)
- Renin angiotensin system (RAS) fingerprint (time frame: inclusion to day 29, daily evaluation)
  - For sub-study B only: RAS fingerprint measures metabolites involved in the renin-angiotensin system. The influence of randomised treatment with candesartan (RAS blockade) will be analysed.
- SpO2/FiO2 ratio (time frame: inclusion to day 29, daily evaluation)
  - For sub-study C only
- PaO/FiO2 ratio (time frame: inclusion to day 29, daily evaluation)
  - For sub-study C only, for ICU patients only
- Modified Sequential Organ Failure Assessment (time frame: inclusion to day 29, daily evaluation)
  - For sub-study C only
- C-reactive protein (time frame: baseline, day 2, 3, 4, 5, 7)
- Interleukin-6 (time frame: baseline, day 2, 3, 4, 5, 7)
- Procalcitonin (time frame: baseline, day 2, 3, 4, 5, 7)
- IgM concentrations (time frame: baseline, day 2, 3, 4, 5, 7)
- IgA concentrations (time frame: baseline, day 2, 3, 4, 5, 7)
- Differential blood counts (time frame: baseline, day 2, 3, 4, 5, 7)

Starting date	16 April 2020
Contact information	Bernd Jilma - Medical University of Vienna
Notes	• Recruitment status: recruiting (hydroxychloroquine/chloroquine arm stopped) • Prospective completion date: 31 March 2022 • Date last update was posted: 2 March 2021 • Sponsor/funding: Medical University of Vienna, Kaiser Franz Josef Hospital, SMZ-Ost Donauspital, Otto Wagner Hospital, Hospital Hietzing, Wilhelminenspital Vienna, Medical University Innsbruck, Medical University of Graz, Kepler University Hospital

NCT04843761

Study name	'ACTIV-3b: therapeutics for severely ill inpatients with COVID-19 (TESICO)'
Methods	Trial design: RCT • Allocation: randomised • Intervention model: parallel assignment • Masking: triple (participant, care provider, investigator) • Primary purpose: treatment Sample size: NR • Estimated enrolment: 640 participants

NCT04843761 *(Continued)*

	Setting: inpatient Language: English Number of centres: 51 Type of intervention: drug
Participants	**Inclusion criteria:** • Signed informed consent • Requiring admission to hospital for acute medical care (not for purely public health or quarantine purposes) • Current respiratory failure (i.e. receipt of high-flow nasal cannula, non-invasive ventilation, invasive mechanical ventilation, or ECMO (extracorporeal membrane oxygenation) used to treat acute hypoxaemic respiratory failure) • SARS-CoV-2 (COVID-19) infection, documented by a nucleic acid test (NAT) or equivalent testing with most recent rest within 14 days prior to randomisation • Respiratory failure is believed to be due to SARS-CoV-2 pneumonia **Exclusion criteria:** • Known allergy to investigational agent or vehicle • More than 4 days since initiation of support for respiratory failure • Chronic/home mechanical ventilation (invasive or non-invasive) for chronic lung or neuromuscular disease (non-invasive ventilation used solely for sleep-disordered breathing is not an exclusion) • Moribund patient (i.e. not expected to survive 24 hours) • Active use of "comfort care" or other hospice-equivalent standard of care • Expected inability to participate in study procedures • In the opinion of the investigator, any condition for which participation would not be in the best interest of the participant or that could limit protocol-specified assessments • Previous enrolment in TESICO **Agent-specific exclusion criteria** • Prior receipt of any dose of remdesivir during present illness (remdesivir agent) • GFR (glomerular filtration rate) < 30 mL/min and not receiving dialysis (remdesivir agent) • ALT (alanine aminotransferase) or AST (aspartate aminotransferase) > 10 times upper limit of normal (remdesivir agent) • Unwillingness to commit to avoid sex that may result in pregnancy for at least 7 days after completion of remdesivir vs placebo (remdesivir agent) • Refractory hypotension (aviptadil agent) • Severe diarrhoea (aviptadil agent) • Current *C. difficile* infection (aviptadil agent) • Pregnancy or current breast-feeding (aviptadil agent) • End-stage liver disease (aviptadil agent)

Interventions	**Details of intervention:**
	
	• Drug: aviptadil placebo + remdesivir + SOC
	  ○ Dose: RDV 200 mg loading dose (day 1), 100 mg (once daily, 9 days) maintenance doses
	  ○ Dose: aviptadil placebo: 0.9% sodium chloride solution over 12 hours per day for 3 days
	  ○ Route of administration: both intravenous
	
	Treatment details of control group:
	
	• Drug: remdesivir placebo
	  ○ Dose: RDV placebo 200 mg loading dose (day 1), 100 mg (once daily, 9 days) maintenance dose

NCT04843761 *(Continued)*

- Route of administration: intravenous

Concomitant therapy: corticosteroid (in line with NIH treatment guidelines, corticosteroids such as dexamethasone, prednisone, methylprednisolone or hydrocortisone may be administered as SOC)

Outcomes

Primary outcome:

Recovery, assessed at 90 days

- Recovery categorised as 1 (Best): At home and not receiving new supplemental oxygen for ≥ 77 consecutive days; 2: At home and not receiving new supplemental oxygen for 49 to 76 consecutive days; 3: At home and not receiving new supplemental oxygen for 1 to 48 consecutive days; 4: Discharged from hospital but either not yet home or home but receiving new supplemental oxygen; 5: Still hospitalised or receiving hospice care; 6 (Worst): Dead

Secondary outcomes:

- All-cause mortality (time frame: through day 90)
- Time to death (time frame: through day 90)
- Composite of time to recovery, days at home off new supplemental oxygen and time to death (time frame: through day 90)
- Composite of alive, at home, and off new supplemental oxygen (time frame: through day 90)
- Composite of recovered, alive and not recovered, and dead (time frame: through day 90)
  - Recovery defined as alive, at home, and off new supplemental oxygen
- Time from randomisation to recovery (time frame: through day 90)
  - Recovery defined as alive, at home, and off oxygen (treating death as competing risk)
- Days alive outside short-term acute care hospital (time frame: up to day 90)
- Incidence of clinical organ failure or serious infections (time frame: through day 28)
  - Defined as any one or more of: worsening respiratory dysfunction; cardiac and vascular dysfunction; renal dysfunction; hepatic dysfunction; neurological dysfunction, haematological dysfunction; serious infection
- Composite of death, clinical organ failure or serious infections (time frame: through day 90)
- Composite of cardiovascular events and thromboembolic events (time frame: through day 28)
- Composite of cardiovascular events and thromboembolic events (time frame: through day 90)
- Composite of grade 3 and 4 clinical adverse events, serious adverse events (SAEs) or death (time frame: through days 5 and 28)
- Incidence of infusion reactions (time frame: through day 180)
  - Percentage of participants for whom infusion was interrupted or stopped prior to completion for any reason (time frame: through day 90)
  - Percentage of participants for whom infusion was interrupted or stopped prior to completion due to adverse event (time frame: through day 90)
- Composite of hospital readmissions or death (time frame: through day 180)
- Incidence of no home use of supplemental oxygen above pre-morbid oxygen use (time frame: 14 days)
  - Measured as: alive at home for an uninterrupted 14-day period and no use of continuous supplemental oxygen at end of 14-day time period.
- Time to hospital discharge from initial hospitalisation (time frame: through day 180)
- Composite of death or serious clinical COVID-19 related events (time frame: through day 90)
- Pulmonary ordinal outcome (time frame: days 1 to 7, 14, and 28)
  - Oxygen requirements measured by 7 categories (1 = least severe, 7 = most severe). The participant's highest (i.e. most severe) observed score is used.
- Composite of SAEs or death (time frame: through day 180)
- Incidence of home use of supplemental oxygen above pre-morbid oxygen use (time frame: through day 180)
  - Measured as: alive at home and no use of continuous supplemental oxygen for an uninterrupted 14-day period
- In category 4, 5 or 6 at day 90 vs in categories 1 to 3 at day 90 (time frame: day 90)

NCT04843761 *(Continued)*

	• In category 5 or 6 at day 90 vs in categories 1 to 4 at day 90 (time frame: day 90) ○ Categories are 1 (Best): At home an off oxygen for ≥ 77 consecutive days; 2: At home and off oxygen for 49 to 76 consecutive days; 3: At home and off oxygen for 1 to 48 consecutive days; 4: Not hospitalised and either at home on oxygen or not at home; 5: Hospitalised for medical care or in hospice care; 6 (Worst): Dead
Starting date	20 April 2021
Contact information	Samuel Brown, MD Intermountain Medical Center/University of Utah
Notes	• Recruitment status: active, not recruiting • Prospective completion date: April 2023 • Date last update was posted: 3 June 2022 • Sponsor/funding: National Institute of Allergy and Infectious Diseases (NIAID)

NCT04978259

Study name	'Long-term follow-up of a randomized multicenter trial on impact of long-COVID in hospitalized COVID-19 patients - SOLIDARITY Finland Long COVID-19'
Methods	Trial design: RCT • Allocation: randomised • Intervention model: parallel assignment • Masking: open-label • Primary purpose: treatment Sample size: NR • Estimated enrolment: 202 participants Setting: inpatient Language: English Number of centres: 1 (University of Helsinki) Type of intervention: drug

Participants	**Inclusion criteria:**
	• Alive patients who attended the SOLIDARITY Finland remdesivir sub-study
	• Eligibility criteria for SOLIDARITY Finland remdesivir sub-study:
	  ○ Adult patients, 18 years and older
	  ○ Laboratory-confirmed SARS-CoV-2 infection
	  ○ Admitted to the hospital ward or the intensive care unit (ICU)
	  ○ Patient provides written informed consent prior to initiation of the study OR close relative/legal representative provides written informed consent prior to initiation of the study according to the presumed will of the patient when patient is unable to give consent.
	  ○ No anticipated transfer within 72 hours to a non-study hospital
	Exclusion criteria:
	• Severe co-morbidity with life expectancy < 3 months according to investigators' assessment
	• ASAT/ALAT > 5 times the upper limit of normal

NCT04978259 *(Continued)*

- Acute co-morbidity within 7 days before inclusion such as myocardial infarction or unstable angina pectoris (not including troponin elevation due to infection)
- Pregnancy or breastfeeding
- Any reason why, in the opinion of the investigators, the patient should not participate
- Patient participates in a potentially confounding drug or device trial during the course of the study
- Already receiving the study drug
- Renal failure (eGRF < 30 mL/min) or dialysis/continuous veno-venous haemofiltration

Interventions

Intervention details

- Drug: remdesivir
  - Intravenous remdesivir during hospital stay up to 10 days in addition to standard care

Treatment details of control group:

- Local standard of care

Outcomes

Primary study outcomes

- Long-COVID symptoms (time frame: at one year from hospital admission)
  - Specific questionnaire for symptoms and their severity
- Long-COVID symptoms (time frame: at 2 years from hospital admission)
  - Specific questionnaire for symptoms and their severity
- Quality of life (QoL) (time frame: at 1 year from hospital admission)
  - EQ-5D-5L questionnaire assesses the following domains:
    - 1. Mobility
    - 2. Self-care
    - 3. Usual activities
    - 4. Pain and discomfort
    - 5. Anxiety and depression
    - 6. Visual analogue scale of subjective perception of overall health. Questions 1 to 5 are ordinal variables and the trouble severity has 5 degrees of severity from no trouble to the most extreme form of trouble
  - Question 6 is a VAS scale from 0 to 100, where 0 represents the worst and 100 the best possible overall state of health
- Quality of life (QoL) (time frame: at 2 years from hospital admission)
  - EQ-5D-5L questionnaire assesses the following domains:
    - 1. Mobility
    - 2. Self-care
    - 3. Usual activities
    - 4. Pain and discomfort
    - 5. Anxiety and depression
    - 6. Visual analogue scale of subjective perception of overall health
  - Questions 1 to 5 are ordinal variables and the trouble severity has 5 degrees of severity from no trouble to the most extreme form of trouble. Question 6 is a VAS scale from 0 to 100, where 0 represents the worst and 100 the best possible overall state of health.

Other outcomes:

- Mortality (time frame: long-term at 1 year)
  - Obtained from health care registries
- Incidence of comorbidity (time frame: long-term at 1 year, obtained from registries)
  - Obtained from health care registries
- Lung function (time frame: 2 years post-discharge)
  - Spirometry
- Lung function (time frame: 2 years post-discharge)
  - Lung diffusion capacity

NCT04978259 *(Continued)*	• Lung function (time frame: 2 years post-discharge) ○ 6-minute walking test • Whole-genome sequencing (time frame: 2 years post-discharge)
Starting date	24 July 2021
Contact information	Kari AO Tikkinen, University of Helsinki
Notes	• Recruitment status: recruiting • Prospective completion date: 31 December 2023 • Date last update was posted: 25 April 2022 • Sponsor/funding: Clinical Urology and Epidemiology Working Group

Abbreviations
ALT/ALAT = alanine transaminase
AST/ASAT = aspartate transaminase
ECMO = extracorporeal membrane oxygenation
eGFR = estimated glomerular filtration rate
ICU = intensive care unit
IGA = immunoglobulin A
IGM = immunoglobulin M
INR = international normalised ratio
NIAID = National Institute of Allergy and Infectious Diseases
NR = not reported
PaO_2/FiO_2 = ratio of arterial oxygen partial pressure to fractional inspired oxygen
PCR = polymerase chain reaction
RCT = randomised controlled trial
RDV = remdesivir
RT-PCR = reverse transcription polymerase chain reaction
SaO_2 = arterial oxygen saturation
SAE = serious adverse events
SoC = standard of care
WHO = World Health Organization

RISK OF BIAS

Legend: ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

Risk of bias for analysis 1.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beigel 2020	✓	✓	✓	✓	✓	✓
Spinner 2020	✓	✓	✓	✓	✓	✓
Wang 2020	~	✓	✓	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
WHO Solidarity Trial Consortium 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.3 In-hospital mortality at up to day 150

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
WHO Solidarity Trial Consortium 2022	✓	✓	✓	✓	~	~

Risk of bias for analysis 1.4 All-cause mortality (time-to-event)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beigel 2020	✓	✓	✓	✓	✓	✓
WHO Solidarity Trial Consortium 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.5 Clinical improvement: alive and ready to discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beigel 2020	✓	✓	✓	✓	✓	✓
Spinner 2020	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Wang 2020	~	✓	✓	✓	✓	~
WHO Solidarity France 2021	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.6 Clinical improvement: alive and ready to discharge (time-to-event)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Spinner 2020	✓	✓	✓	✓	✓	✓
WHO Solidarity France 2021	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.7 Clinical worsening: new need for invasive mechanical ventilation or death

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
WHO Solidarity France 2021	✓	~	✓	~	✓	~

Risk of bias for analysis 1.8 Clinical worsening: new need for invasive mechanical ventilation or death (time-to-event)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beigel 2020	✓	✓	✓	✓	✗	✗
WHO Solidarity France 2021	✓	~	✓	~	✓	~

Risk of bias for analysis 1.9 Adverse events, any grade

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beigel 2020	✓	~	~	✓	✓	~
Spinner 2020	✓	✓	~	~	✓	~
Wang 2020	~	✓	~	✓	✓	~
WHO Solidarity France 2021	✓	✓	✓	~	~	~

Risk of bias for analysis 1.10 Adverse events, grade 3 to 4

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beigel 2020	✓	~	~	✓	✓	~
Spinner 2020	✓	✓	~	✓	~	~
Wang 2020	~	✓	~	✓	✓	~
WHO Solidarity France 2021	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.11 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beigel 2020	✓	~	~	✓	✓	~
Spinner 2020	✓	✓	~	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Wang 2020	~	✓	~	✓	✓	~
WHO Solidarity France 2021	✓	✓	✓	~	✓	~

Risk of bias for analysis 1.12 Ventilator-free days at day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
WHO Solidarity Canada 2022	✓	✗	✗	~	~	✗

Risk of bias for analysis 2.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.1.1 Age < 50 years						
WHO Solidarity Trial Consortium 2022	✓	✓	✓	✓	✓	✓
Subgroup 2.1.2 Age 50 to 69 years						
WHO Solidarity Trial Consortium 2022	✓	✓	✓	✓	✓	✓
Subgroup 2.1.3 Age > 69 years						
WHO Solidarity Trial Consortium 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.1.1 ≤ 10 days of symptom onset						
Wang 2020	~	✓	✓	✓	✓	~
Subgroup 3.1.2 > 10 days of symptom onset						
Wang 2020	~	✓	✓	✓	✓	~

Risk of bias for analysis 4.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.1.1 No oxygen at baseline						
Beigel 2020	✓	✓	✓	✓	✓	✓
Spinner 2020	✓	✓	✓	✓	✓	✓
WHO Solidarity Trial Consortium 2022	✓	✓	✓	✓	✓	✓
Subgroup 4.1.2 Low-flow oxygen at baseline						
Beigel 2020	✓	✓	✓	✓	✓	✓
Subgroup 4.1.3 Low-flow or high-flow oxygen at baseline						
WHO Solidarity Trial Consortium 2022	✓	✓	✓	✓	✓	✓
Subgroup 4.1.4 Mechanical ventilation at baseline						
Beigel 2020	✓	✓	✓	✓	✓	✓
WHO Solidarity Trial Consortium 2022	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.2 In-hospital mortality at up to day 150

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.2.1 No oxygen at baseline						
WHO Solidarity Trial Consortium 2022	✓	✓	✓	✓	~	~
Subgroup 4.2.2 Low-flow or high-flow oxygen at baseline						
WHO Solidarity Trial Consortium 2022	✓	✓	✓	✓	~	~
Subgroup 4.2.3 Mechanical ventilation at baseline						
WHO Solidarity Trial Consortium 2022	✓	✓	✓	✓	~	~

Risk of bias for analysis 5.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 5.1.1 5-day remdesivir						
Spinner 2020	✓	✓	✓	✓	✓	✓
Subgroup 5.1.2 10-day remdesivir						
Spinner 2020	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Gottlieb 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.2 Clinical improvement: symptom alleviation at up to day 14

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Gottlieb 2021	✓	✓	✗	✗	~	✗

Risk of bias for analysis 6.3 Clinical worsening: admission to hospital or death at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Gottlieb 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.4 Serious adverse events

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Gottlieb 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.5 Adverse events, any grade

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Gottlieb 2021	✓	✓	✓	✓	✓	✓

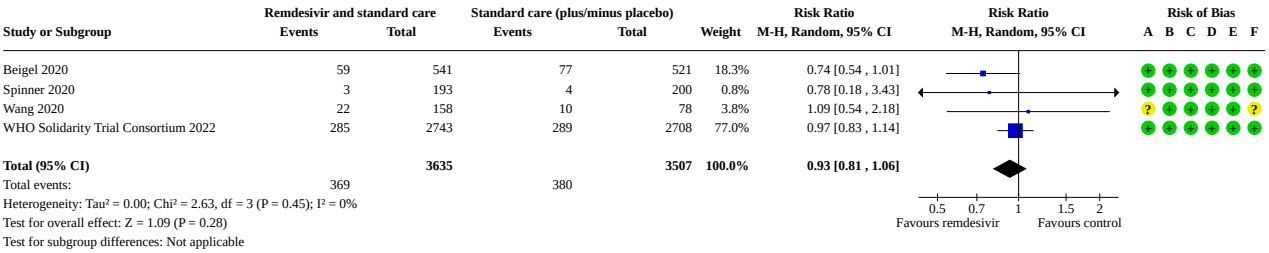
DATA AND ANALYSES

Comparison 1. Remdesivir and standard care versus standard care (plus/minus placebo) in moderate to severe COVID-19

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 All-cause mortality at up to day 28	4	7142	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.81, 1.06]
1.2 All-cause mortality at up to day 60	1	1281	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.69, 1.05]
1.3 In-hospital mortality at up to day 150	1	8275	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.84, 1.03]
1.4 All-cause mortality (time-to-event)	2	6513	Hazard Ratio (IV, Random, 95% CI)	0.88 [0.67, 1.16]
1.5 Clinical improvement: alive and ready to discharge	4	2514	Risk Ratio (M-H, Random, 95% CI)	1.11 [1.06, 1.17]
1.6 Clinical improvement: alive and ready to discharge (time-to-event)	2	1225	Hazard Ratio (IV, Random, 95% CI)	1.06 [0.93, 1.20]
1.7 Clinical worsening: new need for invasive mechanical ventilation or death	1	683	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.52, 0.94]
1.8 Clinical worsening: new need for invasive mechanical ventilation or death (time-to-event)	2	1734	Hazard Ratio (IV, Random, 95% CI)	0.67 [0.54, 0.82]
1.9 Adverse events, any grade	4	2498	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.92, 1.18]
1.10 Adverse events, grade 3 to 4	4	2498	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.84, 1.01]
1.11 Serious adverse events	4	2498	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.65, 1.07]

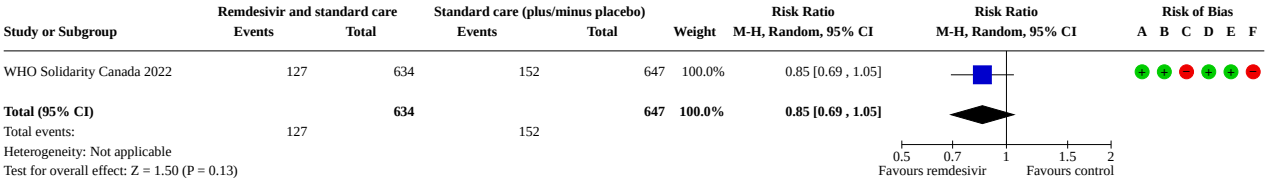
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.12 Ventilator-free days at day 28	1	1281	Mean Difference (IV, Random, 95% CI)	1.90 [0.61, 3.19]

Analysis 1.1. Comparison 1: Remdesivir and standard care versus standard care (plus/minus placebo) in moderate to severe COVID-19, Outcome 1: All-cause mortality at up to day 28



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Remdesivir and standard care versus standard care (plus/minus placebo) in moderate to severe COVID-19, Outcome 2: All-cause mortality at up to day 60

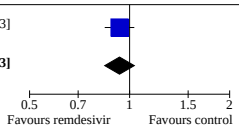


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: Remdesivir and standard care versus standard care (plus/minus placebo) in moderate to severe COVID-19, Outcome 3: In-hospital mortality at up to day 150

Study or Subgroup	Remdesivir and standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
WHO Solidarity Trial Consortium 2022	602	4146	643	4129	100.0%	0.93 [0.84 , 1.03]	+ + + + ? ?
Total (95% CI)		**4146**		**4129**	**100.0%**	**0.93 [0.84 , 1.03]**	
Total events:	602		643				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.34 (P = 0.18)
Test for subgroup differences: Not applicable

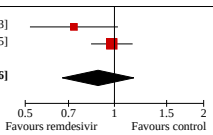


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: Remdesivir and standard care versus standard care (plus/minus placebo) in moderate to severe COVID-19, Outcome 4: All-cause mortality (time-to-event)

Study or Subgroup	log[Hazard Ratio]	SE	Remdesivir and standard care Total	Standard care (plus/minus placebo) Total	Weight	Hazard Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
Beigel 2020	-0.314711	0.174362	541	521	36.4%	0.73 [0.52 , 1.03]	+ + + + + +
WHO Solidarity Trial Consortium 2022	-0.020203	0.082342	2743	2708	63.6%	0.98 [0.83 , 1.15]	+ + + + + +
Total (95% CI)			**3284**	**3229**	**100.0%**	**0.88 [0.67 , 1.16]**	

Heterogeneity: Tau² = 0.02; Chi² = 2.33, df = 1 (P = 0.13); I² = 57%
Test for overall effect: Z = 0.90 (P = 0.37)
Test for subgroup differences: Not applicable

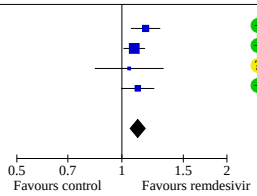


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: Remdesivir and standard care versus standard care (plus/minus placebo) in moderate to severe COVID-19, Outcome 5: Clinical improvement: alive and ready to discharge

Study or Subgroup	Remdesivir and standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Beigel 2020	357	541	294	521	26.3%	1.17 [1.06 , 1.29]	+ + + + + +
Spinner 2020	178	193	170	200	48.5%	1.09 [1.01 , 1.17]	+ + + + + +
Wang 2020	92	150	45	77	4.8%	1.05 [0.84 , 1.32]	? + + + + ?
WHO Solidarity France 2021	265	414	241	418	20.5%	1.11 [1.00 , 1.24]	+ + + ? + ?
Total (95% CI)		**1298**		**1216**	**100.0%**	**1.11 [1.06 , 1.17]**	
Total events:	892		750				

Heterogeneity: Tau² = 0.00; Chi² = 1.96, df = 3 (P = 0.58); I² = 0%
Test for overall effect: Z = 4.13 (P < 0.0001)
Test for subgroup differences: Not applicable

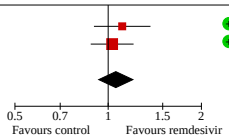


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.6. Comparison 1: Remdesivir and standard care versus standard care (plus/minus placebo) in moderate to severe COVID-19, Outcome 6: Clinical improvement: alive and ready to discharge (time-to-event)

Study or Subgroup	log[Hazard Ratio]	SE	Remdesivir and standard care Total	Standard care (plus/minus placebo) Total	Weight	Hazard Ratio IV, Random, 95% CI
Spinner 2020	0.10436	0.107189	193	200	36.5%	1.11 [0.90 , 1.37]
WHO Solidarity France 2021	0.029559	0.08124	414	418	63.5%	1.03 [0.88 , 1.21]
Total (95% CI)			**607**	**618**	**100.0%**	**1.06 [0.93 , 1.20]**

Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.88 (P = 0.38)
Test for subgroup differences: Not applicable

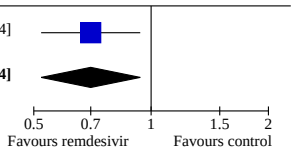


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.7. Comparison 1: Remdesivir and standard care versus standard care (plus/minus placebo) in moderate to severe COVID-19, Outcome 7: Clinical worsening: new need for invasive mechanical ventilation or death

Study or Subgroup	Remdesivir and standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
WHO Solidarity France 2021	60	339	87	344	100.0%	0.70 [0.52 , 0.94]
Total (95% CI)		**339**		**344**	**100.0%**	**0.70 [0.52 , 0.94]**
Total events:	60		87			

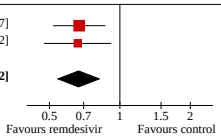
Heterogeneity: Not applicable
Test for overall effect: Z = 2.39 (P = 0.02)
Test for subgroup differences: Not applicable



Analysis 1.8. Comparison 1: Remdesivir and standard care versus standard care (plus/minus placebo) in moderate to severe COVID-19, Outcome 8: Clinical worsening: new need for invasive mechanical ventilation or death (time-to-event)

Study or Subgroup	log[Hazard Ratio]	SE	Remdesivir plus standard care Total	Standard care (plus/minus placebo) Total	Weight	Hazard Ratio IV, Random, 95% CI
Beigel 2020	-0.400478	0.131294	533	518	62.2%	0.67 [0.52 , 0.87]
WHO Solidarity France 2021	-0.415515	0.168552	339	344	37.8%	0.66 [0.47 , 0.92]
Total (95% CI)			**872**	**862**	**100.0%**	**0.67 [0.54 , 0.82]**

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.94); I² = 0%
Test for overall effect: Z = 3.92 (P < 0.0001)
Test for subgroup differences: Not applicable

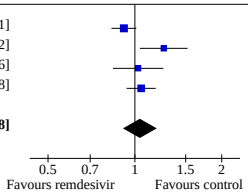


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.9. Comparison 1: Remdesivir and standard care versus standard care (plus/minus placebo) in moderate to severe COVID-19, Outcome 9: Adverse events, any grade

Study or Subgroup	Remdesivir and standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Beigel 2020	305	532	323	516	31.0%	0.92 [0.83 , 1.01]
Spinner 2020	113	193	93	200	20.6%	1.26 [1.04 , 1.52]
Wang 2020	102	155	50	78	19.5%	1.03 [0.84 , 1.26]
WHO Solidarity France 2021	241	406	236	418	28.9%	1.05 [0.94 , 1.18]
Total (95% CI)		**1286**		**1212**	**100.0%**	**1.04 [0.92 , 1.18]**
Total events:	761		702			

Heterogeneity: Tau² = 0.01; Chi² = 9.41, df = 3 (P = 0.02); I² = 68%
Test for overall effect: Z = 0.61 (P = 0.54)
Test for subgroup differences: Not applicable

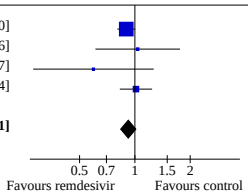


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.10. Comparison 1: Remdesivir and standard care versus standard care (plus/minus placebo) in moderate to severe COVID-19, Outcome 10: Adverse events, grade 3 to 4

Study or Subgroup	Remdesivir and standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Beigel 2020	273	532	295	516	73.0%	0.90 [0.80 , 1.00]
Spinner 2020	24	193	24	200	3.2%	1.04 [0.61 , 1.76]
Wang 2020	13	155	11	78	1.6%	0.59 [0.28 , 1.27]
WHO Solidarity France 2021	128	406	130	418	22.2%	1.01 [0.83 , 1.24]
Total (95% CI)		**1286**		**1212**	**100.0%**	**0.92 [0.84 , 1.01]**
Total events:	438		460			

Heterogeneity: Tau² = 0.00; Chi² = 2.57, df = 3 (P = 0.46); I² = 0%
Test for overall effect: Z = 1.71 (P = 0.09)
Test for subgroup differences: Not applicable

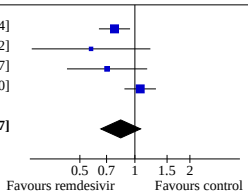


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.11. Comparison 1: Remdesivir and standard care versus standard care (plus/minus placebo) in moderate to severe COVID-19, Outcome 11: Serious adverse events

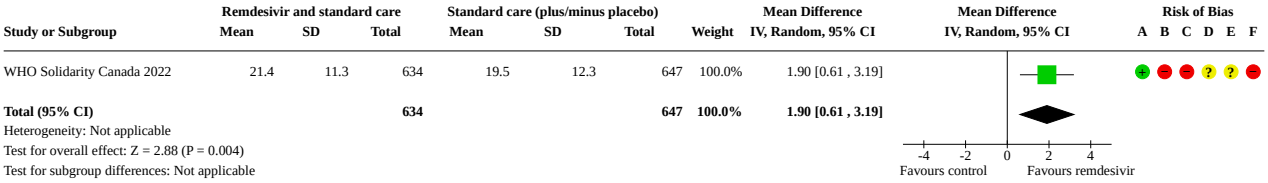
Study or Subgroup	Remdesivir and standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Beigel 2020	130	532	163	516	37.4%	0.77 [0.64 , 0.94]
Spinner 2020	10	193	18	200	9.1%	0.58 [0.27 , 1.22]
Wang 2020	28	155	20	78	16.3%	0.70 [0.43 , 1.17]
WHO Solidarity France 2021	135	406	130	418	37.2%	1.07 [0.88 , 1.30]
Total (95% CI)		**1286**		**1212**	**100.0%**	**0.84 [0.65 , 1.07]**
Total events:	303		331			

Heterogeneity: Tau² = 0.03; Chi² = 7.37, df = 3 (P = 0.06); I² = 59%
Test for overall effect: Z = 1.40 (P = 0.16)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.12. Comparison 1: Remdesivir and standard care versus standard care (plus/minus placebo) in moderate to severe COVID-19, Outcome 12: Ventilator-free days at day 28

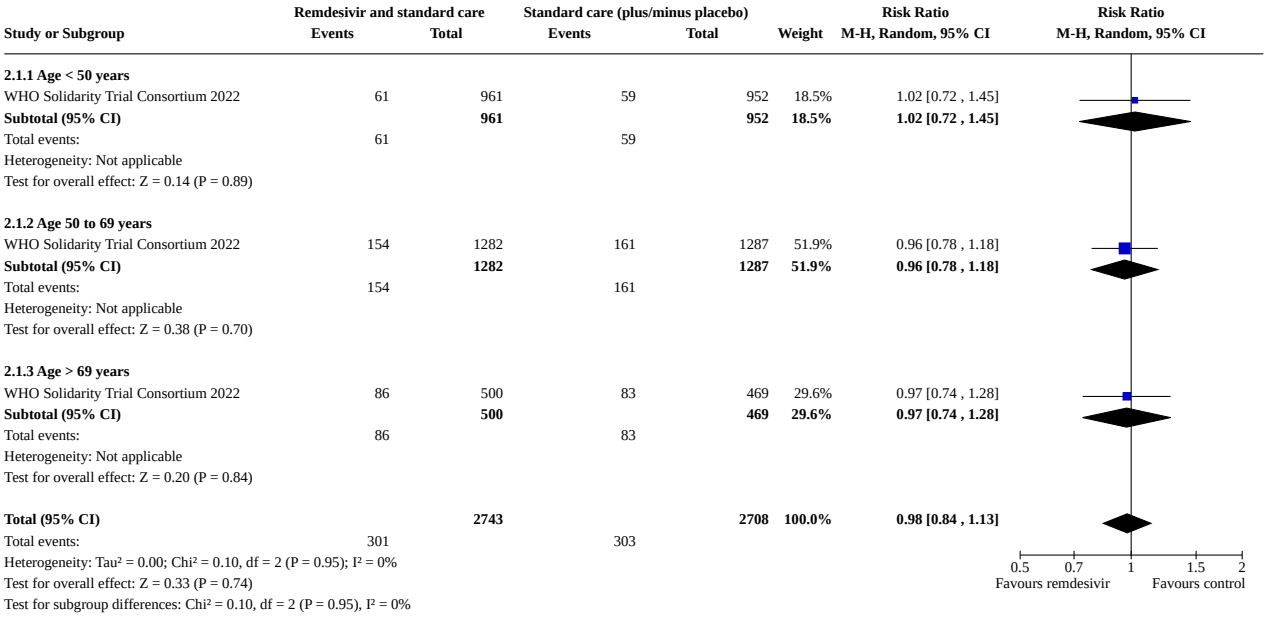


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 2. Subgroup analysis (age of participants): remdesivir and standard care versus standard care (plus/minus placebo)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 All-cause mortality at up to day 28	1	5451	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.84, 1.13]
2.1.1 Age < 50 years	1	1913	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.72, 1.45]
2.1.2 Age 50 to 69 years	1	2569	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.78, 1.18]
2.1.3 Age > 69 years	1	969	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.74, 1.28]

Analysis 2.1. Comparison 2: Subgroup analysis (age of participants): remdesivir and standard care versus standard care (plus/minus placebo), Outcome 1: All-cause mortality at up to day 28

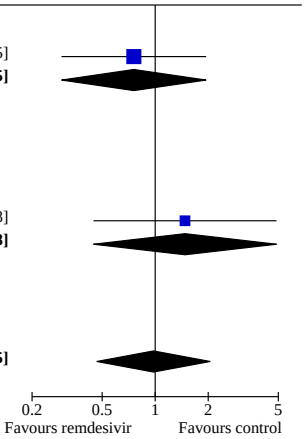


Comparison 3. Subgroup analysis (timing of first dose administration with illness onset): remdesivir and standard care versus standard care (plus/minus placebo)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 All-cause mortality at up to day 28	1	233	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.47, 2.05]
3.1.1 ≤ 10 days of symptom onset	1	118	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.29, 1.95]
3.1.2 > 10 days of symptom onset	1	115	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.45, 4.88]

Analysis 3.1. Comparison 3: Subgroup analysis (timing of first dose administration with illness onset): remdesivir and standard care versus standard care (plus/minus placebo), Outcome 1: All-cause mortality at up to day 28

Study or Subgroup	Remdesivir and standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 ≤ 10 days of symptom onset						
Wang 2020	8	71	7	47	61.6%	0.76 [0.29 , 1.95]
Subtotal (95% CI)		**71**		**47**	**61.6%**	**0.76 [0.29 , 1.95]**
Total events:	8		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
3.1.2 > 10 days of symptom onset						
Wang 2020	12	84	3	31	38.4%	1.48 [0.45 , 4.88]
Subtotal (95% CI)		**84**		**31**	**38.4%**	**1.48 [0.45 , 4.88]**
Total events:	12		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
Total (95% CI)		**155**		**78**	**100.0%**	**0.98 [0.47 , 2.05]**
Total events:	20		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.74, df = 1 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.06 (P = 0.95)						
Test for subgroup differences: Chi² = 0.74, df = 1 (P = 0.39), I² = 0%						

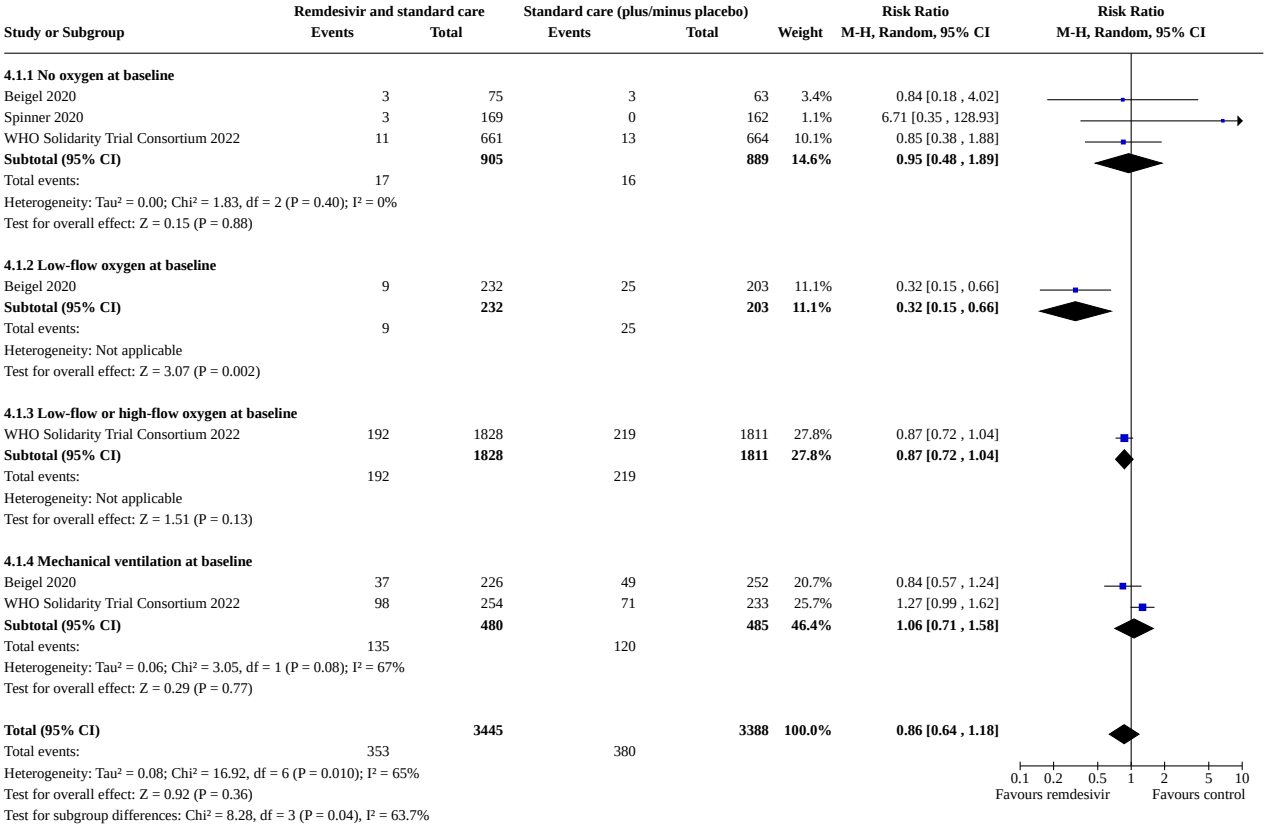


Comparison 4. Subgroup analysis (severity of condition, based on respiratory support at baseline): remdesivir and standard care versus standard care (plus/minus placebo)

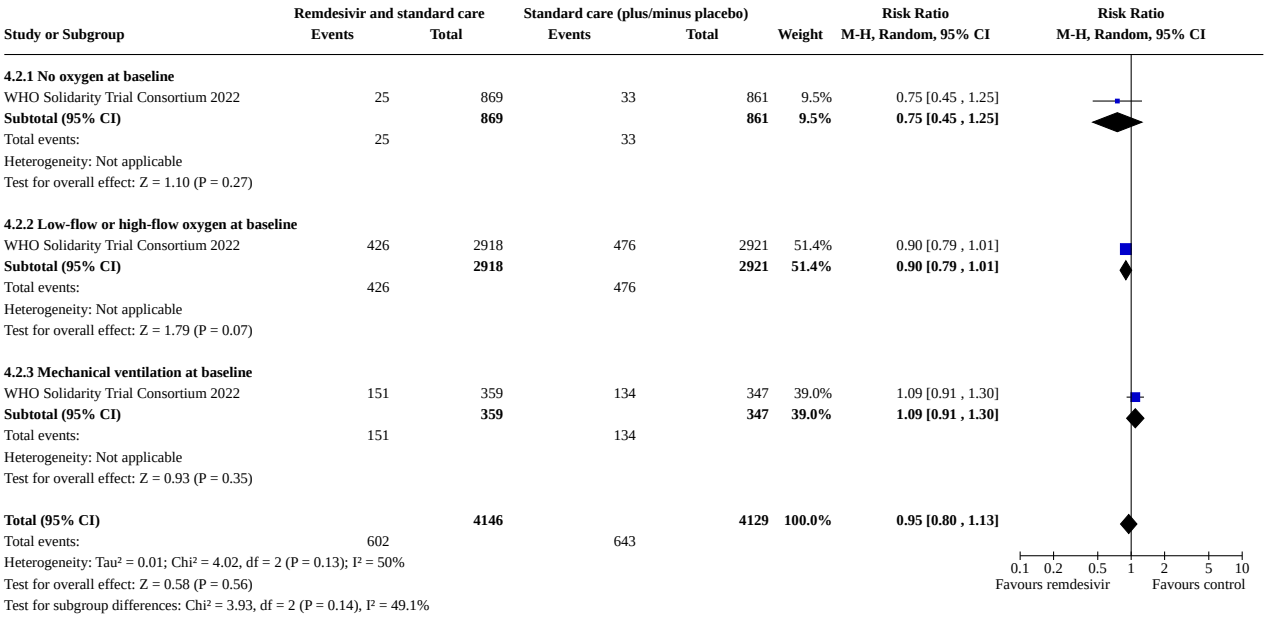
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 All-cause mortality at up to day 28	3	6833	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.64, 1.18]
4.1.1 No oxygen at baseline	3	1794	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.48, 1.89]
4.1.2 Low-flow oxygen at baseline	1	435	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.15, 0.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1.3 Low-flow or high-flow oxygen at baseline	1	3639	Risk Ratio (M-H, Random, 95% CI)	0.87 [0.72, 1.04]
4.1.4 Mechanical ventilation at baseline	2	965	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.71, 1.58]
4.2 In-hospital mortality at up to day 150	1	8275	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.80, 1.13]
4.2.1 No oxygen at baseline	1	1730	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.45, 1.25]
4.2.2 Low-flow or high-flow oxygen at baseline	1	5839	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.79, 1.01]
4.2.3 Mechanical ventilation at baseline	1	706	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.91, 1.30]

Analysis 4.1. Comparison 4: Subgroup analysis (severity of condition, based on respiratory support at baseline): remdesivir and standard care versus standard care (plus/minus placebo), Outcome 1: All-cause mortality at up to day 28



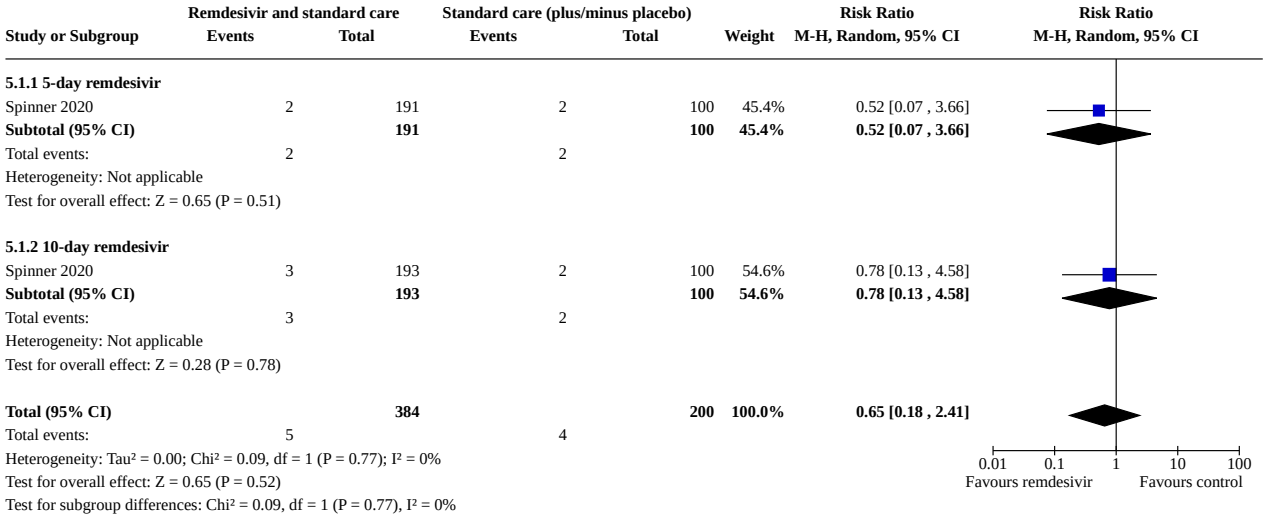
Analysis 4.2. Comparison 4: Subgroup analysis (severity of condition, based on respiratory support at baseline): remdesivir and standard care versus standard care (plus/minus placebo), Outcome 2: In-hospital mortality at up to day 150



Comparison 5. Subgroup analysis (duration of remdesivir application): remdesivir and standard care versus standard care (plus/minus placebo)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 All-cause mortality at up to day 28	1	584	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.18, 2.41]
5.1.1 5-day remdesivir	1	291	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.07, 3.66]
5.1.2 10-day remdesivir	1	293	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.13, 4.58]

Analysis 5.1. Comparison 5: Subgroup analysis (duration of remdesivir application): remdesivir and standard care versus standard care (plus/minus placebo), Outcome 1: All-cause mortality at up to day 28



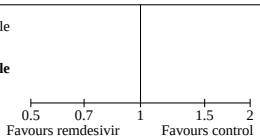
Comparison 6. Remdesivir and standard care versus standard care (plus/minus placebo) in mild COVID-19

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 All-cause mortality at up to day 28	1	562	Risk Ratio (M-H, Random, 95% CI)	Not estimable
6.2 Clinical improvement: symptom alleviation at up to day 14	1	126	Hazard Ratio (IV, Random, 95% CI)	1.41 [0.73, 2.71]
6.3 Clinical worsening: admission to hospital or death at up to day 28	1	562	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.11, 0.75]
6.4 Serious adverse events	1	562	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.10, 0.70]
6.5 Adverse events, any grade	1	562	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.76, 1.10]

Analysis 6.1. Comparison 6: Remdesivir and standard care versus standard care (plus/minus placebo) in mild COVID-19, Outcome 1: All-cause mortality at up to day 28

Study or Subgroup	Remdesivir and standard care Events	Total	Standard care (plus/minus placebo) Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Gottlieb 2021	0	279	0	283		Not estimable		+ + + + + +
Total (95% CI)		**279**		**283**		**Not estimable**		
Total events:	0		0					

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

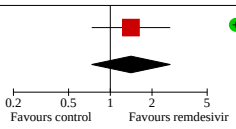


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.2. Comparison 6: Remdesivir and standard care versus standard care (plus/minus placebo) in mild COVID-19, Outcome 2: Clinical improvement: symptom alleviation at up to day 14

Study or Subgroup	log[Hazard Ratio]	SE	Remdesivir and standard care Total	Standard care (plus/minus placebo) Total	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
Gottlieb 2021	0.34359	0.332723	66	60	100.0%	1.41 [0.73 , 2.71]		+ + - - ? -
Total (95% CI)			**66**	**60**	**100.0%**	**1.41 [0.73 , 2.71]**		

Heterogeneity: Not applicable
Test for overall effect: Z = 1.03 (P = 0.30)
Test for subgroup differences: Not applicable

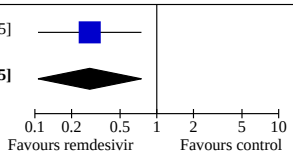


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.3. Comparison 6: Remdesivir and standard care versus standard care (plus/minus placebo) in mild COVID-19, Outcome 3: Clinical worsening: admission to hospital or death at up to day 28

Study or Subgroup	Remdesivir Events	Total	Placebo or standard care alone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI	Risk of Bias A B C D E F
Gottlieb 2021	5	279	18	283	100.0%	0.28 [0.11 , 0.75]		+ + + + + +
Total (95% CI)		**279**		**283**	**100.0%**	**0.28 [0.11 , 0.75]**		
Total events:	5		18					

Heterogeneity: Not applicable
Test for overall effect: Z = 2.54 (P = 0.01)
Test for subgroup differences: Not applicable

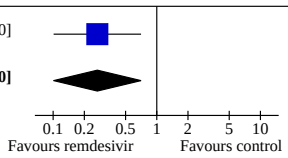


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.4. Comparison 6: Remdesivir and standard care versus standard care (plus/minus placebo) in mild COVID-19, Outcome 4: Serious adverse events

Study or Subgroup	Remdesivir Events	Remdesivir Total	Placebo or standard care alone Events	Placebo or standard care alone Total	Weight	Risk Ratio M-H, Random, 95% CI
Gottlieb 2021	5	279	19	283	100.0%	0.27 [0.10 , 0.70]
Total (95% CI)		**279**		**283**	**100.0%**	**0.27 [0.10 , 0.70]**
Total events:	5		19			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.67 (P = 0.008)
Test for subgroup differences: Not applicable

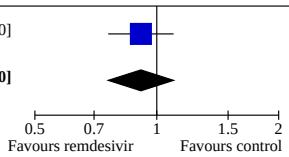


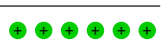
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.5. Comparison 6: Remdesivir and standard care versus standard care (plus/minus placebo) in mild COVID-19, Outcome 5: Adverse events, any grade

Study or Subgroup	Remdesivir Events	Remdesivir Total	Placebo or standard care alone Events	Placebo or standard care alone Total	Weight	Risk Ratio M-H, Random, 95% CI
Gottlieb 2021	118	279	131	283	100.0%	0.91 [0.76 , 1.10]
Total (95% CI)		**279**		**283**	**100.0%**	**0.91 [0.76 , 1.10]**
Total events:	118		131			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.95 (P = 0.34)
Test for subgroup differences: Not applicable





Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

ADDITIONAL TABLES

Table 1. Glossary

Phrase/Word	Meaning/Description
Acute respiratory distress syndrome (ARDS)	ARDS is characterised by a massive response of the respiratory system to a wide variety of external and internal noxious stimuli. There is a disturbance of oxygen uptake and an acute onset. ARDS is the common end route of a wide variety of diseases leading to a severe systemic inflammatory response. The condition should be distinguished from disturbances of respiration caused by cardiac diseases.
Adverse event	An adverse event in the context of clinical trials is an unwanted medical occurrence in patients receiving a pharmacological or non-pharmacological treatment, or both. An adverse event may not necessarily be considered to be related to the treatment.
Antimicrobials	Drugs used to treat diseases caused by micro-organisms (bacteria, fungi, viruses, parasites).
Antiviral (medicine)	An agent that is directed against viruses

Table 1. Glossary *(Continued)*

Bias	(Unconscious) distortion and misinterpretation of research results, especially those obtained experimentally. The most important sources for bias are as follows. • Selection bias: people are more likely to be included in the study if they have a certain characteristic (age, gender, ethnicity, social class, etc.). • Information bias: the data collected as part of the study is subject to error. • Publication bias: studies that show statistically significant results are published preferentially. • Confounding: the result of a study is distorted by interference.
Controlled non-randomised study	A study in which the effects of a pharmacological or non-pharmacological measure, or both, are compared between different groups of participants. The term 'controlled' means that the measure under investigation (intervention, verum) is compared with another measure (placebo or another intervention). The group of participants receiving the intervention under study is known as the intervention group. The group of participants who do not receive the intervention is known as the control group. A controlled non-randomised study is easier to conduct than a randomised controlled trial, but has much less power (see bias).
Convalescent plasma	Blood plasma from patients who have had a disease (e.g. COVID-19). Transfer of convalescent plasma to naive patients (patients who do not have antibodies themselves) leads to an increase in the immune defence of the receiving patient because convalescent plasma contains antibodies.
Corticosteroids	Hormones that are mainly produced in the adrenal cortex. Corticosteroids influence many biological processes in the organism, and are in particular closely linked to the immune system. Important naturally occurring representatives are cortisone and cortisol. Examples of synthetically produced corticosteroids are dexamethasone and budesonide.
Dichotomous	Dichotomy describes a system that can have exactly two mutually exclusive states. Example: either one has a certain disease (state A), or one does not have this disease (state B). The co-occurrence of state A and state B is impossible.
Ebola	Ebola is a viral disease that is often severe. The Ebola virus belongs to the *Filoviridae* (from Latin 'filum' = filamentous). There are at least six different species of the virus. Ebola virus was previously called haemorrhagic fever because it is accompanied by high fever and severe internal and external bleeding.
Heterogeneous	Heterogeneity can be translated as 'non-uniformity'. It is the opposite of homogeneity. In the context of meta-analyses, heterogeneity is a measure of the comparability of clinical trials. For example, studies that examine different populations (e.g. children versus adults) have limited comparability and can lead to misleading conclusions when the data from such studies are pooled in a meta-analysis.
Hydroxychloroquine	A drug related to chloroquine, which is used mainly for the treatment of rheumatoid arthritis, lupus erythematosus, and the prevention of malaria.
Immunocompromised status	Immunocompromised are people who have a congenital or acquired disorder of the immune response. Examples of acquired disorders include infection with HIV. Long-term treatment with certain drugs (e.g. corticosteroids) can also lead to disorders/weakening of the immune response.
Interventions	The term 'intervention' in the context of clinical trials refers to the measure whose effect (superiority, inferiority, non-inferiority) on a specific condition is to be assessed in comparison to other measures. An intervention need not always consist of the administration of a specific drug (so-called non-pharmacological interventions).
Mechanical ventilation	Mechanical ventilation is the term used to describe a procedure in which oxygen is supplied to the patient with the aid of ventilators or other devices. This measure is very restrictive and not without risk, and is therefore used only if the patient can no longer take in enough oxygen through his or her natural breathing (spontaneous respiration). In **this review**, the following procedures are subsumed under the term 'mechanical ventilation'.

Table 1. Glossary *(Continued)*

	• High-flow nasal cannula: oxygen is applied to the patient through the nose at a high flow rate. In addition to the oxygen, the patient can still breathe room air. • Non-invasive mechanical ventilation: the patient is assisted in breathing by applying pressure during exhalation and/or inhalation, for example via a tight-fitting mask or a ventilation helmet. As a rule, the patient is awake during this process. Sensitive guidance of the patient is particularly important. • Invasive mechanical ventilation: the patient is intubated (a breathing tube is inserted into the trachea) and ventilated by a machine.
Middle East respiratory syndrome (MERS)	MERS is a respiratory disease caused by a coronavirus (MERS-CoV). Most cases of the disease are asymptomatic. Diarrhoea is a common accompanying symptom. In severe cases, pneumonia develops.
Monoclonal antibody (MAB)	Antibodies in general are produced by the organism (specifically the immune system) when it is exposed to an antigen (for example, pathogenic micro-organisms and viruses). By reacting with specific parts of the antigen, the antibody can render it harmless. So-called monoclonal antibodies are produced by infecting mice with an antigen, for example. The immune system (especially the B cells) of the infected mouse then produces antibodies that are specifically active against the antigen. These cells accumulate in the spleen of the infected mouse. These cells are then isolated from the animal's spleen in a complicated process and multiplied in vitro (i.e. in the test tube). The resulting monoclonal antibodies are all derived from genetically identical cells and are directed against a specific antigen. Monoclonal antibodies are administered in medicine when the patient does not produce any antibodies or produces too few of his or her own. In addition, these specific antibodies also enable the identification of antigens in the detection of various diseases.
Nasal prongs	Nasal prongs, or nasal cannula, is a device used to deliver low-flow oxygen to the nose through a small plastic tube.
Observational study	Data collection in a specific population under a specific research question. The essential characteristic of an observational study is that no intervention/experiment is carried out.
Placebo	A placebo is a dummy drug that does not contain a pharmacologically active substance.
Randomised controlled trial	A randomised controlled trial is the best way to obtain conclusions regarding the efficacy and effectiveness of a pharmacological or non-pharmacological intervention, or both. The term 'controlled' means that the measure under investigation (intervention, verum) is compared with another measure (placebo or another intervention). The term 'randomised' means that the participants in the study are randomly assigned to one of two or more prespecified treatment groups. The group of participants receiving the intervention under study is known as the intervention group. The group of participants who do not receive the intervention is known as the control group.
Severe acute respiratory syndrome (SARS)	A disease caused by SARS-CoV, which, similar to COVID-19, results in fever and muscle pain in combination with other flu-like signs. In severe cases, atypical pneumonia may occur.
Systematic review	Scientific process of critical judgement of the data available with regard to a specific question. A 'systematic' approach is taken. This includes: • formulation of a research question; • systematic and comprehensive search for data (studies); • clearly defined criteria that the identified studies must fulfil in order to be included in the evaluation; • repeatable and uniform guidelines for data analysis. A systematic review can include a meta-analysis, but this is not required. The aim of a systematic review is to answer the defined research question, or, if this is not possible, to identify gaps in the scientific coverage of the research question.

Table 2. Characteristics of ongoing studies

Study ID	Comparison	Aimed enrolment (n)	Expected completion date
NCT04252664	Remdesivir compared to placebo	308	Recruiting suspended, no publication available yet
NCT04351724	Remdesivir compared to standard care	NR (remdesivir arm); 500 (all study arms)	Recruiting
NCT04978259	Remdesivir compared to standard care	202	Recruiting
NCT04843761	Remdesivir compared to placebo	640	Active, not recruiting

NR = not reported

Table 3. Overview of included studies

NA	Beigel 2020[a]	Spinner 2020	Wang 2020	WHO Solidarity Trial Consortium 2022	Mahajan 2021	Gottlieb 2021	WHO Solidarity Canada 2022	WHO Solidarity France 2021	WHO Solidarity Norway 2021
	(By date of publication)								
Setting	• Inpatient • Multinational	• Inpatient • Multinational	• Inpatient • China	• Inpatient • Multinational	• Inpatient • India	• Outpatient • Multinational	• Inpatient • Canada	• Inpatient • France, Belgium, Austria, Portugal, Luxembourg	• Inpatient • Norway
Design	• Randomised • Double-blind • Placebo-controlled	• Randomised • Open-label • Controlled	• Randomised • Double-blind • Placebo-controlled	• Randomised • Open-label • Controlled	• Randomised • Open-label • Controlled	• Randomised • Double-blind • Placebo-controlled	• Randomised • Open-label • Controlled	• Randomised • Open-label • Controlled	• Randomised • Open-label • Controlled
Study protocol	Reported	Reported	Reported	Reported	Not reported	Reported	Reported (WHO Trial Consortium)	Reported (WHO Trial Consortium)	Reported (WHO Trial Consortium)
Statistical analysis plan	Reported	Reported	Reported	Reported	Not reported	Reported	Reported (WHO Trial Consortium)	Reported (WHO Trial Consortium)	Reported (WHO Trial Consortium)
Intervention (remdesivir) **(duration of application (days))**	10	5 or 10	10	10	5	3	10	10	10
Control	SoC	Placebo + SoC	Placebo + SoC	SoC	SoC	SoC	SoC	SoC	SoC

Table 3. Overview of included studies *(Continued)*

Allocated participants (n)	1062	596	236	8320	82	584	1282	857	101
Number of participants per trial arm (allocated/evaluated)	Intervention: 541/541 Placebo + SoC: 521/521	5-day intervention: 199/191 10-day intervention: 197/193 SoC: 200/200	Intervention: 158/158 Placebo + SoC: 78/78	Intervention: 4169/4146 SoC: 4151/4129	Intervention: 41/34 SoC: 41/36	Intervention: 292/279 Placebo: 292/283	Intervention: 634/634 SoC: 648/647 **Participants enrolled separate from WHO Solidarity Trial :** Intervention: 170 SoC: 153	Intervention: 429/414 SoC: 428/418 **Participants enrolled separate from WHO Solidarity Trial:** Intervention: 210 SoC: 207	Intervention: 43/42 SoC: 58/57 **No participants enrolled separate from WHO Solidarity Trial**
	Severity of condition according to the level of respiratory support at baseline (n/N (%))								
Ambulatory, symptomatic disease	NA	NA	NA	NA	NA	Intervention: 279 (100) Placebo: 283 (100)	NA	NA	NA
Hospitalised, without oxygen support	Intervention: 75 (13.9) Placebo: 63 (12.1)	**Not requiring ongoing medical care** 5-day intervention: 0 (0.0) 10-day intervention: 6 (3.2) SoC: 2 (1.0)	Intervention: 0 (0.0) Placebo + SoC: 3 (3.8)	Intervention: 869 (21) SoC: 861 (20.9)	NA	NA	Intervention: 71/634 (11.2) SoC: 54/647 (8.4)	Intervention: 6/414 (1.4) SoC: 6/418 (1.4)	NA

Table 3. Overview of included studies *(Continued)*

		Requiring ongoing medical care 5-day intervention: 160 (83.8) 10-day intervention: 163 (84.5) SoC: 160 (80.0)							
Low-flow supplemental oxygen	Intervention: 232 (42.9) Placebo: 203 (39.0)	5-day intervention: 29 (15.2) 10-day intervention: 23 SoC: 36 (18.0)	Intervention: 129 (81.6) Placebo + SoC: 65 (83.3)	**Low-flow and high-flow oxygen** Intervention: 2918 (70.4) SoC: 2921 (70.7)	Intervention: 27 (79.4) SoC: 26 (72.2)	NA	Intervention: 334/634 (52.7) SoC: 363/647 (56.2)	Intervention: 247/414 (59.6) SoC: 245/418 (58.6)	NA
High-flow oxygen or non-invasive mechanical ventilation	Intervention: 95 (17.6) Placebo: 98 (18.8)	5-day intervention: 2 (1.0) 10-day intervention: 1 (0.5) SoC: 2 (1.0)	Intervention: 28 (17.2) Placebo + SoC: 9 (11.5)	NA	Intervention: 7 (20.6) SoC: 10 (27.8)	NA	Intervention: 171/634 (27.0) SoC: 176/647 (27.3)	Intervention: 86/414 (20.7) SoC: 93/418 (22.2)	NA
Invasive mechanical ventilation	Intervention: 131 (24.2) Placebo: 154 (29.6)	NA	Intervention: 0 (0) Placebo + SoC: 1 (1.3)	**Non-invasive and invasive mechanical ventilation** Intervention: 359 (8.7) SoC: 347 (8.4)	NA	NA	Intervention: 58/634 (9.1) SoC: 54/647 (8.3)	Intervention: 75/414 (18.1) SoC: 74/418 (17.7)	NA
	Demographics								

Table 3. Overview of included studies *(Continued)*

Age (years)	**Mean (SD)** Intervention: 58.6 (14.6) Placebo: 59.2 (15.4)	**Median (IQR)** 5-day intervention: 58 (48 to 66) 10-day intervention: 56 (45 to 66) SoC: 57 (45 to 66)	**Median (IQR)** Intervention: 66 (57 to 73) Placebo: 64 (53 to 70)	**n/Total** **< 50** Intervention: 1310 (31.6) SoC: 1326 (32.1) **50 to 69** Intervention: 1920 (46.3) SoC: 1908 (46.2) **≧ 70** Intervention: 916 (22.1) SoC: 895 (21.7)	**Mean (SD)** Intervention: 58.09 (12.1) SoC: 57.41 (14.1)	**Mean (SD)** Intervention: 50 (15) Placebo: 51 (15)	**Median (IQR)** Intervention: 65 (53 to 77) SoC: 66 (54 to 74)	**Median (IQR)** Intervention: 63 (55 to 73) SoC: 64 (54 to 72)	**Mean (SD)** Intervention: 59.7 (± 16.5) SoC: 58.1 (15.7)
Gender (male (n(%)))	Intervention: 352 (65.1) Placebo: 332 (63.7)	5-day intervention: 114 (59.7) 10-day intervention: 118 (61.1) SoC: 125 (62.5)	Intervention: 89 (56.3) Placebo: 51 (65.4)	Intervention: 2601 (62.7) SoC: 2639 (63.9)	Intervention: 21 (61.8) SoC: 27 (75.0)	Intervention: 148 (53) Placebo: 145 (51.2)	Intervention: 374/634 (59) SoC: 392/647 (60.6)	Intervention: 291/414 (70.3) SoC: 288/418 (68.9)	Intervention: 29(69.0) SoC: 43(75.4)
Participants with a PCR confirmed SARS-CoV-2 infection	NA	NA	NA	NA	NA	Intervention: 215 of 279 patients (77.1%) Placebo: 213 of 283 patients (75.3%)	NA	NA	NA

Table 3. Overview of included studies *(Continued)*

	Comorbidities at baseline (n (%))								
Diabetes	Intervention: 164 (30.8) Placebo: 158 (30.4)	5-day intervention: 71 (37) 10-day intervention: 85 (44) SoC: 76/200 (38)	Intervention: 40 (25) Placebo: 16 (21)	Intervention: 1129 (27.2) SoC: 1120 (27.1)	Intervention: 21 (62) SoC: 21 (58)	Intervention: 173 (62) Placebo: 173 (61.1)	Intervention: 155/634 (33.6) SoC: 188 /647 (38.4)	Intervention: 104/414 (26) SoC: 113/418 (27)	Intervention: 9(22) SoC: 9 (15.8)
Hypertension	Intervention: 269 (50.6) Placebo: 264 (50.9)	5-day intervention: 82 (43) 10-day intervention: 85 (44) SoC: 81 (41)	Intervention: 73 (46) Placebo: 30 (38)	Not reported	Intervention: 15 (44) SoC: 17 (47)	Intervention: 138 (49.5) Placebo: 130 (45.9)	Not reported	Not reported	Intervention: 15 (36.6) SoC: 14 (24.6)
Cardiovascular or cerebrovascular disease	Not reported	5-day intervention: 111 (58) 10-day intervention: 111 (58) SoC: 107 (54)	Intervention: 15 (9) Placebo: 2 (3)	**Heart disease** Intervention: 929 (22.4) SoC: 935 (22.6)	Intervention: 4 (12) SoC: 5 (14)	Intervention: 20 (7.2) Placebo: 24 (8.5)	Intervention: 120/634 (26) SoC: 135/647 (27.6)	Intervention: 111/414 (27) SoC: 118/418 (28)	**Chronic cardiac disease** Intervention: 6 (14.6) SoC: 12 (21.1)
Chronic lung disease	Not reported	Not reported	Not reported	Intervention: 284 (6.9) SoC: 281 (6.8)	Not reported	Intervention: 67 (24) Placebo: 68 (24)	Intervention: 67/634 (14.5) SoC: 65/647 (13.3)	Intervention: 71/414 (17) SoC: 75/418 (18)	Intervention: 4 (9.8) SoC: 3 (5.3)
Asthma	Not reported	5-day intervention: 22 (12) 10-day intervention: 31 (16) SoC: 28 (14)	Not reported	Intervention: 247 (6) SoC: 242 (5.9)	Intervention: 1 (3) SoC: 0 (0)	Not reported	Intervention: 49/634 (10.6) SoC: 55/647 (11.2)	Not reported	Not reported

Table 3. Overview of included studies *(Continued)*

Obesity	Intervention: 242 (46) Placebo: 234 (45)	BMI (median (IQR)) 5-day intervention: 27 (24 to 30) 10-day intervention: 28 (25 to 32) SoC: 27 (24 to 31)	Not reported	Not reported	Not reported	Intervention: 154 (55.2) Placebo: 156 (55.1)	Not reported	Intervention: 138/414 (34) SoC: 140/418 (34)	Intervention: 11 (28.9) SoC: 9 (18.4)
CLD	Not reported	Not reported	Not reported	Intervention: 57 (1.4) SoC: 72 (1.7)	Not reported	Intervention: 1 (0.4) Placebo: 1 (0.4)	Intervention: 8/634 (1.7) SoC: 19/647 (3.9)	Intervention: 15/414 (4) SoC: 15/418 (4)	Not reported
CKD	Not reported	Not reported	Not reported	Not reported	Intervention: 2 (6) SoC: 1 (3)	Intervention: 7 (2.5) Placebo: 11 (3.9)	Not reported	Intervention: 19/414 (5) SoC: 32/418 (8)	Not reported
Other	Not reported	Not reported	Not reported	Not reported	**Hyperlipidaemia** Intervention: 4 (12) SoC: 3 (8) **Hypothyroidism** Intervention: 4 (12) SoC: 3 (8)	**Current cancer** Intervention: 12 (4.3) Placebo: 18 (6.4) **Immune compromise** Intervention: 14 (5) Placebo: 9 (3.2)	**HIV positive** Intervention: 1/634 (0.2) SoC: 1/647 (0.2)	**Auto-inflammatory disease** Intervention: 17/414 (4) SoC: 24/418 (6) **Malignant haemopathy** Intervention: 16/414 (4) SoC: 19/418 (5) **Chronic neurological disorder including dementia** Intervention: 18/414 (4) SoC: 16/418 (4) **Active malignant neoplasm** Intervention: 13/414 (3)	Not reported

Table 3. Overview of included studies *(Continued)*

								SoC: 15/418 (4) **Transplantation** Intervention: 2/414 (< 1) SoC: 9/418 (2) **Asplenia** Intervention: 1/414 (< 1) SoC: 3 /418(1) **AIDS/HIV not on ART** Intervention: 0/414 SoC: 2/418 (< 1)	
	Concomitant medications (n(%))								
Corticosteroids	Intervention: 115 (21.6) Placebo: 126 (24.4)	5-day intervention: 33 (17) 10-day intervention: 29 (15) SoC: 38 (19)	Intervention: 60 (38) Placebo: 31 (40)	Intervention: 2782 (67.1) SoC: 2820 (68.3)	Not reported	Not reported	Intervention: 553/634 (87.2) SoC: 564/647 (87.2)	**General route** Intervention: 164/414 (39.6) SoC: 169/418 (40.4) **Inhaled route** Intervention: 27/414 (6.5) SoC: 35/418 (8.4)	Intervention: 1 (2.4) SoC: 2 (3.6)
HCQ/CQ	Intervention: 184 (35) Placebo: 189 (37)	5-day intervention: 16 (8) 5-day intervention: 22 (11) SoC: 89 (45)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Lopinavir-ritonavir	Not reported	5-day intervention: 10 (5) 10-day intervention: 11 (6)	Intervention: 27 (17) Placebo: 31 (40)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Table 3. Overview of included studies *(Continued)*

		SoC: 43 (22)							
MAB (e.g. interleukin 6)	Intervention: 23 (4.3) Placebo: 26 (5.0)	5-day intervention: 1 (1) 10-day intervention: 1 (1) SoC: 10 (5)	Not reported	Intervention: 174 (4.2) SoC: 199 (4.8)	Not reported	Not reported	**Tocilizumab** Intervention: 14/634 (2.2) SoC: 5/647 (0.8)	**Tocilizumab** Intervention: 5/414 (1.2) SoC: 2/418 (0.5)	Not reported
Azithromycin	Not reported	5-day intervention: 35 (18) 10-day intervention: 41 (21) SoC: 62 (31)	Not reported	Not reported	Not reported	Not reported	Not reported	Intervention: 11/414 (2.7) SoC: 4/418 (1)	Not reported
Other	**Antibiotics** Intervention: 420 (79) Placebo: 443 (86) **Vasopressors** Intervention: 147 (28) Placebo: 195 (38) **Other anti-inflammatory** **medications** Intervention: 42 (8) Placebo: 37 (7)	Not reported	**Antibiotics** Intervention: 121 (77) Placebo: 63 (81) **Interferon alfa-2b** Intervention: 29 (18) Placebo: 15 (19)	**Convalescent plasma** Intervention: 125 (3) SoC: 151 (3.7) **Non-trial interferon** Intervention: 5 (0.1) SoC: 30 (0.7) **Non-trial antiviral** Intervention: 115 (2.8) SoC: 262 (6.4)	Not reported	Not reported	Not reported	**Antibiotics** Intervention: 178/414 (43) SoC: 166/418 (39.7) **Interleukin-1 inhibitors** Intervention: 3/414 (0.7) SoC: 1/418 (0.2) **Angiotensin-receptor blockers** Intervention: 33/414 (8) SoC: 42/418 (10) **Anticoagulants** Intervention: 212/414 (51.2) SoC: 224/418 (53.6) **Vasopressors** Intervention: 107/414 (25.8)	**Other immunomodulatory drugs** Intervention: 1 (2.4) SoC: 1 (1.8) **ACE inhibitors** Intervention: 2 (4.9) SoC: 4 (7.1) **Angiotensin II receptor blockers**

Table 3. Overview of included studies *(Continued)*

	Other biologic therapies Intervention: 21 (4) Placebo: 13 (3)				
	Other putative SARS-CoV-2 medications Intervention: 8 (2) Placebo: 14 (3)				
	Other antiviral medications Intervention: 10 (2) Placebo: 8 (2)				
			SoC: 124/418 (29.7) **NMBA** Intervention: 97/414 (23.4) SoC: 113/418 (27) **Inhaled nitric oxide** Intervention: 15/414 (3.6) SoC: 17/418 (4.1)	Intervention: 11 (26.8) SoC: 7 (12.5)	

[a]Missing data at baseline (n/N): intervention: 8/541, placebo: 3/521.
ACE = angiotensin converting enzyme
BMI = body mass index
CKD = chronic kidney disease
CLD = chronic liver disease
COPD = chronic obstructive pulmonary disease
HCQ/CQ = hydroxychlorquine/chloroquine
IQR = interquartile range
MAB = monoclonal antibodies
NA = not available/not applicable
NMBA = neuromuscular blocking agent(s)
RDV = remdesivir
SD = standard deviation
SoC = standard of care
WHO = World Health Organization

Table 4. Outcomes

Primary outcomes (included in summary of findings)		
Review version 1	**Review update 1**	
	Hospitalised	**Non-hospitalised**
All-cause mortality at day 28, day 60, time-to-event, and at hospital discharge	**All-cause mortality** at**day 28**, **day 60,** and **up to longest follow-up** **In-hospital mortality at up to longest follow-up**	**All-cause mortality** at **day 28, up to longest follow-up,** and **time-to-event**

Clinical status, at **day 28**, **day 60**, and **up to longest follow-up**, including:
 	
• **improvement of clinical status:**
  ○ weaning or liberation from invasive mechanical ventilation in surviving participants;
  ○ ventilator-free days;
  ○ duration to liberation from invasive mechanical ventilation;
  ○ liberation from supplemental oxygen in surviving participants;
  ○ duration to liberation from supplemental oxygen.
• **worsening of clinical status:**
  ○ new need for mechanical ventilation;
  ○ new need for invasive mechanical ventilation;
  ○ new need for non-invasive mechanical ventilation or high-flow oxygen;
  ○ new need for oxygen by mask or nasal prongs.
	Clinical status at**day 28, up to longest follow-up**, and**time-to-event** including:
	
	• **improvement of clinical status,** defined as**:**
	  ○ proportion of participants alive and ready to be discharged
	• **worsening of clinical status,** defined as:
	  ○ proportion of participants with new need for invasive mechanical ventilation or deceased
		Clinical status at**day 14, day 28, up to longest follow-up**, and**time-to-event** including:
		
		• **improvement of clinical status,** defined as**:**
		  ○ proportion of participants with symptom resolution (all symptoms resolved)
		• **worsening of clinical status,** defined as:
		  ○ proportion of participants admitted to hospital or deceased

Quality of life	—	**Quality of life**
Serious adverse events	**Serious adverse events**	**Serious adverse events**
Adverse events • Any grade • Grade 1 to 2 • Grade 3 to 4	**Adverse events (any grade)**	**Adverse events (any grade)**
Secondary outcomes		
Review version 1	**Review update 1**	
	Hospitalised	**Non-hospitalised**
	Moved from primary to secondary outcome: • All-cause mortality (time-to-event) • Quality of life	—

Table 4. Outcomes *(Continued)*

	• Adverse events grade 3 and 4	
	Ventilator-free days	—
Need for dialysis at up to 28 days	—	—
Need for admission to intensive care unit (ICU)	—	—
Duration of ICU length of stay, or time to discharge from ICU	—	—
Duration of hospitalisation, or time to discharge from hospital	—	—
Viral clearance	—	—

APPENDICES

Appendix 1. Search strategies

Cochrane COVID-19 Study Register

Search string: remdesivir* OR GS5734 OR "GS 5734"

Study characteristics:
1) "Intervention assignment": "Randomised" OR "Unclear"
2) "Study type": "Interventional" AND "Study design": "Parallel/Crossover" OR "Unclear" OR "Other"

= 428 references

Web of Science Core Collection (Advanced search)

#1 TI=(remdesivir* OR GS5734 OR "GS 5734") OR AB=(remdesivir* OR GS5734 OR "GS 5734")

#2 TI=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2") OR AB=(COVID OR COVID19 OR "SARS-CoV-2" OR "SARS-CoV2" OR SARSCoV2 OR "SARSCoV-2" OR "SARS coronavirus 2" OR "2019 nCoV" OR "2019nCoV" OR "2019-novel CoV" OR "nCov 2019" OR "nCov 19" OR "severe acute respiratory syndrome coronavirus 2" OR "novel coronavirus disease" OR "novel corona virus disease" OR "corona virus disease 2019" OR "coronavirus disease 2019" OR "novel coronavirus pneumonia" OR "novel corona virus pneumonia" OR "severe acute respiratory syndrome coronavirus 2")

#3 #1 AND #2

#4 TI=(random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII") OR AB=(random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

#5 #3 AND #4
Indexes=SCI-EXPANDED, ESCI

= 795 references

WHO COVID-19 Global literature on coronavirus disease

Title, abstract, subject: (remdesivir* OR GS5734 OR "GS 5734") AND (random* OR placebo OR trial OR groups OR "phase 3" or "phase3" or p3 or "pIII")

without MEDLINE, EMBASE, Web of Science, PMC, and PubMed = 569 references

WHAT'S NEW

Date	Event	Description
23 May 2022	New citation required and conclusions have changed	Conclusions adapted: conclusion for outpatients added
23 May 2022	New search has been performed	Review updated: three further studies for inpatients and one study for outpatients included

HISTORY

Review first published: Issue 8, 2021

CONTRIBUTIONS OF AUTHORS

FG: clinical expertise, study selection, data extraction and assessment, conception and writing of the manuscript.

KA: methodological expertise, study selection, data extraction and assessment, conception and writing of the manuscript.

KD: methodological expertise, study selection, data extraction and assessment.

VT: clinical expertise, study selection, data extraction and assessment, writing of the manuscript.

MIM: Information Specialist, development of the search strategy, writing of the manuscript.

NS: methodological expertise and advice, writing and proofreading of the manuscript.

CB: methodological expertise and advice, conception, writing and proofreading of the manuscript.

AM: clinical expertise, data extraction and assessment, writing of the manuscript.

MG: clinical expertise, data extraction and assessment.

FF: clinical expertise and advice, conception, writing and proofreading of the manuscript.

MS: clinical expertise and advice, conception, writing and proofreading of the manuscript.

DECLARATIONS OF INTEREST

FG: works as an Intensive Care Medicine Consultant and is member of the CEOsys project. The latter was funded in 2021 by the Network of University Medicine (Nationales Forschungsnetzwerk der Universitätsmedizin (NUM)) by the Federal Ministry of Education and Research of Germany (Bundesministerium für Bildung und Forschung (BMBF)), grant number 01KX2021, paid to the institution.

KA: is member of the CEOsys project, which was funded in 2021 by the Network of University Medicine (Nationales Forschungsnetzwerk der Universitätsmedizin (NUM)) by the Federal Ministry of Education and Research of Germany (Bundesministerium für Bildung und Forschung (BMBF)), grant number 01KX2021, paid to the institution.

KD: is member of the CEOsys project, which was funded in 2021 by the Network of University Medicine (Nationales Forschungsnetzwerk der Universitätsmedizin (NUM)) by the Federal Ministry of Education and Research of Germany (Bundesministerium für Bildung und Forschung (BMBF)), grant number 01KX2021, paid to the institution.

VT: works as an Intensive Care Medicine Consultant and is member of the CEOsys project (no direct funding).

MIM: is member of the CEOsys project, which was funded in 2021 by the Network of University Medicine (Nationales Forschungsnetzwerk der Universitätsmedizin (NUM)) by the Federal Ministry of Education and Research of Germany (Bundesministerium für Bildung und Forschung (BMBF)), grant number 01KX2021, paid to the institution. MIM is part of Cochrane Metabolic and Endocrine Disorders; she was not part of the editorial process.

NS: none known; she is Co-ordinating Editor of Cochrane Haematology, but was not involved in the editorial process for this review.

CB: none known.

AM: has no relevant conflicts of interest to declare. Affiliation with not-for-profit organisation: co-ordination of Section COVRIIN and work in Office of STAKOB (Competence and Treatment Centres for high consequence infectious diseases) at Robert Koch Institute Centre for Biological Threats and Special Pathogens (ZBS), Section Clinical Management and Infection Control.

MG: works as an Intensive Care Medicine Consultant and is member of the CEOsys project, which was funded in 2021 by the Network of University Medicine (Nationales Forschungsnetzwerk der Universitätsmedizin (NUM)) by the Federal Ministry of Education and Research of Germany (Bundesministerium für Bildung und Forschung (BMBF)), grant number 01KX2021, paid to the institution.

FF: works as an Intensive Care Medicine Consultant and is member of the CEOsys project (no direct funding).

MS: has no known conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- University Hospital of Cologne, Germany

  Cochrane Cancer, Department of Internal Medicine
- University Hospital RWTH Aachen, Germany

  Department of Intensive Care Medicine
- Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Germany

  Department of Infectious Diseases and Respiratory Medicine
- University Hospital Leipzig, Germany

  Department of Anesthesiology and Intensive Care Medicine

External sources

- Federal Ministry of Education and Research, Germany

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between protocol and review (first version)

Types of outcome measures

We specified outcomes regarding the effectiveness and safety of remdesivir for individuals with COVID-19 and either moderate to severe or mild to asymptomatic disease after a guideline consortium (CEOsys) that took place after protocol registration. This approach was implemented in all reviews of CEOsys. We created outcome categories and added/specified the following outcomes for hospitalised participants with moderate or severe COVID-19, as follows.

- **All-cause mortality** at day 28, day 60, time-to-event, and at hospital discharge.
- **Clinical status**, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020c), WHO Ordinal Scale for Clinical Improvement (WHO 2020c)) at day 28, day 60, and up to longest follow-up, including:
  - Improvement of clinical status:
    - weaning or liberation from invasive mechanical ventilation in surviving participants;
    - ventilator-free days;
    - duration to liberation from invasive mechanical ventilation;
    - liberation from supplemental oxygen in surviving participants;
    - duration to liberation from supplemental oxygen.
  - Worsening of clinical status:
    - new need for mechanical ventilation;
    - new need for invasive mechanical ventilation;
    - new need for non-invasive mechanical ventilation or high-flow oxygen;
    - new need for oxygen by mask or nasal prongs.
- Need for dialysis at up to 28 days.

- **Quality of life**, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days, up to 30 days, and the longest follow-up available.
- Need for admission to intensive care unit (ICU).
- Duration of ICU length of stay, or time to discharge from ICU.
- Duration of hospitalisation, or time to discharge from hospital.
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline and up to three, seven, and 15 days.
- **Serious adverse events**, defined as number of participants with event.
- **Adverse events** (any grade, grade 1 to 2, grade 3 to 4), defined as number of participants with event.

We combined three different types of advanced respiratory support (high-flow oxygen, non-invasive mechanical ventilation, and invasive mechanical ventilation) as one outcome measure with the term 'mechanical ventilation' for the following reasons.

- Their application in clinical routine usually gives indirect evidence about a clinically relevant worsening of organ functions in an individual patient.
- Their application is accompanied by a need for higher level of monitoring and care (e.g. admission to ICU).
- For the individual patient, the application of each of these advanced respiratory support devices means a relevant loss of independence and quality of life, compared to application of low-flow oxygen therapy or hospitalisation without any respiratory support.

Assessment of heterogeneity

We clarified our approach to exploring heterogeneity. We intended to conduct subgroups by type of respiratory support at baseline irrespective of the amount of statistical variation observed between the studies. We used sensitivity analysis rather than subgroup analysis to explore heterogeneity if the I^2 was over 80%.

Types of subgroup analyses

We expanded the subgroup analysis, and additionally plan to conduct separate analysis if more data become available in the next updates of this review, for the following.

- Age of participants (divided into applicable age groups, e.g. 18 to 65 years, 65 to 79 years, 80 years and older).
- Pre-existing conditions (e.g. diabetes, respiratory disease, hypertension, immunosuppression, obesity, cardiac injury).
- Timing of first dose administration with illness onset.
- Severity of condition:
  - no oxygen versus low-flow oxygen versus mechanical ventilation (including high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, and extracorporeal membrane oxygenation).
- Duration of remdesivir application:
  - 5-day course of remdesivir versus 10-day course of remdesivir.

Although we contacted all study authors, especially in terms of detailed description of the extent of respiratory support (e.g. low- versus high-flow oxygen, non-invasive versus invasive mechanical ventilation), there remained differences in the reporting of severity of illness and incomplete data sets, which resulted in a relevant obstacle to the planned subgroup analysis.

Differences between reviews (first version versus first update)

Considerations for the update

The update of this living systematic review included additional data of two studies, the final results from the large WHO Solidarity trial, as well as three separately published add-on or sub-trials of the aforementioned multinational Solidarity trial (Abd-Elsalam 2021; Gottlieb 2021; WHO Solidarity Canada 2022; WHO Solidarity France 2021; WHO Solidarity Norway 2021; WHO Solidarity Trial Consortium 2022), with consequential change in prioritised outcomes, credibility, and thus estimated effects. The process was supported by Cochrane specialists and in accordance with the "Guidance for the production and publication of Cochrane living systematic reviews: Cochrane Reviews in living mode" (Cochrane LSR). The following adaptions have been implemented:

Abstract

The text has been adapted according to changes in inclusion of outpatient participants, outcome set, results, and conclusion.

Plain language summary

The text has been adapted according to changes in inclusion of outpatient participants, outcome set, results, and conclusion.

Background

The text has been adapted according to current knowledge on SARS-CoV-2 and COVID-19, as well as implementation and recommendations on the use of remdesivir.

Objectives

The text has been adapted according to inclusion of participants independent of care setting and approach for a living review removed.

Methods

Types of outcome measures

After the initial review, knowledge and experience in patient-relevant outcome measures became more profound and adaptions to address former discrepancies were necessary. Changes to the outcome set are in line with further reviews produced within the German research project 'CEOsys' (COVID-19 Evidence-Ecosystem; CEOsys 2021), which have been published more recently with Cochrane (Griesel 2022; Kramer 2022). The main intention of all adaptions is to provide a clear representation of estimated effects, most crucial for affected people.

Hospitalised individuals with moderate to severe COVID-19

Primary outcomes

- All-cause mortality at up to day 28, day 60, and up to longest follow-up.
- In-hospital mortality at up to longest follow-up.
- Clinical improvement: proportion of participants alive and ready to be discharged at up to day 28, up to longest follow-up, and time-to-event. Participants should be discharged without clinical deterioration or death.
- Clinical worsening: proportion of participants with new need for invasive mechanical ventilation or deceased within 28 days, up to longest follow-up, and time-to-event.
- Adverse events (any grade) during the study period, defined as number of participants with any event.
- Serious adverse events during the study period, defined as number of participants with any event.

Secondary outcomes

- All-cause mortality, time-to-event.
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHO Quality of Life 100-question patient-reported questionnaire (WHOQOL-100)) at up to seven days, up to 28 days, and longest follow-up available.
- Adverse events grades 3 and 4.
- Ventilator-free days (defined as days alive and free from mechanical ventilation).

Non-hospitalised individuals with asymptomatic SARS-CoV-2 infection or mild COVID-19

Primary outcomes

- All-cause mortality at day 28, up to longest follow-up, and time-to-event.
- Clinical improvement: proportion of participants with symptom resolution (all symptoms resolved) at up to day 14, day 28, up to longest follow-up, and time-to-event.
- Clinical worsening: proportion of participants admitted to the hospital or deceased within 14 days, 28 days, up to longest follow-up, and time-to-event.
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days, up to 28 days, and longest follow-up available.
- Serious adverse events during the study period, defined as number of participants with any event.
- Adverse events (any grade) during the study period, defined as number of participants with any event.

The key outcome measures (all-cause mortality, clinical course, adverse and serious adverse events) remain as *primary outcomes*. However, the definition of measures for clinical deterioration or improvement were adapted to eliminate the competing risk of death. Additionally, we decided to condense the former measures of clinical status into one surrogate for each direction (deterioration or improvement) to allow a more precise statement. Outcome measures subordinate to primary outcomes are now listed as *secondary outcomes*. *All-cause mortality (time-to-event)*, q*uality of life,adverse events (grade 3 and 4), ventilator-free days* have been graded as "secondary" due to continuing lack of reporting and hence limited informative value. *Need for dialysis, admission to intensive care unit (ICU), duration of ICU length of stay or time to discharge from ICU, duration of hospitalisation or time to discharge from hospital* and *viral clearance* have been eliminated from the core outcome set because of redundancy and to provide a compact overview.

New data on the usage of remdesivir in the outpatient setting led us to add this potential population in our analyses: *non-hospitalised individuals with asymptomatic SARS-CoV-2 infection or mild disease*.

Subgroup analyses

In the first version of this review we conducted subgroup analyses for all-cause mortality at up to day 28 exclusively. We performed additional analyses where longer follow-up data on mortality were available.

Sensitivity analyses

We removed the analysis "Comparison of adolescent and adult participants versus adult participants", as we considered this to be more appropriate for subgroup analysis (age of participants). Since only 1.4% in the population of non-hospitalised participants and less than 0.1% in the population of the hospitalised participants were adolescent (12 to 18 years of age), we judged the influence on analyses to be infinitesimal.

Results

We have adapted the text according to changes in study characteristics and effects of intervention. We moved two studies from *ongoing* to *awaiting classification*. One study, formerly included, has been excluded due to retraction.

Discussion

We have adapted the text according to changes in effects of intervention, integration in current pandemic status (e.g. vaccination, variants of concerns), and current literature on the intervention.

Authors' conclusion

We have adapted the text according to changes in effects of intervention.

Tables and figures

We added an additional summary of findings table for the population of participants with asymptomatic SARS-CoV-2 infection or mild COVID-19. Only primary outcomes were displayed according to changes in outcome set (Table 4). We added an additional table to display changes in the outcome set (Table 4). We have adapted Table 1, Table 2, and Table 3 according to changes. We have removed the former Table "Narrative summary of outcomes of included studies" due to accumulation of redundant information. We have adapted the PRISMA flow diagram according to changes in the search.

Living systematic review considerations

For the first version of this review, we followed a living systematic review approach and our Information Specialist (MIM) provided us with new search records weekly, which we screened, extracted, evaluated, and integrated following the guidance for Cochrane living systematic reviews (Cochrane LSR). We manually checked platform trials that were previously identified for additional treatment arms. We waited until the accumulating evidence changed our conclusions in the implications for research and practice before republishing the update of the review.

This update represents a major update, providing a comprehensive review of current available RCTs according to Cochrane methodological standards conducted in a team effort by clinicians and methodologists. We believe that relevant changes in international recommendations, pandemic course, and exposition of the population should determine the necessity of future updates rather than specific time frames. We have therefore refrained from maintaining this review as a living systematic review, as originally planned.

NOTES

Parts of the review's Methods section are adopted from templates of Cochrane Haematology and a similar protocol published by Piechotta 2020, and the corresponding review (Piechotta 2021).

INDEX TERMS

Medical Subject Headings (MeSH)

*COVID-19; COVID-19 Drug Treatment; Disease Progression; Randomized Controlled Trials as Topic; SARS-CoV-2

MeSH check words

Humans; Middle Aged