National Institute for Health and Care Excellence

NICE COVID-19 rapid guideline: managing COVID-19

[P] Evidence review for remdesivir for people in hospital

NICE guideline NG191

June 2022

Guideline version (Final)

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Objective

This evidence review aims to update existing NICE rapid guidance on the use of remdesivir for people in hospital with COVID-19, which was published in May 2021.

Review question

A description of the relevant population, intervention, comparison and outcomes (PICO) for this review was developed by NICE for the topic (see appendix A for more information). The review question for this evidence review is:

What is the effectiveness and safety of remdesivir for adults, young people and children hospitalised with COVID-19?

Methodology

The evidence review was developed using NICE interim process and methods for guidelines developed in response to health and social care emergencies.

The original NICE recommendations were published on 27 May 2021, based on an evidence review developed by NICE, in collaboration with the Australian National COVID-19 Clinical Evidence Taskforce. Ongoing surveillance was conducted from publication to identify any new emerging evidence to be considered as triggers for an update.

A multi-faceted search approach was used to identify studies for consideration in this review.

A focused search of the following databases was conducted on 10 March 2022: MEDLINE ALL (Ovid); Embase (Ovid); Cochrane CENTRAL (Wiley); and the World Health Organization COVID-19 database (WHO website). Preprints were searched using the standard NICE process. Full search strategies for each database are provided in appendix B.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

Potentially relevant studies identified in surveillance searches were also assessed for eligibility for inclusion in the evidence review to 3 June 2022.

Included studies

The focused search identified 519 records.

Relevant references were screened for eligibility against the protocol using their titles and abstracts. 36 full text references were obtained and assessed for relevance against the criteria in the review protocol (see appendix A). 26 full text references were excluded. Details of excluded studies are provided in appendix E.

In addition, 1 study was identified through surveillance searches.

4 studies were included in the previous version of the evidence review published in May 2021 (Beigel 2020, Goldman 2020, Spinner 2020, Wang 2020).

In total, 11 studies are included in this updated evidence review, 7 of which are new to this review and 4 of which were in the previous version of the evidence review. A summary of the included studies is shown in Table 1.

Analysis plan

The previous version of the evidence review included interim results from the WHO-SOLIDARITY trial, which had been published on 20 December, 2020. The full dataset from WHO-SOLIDARITY was published online on 2 May 2022, which was then incorporated into the review meaning the interim results were then taken out of the review and replaced with final results.

The Ader 2022 [DISCOVERY], Barrat-Due 2021 [NOR-SOLIDARITY] and Ali 2022 [CATCO] trials were previously partially reported as part of the WHO-SOLIDARITY trial. Once it became apparent that there was a risk of double-counting patients across these trials, the systematic review Lee 2022 was included as part of this evidence review. Lee 2022 included data obtained directly from study authors of DisCoVeRy and CATCO for the subset of patients that did not overlap with WHO-SOLDARITY. The differences between data from Lee 2022 and the DisCoVeRy and CATCO studies are highlighted in appendix H.

10 studies (Abd-Elsalam 2021, Ader 2022 [DisCoVeRy], Ali 2022 [CATCO], Barratt-Due 2021 [NOR-SOLIDARITY], Beigel 2020 [ACTT-1], Mahajan 2021, WHO-SOLIDARITY 2022, Spinner 2020, Wang 2020, Lee 2022) compared remdesivir to standard care; 1 study (Goldman 2020) compared a 10-day course of remdesivir to a 5-day course of remdesivir.

Table 1: Summary of included studies

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
New at this update Abd-Elsalam 2021 Egypt 16 June 2020 to 19 December 2020	RCT	Level of respiratory support at baseline not reported but mean O_2 saturation was 87-90%. Respiratory rate 22.42 to 21.78 (bpm)	200 adults (18-80 years; mean age 53.53 years SD 15.2, 60% male) with confirmed COVID-19 who were hospitalised. Comorbidities: 34% with hypertension 33% with diabetes Exclusion criteria included history of renal impairment, contraindications to remdesivir and pregnant or lactating mothers.	Intravenous remdesivir 200mg day 1, then 100mg for up to 10 days	Standard care (zinc, acetylcysteine, lactoferrin and vitamin C) Corticosteroids were not part of standard care.	Mortality Need for mechanical ventilation Duration of hospital stay
New at this update Ader 2022 [DisCoVeRy] Pre-print Austria, Belgium, France, Luxembourg, Portugal 22 March 2020 to 21 January 2021	RCT	Level of respiratory support at baseline: Low flow O_2: 60% High flow O_2 or NIV: 22% IMV or ECMO: 18% 35.1% received corticosteroids overall	857 adults (≥18 years; median age 64 [IQR 54-73]; 70% male) admitted to hospital with laboratory confirmed COVID-19 with an oxygen saturation of 94% or less on room air or requirement for respiratory support. Comorbidities 74% had at least one comorbidity such as obesity, diabetes, chronic cardiac and pulmonary disease. Participants with a history of ribavirin use and severe chronic kidney disease were excluded. Pregnant and breastfeeding mothers were excluded.	Intravenous remdesivir 200mg day 1, then 100mg for up to 10 days	Standard care (incl. corticosteroids)	Mortality Ventilator free days Oxygenation free days Days to hospital discharge Days to improvement on ordinal scale Adverse events Change from baseline viral load

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
New at this update Ali 2022 [CATCO 2022] Canada 14 August 2020 to 21 April 2021	RCT	Level of respiratory support at baseline: No O2 or Low flow O_2: 65% High flow or NIV O_2: 27.1% IMV: 8.7% 87.2% were receiving corticosteroids at baseline	1267 adults (median age 65-66 years; 40% female) who were hospitalised in Canada with COVID-19. 1 participant was pregnant. Comorbidities: A range of pre-existing co-morbidities were reported including: 36% with diabetes 28% with COPD 10.9% with asthma 26.8% with CVD Key exclusion criteria included participants who were not expected to survive beyond 24 hours and those already receiving remdesivir at the time of enrolment.	Intravenous remdesivir 200mg day 1, then 100mg for up to 10 days	Standard care (incl. corticosteroids)	Mortality (at 28 days and 60 days) Need for new mechanical ventilation Duration of hospital stay Oxygen free days Ventilator free days Safety: New hepatic dysfunction Safety: New dialysis
New at this update Barratt-Due 2021 [NOR-SOLIDARITY 2021] Norway 28 March 2020 to 04 October 2020	RCT	COVID-19 severity not reported but in hospital because of COVID-19 Level of respiratory support not reported. 8% were receiving	101 adults (≥18 years; mean age 59.8 years SD 15.3; 34.3% female) with PCR confirmed COVID-19 admitted to a hospital ward of intensive care unit. Comorbidities: Chronic cardiac disease: 15.6% Chronic pulmonary disease: 5.6% Hypertension: 30.6% Diabetes: 17.2% Obesity: 26.8% People with severe comorbid conditions or a life expectancy of	Intravenous remdesivir 200mg day 1, then 100mg for up to 10 days	Standard care (incl. corticosteroids)	Mortality Discharge from hospital Adverse events Serious adverse events

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
		corticosteroids at baseline	3 months were excluded. Pregnant women and or breast feeding women were also excluded.			
Beigel 2020 [ACTT-1] North America (79.8%), Europe (15.3%), Asia (4.9%) 21 February 2020 to 19 April 2020	RCT	No O_2 support: 13% Low flow O_2: 41% High flow O_2 or NIV: 18.2% IMV or ECMO: 26.8% This trial was conducted before corticosteroid use became standard care.	1062 adults (mean age 58.9 years SD 15; 64.4% male) hospitalised with COVID-19 who had evidence of lower respiratory tract infection. Comorbidities: 2 or more underlying comorbidities (55.2%). Comorbidities included type II diabetes (30%), hypertension (50%), and obesity (45 Exclusion: ALT/AST>5 times limit of normal, eGFR<30 or dialysis, pregnant or breast feeding, allergy to medication, or anticipated/transfer discharge ≤ 72 hours.	Intravenous remdesivir 200mg day 1, then 100mg for up to 10 days	Placebo	Time to recovery Mortality Need for mechanical ventilation
Goldman 2020 United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan	RCT	Level of respiratory support at baseline: No O_2 support: 39.5%	408 adults (median age 61-62 years; 64% male) hospitalised with PCR confirmed COVID-19 Comorbidities: Diabetes 23% Hyperlipidaemia 22.5%	Intravenous remdesivir 200mg day 1, then 100mg for up to 5 days	Intravenous remdesivir 200mg day 1, then 100mg for up to 10 days	Death at day 14 Serious adverse events Adverse events

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
March 2021		Low flow O_2: 55% High flow O_2 or NIV: 39% IMV or ECMO: 3.5%	Hypertension 50% Asthma 12.5% Exclusion: IMV and ECMO at screening, multiorgan failure, ALT/AST>5 times limit of normal, or estimated creatinine clearance <50ml/min; concurrent treatment with other agents with putative activity against COVID-19.			Acute respiratory failure or ARDS Septic shock Discontinued due to adverse event Clinical recovery day 14 Discharged from hospital
New at this update Lee 2022 *From this study, only subgroup data from the DisCoVeRy and CATCO trials were included in the analysis. The PICO information given here is broader and relevant for the full systematic review*	SR	Level of respiratory support at baseline: No O_2 support: 24% Hi or Low Flow O2 support [no ventilation]: 65% IMV or ECMO: 11%	Inclusion: RCTs comparing remdesivir with standard care or placebo among adults hospitalised with COVID-19 Search period: 1 Jan 2020 – 1 Jan 2022 Results: 8 RCTs including 9,157 adult patients hospitalised with COVID-19 were included in the meta-analysis	A range of protocols were used in included RCTs from IV remdesivir for 5 days or 10 days	Placebo or standard care (incl. corticosteroids)	Mortality

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
New at this update Mahajan 2021 June 2020 to December 2020	RCT	Level of respiratory support: Low flow O_2: 75.8% High flow or NIV O_2: 24.2% Level of corticosteroid use not reported.	82 adults (ages 18 to 60 years; mean age 57.74 SD 13.1; 65.5% male) hospitalised with PCR-confirmed COVID-19 Comorbidities: 60% with diabetes 10% with hypothyroidism 10% with hyperlipidaemia 4.3% with CKS 45.7% with hypertension People receiving mechanical ventilation or with multi organ failure were not included in the study.	Intravenous remdesivir 200mg day 1, then 100mg for 5 days	Standard care (incl. corticosteroids, heparins)	Need for supplemental oxygen Need for mechanical ventilation Mortality
New at this update* WHO-SOLIDARITY 2022 [WHO-SOLIDARITY] Global 22 March 2020 to 29 January 2021 **Previous evidence review included interim study results (Pan 2020)*	RCT	Level of respiratory support No O_2 support: 21% Low or high flow O_2: 70.5% Ventilation (type not specified): 8.5% 67.7% received corticosteroids overall	8275 adults (≥18 years; 63% male) hospitalised with COVID-19 Age was stratified: 31.8% aged <50 years; 46% aged 50-69 years; 21.8% aged ≥70 years Comorbidities: Diabetes 27% Heart disease 22.5% Exclusion: received any trial drug, expected to be transferred within 72 hours and contraindications.	Intravenous remdesivir 200mg day 1, then 100mg for up to 10 days	Standard care (incl. corticosteroids).	Mortality Need for mechanical ventilation

Study & Country	Study type	COVID-19 severity	Population	Intervention	Comparator	Outcomes
Spinner 2020 105 hospitals in the United States, Europe, and Asia 15 March 2020 to 18 April 2020	RCT	Level of respiratory support No O_2 support: 84% Low flow O_2: 15% High flow O_2 or NIV: 1% 16% were receiving corticosteroids at baseline	596 adults (median age 56-58; 61% male) hospitalised with PCR confirmed COVID-19 Comorbidities: Cardiovascular disease (56%), diabetes (40%), and hypertension (42%). Exclusions: Alanine aminotransferase or aspartate amino transferase > 5 times upper limit of normal or creatinine clearance of <50mL/min	Intravenous remdesivir 200mg day 1, then 100mg for up to 5 or 10 days	Standard care (incl. corticosteroids, hydroxychloroquine, azithromycin, among others).	Clinical status on day 11 on a 7-point ordinal scale ranging from death (1) to discharged (7)
Wang 2020 China 6 February 2020 to 12 March 2020	RCT	Level of respiratory support Low flow O_2 82.5% High flow O_2 or NIV 15% 65.5% received corticosteroids overall	237 adults (median age 64-66 years; 56% male) Comorbidities: hypertension (46%), diabetes (25%), and coronary heart disease (9%). People with severe comorbid conditions were excluded. Pregnant women were also excluded.	Intravenous remdesivir 200mg day 1, then 100mg for up to 10 days	Standard care – includes concomitant use of lopinavir–ritonavir, interferons, and corticosteroids	Time to clinical improvement [decline of 2 levels on a 6-point ordinal scale]

See appendix F for full evidence tables

Results

What is the effectiveness and safety of remdesivir for adults, young people and children hospitalised with COVID-19?

Remdesivir vs standard care, standard care plus placebo or placebo

Key results

Compared with standard care, remdesivir reduces death at day 28 in hospitalised people who require no or low-flow oxygen.

There is no evidence that remdesivir is more effective than placebo or standard care in treating hospitalised patients with COVID-19 who require high-flow oxygen supplementation, non-invasive ventilation or invasive ventilation compared to standard care.

What is the evidence informing this conclusion?

Evidence comes from 10 randomised controlled trials and 1 systematic review that compared remdesivir to standard care or placebo in nearly 10,000 adults hospitalised with COVID-19 (Abd-Elsalam 2021, Ader 2022 [DisCoVeRy], Ali 2022 [CATCO], Barratt-Due 2021 [NOR-SOLIDARITY], Beigel 2020 [ACTT-1], Goldman 2020, Mahajan 2021, WHO-SOLIDARITY 2022, Spinner 2020, Wang 2020, Lee 2022). The majority of evidence is from the WHO SOLIDARITY and ACTT-1 trials, which randomised 8275 and 1062 patients, respectively, hospitalised with COVID-19 and requiring varying levels of oxygen support at baseline (see Table 1). Of the 10 RCTs included in this review, 9 compared remdesivir to standard care while 1 study (Beigel 2020) compared remdesivir to placebo. For patients who require supplemental oxygen, corticosteroids are currently part of standard care for COVID-19 in hospital in the UK. Beigel 2020 and Abd-Elsalam 2021 did not report use of corticosteroids as part of the standard care.

Eight RCTs included in this comparison evaluated mortality at 28 days after starting treatment. The WHO-SOLIDARITY study evaluated in-hospital mortality, regardless of whether before or after day 28. The majority of studies also reported the need for invasive mechanical ventilation or oxygen supplementation during the trial. Other outcomes evaluated included clinical recovery, discharge from hospital, duration of hospital stay, respiratory failure or acute respiratory distress syndrome (ARDS), time to recovery, time to improvement, oxygen or ventilator-free days by day 28, serious adverse events and adverse events including septic shock.

Ader 2022 [DISCOVERY], Barrat-Due 2021 [NOR-SOLIDARITY] and Ali 2022 [CATCO] trials were previously partially reported as part of the WHO-SOLIDARITY trial. The DisCoVeRy and CATCO trials reported on the same outcomes as WHO-SOLIDARITY [mortality, progression to ventilation and discharge from hospital] while NOR-SOLIDARITY reported on other outcomes.

Therefore, to avoid duplication for the outcome of mortality, we obtained mortality data for Ader 2022 [DisCoVeRy] and Ali 2022 [CATCO] from Lee 2022 which performed a meta-analyses of mortality in people treated with remdesivir vs. standard care. The authors of the Lee 2022 systematic review obtained data directly from the researchers on the subset of patients who were not already included in the WHO-SOLIDARITY 2022 report. See Appendix H of the evidence review document for differences between published data in the DisCoVeRy and CATCO trials vs. data extracted from the Lee 2022 systematic review.

Since data was not available to distinguish between patients included in WHO-SOLIDARITY vs those not included in WHO-SOLIDARITY for the outcomes progression to ventilation and discharge from hospital, Ader 2022 [DisCoVeRy] and Ali 2022 [CATCO] were excluded from the meta-analyses for these outcomes to prevent double counting of data.

The evidence for mortality was divided into 2 analyses based on the level of respiratory support required. This is because it is expected that antivirals will most likely be more effective in the early stages of disease progression. The levels of respiratory support have been used as a proxy to measure disease progression in the trials. Low levels of respiratory support were considered to be no oxygen

supplementation or low-flow oxygen supplementation. Higher levels of respiratory support included high-flow oxygen supplementation, non-invasive ventilation (NIV) [such as Bilevel Positive Airway Pressure (BiPAP) and Continuous Positive Airway Pressure (CPAP)] and invasive ventilation.

The WHO-SOLIDARITY trial did not report data separately for patients on low-flow vs. high-flow oxygen. Subgroups presented in this study were: patients on no oxygen supplementation, patients on oxygen supplementation (any), and patients on ventilation (any). In a previous panel discussion, it was agreed that subgroups of patients on no oxygen supplementation and those on oxygen supplementation would be included in meta-analyses of “low levels of respiratory support” as it was likely that the majority of those patients on oxygen supplementation were on low-flow oxygen supplementation.

Publication status

All studies were full publications.

Study characteristics

Mean or median age in the studies ranged between 53 and 69 years and the proportion of men ranged between 56% and 70%.

The severity of COVID-19 across the studies were generally defined as moderate-to-severe. Moderate was mostly defined as people who either did not require oxygen at baseline or required low-flow oxygen supplementation. Severe was defined as people who required high-flow oxygen supplementation or non-invasive mechanical ventilation (NIV) at baseline or invasive mechanical ventilation (IMV). There was variability in disease severity and the corresponding levels of oxygen support and ventilation required among patients at baseline (see Table 2).

The dosage of remdesivir was consistent across all studies (200mg loading dose followed by 100mg daily) but the duration of the course ranged between 5 and 10 days.

All studies used the intravenous (IV) route of administration for remdesivir.

Children and pregnant women were excluded from almost all the trials. Ali 2021 included one pregnant woman. Spinner 2020 included children aged 12-17 but didn't report data for this group separately. Most studies also excluded patients with organ failure or severe comorbid conditions.

Table 2 : Levels of respiratory support at baseline

Level of respiratory support at baseline	Beigel 2020 (n=1062)	Wang 2020 (n=236)	Spinner 2020 (n=584)	WHO-SOLIDARITY 2022 (n=8275)	Abd-Elsalam 2021 (n=100)	Ader 2022 (n=857)***	Ali 2022 (n=1267)***	Barratt-Due 2021 (n=99)	Mahajan 2021 (n=70)
No oxygen or low-flow oxygen supplementation	573 (54%)	197 (83%)	584 (100%)	7569 (91.5%)*	*200** (100%)*	493 (60%)	822 (65%)	*Not specified*	53 (76%)
High-flow oxygen supplementation or NIV	193 (18%)	39 (17%)	0 (0%)	N/A	*N/A*	179 (22%)	347 (27%)	*Not specified*	17 (24%)
Invasive mechanical ventilation	285 (27%)	0 (0%)	0 (0%)	487 (8.5%)	0 (0%)	149 (18%)	112 (8%)	*Not specified*	0 (0%)

**Note that in the WHO-SOLIDARITY trial, subgroups provided were "No oxygen at baseline" [21%], "Low-flow or high-flow oxygen at baseline" [70.5%], and "Ventilation (any type) at baseline" [8.5%]*

***Note that in the Abd-Elsalam study, levels of respiratory support at baseline were not specified. Study authors clarified that none of the patients in the trial required ventilation at baseline.*

**** Note that, due to overlap with WHO-SOLIDARITY 2022, data from the Lee 2022 systematic review was used in place of data from Ali and Ader in meta-analyses of mortality by level of respiratory support.*

What are the main results?

All-cause mortality at day 28 (Updated)

People not receiving oxygen or receiving low-flow oxygen supplementation at baseline (Updated)

Data for mortality from 8 studies (n=10,483) reporting no or low-flow oxygen support at baseline (Ali 2022, Ader 2022 [DisCoVeRy]. Beigel 2020, WHO-SOLIDARITY 2022, Spinner 2020, Abd-Elsalam 2021, Mahajan 2021 and Wang 2020) were included in the meta-analysis. Barratt-Due 2021 [NOR-SOLIDARITY] did not specify baseline level of oxygen support so was excluded from this analysis. Data from a

systematic review by Lee 2022 was used in place of published data from Ali 2022 [CATCO] and Ader 2022 [DisCoVeRy] trials to avoid double-counting patients included in the WHO-SOLIDARITY trial.

The analysis found a statistically significant reduction in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving low-flow or no oxygen supplementation (RR 0.81 95% CI 0.68 to 0.96).

Two studies (Beigel 2020 and Abd-Elsalam 2021) did not report use of corticosteroids as part of standard care in the trials. A sensitivity analysis removing these two studies from the analysis did not differ from the overall results (RR 0.87 95% CI 0.78 to 0.97).

People receiving high-flow oxygen supplementation, NIV or IMV at baseline (Updated)

Data for mortality from 5 studies (n= 1,486) reporting high-flow oxygen support, NIV or IMV at baseline (Ader 2022, Ali 2022, Beigel 2020, WHO-SOLIDARITY 2022, and Wang 2020) were included in the meta-analysis. Barratt-Due 2021 [NOR-SOLIDARITY] did not specify baseline level of oxygen support so was excluded from this analysis. Data from Lee 2022 was used in place of published data from Ali 2022 [CATCO] and Ader 2022 [DisCoVeRy] trials to avoid double-counting patients included in the WHO-SOLIDARITY trial.

The analysis found no significant difference in all-cause mortality at 28 days for remdesivir compared to standard care in people who are receiving high-flow oxygen supplementation, NIV or IMV (RR 1.08 95% CI 0.93 to 1.25).

One study (Beigel 2020) did not report use of corticosteroids as part of standard care in the trials. A sensitivity analysis removing this study from the analysis did not differ from the overall results (RR 1.10 95% CI 0.92 to 1.30).

For the following outcomes it was not possible to split the data by level of respiratory support:

Invasive mechanical ventilation or ECMO (Updated)

Data for the need for invasive mechanical ventilation or ECMO from 4 studies (Abd-Elsalam 2021, Beigel 2020, Mahajan 2021, WHO-SOLIDARITY 2022) were included in the meta-analysis (n= 8,605). The analysis found no significant difference in need for invasive mechanical ventilation or ECMO at day 28 with remdesivir compared with standard care, in hospitalised patients not on invasive ventilation at baseline (RR 0.85 95% CI 0.65 to 1.13).

Data from Ali 2022 [CATCO] and Ader 2022 [DisCoVeRy] were excluded from this analysis as it was not possible to avoid double-counting with WHO-SOLIDARITY 2022.

Most studies in this analysis did not report this outcome by baseline level of support so it was not possible to do separate analyses for those on no/low-flow oxygen and those on high-flow oxygen or NIV. Only WHO-SOLIDARITY 2022 reported separately on need for IMV or ECMO among patients not receiving oxygen at baseline. Data for this subgroup did not differ from the overall results (RR 0.97 95% CI 0.63 to 1.49).

Need for oxygen supplementation [high-flow oxygen or NIV] (Updated)

Data for this outcome from 3 studies (Ali 2022, Beigel 2020 and Mahajan 2021) were included in this meta-analysis (n= 906). The analysis found a statistically significant reduction in the need for high-flow oxygen or NIV for those treated with remdesivir compared to standard care.

Clinical recovery (No change)

Data for this outcome from 3 studies (Beigel 2020, Wang 2020, Spinner 2020) were included in this meta-analysis (n= 1,876). It found no statistically significant difference in clinical recovery at day 28 between remdesivir and standard care. Clinical recovery was defined as the first day in which a patient satisfied categories 1, 2 or 3 on the 8-point WHO ordinal scale (Beigel 2020) or improvement from a baseline score of 2 to 5 to a score of 6 or 7 on a 7-point ordinal scale (Spinner 2020).

Respiratory failure or ARDS (No change)

Data for this outcome from 2 studies (Beigel 2020, Wang 2020) were included in this

meta-analysis (n= 1,296). It found no statistically significant difference in respiratory failure or ARDS at day 28 with remdesivir compared with standard care in hospitalised patients not on invasive ventilation at baseline.

Septic Shock (No change)

Data for this outcome from 2 studies (Beigel 2020, Wang 2020) were included in the meta-analysis (n=1,296). It found no statistically significant difference in septic shock at day 28 between remdesivir and standard care.

Adverse events (Updated)

Data for this outcome from 6 studies (Ader 2022, Ali 2022, Barratt-Due 2021, Beigel 2020, Spinner 2020, Wang 2020) were included in the meta-analysis (n= 4,123). It found no statistically significant difference in adverse events at the end of follow up between remdesivir and standard care.

Serious adverse events (Updated)

Data for this outcome from 5 studies (Ader 2022, Barratt-Due 2021, Beigel 2020, Spinner 2020, Wang 2020) were included in the meta-analysis (n= 2,536). It found no statistically significant difference in serious adverse events at the end of follow up between remdesivir and standard care.

Discontinuation due to adverse events (No change)

Data for this outcome from 3 studies (Beigel 2020, Spinner 2020, Wang 2020) were included in the meta-analysis (n= 1,880). It found no statistically significant difference in discontinuation due to adverse events during treatment with remdesivir compared with standard care.

Discharge from hospital (Updated)

Data from WHO-SOLIDARITY 2022 was used for this outcome (n= 8,275). This analysis found no statistically significant difference in discharge from hospital with remdesivir compared with standard care. Data from Ader 2022 [DisCoVeRy] was

excluded from this analysis as it was not possible to avoid double-counting with WHO-SOLIDARITY 2022.

Time to recovery (No change)

Data for this outcome from 2 studies (Beigel 2020, Spinner 2020) were included in the meta-analysis (n=1643). It found a statistically significant decrease in time to improvement between remdesivir and standard care.

Time to improvement (Updated)

Data for this outcome from 3 studies (Ader 2022, Spinner 2020, Wang 2020) were included in the meta-analysis (n=1642). It found no statistically significant difference in time to improvement between remdesivir and standard care.

Duration of hospital stay (New at this update)

One study (Ali 2022) reported on duration of hospital stay for those treated with remdesivir compared to standard care (n= 200). The study found a statistically significant decrease in days in hospital for those treated with remdesivir compared with standard care.

Oxygen-free days (New at this update)

One study (Ali 2022) reported on the number of oxygen-free days at day 28 for those treated with remdesivir compared to standard care (n= 1,168). The study found a statistically significant increase in oxygen-free days among those treated with remdesivir compared with standard care.

Ventilator-free days (New at this update)

One study (Ali 2022) reported on the number of ventilator-free days at day 28 for those treated with remdesivir compared to standard care (n= 1,168). The study found a statistically significant increase in ventilator-free days among those treated with remdesivir compared with standard care.

Our confidence in the results

All but one outcome (Respiratory failure or ARDS) were downgraded for risk of bias. In the case of the mortality outcomes, there was a risk of double-counting patients from the WHO-SOLIDARITY trial in the add-on trials [DisCoVeRy and CATCO]. For these outcomes, we noted a serious risk of bias due to uncertainty over how the trialists managed data across the studies, but we also used data from the Lee 2022 systematic review to minimise the risk of double-counting.

All studies were open-label. For outcomes that were considered subjective and where clinical judgement could be influenced by knowledge of treatment allocation, a rating of moderate risk of bias was given for the domain of outcome assessment.

Outcomes were downgraded for inconsistency where there was evidence of statistical heterogeneity (I2>50%). These included invasive mechanical ventilation or ECMO, serious adverse events, respiratory failure or ARDS, clinical recovery, adverse events, and discontinuation due to adverse events. Analyses which were not split by level of respiratory support may also be considered as clinically heterogenous.

All included studies met the PICO eligibility criteria so outcomes were not downgraded for indirectness. However, it is noted that all studies were carried out before the rollout of COVID-19 vaccination. Two studies (Abd-Elsalam 2021 and Beigel 2020) did not use corticosteroids as standard of care which is routinely used in the UK for people hospitalised for COVID-19. However, a sensitivity analysis without these studies showed no difference to the overall results.

Outcomes were downgraded for imprecision where the 95% confidence interval crossed the line of no effect.

Outcomes rated as moderate certainty included: all-cause mortality (no oxygen or low flow oxygen), need for oxygen supplementation, time to recovery).

Outcomes rated as low certainty included: all-cause mortality (High flow O2, NIV or IMV), invasive mechanical ventilation or ECMO, respiratory failure or ARDS, time to improvement, duration of hospital stay, oxygen-free days and ventilator-free days.

All the remaining outcomes were rated as very low certainty.

See appendix G for forest plots and appendix I for full GRADE profiles.

Remdesivir for 5 days vs remdesivir for 10 days

There remains uncertainty whether a 5-day course of remdesivir is more effective and safer than a 10-day course.

What is the evidence informing this recommendation?

Evidence comes from two randomised trials that compared 5-day to 10-day treatment with remdesivir in 781 hospitalised patients with moderate to critical COVID-19 (Goldman 2020; Spinner 2020).

Study characteristics

Mean or median age ranged between 56 to 62 years and women comprised 32 to 40% of patients across both studies. Pregnant people and children were ineligible, with the exception of 1 trial (Spinner 2020) which included children over 12 years weighing 40kg or more.

The majority of people (84%) in 1 trial (Spinner 2020) were not receiving oxygen supplementation at baseline. In the second trial 55% were receiving oxygen supplementation at baseline and 30.5% were ventilated (Goldman 2020).

What are the main results?

Critical outcomes

All-cause mortality
Moderate quality evidence from 2 studies found no statistically significant difference in all-cause mortality at 14 days with remdesivir 5-day treatment compared to 10-day treatment (16 fewer deaths per 1000 people [RR 0.73 95% CI 0.40 to 1.33; 781 people in 2 studies]).

Low quality evidence from 1 study found no statistically significant difference in all-

cause mortality at 28 days with remdesivir 5-day treatment compared to 10-day treatment (5 fewer deaths per 1000 people [RR 0.67 95% CI 0.11 to 3.99; 384 people in 1 study]).

Serious adverse events
Moderate quality evidence from 2 studies found a statistically significant reduction in serious adverse events with remdesivir 5-day treatment compared to 10-day treatment (72 fewer events per 1000 people [RR 0.64 95% CI 0.47 to 0.87; 781 people in 2 studies]).

Important outcomes

Acute respiratory failure or ARDS
Low quality evidence from 1 study found a statistically significant reduction in acute respiratory failure or ARDS at 30 days with remdesivir 5-day treatment compared to 10-day treatment (62 fewer events per 1000 people [RR 0.47 95% CI 0.24 to 0.94; 397 people in 1 study]).

Septic shock
Very low-quality evidence from 1 study found no statistically significant difference in septic shock at 30 days with remdesivir 5-day treatment compared to 10-day treatment (15 fewer events per 1000 people [RR 0.39 95% CI 0.08 to 2.01; 397 people in 1 study]).

Clinical recovery
Low quality evidence from 1 study found a statistically significant increase in clinical recovery at 14 days with remdesivir 5-day treatment compared to 10-day treatment (108 more events per 1000 people [RR 1.20 95% CI 1.02 to 1.14; 397 people in 1 study]).

Adverse events
Moderate quality evidence from 2 studies found no statistically significant difference in adverse events with remdesivir 5-day treatment compared to 10-day treatment (46 fewer events per 1000 people [RR 0.93 95% CI 0.84 to 1.03; 781 people in 2

studies]) .

Discontinuation due to adverse events
Low quality evidence from 2 studies found no statistically significant difference in discontinuation due to adverse events at 14 days with remdesivir 5-day treatment compared to 10-day treatment (23 fewer events per 1000 people [RR 0.59 95% CI 0.30 to 1.15; 781 people in 2 studies]).

Discharge from hospital
Moderate quality evidence from 2 studies found no statistically significant difference in discharge from hospital at 14 days with remdesivir 5-day treatment compared to 10-day treatment (38 more events per 1000 people [RR 1.06 95% CI 0.93 to 1.20; 781 people in 2 studies]).

Low quality evidence from 1 study found no statistically significant difference in discharge from hospital at 28 days with remdesivir 5-day treatment compared to 10-day treatment (9 fewer events per 1000 people [RR 0.99 95% CI 0.92 to 1.06; 384 people in 1 study]).

Our confidence in the results

Certainty of the evidence is moderate for the following outcomes: death within 14 days, serious adverse events, adverse events and discharge from hospital within 14 days. Certainty is low for death within 28 days, acute respiratory failure or ARDS, clinical recovery or discontinuation due to adverse event within 14 days and discharge from hospital within 28 days. This judgement is based on serious risk of bias (problems with randomisation, lack of blinding), serious imprecision (low event rate for the outcome of death within 14 days) and very serious imprecision (reliance on a single study with few patients and/or few events). Certainty of the evidence is very low for septic shock due to lack of blinding and reliance on a single study with few patients and few events.

See appendix G for forest plots and appendix I for full GRADE profiles.

Evidence to decision

Benefits and harms

Ten randomised controlled trials and 1 systematic review were included as part of the evidence review for remdesivir for people in hospital and needing supplementary oxygen. These studies compared the outcomes between people having remdesivir and people having placebo or standard care. The outcome of all-cause mortality was evaluated based on the level of respiratory support that people needed at baseline. For all other outcomes, including invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO), adverse events, serious adverse events, stopping treatment because of adverse events, clinical recovery, oxygen-free days, ventilator-free days, duration of hospital stay and hospital discharge, it was not possible to split the data by level of respiratory support.

When considering the benefits and harms of remdesivir treatment, the panel focused on the outcome of all-cause mortality. This was evaluated separately for people not having oxygen support or having low-flow supplemental oxygen at baseline and for people having high-flow supplemental oxygen, non-invasive ventilation (NIV) or IMV at baseline. Although not always described in the evidence, the panel considered that continuous positive airway pressure (CPAP) was included as a type of NIV.

The panel noted difficulties in disaggregating data on different modalities of respiratory support to inform subgroup analysis. Notably, the WHO-SOLIDARITY trial did not report high-flow and low-flow oxygen separately. Also, it did not distinguish between NIV and IMV. The subgroups presented in this trial were people not having supplemental oxygen at baseline, people having supplemental oxygen at baseline and people having ventilation at baseline. However, the panel agreed that subgroup data should be distinguished between high-flow oxygen, NIV or IMV and low-flow oxygen modalities in the pooled meta-analysis of included studies. For the WHO-SOLIDARITY trial, the panel agreed to include people having supplemental oxygen in the meta-analyses for people having low-flow or no oxygen at baseline. Also, people having ventilation were included in the meta-analyses for people having high-flow oxygen, NIV or IMV at baseline.

The panel noted that there was a statistically significant reduction in all-cause mortality among people having no or low-flow oxygen. There was no difference in mortality between remdesivir and control among people having high-flow oxygen, NIV or IMV at baseline.

The panel discussed a clinical rationale for this trend, based on the mechanism of action of antiviral treatments. This hypothesis states that antivirals are expected to be:

- most effective early in the disease course, when viral replication is a driver of disease
- less likely to be effective in the later stages in the disease course, when it enters the hyperinflammatory phase when people are more likely to need more extensive respiratory support.

Note that the studies included in this evidence review did not provide data on viral load.

Evidence from randomised controlled trials of remdesivir compared with standard care shows that remdesivir has an acceptable safety profile. There was no statistically significant difference in adverse events, serious adverse events, stopping because of adverse events, respiratory failure or acute respiratory distress syndrome, or septic shock among people having remdesivir compared with standard care.

The panel noted that the direction of effect was consistently in favour of remdesivir across studies for people having low-flow oxygen or no oxygen. They agreed that a 'consider' recommendation for people on low-flow oxygen and not on high-flow oxygen, NIV or IMV would allow for clinical discretion in making individualised treatment decisions. They also agreed that it would reflect the level of uncertainty in the evidence.

Because of the uncertainty of the evidence, the panel advised that people in hospital with COVID-19 and having high-flow oxygen, NIV or IMV should not have remdesivir except in the context of an ongoing clinical trial. The panel discussed that additional clinical research would be helpful to understand with certainty the benefits or potential harms of remdesivir for people having high-flow oxygen, NIV or IMV.

Based on the results of 2 studies that compared 10-day with 5-day courses of remdesivir, the current evidence does not suggest any greater benefit for a 10-day duration but suggests an increased risk of harm. The panel also acknowledged that, if disease progression results in the need for more respiratory support while using remdesivir, there may be no benefit in completing the full course. For these reasons, along with resource impact considerations (see also Resources), the panel agreed to recommend remdesivir for up to 5 days.

The panel noted the unclear additive benefit of remdesivir when used with dexamethasone, particularly because the 2 main trials, SOLIDARITY and ACTT-1, were done before the routine use of dexamethasone.

The panel also reviewed data from an observational study but did not consider this to have any effect on the recommendations.

Certainty of the evidence

For outcomes relevant to the benefit of remdesivir treatment (including all-cause mortality, need for mechanical ventilation, need for oxygen supplementation, clinical recovery, duration of hospital stay, discharge from hospital, oxygen-free days, ventilator-free days, time to improvement and time to recovery), the certainty of evidence was very low to moderate.

Certainty of the evidence was moderate for all-cause mortality in people who need low-flow supplemental oxygen or no oxygen because of serious risk of bias. This is because there is a risk that people enrolled in the WHO-SOLIDARITY were also included in published results of add-on trials, including CATCO (Ali 2022) in Canada and DisCoVeRy (Ader 2022) in France. The certainty of the evidence for all-cause

mortality in people who need high-flow oxygen, NIV or IMV was downgraded further for imprecision because the confidence interval crossed the line of no effect.

For outcomes relevant to the safety of remdesivir (including adverse events, serious adverse events, stopping because of adverse events, respiratory failure or ARDS, and septic shock), the certainty of the evidence was low to very low. This is because of inconsistency in outcomes resulting from statistical heterogeneity in the meta-analysis, imprecision when the confidence interval crossed the line of no effect and serious risk of bias because 2 of the included studies were unblinded.

Values and preferences

The panel were not aware of any systematically collected data on peoples' preferences and values. They identified critical outcomes that would be important for decision making. These included all-cause mortality, the need for IMV and serious adverse events. It is likely that these outcomes would also be of similar importance to people with COVID-19. In addition, other outcomes including less serious adverse events, discharge from hospital, duration of hospital stay and longer-term outcomes such as functional independence are likely to be of particular importance to people with COVID-19. These outcomes were not as commonly reported in studies. The outcome of functional independence was not reported at all in studies included in this review.

The panel inferred that, in view of the probable mortality benefits for people with COVID-19 who need low-flow supplemental oxygen, most would choose remdesivir.

Resources

Cost effectiveness was not assessed as part of the evidence review.

The panel raised concerns about opportunity costs where remdesivir is being used in critical care, and the importance of not diverting resources away from best supportive care. The panel noted the value of targeting treatment to optimise use of resources. The panel also noted the lack of evidence showing any benefit of a 10-day over a 5-day regimen, a direction of effect indicating potential harms of the 10-

day duration and the resource impact for a longer treatment duration. See also the benefits and harms section.

Equity

The panel noted an absence of evidence from randomised controlled trials on remdesivir use in children. However, it was considered unlikely that most children would benefit from this intervention because most children will recover without the need for it.

Children are often excluded from clinical trials. It was suggested that the recommendation for use of remdesivir only in clinical trials for people who need high-flow oxygen, NIV or IMV could lead to inequity if adults could have remdesivir as part of a trial, but children could not. However, the proposed inequity is outweighed by the possibility of harm from remdesivir use in people who need high-flow or more intensive oxygen therapy.

The panel also noted a lack of evidence from randomised controlled trials on remdesivir use in people who were immunocompromised. The studies included in this review did not exclude people in this subgroup, but it was not possible to analyse the effect of remdesivir in them. The panel decided to refer to NHS England's Interim Clinical Commissioning Policy on remdesivir for people in hospital with COVID-19, which includes people who are significantly immunocompromised. This policy states that ‘for significantly immunocompromised patients hospitalised for COVID-19 symptoms, a course of remdesivir can be extended to a maximum of 10 days’.

No evidence for using remdesivir in pregnancy was identified. The marketing authorisation confirms the lack of evidence, and notes that remdesivir should be avoided in pregnancy unless 'the clinical condition of the women requires treatment with it'. Any decisions to use remdesivir in someone who is pregnant should involve them and a multidisciplinary team, if possible. People who are pregnant are often excluded from clinical trials, which could lead to inequity if some people could have remdesivir as part of a clinical trial but not if they are pregnant. However, the proposed inequity is outweighed by the possibility of harm from remdesivir use in people who need high-flow or more intensive oxygen therapy.

Some people with COVID-19 may have treatment through virtual wards. However, supporting information published by NHS England about virtual wards does not include criteria for specific treatments, including remdesivir, in this acute setting. No evidence was identified on remdesivir use in hospital-led acute care in the community, including hospital at home and virtual wards. But new evidence and intelligence on policy changes to services will be monitored through surveillance.
No other equity issues were identified.

Acceptability

The panel were not aware of any systematically collected evidence about acceptability. A potential deterring factor to acceptability could be that the certainty of current evidence is very low to moderate. However, the panel noted the consistent direction of effect in favour of remdesivir for those on lower levels of respiratory support.

It is anticipated that, when considering the risks and benefits of treatment, most people who are admitted to hospital with COVID-19 pneumonia and need low-flow supplemental oxygen would choose to have remdesivir.

It is anticipated that, when considering the risks and benefits of treatment, most people who are admitted to hospital with COVID-19 pneumonia and need high-flow oxygen, NIV or IMV would choose not to have remdesivir.

Feasibility

Although there is no systematically collected evidence about feasibility, the panel noted that current widespread use of remdesivir in clinical practice is an indicator of feasibility.

Appendices

Appendix A: PICO table

Review question:

What is the effectiveness and safety of remdesivir for adults, young people and children with COVID-19?

Criteria	Notes
Population	Hospitalised adults, young people and children with confirmed COVID-19.
Interventions	Remdesivir
Comparators	Standard care alone, standard care plus placebo or placebo alone Note: Standard care comprises best supportive care and in certain circumstances the use of additional drugs (such as dexamethasone, remdesivir).
Outcomes	**Effectiveness outcomes** • Mortality • Invasive mechanical ventilation (IMV) or intensive care admission (requirement and duration) • Hospitalisation (requirement and duration) • Supplemental oxygen (requirement and duration) • High-flow oxygen, continuous positive airway pressure or non-invasive ventilation (requirement and duration) • Symptom resolution or clinical recovery (number and time until) • Clinical worsening / deterioration (number and time until)

	• Sustained recovery (development of long-term effects of COVID measured at least 4 weeks from onset of acute COVID-19) • Virological clearance (negative PCR) / viral load **Safety outcomes** • Adverse events • Discontinuation due to adverse events The definitions of mechanical ventilation, non-invasive ventilation and other forms of respiratory support such as high flow nasal oxygen (HFNO) therapy or continuous positive airway pressure or non-invasive bilevel ventilation may differ across the studies. In the context of UK practice the following definitions should be considered: **Advanced respiratory support:** Invasive mechanical ventilation, bilevel positive airway pressure (BiPAP) via translaryngeal tube or tracheostomy, continuous positive airway pressure (CPAP) via translaryngeal tube, or extracorporeal respiratory support) **Non-invasive ventilation:** includes HFNO, CPAP, CPAP via tracheostomy, and non-invasive bilevel ventilation. Note: oxygen via (low flow) nasal cannulae or face mask does not fall within the categories above.
Settings	All settings in which patients are under the care of a secondary care clinical team for the management of COVID-19
Subgroups	• Adults > 50 years • Children <12 years of age • Disease severity at baseline (mild/moderate/severe/critical)

	• Gender • Ethnic background • Pregnant women • Comorbidities (chronic obstructive pulmonary disease, hypertension, diabetes, coronary heart disease, chronic kidney disease, cancer, cerebral vascular disease, obesity) • Time from symptom onset (≤7 days vs. > 7 days) • Vaccination status • Seronegative vs. seropositive • PCR confirmed COVID vs. not confirmed • COVID-19 variants • Asymptomatic with positive test vs. symptomatic with positive test
Study types	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If no systematic reviews or RCT evidence is available progress to: • Non-randomised controlled trials • Systematic reviews of non-randomised controlled trials • Cohort studies • Before and after studies • Interrupted time series studies

	Preprints will be considered as part of the evidence review.
Countries	Any
Timepoints	From 2020 onwards
Other exclusions	• Non-English language papers, studies that are only available as abstracts, and narrative reviews • Animal studies • Editorials, letters, news items, case reports and commentaries, conference abstracts and posters theses and dissertations
Equality issues	Sex, age, ethnicity, religion or beliefs, people with a learning disability and disabled people, socioeconomic status, people who are pregnant or breastfeeding, people whose first language isn't English, people who are homeless, refugees, asylum seekers, migrant workers and people who are homeless.

Appendix B: Literature search strategy/Data source

Search design and peer review

This search was developed in compliance with Appendix L of NICE's manual on developing guidelines.
A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 10 March 2022. This search report is compliant with the requirements of PRISMA-S.
The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.
The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Limits and restrictions

The searches were limited to 1 March 2021 to current as Surveillance of remdesivir for NG191 started on 23 March 2021 and this was backdated to the beginning of that month to ensure no papers were missed.
English language papers were prioritised given the rapid nature of the review.
The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Search filters

Limits were applied in line with the PICO for this topic.
The MEDLINE RCT filter was McMaster Therapy – Medline - "best balance of sensitivity and specificity" version. The standard NICE modifications were used: randomized.mp changed to randomi?ed.mp.

> Haynes RB et al. (2005) Optimal search strategies for retrieving scientifically strong studies of treatment from Medline: analytical survey. *BMJ*, 330, 1179-1183.

The Embase RCT filter was McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

> Wong SSL et al. (2006) Developing optimal search strategies for detecting clinically sound treatment studies in EMBASE. *Journal of the Medical Library Association*, 94(1), 41-47.

Key decisions

NICE's approach to retrieving preprints has evolved throughout the pandemic:

- Prior to 20th April 2020 MedRxiv and BioRxiv were searched directly.
- From 20th April 2020 an automated process was used to download the entire MedRxiv and BioRxiv COVID-19 and SARS-COV-2 collection into EPPI Reviewer 5 and update the results on a daily basis. Individual topic searches were conducted within EPPI Reviewer to get round limitations of the native search functionality in MedRxiv and BioRxiv.
- From 19th August 2021, results from additional preprint servers were added to the EPPI Reviewer database on a weekly basis. The additional results were sourced from the aggregator sites Europe PMC and the NIH Office of Portfolio Analysis COVID-19 database. These sites index multiple preprint servers, including Arxiv, MedRxiv, BioRxiv, Research Square, SSRN and preprints.org. The NIH database is pre-sifted for COVID-19 related references. Europe PMC is broader, and so we initially used their stock strategy to narrow the results down to a subset that were related to COVID-19. References added to the aggregator sites from the 10th August 2021 were downloaded, but searches of these sources were not backdated further.

The preprint search in EPPI was limited to the title field to maintain the relevance of the results.

The development of NICE's main database search strategy for Covid-19 is covered in: Levay P and Finnegan A (2021) The NICE COVID-19 search strategy for Ovid MEDLINE and Embase: developing and maintaining a strategy to support rapid guidelines. MedRxiv preprint. https://doi.org/10.1101/2021.06.11.21258749

The names for the drug were checked in the BNF (3 February 2022) and the searches for the Ansems et al. Cochrane review.

> Ansems K, et al. (2021) Remdesivir for the treatment of COVID-19. *Cochrane Database of Systematic Reviews*, Issue 8. Art. No.: CD014962. DOI: 10.1002/14651858.CD014962.

The clinical trial ID numbers used in the search were obtained from the National Institute for Health Research Innovation Observatory (NIHRIO) Covid-19 Therapeutics and Vaccines in Clinical Development Scan spreadsheet. This was last updated on 3 March 2022. There were 74 trials in total. All remdesivir trials were used, they were not reviewed for relevance to the current PICO.

The MEDLINE and CENTRAL searches were done in the format:

> (COVID-19 AND Remdesivir AND RCT Filter) OR Trial numbers

Embase was done a different format:

> ((COVID-19 AND Remdesivir) OR Trial numbers) AND RCT Filter

This change was made because the Embase search was retrieving articles that had long lists of clinical trials attached to them, which were not directly relevant. These were discussion pieces and reviews. None of the ones reviewed were clinical trial reports on remdesivir. Similarly, the Emtree term for remdesivir was focussed to increase the relevance of the results. About half of the records indexed with this term actually have the drug name in the title or abstract, highlighting that it is used broadly. Making these changes reduced the Embase results from 508 to 200. Around 30 were reviewed on screen and none of the ones that would be excluded were relevant.

Clinical/public health searches

Main search – Databases

Database	Date searched	Database platform	Database segment or version	No. of results downloaded
MEDLINE ALL	10/03/2022	Ovid	Ovid MEDLINE(R) ALL <1946 to March 09, 2022>	141
Embase	10/03/2022	Ovid	Embase <1974 to 2022 March 09>	200
Cochrane CENTRAL	10/03/2022	Wiley	Cochrane Central Register of Controlled Trials Issue 2 of 12, February 2022	58
Preprints	10/03/2022	EPPI-R	Last updated 10 March 2022 0838	103
WHO Covid-19 Database	10/03/2022	WHO	Searched on 10 March 2022	17

Main search – Additional methods

Additional method	Date searched	No. of results downloaded
Surveillance	24/02/2022	390

Search results

Records	
Total number of records	909
Number of duplicates	232
Total number after deduplication	677

Search strategy history

Database name: MEDLINE ALL

Ovid MEDLINE(R) ALL <1946 to March 09, 2022>
1 SARS-CoV-2/ or COVID-19/ 146598
2 (corona* adj1 (virus* or viral*)).ti,ab. 2867
3 (CoV not (Coefficien* or "co-efficien*" or covalent* or Covington* or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk*" or CoVR or CoVS)).ti,ab. 69523
4 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. 239227
5 or/1-4 246714
6 limit 5 to yr="2020-Current" 233567
7 (Remdesivir* or "GS-5734" or GS5734 or Veklury*).tw,kw,kf. 2310
8 6 and 7 2229
9 randomized controlled trial.pt. 560636
10 randomi?ed.mp. 988578
11 placebo.mp. 233540
12 or/9-11 1050775
13 8 and 12 281
14 (NCT04944082 or IRCT20200405046953N1 or NCT04745351 or "2020-005416-22" or "202000541622" or NCT04560231 or NCT04330690 or NCT04488081 or NCT04323761 or NCT04610541 or "PER-010-20" or PER01020 or IRCT20200404046937N5 or NCT04546581 or NCT04492475 or NCT04871633 or NCT04575064 or NCT04501978 or IRCT20150107020592N31 or IRCT20151227025726N28 or NCT04843761 or "2020-000982-18" or "202000098218" or NCT04345419 or IRCT20161206031255N4 or "2020-001366-11" or "202000136611" or IRCT20171122037571N2 or IRCT20210510051248N1 or NCT04501952 or "CTRI 2021 08 035537" or CTRI202108035537 or "2020-004928-42" or "202000492842" or NCT04391309 or IRCT20200329046892N2 or NCT04492501 or NCT04779047 or NCT04853901 or NCT04583969 or NCT04583956 or NCT04596839 or "2020-002060-31" or "202000206031" or NCT04593940 or NCT04257656 or IRCT20210709051824N1 or NCT04351724 or NCT04713176 or "CTRI 2021 02 031430" or CTRI202102031430 or NCT05185284 or NCT04647695 or NCT04409262 or NCT04480333 or IRCT20200721048159N4 or NCT04647669 or NCT04252664 or IRCT20201229049872N1 or NCT05024006 or NCT05041907 or NCT04292730 or NCT04292899 or NCT05226533 or NCT04302766 or "CTRI 2020 12 029615" or CTRI202012029615 or NCT04539262 or NCT04280705 or IRCT20210324050760N1 or NCT04640168 or NCT04315948 or NCT04693026 or LBCTR2020043495 or NCT04988035 or IRCT20200426047212N2 or NCT04349410 or "JPRN-jRCT2031190264" or JPRNjRCT2031190264 or NCT04738045 or NCT04978259 or NCT04401579 or NCT04678739 or NCT04727775 or NCT04970719 or NCT04410354 or NCT04321616 or NCT04431453 or ISRCTN83971151 or NCT04694612 or "2020-005416-22" or "202000541622" or "2020-001453-49" or "202000145349" or "2020-002542-16" or "202000254216" or "JPRN-jRCT2031200174" or JPRNjRCT2031200174 or "JPRN-jRCT2031200092" or JPRNjRCT2031200092 or "2020-001549-38" or

"202000154938" or "2020-003278-37" or "202000327837" or "CTRI 2021 01 030830" or CTRI202101030830 or "2020-003510-12" or "202000351012" or "PER-101-20" or PER10120 or "2020-001302-30" or "202000130230" or "2020-002275-34" or "202000227534" or "2020-000842-32" or "202000084232" or ISRCTN85762140 or "2020-000841-15" or "202000084115" or ISRCTN15874265 or "2020-001052-18" or "202000105218" or ISRCTN13035264 or "JPRN-jRCT2031200252" or JPRNjRCT2031200252 or "2020-000936-23" or "202000093623" or "JPRN-jRCT2031200035" or JPRNjRCT2031200035 or "2020-001803-17" or "202000180317").af. 32
15 13 or 14 290
16 Animals/ not humans/ 4935634
17 15 not 16 289
18 (letter or historical article or comment or editorial or news or case reports).pt. 4603923
19 17 not 18 271
20 limit 19 to english language 266
21 limit 20 to ed=20210301-20220310 99
22 limit 20 to dt=20210301-20220310 113
23 21 or 22 141

Database name: Embase

Embase <1974 to 2022 March 09>
1 exp severe acute respiratory syndrome coronavirus 2/ or coronavirus disease 2019/ or experimental coronavirus disease 2019/ 208137
2 (corona* adj1 (virus* or viral*)).ti,ab. 3474
3 (CoV not (Coefficien* or co-efficien* or covalent* or covington or covariant* or covarianc* or "cut-off value*" or "cutoff value*" or "cut-off volume*" or "cutoff volume*" or "combined optimi?ation value*" or "central vessel trunk" or CoVR or CoVS)).ti,ab. 74442
4 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel*" or Ncov* or "n-cov" or "SARS-CoV-2*" or "SARSCoV-2*" or SARSCoV2* or "SARS-CoV2*" or "severe acute respiratory syndrome*" or COVID*2).ti,ab. 254612
5 or/1-4 273143
6 limit 5 to yr="2020-Current" 258284
7 (Remdesivir* or "GS-5734" or GS5734 or Veklury*).tw,kw,kf. 3011
8 *remdesivir/ 906
9 7 or 8 3048
10 6 and 9 2943
11 (NCT04944082 or IRCT20200405046953N1 or NCT04745351 or "2020-005416-22" or "202000541622" or NCT04560231 or NCT04330690 or NCT04488081 or NCT04323761 or NCT04610541 or "PER-010-20" or PER01020 or IRCT20200404046937N5 or NCT04546581 or NCT04492475 or NCT04871633 or NCT04575064 or NCT04501978 or IRCT20150107020592N31 or IRCT20151227025726N28 or NCT04843761 or "2020-000982-18" or "202000098218" or NCT04345419 or IRCT20161206031255N4 or "2020-001366-11" or "202000136611" or IRCT20171122037571N2 or IRCT20210510051248N1 or NCT04501952 or "CTRI 2021 08 035537" or CTRI202108035537 or "2020-004928-42" or "202000492842" or NCT04391309 or IRCT20200329046892N2 or NCT04492501 or NCT04779047 or NCT04853901 or NCT04583969 or NCT04583956 or NCT04596839 or "2020-002060-31" or "202000206031" or

NCT04593940 or NCT04257656 or IRCT20210709051824N1 or NCT04351724 or NCT04713176 or "CTRI 2021 02 031430" or CTRI202102031430 or NCT05185284 or NCT04647695 or NCT04409262 or NCT04480333 or IRCT20200721048159N4 or NCT04647669 or NCT04252664 or IRCT20201229049872N1 or NCT05024006 or NCT05041907 or NCT04292730 or NCT04292899 or NCT05226533 or NCT04302766 or "CTRI 2020 12 029615" or CTRI202012029615 or NCT04539262 or NCT04280705 or IRCT20210324050760N1 or NCT04640168 or NCT04315948 or NCT04693026 or LBCTR2020043495 or NCT04988035 or IRCT20200426047212N2 or NCT04349410 or "JPRN-jRCT2031190264" or JPRNjRCT2031190264 or NCT04738045 or NCT04978259 or NCT04401579 or NCT04678739 or NCT04727775 or NCT04970719 or NCT04410354 or NCT04321616 or NCT04431453 or ISRCTN83971151 or NCT04694612 or "2020-005416-22" or "202000541622" or "2020-001453-49" or "202000145349" or "2020-002542-16" or "202000254216" or "JPRN-jRCT2031200174" or JPRNjRCT2031200174 or "JPRN-jRCT2031200092" or JPRNjRCT2031200092 or "2020-001549-38" or "202000154938" or "2020-003278-37" or "202000327837" or "CTRI 2021 01 030830" or CTRI202101030830 or "2020-003510-12" or "202000351012" or "PER-101-20" or PER10120 or "2020-001302-30" or "202000130230" or "2020-002275-34" or "202000227534" or "2020-000842-32" or "202000084232" or ISRCTN85762140 or "2020-000841-15" or "202000084115" or ISRCTN15874265 or "2020-001052-18" or "202000105218" or ISRCTN13035264 or "JPRN-jRCT2031200252" or JPRNjRCT2031200252 or "2020-000936-23" or "202000093623" or "JPRN-jRCT2031200035" or JPRNjRCT2031200035 or "2020-001803-17" or "202000180317").af. 539
12 10 or 11 3314
13 random:.tw. 1763737
14 placebo:.mp. 490602
15 double-blind:.tw. 228261
16 or/13-15 2030007
17 12 and 16 483
18 nonhuman/ not human/ 4945712
19 17 not 18 479
20 (letter or editorial).pt. 1933740
21 19 not 20 460
22 "case report".sh. 2715973
23 21 not 22 442
24 limit 23 to english language 437
25 (conference abstract* or conference review or conference paper or conference proceeding).db,pt,su. 5115212
26 24 not 25 378
27 limit 26 to medline 36
28 26 not 27 342
29 limit 28 to dc=20210301-20220310 200

Database name: Cochrane CENTRAL

#1 MeSH descriptor: [SARS-CoV-2] this term only 803
#2 MeSH descriptor: [COVID-19] this term only 1377
#3 (corona* near/1 (virus* or viral*)):ti,ab,kw 296
#4 (CoV NOT (Coefficien* or "co-efficient" or “co-efficiency” or “co-efficiencies” or covalent* or Covington* or covariant* or covarianc* or "cut-off value" or "cut-off

values" or "cutoff value" or "cutoff values" or "cut-off volume" or "cut-off volumes" or "cutoff volume" or "cutoff volumes" or "combined optimisation value" or "combined optimisation values" or "combined optimization value" or "combined optimization values" or "central vessel trunk" or "central vessel trunks" or CoVR or CoVS)):ti,ab,kw 641
#5 (coronavirus* or 2019nCoV* or 19nCoV* or "2019 novel" or Ncov* or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or SARSCoV2* or "SARS-CoV2" or "severe acute respiratory syndrome" or "severe acute respiratory syndromes" or covid19 or covid-19 or covid):ti,ab,kw 10138
#6 {or #1-#5} 10188
#7 (Remdesivir* or "GS-5734" or GS5734 or Veklury*):ti,ab,kw 280
#8 #6 and #7 271
#9 conference:pt 195680
#10 #8 not #9 242
#11 (clinicaltrials or trialsearch):so 391193
#12 #10 not #11 95
#13 #10 not #11 in Trials 91
#14 #10 not #11 with Publication Year from 2021 to 2022, in Trials 58

Database name: Preprints

Preprints were searched via EPPI reviewer v5
Title: Has Any: Remdesivir* GS5734 Veklury*
Title: Has Phrase: "GS-5734"

Database name: WHO COVID-19 Database

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel-coronavirus-2019-ncov

(remdesivir* OR "GS-5734" OR gs5734 OR veklury*) AND type_of_study:("clinical_trials") AND (year_cluster:[2021 TO 2022]) AND db:("ProQuest Central" OR "Web of Science" OR "other preprints" OR "Academic Search Complete" OR "PMC" OR "GIM" OR "Indonesian Research" OR "SSRN" OR "Scopus")

17 results

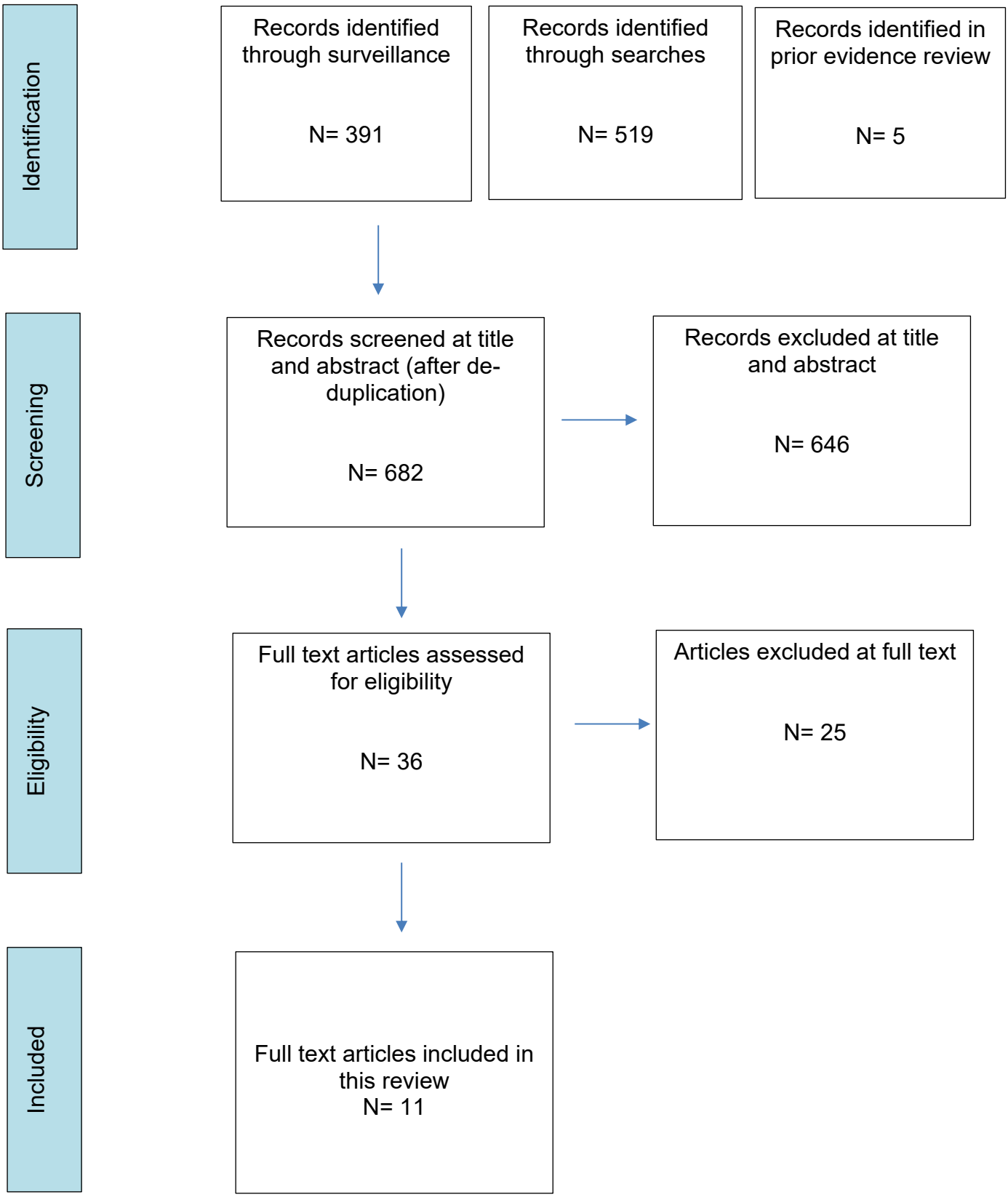
Additional search methods

Source name: Surveillance

Overall COVID-19 Surveillance process	The NICE COVID-19 Surveillance process began on 30 March 2020 to cover new journal articles, reports, policy, guidelines, pre-prints and other documents on COVID-19 and SARS-CoV-2 published since 16 March 2020. Weekly and monthly searches are performed of MEDLINE, Embase, bioRxiv and medRxiv, other pre-print sources, BMJ Best Practice, NICE Evidence Search, TRIP database, Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials (CENTRAL). A number of websites are checked manually (listed in "COVID-19 rapid guideline: Vaccine-induced Immune Thrombocytopenia and Thrombosis (VITT): Search strategies. NICE guideline 200"). The search is

	limited to items published in English. Animal studies, letters, comments, editorial, case reports and conference reports are also excluded. The results of these Surveillance searches are processed on a weekly basis using a combination of automated and manual processes. The references that are of potential relevance to NICE are marked and placed into a group for the guidelines or other products to which they relate. These groups use the codeset function in EPPI-R5. By the end of 2021, the Surveillance master EPPI review contained over 250,000 unique records.
Surveillance for remdesivir	The Surveillance process started to monitor remdesivir in relation to NICE guideline 191 COVID-19 rapid guideline 191: managing COVID-19 from 23 March 2021. Any items of potential relevance were added to a set in EPPI Reviewer.
Date of search	The set in EPPI Reviewer relating to remdesivir was downloaded on 5 March 2022. The date of the last search for Surveillance was 24 February 2022.
Number of results	390

Appendix C: PRISMA diagram



Appendix D: Included studies

Abd-Elsalam, Sherief, Ahmed, Ossama Ashraf, Mansour, Noha O. et al. (2021) Remdesivir Efficacy in COVID-19 Treatment: A Randomized Controlled Trial. The American Journal of Tropical Medicine and Hygiene: tpmd210606
Ader F, Bouscambert-Duchamp M, Hites M et al. (2022) Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial. The Lancet. Infectious diseases 22(2): 209-221
Ali K, Azher T, Baqi M et al. (2022) Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne
Barratt-Due, Andreas, Olsen, Inge Christoffer, Nezvalova-Henriksen, Katerina et al. (2021) Evaluation of the Effects of Remdesivir and Hydroxychloroquine on Viral Clearance in COVID-19. Annals of Internal Medicine 174(9): 1261-1269
Beigel JH, Tomashek KM, Dodd LE et al. (2020) Remdesivir for the Treatment of Covid-19 - Final Report. The New England journal of medicine 383(19): 1813-1826
Goldman JD, Lye DCB, Hui DS et al. (2020) Remdesivir for 5 or 10 Days in Patients with Severe Covid-19. The New England journal of medicine 383(19): 1827-1837
Lee TC; Murthy S; Del Corpo O; Senécal J; Butler-Laporte G; Sohani ZN; Brophy JM; McDonald EG (2022) Remdesivir for the treatment of COVID-19: A systematic review and meta-analysis. Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases
Mahajan, Lakshmi; Singh, A P; Gifty (2021) Clinical outcomes of using remdesivir in patients with moderate to severe COVID-19: A prospective randomised study. Indian journal of anaesthesia 65(suppl1): 41-s46
Spinner CD, Gottlieb RL, Criner GJ et al. (2020) Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. JAMA 324(11): 1048-1057
Wang Y, Zhang D, Du G et al. (2020) Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet (London, England) 395(10236): 1569-1578
WHO Solidarity Trial Consortium (2022) Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Soldarity randomised trial and updated meta-analyses; The Lancet

Appendix E: Excluded studies at full text screening

Study reference	Reason for exclusion
Thiede, Joshua M, Gress, Abigail R, Libby, Samuel D et al. (2021) Immune Profiling to Determine Early Disease Trajectories Associated With Coronavirus Disease 2019 Mortality Rate: A Substudy from the ACTT-1 Trial. The Journal of infectious diseases 223(8): 1339-1344	Post- hoc analysis
Olender, S, Walunas, TL, Martinez, E et al. (2021) Remdesivir versus standard of care for severe COVID-19. Topics in antiviral medicine 29(1): 139	Compares one arm of an RCT to observational data - does not match review protocol
Gottlieb, Robert L, Vaca, Carlos E, Paredes, Roger et al. (2022) Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. The New England journal of medicine 386(4): 305-315	Population not relevant - Not hospitalised
Olender, Susan A, Walunas, Theresa L, Martinez, Esteban et al. (2021) Remdesivir Versus Standard-of-Care for Severe Coronavirus Disease 2019 Infection: An Analysis of 28-Day Mortality. Open forum infectious diseases 8(7): ofab278	Post hoc analysis that compares one arm of an RCT to real-world evidence - study type does not fit review protocol
Hosseini, Hamed, Sadeghi, Anahita, Tabarsi, Payam et al. Another step toward final call on Remdesivir efficacy as a treatment for hospitalized COVID-19 patients: a multicenter open-label trial. medrxiv preprint	Single arm (no control)
Abeldano Zuniga, Roberto Ariel, Coca, Silvia Mercedes, Abeldano, Giuliana Florencia et al. (2021) Clinical effectiveness of drugs in hospitalized patients with COVID-19: a systematic review and meta-analysis. Therapeutic advances in respiratory disease 15: 17534666211007214	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Al-Abdouh, Ahmad, Bizanti, Anas, Barbarawi, Mahmoud et al. (2021) Remdesivir for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials. Contemporary clinical trials 101: 106272	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Alexander Paul, E, Piticaru, Joshua, Lewis, Kim et al. Remdesivir use in patients with coronavirus COVID-19 disease: a systematic review and meta-analysis. medrxiv preprint	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Ansems, Kelly, Grundeis, Felicitas, Dahms, Karolina et al. (2021) Remdesivir for the treatment of COVID-19. The Cochrane database of systematic reviews 8: cd014962	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Bansal, V., Mahapure, K.S., Bhurwal, A. et al. (2020) Mortality Benefit of Remdesivir in COVID-19: A Systematic Review and Meta-Analysis. Frontiers in Medicine 7: 606429	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Choupoo, N.S., Das, S.K., Haldar, R. et al. (2020) Evaluating the efficacy and safety of the existing repurposed pharmacological agents for treating covid-19: A meta-analysis and systemic review of clinical trials. Indian Journal of Critical Care Medicine 24(11): 1106-1113	Systematic review – did not include any remdesivir RCTs
Enoki, Yuki, Igarashi, Yuki, Watabe, Yuki et al. (2021) Remdesivir for the treatment of coronavirus COVID-19: A meta-analysis of randomised controlled trials. Journal of global antimicrobial resistance 24: 81-82	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO

Hariyanto, Timotius Ivan, Kwenandar, Felix, Japar, Karunia Valeriani et al. (2021) The effectiveness and safety of remdesivir for the treatment of patients with covid-19: A systematic review and meta-analysis. Anti-Infective Agents 19(3): 333-340	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Konwar, Mahanjit; Maurya, Miteshkumar; Bose, Debdipta (2021) A Meta-Analysis of Safety of Different Regimens of Remdesivir in COVID-19 Patients. Current drug safety	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Lee Todd, C, Murthy, Srinivas, Corpo Olivier C, Del et al. Remdesivir for the Treatment of COVID-19: An Updated Systematic Review and Meta-Analysis. medrxiv preprint	Superseded by full text publication which has been included
NA Lixiang Lou, Sr., NA Hui Zhang, Sr., NA Zeqing Li, Sr. et al. The efficacy and safety of remdesivir in the treatment of patients with COVID-19: a systematic review and meta-analysis. medrxiv preprint	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Okoli, George N, Rabbani, Rasheda, Copstein, Leslie et al. (2021) Remdesivir for coronavirus disease 2019 (COVID-19): a systematic review with meta-analysis and trial sequential analysis of randomized controlled trials. Infectious diseases (London, England) 53(9): 691-699	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Paiva Francisca, Verdugo-Paiva, Acuna Maria, Paz, Sola, Ivan et al. Remdesivir for the treatment of COVID-19: A living systematic review. medrxiv preprint	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Piscoya, Alejandro, Sueng Luis F., Ng-Sueng, Riego Angela Parra, del et al. Efficacy and harms of remdesivir for the treatment of COVID-19: a systematic review and meta-analysis. medrxiv preprint	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Rezagholizadeh, Afra, Khiali, Sajad, Sarbakhsh, Parvin et al. (2021) Remdesivir for treatment of COVID-19; an updated systematic review and meta-analysis. European journal of pharmacology 897: 173926	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Sarfraz, Azza, Sanchez-Gonzalez, Marcos, Michel, Jack et al. (2021) Randomized controlled trials of remdesivir in hospitalized coronavirus disease 2019 patients: A meta-analysis. Turkish Journal of Emergency Medicine 21(2): 43-50	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Sarfraz, Azza, Sarfraz, Zouina, Gonzalez Marcos, Sanchez-Gonzalez et al. Randomized placebo-controlled trials of remdesivir in severe COVID-19 patients: A Systematic Review and Meta-analysis. medrxiv preprint	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Singh, Surjit, Khera, Daisy, Chugh, Ankita et al. (2021) Efficacy and safety of remdesivir in COVID-19 caused by SARS-CoV-2: a systematic review and meta-analysis. BMJ open 11(6): e048416	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Tao, J., Aristotelidis, R., Zanowick-Marr, A. et al. (2021) Evaluation of the Treatment Efficacy and Safety of Remdesivir for COVID-19: a Meta-analysis. SN Comprehensive Clinical Medicine 3(12): 2443-2454	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Thiruchelvam, Kaeshaelya, Kow, Chia Siang, Hadi, Muhammad et al. (2021) The use of remdesivir for the management of patients with moderate-to-severe COVID-19: A systematic review. Expert review of anti-infective therapy	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO

Zhu, Yun, Teng, Zhaowei, Yang, Lirong et al. Efficacy and Safety of Remdesivir for COVID-19 Treatment: An Analysis of Randomized, Double-Blind, Placebo-Controlled Trials. medrxiv preprint	Systematic review - RCTs included in this systematic review were reviewed independently for relevance to PICO
Pan H, Peto R, Henao-Restrepo AM et al. (2020) Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. The New England journal of medicine 384(6): 497-511	Replaced by final results, published on 2 May 2022 in WHO-SOLIDARITY 2022 study

Appendix F: Evidence tables

Abd-Elsalam, 2021

Bibliographic Reference	Abd-Elsalam, Sherief; Ahmed, Ossama Ashraf; Mansour, Noha O.; Abdelaziz, Doaa H.; Salama, Marwa; Fouad, Mohamed Hassan Ahmed; Soliman, Shaimaa; Naguib, Ahmed Mohamed; Hantera, Mohamed Sayed; Ibrahim, Ibrahim S.; Torky, Mohamed; Dabbous, Hany M.; El Ghafar, Mohamed Samir Abd; Abdul-Baki, Enas Abdul-Raouf M.; Elhendawy, Mohammed; Remdesivir Efficacy in COVID-19 Treatment: A Randomized Controlled Trial; The American Journal of Tropical Medicine and Hygiene; 2021

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04345419
Study start date	16-Jun-2020
Study end date	19-Dec-2020
Aim of the study	To assess the efficacy of remdesivir in hospitalised adults with COVID-19
Country/geographical location	Egypt
Study setting	Hospital
Population description	Patients with confirmed COVID-19, who were hospitalised were included in the study. The population included a male majority of participants (60%), with a mean age of 53.53 years (SD 15.2). A majority of patients presented with symptoms (for example cough, fever, headache) and 34% of patients had underlying comorbidities (for example, diabetes, hypertension).
Inclusion criteria	• Patients with mild or moderate symptoms • Aged 18-80 years
Exclusion criteria	• Patients with a history of renal impairment • Patients with alanine aminotransferase and or aspartate aminotransferase levels >5 times the upper limit of normal • Patients with an allergy or contraindication to remdesivir • Pregnant or lactating mothers
Intervention dosage (loading)	200mg
Intervention dosage (maintenance)	100mg daily
Intervention scheduled duration	10-day course

Intervention actual duration	Not reported
Intervention route of administration	Intravenous infusion over 30 to 60 minutes
Comparator (where applicable)	Standard care (zinc, acetylcysteine, lactoferrin and vitamin C). Paracetamol and prophylactic anticoagulant were prescribed when indicated
Methods for population selection/allocation	Patients were randomly assigned at a 1:1 ratio using computer random sequence generator. Treatment allocation was concealed from outcome assessors and patients using sequentially numbered opaque sealed envelopes kept by the hospital pharmacist. Envelopes were opened sequentially only after participant details were written on the envelope.
Methods of data analysis	Shapiro-Wilk test was used to test the normality of the studied variables. Numerical data were expressed as mean and standard deviation. Qualitative data were expressed as frequency and percentage. Comparison between the two groups with respect to continuous variables was done using Student's-test for normally distributed data or Mann-Whitney's test for not normally distributed ones. The chi-squared test was used to compare between the groups with respect to categorical data. Binary logistic regression was used to ascertain the effect of the potential risk factors on the patients' mortality. Two-sided P value, 0.05 was considered statistically significant. Statistical analysis was done using IBM SPSS Statistics version 23.
Attrition/loss to follow-up	Remdesivir group: 5 lost to follow-up Control group: 4 lost to follow-up
Source of funding	Not reported
Study limitations (Author)	The study included only mild-moderate COVID-19 patients which limit its applicability to severely ill patients. The study used an open-label design which could not eliminate the risk of bias of performance. The study also had a small sample size and the lack of assessment of virologic response limits the generalisability of these results. The study also had limited ethnic diversity.
Study limitations (Reviewer)	The study was an open-label randomised trial with small sample size. The population characteristics between both groups were not balanced and as such there may be some variation in response to treatment. Standard care did not include dexamethasone which is current standard care in the UK. The study does not specify level of oxygen support at baseline although oxygen saturation was 87-90%. Follow up time period (for mortality) was not reported.
Other details	

Study arms

Remdesivir (N = 100)

Control (N = 100)

Characteristics

Arm-level characteristics

Characteristic	Remdesivir (N = 100)	Control (N = 100)
Age Mean (SD)	55.04 (14.15)	52.02 (16.25)
Male No of events	n = 66 ; % = 66	n = 53 ; % = 53
History of smoking No of events	n = 24 ; % = 24	n = 26 ; % = 26
Diabetes No of events	n = 39 ; % = 39	n = 27 ; % = 27
Hypertension % No of events	n = 33 ; % = 33	n = 35 ; % = 35

Outcomes

Remdesivir vs Control

Outcome	Remdesivir, , N = 100	Control, , N = 100
Duration of hospital stay (days) Mean (SD)	12.37 (8.96)	16.72 (5.78)
Duration of hospital stay (days) Median (IQR)	10 (8 to 13.75)	16 (12 to 21)
Need for mechanical ventilation No of events	n = 11 ; % = 11	n = 8 ; % = 8
Mortality No of events	n = 9 ; % = 9	n = 7 ; % = 7

Critical appraisal - Remdesivir - RoB

Mortality

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Knowledge of intervention allocation unlikely to have impacted this outcome)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Outcomes in the trial registry differ from the final publication)*
Overall bias and Directness	Risk of bias judgement	Moderate *(Different outcomes reported compared to those in trial registry. Protocol unavailable)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(No corticosteroids as standard care)*

Duration of hospital stay

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Knowledge of treatment allocation could impact this outcome)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Outcomes in the trial registry differ from the final publication)*
Overall bias and Directness	Risk of bias judgement	Moderate *(Different outcomes reported compared to those in trial registry. Protocol unavailable)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(No corticosteroids as standard care)*

Need for mechanical ventilation-

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Knowledge of intervention allocation unlikely to have impacted this outcome)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Some concerns *(Outcomes in the trial registry differ from the final publication)*
Overall bias and Directness	Risk of bias judgement	Moderate *(Different outcomes reported compared to those in trial registry. Protocol unavailable)*
Overall bias and Directness	Overall Directness	Indirectly applicable *(No corticosteroids as standard care)*

Ader, 2022

Bibliographic Reference	Ader F; Bouscambert-Duchamp M; Hites M; Peiffer-Smadja N; Poissy J; Belhadi D; Diallo A; Lê MP; Peytavin G; Staub T; Greil R; Guedj J; Paiva JA; Costagliola D; Yazdanpanah Y; Burdet C; Mentré F; ; Remdesivir plus standard of care versus standard of care alone for the treatment of patients admitted to hospital with COVID-19 (DisCoVeRy): a phase 3, randomised, controlled, open-label trial.; The Lancet. Infectious diseases; 2022; vol. 22 (no. 2)

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04315948
Study start date	22-Mar-2020
Study end date	21-Jan-2021
Aim of the study	To evaluate the clinical efficacy of remdesivir plus standard of care compared with standard of care alone in patients admitted to hospital with COVID-19, with an indication of oxygen ventilator support
Country/geographical location	Austria, Belgium, France, Luxembourg, Portugal
Study setting	Hospital
Population description	857 participants were randomised for treatment. The median age of participants was 64 years (IQ R 54-73), a majority of participants were male (70%), with underlying comorbidities such as obesity, diabetes, chronic cardiac and pulmonary disease. A majority of participants (99%), were on some form of oxygen support upon admission and were classified as moderate to severe COVID-19. Characteristics between treatment arms were balanced.
Inclusion criteria	• Adult patients (aged ≥18 years) admitted to hospital with laboratory-confirmed SARS-CoV-2 infection and illness of any duration • Patients with clinical evidence of hypoxaemic pneumonia, or required oxygen supplementation
Exclusion criteria	• Elevated liver enzymes • Severe chronic kidney disease • Any contraindication to one of the studied treatments or their use in the 29 days before random assignment • Use of ribavirin • Pregnancy or breastfeeding
Intervention dosage (loading)	200mg
Intervention dosage (maintenance)	100mg once daily

Intervention scheduled duration	10 days; cessation was allowed if participants were discharged from hospital after 5 days
Intervention actual duration	Not reported
Intervention route of administration	Intravenous infusion over 1 hour
Comparator (where applicable)	Standard care included: anticoagulants, immunomodulators and dexamethasone
Methods for population selection/allocation	Participants were randomly assigned 1:1:1:1:1 when five groups were initially implemented and were then assigned 1:1 to receive either standard of care or standard of care plus remdesivir, once the other three treatment groups had been stopped for futility. Participants allocated to the standard of care alone or in combination with remdesivir were recruited contemporaneously. Randomisation was done in the electronic case report form to ensure appropriate allocation concealment and used computer-generated blocks of various sizes; it was stratified on the severity of disease at inclusion and on the European administrative region. The disease was defined as moderate in participants not receiving supplemental oxygen or requiring supplemental oxygen through a face mask or nasal prongs (ie, ordinal scale value of 3 or 4); it was defined as severe in participants requiring non-invasive ventilation, a high-flow oxygen device, invasive mechanical ventilation, or ECMO (ie, ordinal scale value of 5 or 6). Allocated treatment was not masked to participants nor the study investigator.
Methods of data analysis	The sample size was determined assuming the following scenario under the standard of care for each item of the ordinal scale at day 15: item 1, 42%; item 2, 38%; item 3, 8%; item 4, 7%; item 5, 2%; item 6, 1%; item 7, 2%. At the time of the trial design (March 2020), there was substantial uncertainty with these assumptions. We powered the study for an odds ratio (OR) of 1·5 (an OR greater than 1 indicates the superiority of the experimental treatment over the control for each ordinal scale category), with 90% power and using an overall one-sided type I error rate of 0·05. This size effect appeared statistically relevant, meaning that 52% of patients would be discharged with no limitation of activity at day 15 in the remdesivir group, instead of 42% of patients in the control group. We determined that the inclusion of 450 participants in each treatment group was required; this number was increased to 475 participants per group to account for unevaluable participants. An independent data safety and monitoring board (DSMB) externally reviewed the trial data at regular intervals regarding treatment efficacy, safety, and futility. Following cessation of hydroxychloroquine on June 17, 2020, and of both groups being treated with lopinavir–ritonavir on June 27, 2020, the trial continued the evaluation of remdesivir. On Jan 13, 2021, the DisCoVeRy DSMB recommended suspending participant recruitment on the basis of the evaluation of an interim report of 842 randomly assigned participants, of whom 776 participants had been evaluated at day 15 (389 on remdesivir and 387 on standard of

care). Calculating conditional power on the basis of the intended recruitment of 900 participants (ie, an additional 124 evaluable participants), the DSMB estimated the chances of reaching 5% significance on the originally hypothesised OR of 1·5 to be 0·02% at the end of the trial. They also found no evidence of efficacy on the WHO scale at day 29, nor on mortality at day 29, and noticed the low recruitment rate in the trial over the past 6 weeks. The decision was endorsed by the DisCoVeRy steering committee on Jan 19, 2021, with subsequent cessation of participant recruitment on Jan 21, 2021. Since April 28, 2021, participants enrolled in the trial are randomly assigned (1:1) to receive either AZ7442 (a combination of two long-acting antibodies derived from convalescent patients) or placebo.

The intention-to-treat population included all randomly assigned participants with a positive SARS-CoV-2 PCR result obtained in the past 9 days, for whom a valid consent form was obtained and who did not receive any investigational treatment in the past 29 days.

The modified intention-to-treat population included participants from the intention-to-treat population who received at least one dose of the treatment allocated by random assignment.

Efficacy analyses were done in the intention-to-treat population. Safety analyses were done in the modified intention-to-treat population. Analyses were stratified by baseline severity but not by region of inclusion due to a small number of inclusions in some regions; all tests were two-sided with a type I error of 0·05. When an endpoint was statistically significant, we did a non-prespecified subgroup analysis according to the baseline severity of COVID-19.

For the seven-point ordinal scale, missing data were imputed using the last observation carried forward method, except in the case of known death or hospital discharge, in which case the ordinal scale was imputed to the value of 7 (death) or 2 (not hospitalised, limitation of activities), respectively. For NEWS-2 oxygenation and mechanical ventilation outcomes, missing data were treated using the last observation carried forward method, except on the day of death, in which case participants were imputed to the worst NEWS-2 value or considered to require oxygen or mechanical ventilation. For time-to-event analyses, participants were censored at day 29, at their date of loss of follow-up, or of study withdrawal, whichever occurred first. For outcomes in which death was not included, participants who died before day 29 were censored at day 29. Missing SARS-CoV-2 viral loads were not imputed. For the analysis of viral load by mixed models, undetectable viral load values (ie, values <1 log10 copies per 10 000 cells) were imputed to half the limit of detection (0·7 log10 copies per 10 000 cells). In the case of several consecutive undetectable values, only the first value was replaced, and the subsequent values were discarded (until the next detectable value if values were available afterwards).

For the seven-point ordinal scale, data were analysed using a proportional odds model. Time-to-event data were analysed using

	a Cox proportional hazards model. An analysis of covariance was done for the comparison of oxygenation and ventilator-free days between groups; in-hospital mortality, 28-day mortality, and the number of participants with detectable SARS-CoV-2 in respiratory tract specimens at each time point were analysed using a Cochran-Mantel-Haenszel test. For safety endpoints, the number of participants with at least one adverse event, with at least one grade 3 or 4 adverse events, and with at least one serious adverse event were compared between groups using a Cochran-Mantel-Haenszel test. Prespecified subgroup analyses for the primary outcome were done using proportional odds models across the following subgroups: age (<50 years, 50–69 years, ≥70 years); sex (female, male); duration of symptoms before random assignment (≤7 days, 8–14 days, >14 days); disease severity (moderate, severe); and country. The evolution of the viral load since the random assignment was analysed using a mixed-effects linear model with a test of treatment effect on the slope, and a non-prespecified subgroup analysis was done across the duration of symptoms before random assignment (≤7 days, 8–14 days, >14 days) and disease severity at random assignment. All analyses were done using SAS version 9.4.
Attrition/loss to follow-up	Not reported
Source of 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.
Study limitations (Author)	The trial was an open-label study that could introduce the risk of bias in the follow-up and management of patients. Due to the fact that several other treatments were concomitantly evaluated at the beginning of the trial, masking was not possible due to the varying administration routes and the subjectivity in the management of cases (for example decisions to begin corticosteroids). No viral load assessments were available at any timepoint for 18% of participants and there was no baseline viral load measurement for 50% of participants. Finally, plasma concentrations of the prodrug remdesivir and GS-441524 were assessed in only 10% of participants and the concentrations of its intracellular active metabolite were not measured. Although the trial was not designed as a pharmacokinetic study, it provides data on remdesivir exposure in patients admitted to hospital with COVID-19, which are currently lacking.
Study limitations (Reviewer)	This was an open-label study indicating that there may be a risk of deviation from intervention. This was not reported or mitigated appropriately in the study. Secondly, as this was an open-label study, the reporting of outcomes may have been affected by the assessors' pre-existing knowledge about the intervention and its effects.
Other details	Not applicable

Study arms

Remdesivir (N = 420)

Updated with 2022 preprint data

Control (N = 423)

Updated with 2022 ~~preprint data~~full publication data

Characteristics

Arm-level characteristics

Characteristic	Remdesivir (N = 420)	Control (N = 423)
Age Median (IQR)	63 (55 to 73)	64 (54 to 72)
Female No of events	n = 124 ; % = 30	n = 131 ; % = 31
Male No of events	n = 296 ; % = 70	n = 292 ; % = 69
Caucasian No of events	n = 248 ; % = 67.4	n = 260 ; % = 69.9
North African No of events	n = 51 ; % = 13.9	n = 63 ; % = 16.9
Sub-Saharan No of events	n = 30 ; % = 8.2	n = 17 ; % = 4.6
Other No of events	n = 39 ; % = 10.6	n = 32 ; % = 8.6
Moderate No of events	n = 256 ; % = 61	n = 255 ; % = 60.3
Severe No of events	n = 164 ; % = 39	n = 168 ; % = 39.7
Room air	n = 6 ; % = 1.4	n = 6 ; % = 1.4

Characteristic	Remdesivir (N = 420)	Control (N = 423)
No of events		
Nasal cannula or face mask No of events	n = 250 ; % = 59.5	n = 249 ; % = 58.9
High-flow oxygen device No of events	n = 72 ; % = 17.1	n = 77 ; % = 18.2
Non-invasive ventilation No of events	n = 15 ; % = 3.6	n = 16 ; % = 4
Invasive mechanical ventilation No of events	n = 77 ; % = 18.3	n = 72 ; % = 17
Extracorporeal membrane oxygenation No of events	n = 0 ; % = 0	n = 2 ; % = 0.5
Obesity No of events	n = 140 ; % = 34	n = 144 ; % = 34.2
Chronic cardiac disease No of events	n = 112 ; % = 26.9	n = 122 ; % = 28.8
Diabetes % No of events	n = 109 ; % = 26.1	n = 116 ; % = 27.4
Chronic pulmonary disease No of events	n = 73 ; % = 17.5	n = 78 ; % = 18.4
Chronic kidney disease Stage 1-3 No of events	n = 21 ; % = 5	n = 34 ; % = 8
corticosteroids No of events	n = 164 ; % = 39.6	n = 169 ; % = 40.4
Tocilizumab No of events	n = 5 ; % = 1.2	n = 2 ; % = 0.5
Anticoagulants No of events	n = 212 ; % = 51.2	n = 224 ; % = 53.6
Median viral load at baseline (Log10 copies per 10,000 cells)	3.2 (1.7 to 4.5)	3.2 (1.8 to 4.4)

Characteristic	Remdesivir (N = 420)	Control (N = 423)
Median (IQR)		

Outcomes

Remdesivir vs Placebo

Outcome	Remdesivir, , N = 420	Control, , N = 423
Death within 28 days No of events	n = 34 ; % = 8.1	n = 38 ; % = 9
Death within 28 days Sample size	n = 420	n = 423
Death within 28 days - Moderate severity No of events	n = 15 ; % = 5.9	n = 15 ; % = 5.9
Death within 28 days - Moderate severity Sample size	n = 256	n = 255
Death within 28 days - Severe severity No of events	n = 19 ; % = 11.6	n = 23 ; % = 13.7
Death within 28 days - Severe severity Sample size	n = 164	n = 168
Ventilator free days until day 29 Median (IQR)	29 (21 to 29)	29 (15 to 29)
Oxygenation free days until day 29 Median (IQR)	17 (1 to 22)	17 (0 to 23)
New mechanical ventilation, ECMO or death within 29 days No of events	n = 58 ; % = 16.9	n = 88 ; % = 25.2
New mechanical ventilation, ECMO or death within 29 days Sample size	n = 343	n = 349
New mechanical ventilation, ECMO or death within 29 days - Moderate severity No of events	n = 33 ; % = 13.2	n = 41 ; % = 28.7

Outcome	Remdesivir, , N = 420	Control, , N = 423
New mechanical ventilation, ECMO or death within 29 days - Moderate severity Sample size	n = 256	n = 255
New mechanical ventilation, ECMO or death within 29 days - Severe severity No of events	n = 25 ; % = 28.7	n = 47 ; % = 50
New mechanical ventilation, ECMO or death within 29 days - Severe severity Sample size	n = 87	n = 94
Days to hospital discharge within 29 days Median (IQR)	15 (10 to 29)	14 (8 to 29)
Days to improvement of two categories of the 7 point ordinal scale or hospital discharge within day 29 Median (IQR)	12 (8 to 24)	12 (7 to 28)
Any adverse event No of events	n = 256 ; % = 62.4	n = 248 ; % = 58.6
Any adverse event Sample size	n = 410	n = 423
Any serious adverse event No of events	n = 147 ; % = 35.9	n = 138 ; % = 32.6
Any serious adverse event Sample size	n = 410	n = 423
Any grade 3 or 4 adverse event No of events	n = 143 ; % = 34.9	n = 150 ; % = 35.5
Any grade 3 or 4 adverse event Sample size	n = 410	n = 423
Day 0 Nominal	44	45
Day 2 Nominal	37	34
Day 4	32	31

Outcome	Remdesivir, , N = 420	Control, , N = 423
Nominal		
Day 7 Nominal	27	29
Day 10 Nominal	24	23
Day 14 Nominal	23	21

Critical appraisal - Remdesivir - RoB

Death within 29 days

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Awareness of treatment allocation unlikely to impact this outcome)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(Awareness of treatment allocation unlikely to impact this outcome)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Ventilator free days until day 29

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Awareness of treatment allocation could have impacted the decision to ventilate)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation could have impacted the decision to ventilate)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Awareness of treatment allocation could have impacted the decision to ventilate)*
Overall bias and Directness	Overall Directness	Directly applicable

Oxygenation free days until day 29

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Awareness of treatment allocation could have impacted the decision to give oxygen)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation could have impacted the decision to give oxygen)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Awareness of treatment allocation could have impacted the decision to give oxygen)*
Overall bias and Directness	Overall Directness	Directly applicable

New mechanical ventilation, ECMO or death within 29 days

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Awareness of treatment allocation could have impacted the decision to ventilate)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation could have impacted the decision to ventilate)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Awareness of treatment allocation could have impacted the decision to ventilate)*
Overall bias and Directness	Overall Directness	Directly applicable

Days to hospital discharge within 29 days

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended	Risk of bias for deviations from the intended interventions	Some concerns *(Awareness of treatment*

Section	Question	Answer
interventions (effect of assignment to intervention)	(effect of assignment to intervention)	*allocation could have impacted decisions around care)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation could have impacted decisions around care)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Awareness of treatment allocation could have impacted decisions around care)*
Overall bias and Directness	Overall Directness	Directly applicable

Days to improvement of two categories of the 7 point ordinal scale or hospital discharge within day 29

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Awareness of treatment allocation could have impacted decisions around care)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation could have impacted decisions around care)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Awareness of treatment allocation could have impacted decisions around care)*
Overall bias and Directness	Overall Directness	Directly applicable

Any adverse event

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Awareness of treatment allocation could have impacted decisions around care)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation could have impacted decisions around care)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Awareness of treatment allocation could have impacted decisions around care)*
Overall bias and Directness	Overall Directness	Directly applicable

Any serious adverse event

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended	Risk of bias for deviations from the intended interventions	Some concerns *(Awareness of treatment*

Section	Question	Answer
interventions (effect of assignment to intervention)	(effect of assignment to intervention)	*allocation could have impacted decisions around care)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation could have impacted decisions around care)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Awareness of treatment allocation could have impacted decisions around care)*
Overall bias and Directness	Overall Directness	Directly applicable

Any grade 3 or 4 adverse event

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Awareness of treatment allocation could have impacted decisions around care)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation could have impacted decisions around care)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Awareness of treatment allocation could have impacted decisions around care)*
Overall bias and Directness	Overall Directness	Directly applicable

Change from baseline viral load

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Awareness of treatment allocation unlikely to impact this outcome)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low *(Awareness of treatment allocation unlikely to impact this outcome)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Ali, 2022

Bibliographic Reference	Ali K; Azher T; Baqi M; Binnie A; Borgia S; Carrier FM; Cavayas YA; Chagnon N; Cheng MP; Conly J; Costiniuk C; Daley P; Daneman N; Douglas J; Downey C; Duan E; Duceppe E; Durand M; English S; Farjou G; Fera E; Fontela P; Fowler R; Fralick M; Geagea A; Grant J; Harrison LB; Havey T; Hoang H; Kelly LE; Keynan Y; Khwaja K; Klein G; Klein M; Kolan C; Kronfli N; Lamontagne F; Lau R; Fralick M; Lee TC; Lee N; Lim R; Longo S; Lostun A; MacIntyre E; Malhamé I; Mangof K; McGuinty M; Mergler S; Munan MP; Murthy S; O'Neil C; Ovakim D; Papenburg J; Parhar K; Parvathy SN; Patel C; Perez-Patrigeon S; Pinto R; Rajakumaran S; Rishu A; Roba-Oshin M; Rushton M; Saleem M; Salvadori M; Scherr K; Schwartz K; Semret M; Silverman M; Singh A; Sligl W; Smith S; Somayaji R; Tan DHS; Tobin S; Todd M; Tran TV; Tremblay A; Tsang J; Turgeon A; Vakil E; Weatherald J; Yansouni C; Zarychanski R; ; ; Remdesivir for the treatment of patients in hospital with

COVID-19 in Canada: a randomized controlled trial.; CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne; 2022

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04330690
Study start date	14-Aug-2020
Study end date	21-Apr-2021
Aim of the study	To estimate the effects of treatment with remdesivir compared with standard care for patients hospitalised with COVID-19
Country/geographical location	Canada
Study setting	Hospital
Population description	The trial reported on data from 1267 participants who were hospitalised in Canada with COVID-19. The median age of participants was 65 years (IQR 53 to 77), with 40% female participants. Most patients were on low flow oxygen (54.5%) at baseline and, had a range of pre-existing co-morbidities (diabetes, chronic respiratory disease, asthma, smoker, chronic cardiovascular disease and chronic liver disease).
Inclusion criteria	• Patients admitted to participating hospitals in Canada with PCR confirmed SARS-CoV-2 infection
Exclusion criteria	• Allergy to study drug • Anticipated transfer to a nonstudy site • Expected to not survive beyond 24 hours • Already receiving remdesivir at time of enrolment
Intervention dosage (loading)	200mg
Intervention dosage (maintenance)	100mg
Intervention scheduled duration	10 days
Intervention actual duration	Not reported
Intervention route of administration	Intravenous infusion
Comparator (where applicable)	Standard care
Methods for population selection/allocation	Patients were randomised through a Web-based server unstratified in a 1:1 ratio. Following the publication of the WHO Solidarity trial

	interim analysis, recruitment was preferentially focused on patients who were not mechanically ventilated
Methods of data analysis	The primary analysis was based upon intention to treat. All-cause mortality and the binary secondary outcomes are reported as proportions, risk ratios, absolute risk difference and 95% confidence intervals (CIs). Secondary outcomes of clinical severity were examined using a proportional odds model, adjusting for baseline severity based on ordinal scale position at baseline. The proportionality assumption for clinical severity outcomes did not hold for some outcomes and therefore some groups were compared using a Wilcoxon rank-sum test. The Fine–Gray model was used to compare the time to discharge alive, accounting for competing risk of death, and present results as subdistribution hazards and 95% CIs. The duration of hospital stay and oxygen-free and ventilator-free days were reported using means and standard deviations (SDs), and medians and interquartile ranges (IQRs); differences between the groups for medians and 95% CIs are based on the Hodges–Lehman approach. Subgroup analyses for the primary outcome of mortality evaluated the treatment effect across the following prespecified subgroups, with tests for interaction: duration of symptoms before enrolment (< 7 d), age younger than 55 years, sex, and severity of symptoms on presentation (defined as the amount of respiratory support, including low-flow oxygen, high-flow nasal oxygen, noninvasive ventilation and invasive mechanical ventilation). There was no imputation for missing data. Given that this study was part of a global adaptive trial, no power calculations were performed. *P* values less than 0.05 denote statistical significance for primary and secondary outcomes, which were not adjusted for multiplicity. All statistical analyses were performed in SAS (version 9.4, Cary, NC).
Attrition/loss to follow-up	Not reported
Source of funding	Not reported
Study limitations (Author)	As this study reports on a smaller number of participants than the WHO Solidarity trial, it is not powered sufficiently to infer statistical significance on the mortality outcome. Furthermore, the study reports on outcomes from a highly resourced health system and as such may not be applicable to healthcare systems worldwide. Information on viral variants was not reported and as such, the effect of remdesivir on different variants cannot be ascertained and lastly achieving follow-up for the patients following discharge was not possible due to strains in the health system.
Study limitations (Reviewer)	Details on allocation concealment were not provided by the study; it was inferred that it followed the methodology in line with the main WHO trial but no further detail was provided about it. The study also does not detail what standard of care regimens were administered to these patients and as such, the effects of remdesivir treatment in combination or as monotherapy cannot be fully elucidated.
Other details	This study reports data from the Canadian centres that participated in the WHO Solidarity trial and reports patient data past the recruitment dates of the WHO Solidarity trial.

Study arms

Remdesivir (N = 634)

Standard of care (N = 647)

Characteristics

Arm-level characteristics

Characteristic	Remdesivir (N = 634)	Standard of care (N = 647)
Age Median (IQR)	65 (53 to 77)	66 (54 to 77)
Female No of events	n = 260 ; % = 41	n = 255 ; % = 39.4
White No of events	n = 269 ; % = 42.4	n = 255 ; % = 39.4
South Asian No of events	n = 90 ; % = 14.2	n = 110 ; % = 17
East Asian No of events	n = 40 ; % = 6.3	n = 42 ; % = 6.5
Indigenous or First Nations No of events	n = 40 ; % = 6.3	n = 28 ; % = 4.3
Black No of events	n = 20 ; % = 3.2	n = 25 ; % = 3.9
Arab No of events	n = 22 ; % = 3.5	n = 24 ; % = 3.7
Latin American No of events	n = 23 ; % = 3.6	n = 21 ; % = 3.2
West Asian No of events	n = 8 ; % = 1.3	n = 12 ; % = 1.9

Characteristic	Remdesivir (N = 634)	Standard of care (N = 647)
Other No of events	n = 9 ; % = 1.4	n = 14 ; % = 2.2
Not available No of events	n = 119 ; % = 18.8	n = 126 ; % = 19.5
Patients in ICU at randomisation No of events	n = 139 ; % = 21.9	n = 135 ; % = 20.9
No organ support No of events	n = 71 ; % = 11.2	n = 54 ; % = 8.4
Low flow oxygen No of events	n = 334 ; % = 52.7	n = 363 ; % = 56.2
High flow nasal oxygen No of events	n = 149 ; % = 23.5	n = 153 ; % = 23.7
Non-invasive ventilation No of events	n = 22 ; % = 3.5	n = 23 ; % = 3.6
Invasive mechanical ventilation No of events	n = 58 ; % = 9.1	n = 54 ; % = 8.3
Diabetes No of events	n = 155 ; % = 33.6	n = 188 ; % = 38.4
Chronic respiratory disease No of events	n = 67 ; % = 14.5	n = 65 ; % = 13.3
Asthma No of events	n = 49 ; % = 10.6	n = 55 ; % = 11.2
Smoker No of events	n = 23 ; % = 5	n = 22 ; % = 4.5
Chronic cardiovascular disease] No of events	n = 120 ; % = 26	n = 135 ; % = 27.6
Chronic liver disease No of events	n = 8 ; % = 1.7	n = 19 ; % = 3.9
Corticosteroid No of events	n = 553 ; % = 87.2	n = 564 ; % = 87.2

Characteristic	Remdesivir (N = 634)	Standard of care (N = 647)
Tocilizumab No of events	n = 14 ; % = 2.2	n = 5 ; % = 0.8

Outcomes

Remdesivir vs Standard of Care

Outcome	Remdesivir, N = 634	Standard of care, N = 647
In-hospital mortality No of events	n = 117 ; % = 18.7	n = 145 ; % = 22.6
In-hospital mortality Sample size	n = 634	n = 647
Mortality by day 60 No of events	n = 127 ; % = 24.8	n = 152 ; % = 28.2
Mortality by day 60 Sample size	n = 512	n = 539
No oxygen therapy at baseline No of events	n = 7 ; % = 10	n = 8 ; % = 15
No oxygen therapy at baseline Sample size	n = 68	n = 54
Oxygen therapy at baseline No of events	n = 36 ; % = 11	n = 58 ; % = 16
Oxygen therapy at baseline Sample size	n = 330	n = 360
High flow oxygen at baseline No of events	n = 45 ; % = 30	n = 52 ; % = 34
High flow oxygen at baseline Sample size	n = 149	n = 153
NIV at baseline No of events	n = 10 ; % = 46	n = 6 ; % = 26
NIV at baseline	n = 22	n = 23

Outcome	Remdesivir, N = 634	Standard of care, N = 647
Sample size		
IMV at baseline No of events	n = 19 ; % = 34	n = 21 ; % = 40
IMV at baseline Sample size	n = 56	n = 52
Need for new mechanical ventilation Sample size calculated by analyst from data in paper No of events	n = 46 ; % = 8	n = 89 ; % = 15
Need for new mechanical ventilation Sample size calculated by analyst from data in paper Sample size	n = 575	n = 593
Duration of hospital stay Median (IQR)	10 (6 to 18)	9 (6 to 17)
For survivors Median (IQR)	9 (6 to 17)	9 (6 to 16)
For non-survivors Median (IQR)	12 (5 to 20)	11 (6 to 20)
Oxygen free days at day 28 Median (IQR)	20 (0 to 24)	19 (0 to 24)
Oxygen free days at day 28 Mean (SD)	15.9 (10.5)	14.2 (11.1)
Ventilator free days at day 28 Median (IQR)	28 (19 to 28)	28 (1 to 28)
Ventilator free days at day 28 Mean (SD)	21.4 (11.3)	19.5 (12.3)
New hepatic dysfunction No of events	n = 82 ; % = 13.1	n = 88 ; % = 13.7
New dialysis No of events	n = 16 ; % = 2.6	n = 15 ; % = 2.3

Critical appraisal - Remdesivir - RoB

In hospital mortality

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Missing data not accounted for)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Missing data unaccounted for)*
Overall bias and Directness	Overall Directness	Directly applicable

Mortality by day 60

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Missing data not accounted for)*

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Missing data unaccounted for)*
Overall bias and Directness	Overall Directness	Directly applicable

Need for new mechanical ventilation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Awareness of treatment allocation may have impacted decisions around care)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Missing data not accounted for)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation may have impacted decisions around care)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Missing data unaccounted for; open label study and subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Duration of hospital stay

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low

Section	Question	Answer
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Awareness of treatment allocation may have impacted decisions around care)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation may have impacted decisions around care)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Open label study and subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Oxygen free days at day 28 (Median, IQR)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Awareness of treatment allocation may have impacted decisions around care)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Missing data not accounted for)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation may have impacted decisions around care)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Missing data unaccounted for; open label study and subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Oxygen free days at day 28 (Mean, SD)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Awareness of treatment allocation may have impacted decisions around care)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Missing data not accounted for)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation may have impacted decisions around care)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Missing data unaccounted for; open label study and subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Ventilator free days at day 28 (Median, IQR)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended	Risk of bias for deviations from the intended interventions	Some concerns *(Awareness of treatment allocation may have*

Section	Question	Answer
interventions (effect of assignment to intervention)	(effect of assignment to intervention)	*impacted decisions around care)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Missing data not accounted for)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation may have impacted decisions around care)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Missing data unaccounted for; open label study and subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Ventilator free days at day 28 (Mean, SD)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Awareness of treatment allocation may have impacted decisions around care)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Missing data not accounted for)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation may have impacted decisions around care)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Missing data unaccounted for; open label study and subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

New hepatic dysfunction

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Awareness of treatment allocation may have impacted decisions around care)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation may have impacted decisions around care)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Open label study and subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

New dialysis

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Awareness of treatment allocation may have impacted decisions around care)*

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Missing data not accounted for)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation may have impacted decisions around care)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Missing data unaccounted for; open label study and subjective outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Barratt-Due, 2021

Bibliographic Reference	Barratt-Due, Andreas; Olsen, Inge Christoffer; Nezvalova-Henriksen, Katerina; Kåsine, Trine; Lund-Johansen, Fridtjof; Hoel, Hedda; Holten, Aleksander Rygh; Tveita, Anders; Mathiessen, Alexander; Haugli, Mette; Eiken, Ragnhild; Kildal, Anders Benjamin; Berg, Åse; Johannessen, Asgeir; Heggelund, Lars; Dahl, Tuva Børresdatter; Skåra, Karoline Hansen; Mielnik, Pawel; Le, Lan Ai Kieu; Thoresen, Lars; Ernst, Gernot; Hoff, Dag Arne Lihaug; Skudal, Hilde; Kittang, Bård Reiakvam; Olsen, Roy Bjørkholt; Tholin, Birgitte; Ystrøm, Carl Magnus; Skei, Nina Vibeche; Tran, Trung; Dudman, Susanne; Andersen, Jan Terje; Hannula, Raisa; Dalgard, Olav; Finbråten, Ane-Kristine; Tonby, Kristian; Blomberg, Bjorn; Aballi, Saad; Fladeby, Cathrine; Steffensen, Anne; Müller, Fredrik; Dyrhol-Riise, Anne Ma; Trøseid, Marius; Aukrust, Pål; Evaluation of the Effects of Remdesivir and Hydroxychloroquine on Viral Clearance in COVID-19; Annals of Internal Medicine; 2021; vol. 174 (no. 9); 1261-1269

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04321616
Study start date	28-Mar-2020
Study end date	04-Oct-2020

Aim of the study	To evaluate the effects of remdesivir on all-cause, in-hospital mortality; the degree of respiratory failure and inflammation and viral clearance in the oropharynx
Country/geographical location	Norway
Study setting	Hospital
Population description	A total of 99 patients were enrolled in the remdesivir vs standard of care treatment groups, with mild-moderate COVID-19. The mean age of participants was 59.8 years (SD 15.3), with 34.3% of participants being female. Participants presented with a range of underlying comorbidities such as diabetes, hypertension, chronic cardiac and pulmonary disease.
Inclusion criteria	• Adults (Aged 18 years or older), with SARS-CoV-2 infection confirmed by PCR • Adults who were admitted to hospital ward or intensive care unit with no anticipated transfer to a non-study hospital
Exclusion criteria	• Patients with severe comorbid conditions, with life expectancy of less than 3 months • Levels of aspartate aminotransferase or alanine aminotransferase more than 5 times the upper limit of normal • Rate corrected QT interval, greater than 470ms • Pregnancy or breastfeeding • Acute occurrence of a comorbid condition in a 7 day period before inclusion • intolerance to study drugs • participation in a potentially confounding trial • concomitant medications interfering with study drugs
Intervention dosage (loading)	200mg remdesivir
Intervention dosage (maintenance)	100mg daily
Intervention scheduled duration	Up to 10 days
Intervention actual duration	Not reported
Intervention route of administration	Intravenous infusion
Comparator (where applicable)	Standard of care
Methods for population selection/allocation	Eligible patients were allocated in an equal ratio using computer randomisation procedures. There were 2 separate allocation lists. The first was the global list, in which the allocation sequence was prepared by an independent statistician appointed by the international trial steering group. A secondary national list was additionally prepared as a backup if allocation according to the global list was not available. The randomisation procedure ensured

	that a patient could be allocated only to available treatment. The randomisation lists were not stratified or blocked; thus, the randomisation can be regarded as simple. The trial was open-label, without placebo control.
Methods of data analysis	This is an add-on study, there are no adjustments for multiple testing as per WHO-SOLIDARITY trial protocol for analysis. Interpretations of results are based on unadjusted CIs. All treatment comparisons are with concurrent controls. Thus, some participants receiving SoC act as controls for both active treatment groups, whereas some act in one or the other. The log-rank statistic was used to test the null hypothesis of no treatment effect on all-cause mortality. The natural logarithm of the average mortality rate ratio was estimated using the (O − E)/V estimator (where O is observed events, E is expected events, and V is variance) from the log-rank statistic with 95% CIs estimated using a normal distribution with 1/V as variance. Hazard ratios, estimated using Cox proportional hazards models, were reported as advised by the journal's editors and reviewers. Because of the low number of deaths in blinded reviews, stratification variables in the primary analyses were not used. Participants who withdrew consent or were alive but still in the hospital at the time of database locking were censored at the last known time of contact. Discharged participants were assumed to be alive and were censored at the time of database locking unless otherwise confirmed. Those who had an end-of-study visit at 3 months were censored at this date. Dichotomous endpoints were analysed using logistic regression without adjustment for any baseline covariates. The estimated average marginal risk difference and corresponding 95% CI were estimated using the delta method. Missing data due to discharge or participant withdrawal were imputed with the best outcome. Continuous outcomes during the first 14 days were analysed using a mixed model with fixed intercept and separate slopes before and after day 7, and random intercept and slope. The difference in slope before day 7 was used to estimate the treatment effect in the first week. We also computed the average marginal point estimate at day 10 as a separate measure of treatment difference. As sensitivity analyses, we added simpler between-group analyses using t-tests and Wilcoxon tests on the change from baseline to day 7 and day 10. Subgroup analyses were done by including the subgroup as an interaction term with the treatment term in the mixed model. High and low baseline subgroups were defined by the overall median. The 90-day outcomes on antibodies against SARS-CoV-2 were analysed using the *t* distribution. Duration of mechanical ventilation and ICU stay are descriptively presented using cumulative probability plots. All statistical analyses were done with Stata, version 16.1 (StataCorp), and R, version 4.0.
Attrition/loss to follow-up	Remdesivir group= 1 Standard of care = 3
Source of funding	National Clinical Therapy Research in the Specialist Health Services - Norway

Study limitations (Author)	The trial had no placebo group. Also median duration of hospitalisation was 5 to 6 days, and most of the patients did not receive the full treatment length of the tested medication.
Study limitations (Reviewer)	Severity of illness was not reported at baseline and neither was level of respiratory support.
Other details	This is the Norwegian arm of the WHO-Solidarity trial (NCT04315948)

Study arms

Remdesivir + SoC (N = 42)

Standard of Care (N = 57)

Characteristics

Arm-level characteristics

Characteristic	Remdesivir + SoC (N = 42)	Standard of Care (N = 57)
Age Mean (SD)	59.7 (16.5)	58.1 (15.7)
Female No of events	n = 13 ; % = 31	n = 14 ; % = 24.6
Chronic cardiac disease No of events	n = 6 ; % = 14.6	n = 12 ; % = 21.1
Chronic pulmonary disease No of events	n = 4 ; % = 9.8	n = 3 ; % = 5.3
Ever smoking No of events	n = 16 ; % = 39	n = 27 ; % = 47.4
Hypertension No of events	n = 15 ; % = 36.6	n = 14 ; % = 24.6
Diabetes No of events	n = 9 ; % = 15.8	n = 7 ; % = 13.5

Characteristic	Remdesivir + SoC (N = 42)	Standard of Care (N = 57)
Obesity No of events	n = 9 ; % = 18.4	n = 16 ; % = 32.7
Steroids No of events	n = 1 ; % = 2.4	n = 2 ; % = 3.6
Other immunomodulatory drugs No of events	n = 1 ; % = 2.4	n = 1 ; % = 1.8
ACE inhibitors No of events	n = 2 ; % = 4.9	n = 4 ; % = 7.1
Angiotensin II receptor blockers No of events	n = 11 ; % = 26.8	n = 7 ; % = 12.5

Outcomes

Remdesivir+SoC vs Standard of care

Outcome	Remdesivir + SoC	Standard of Care
Mortality No of events	n = 3 ; % = 7.1	n = 4 ; % = 7
Mortality Sample size	n = 34	n = 49
Adverse events No of events	n = 34 ; % = 81	n = 33 ; % = 58
Adverse events Sample size	n = 42	n = 87
Serious adverse events No of events	n = 13 ; % = 31	n = 20 ; % = 35
Serious adverse events Sample size	n = 42	n = 87

Critical appraisal - Remdesivir - RoB

Mortality

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation may have had an impact on decisions about care)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Moderate *(Awareness of treatment allocation may have had an impact on decisions about care)*
Overall bias and Directness	Overall Directness	Directly applicable

Serious adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Awareness of treatment allocation may have had an impact on decisions about care)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Awareness of treatment allocation may have had an impact on decisions about care)*
Overall bias and Directness	Overall Directness	Directly applicable

Beigel et al.

Bibliographic Reference	Beigel JH; Tomashek KM; Dodd LE; Mehta AK; Zingman BS; Kalil AC; Hohmann E; Chu HY; Luetkemeyer A; Kline S; Lopez de Castilla D; Finberg RW; Dierberg K; Tapson V; Hsieh L; Patterson TF; Paredes R; Sweeney DA; Short WR; Touloumi G; Lye DC; Ohmagari N; Oh MD; Ruiz-Palacios GM; Benfield T; Fätkenheuer G; Kortepeter MG; Atmar RL; Creech CB; Lundgren J; Babiker AG; Pett S; Neaton JD; Burgess TH; Bonnett T; Green M; Makowski M; Osinusi A; Nayak S; Lane HC; ; Remdesivir for the Treatment of Covid-19 - Final Report.; The New England journal of medicine; vol. 383 (no. 19)

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04280705
Study start date	21-Feb-2020
Study end date	19-Apr-2020
Aim of the study	To evaluate the clinical efficacy and safety of remdesivir as compared with placebo.
Country/geographical location	USA, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, and Singapore.
Study setting	Hospital
Population description	Adults who were hospitalised with Covid-19 and had evidence of lower respiratory tract infection.
Inclusion criteria	Participants 18 years of age or older who were hospitalised with symptoms suggestive of COVID-19 were assessed for eligibility. Participants had to meet one of the following criteria suggestive of lower respiratory tract infection at the time of enrolment: radiographic infiltrates by imaging study, peripheral oxygen saturation (SpO2) ≤94% on room air, or requiring supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO). There was no limit to the duration of symptoms prior to enrolment. Participants had to have a laboratory-confirmed SARS-CoV-2 infection as determined by a positive reverse transcription, polymerase-chain-reaction (RT-PCR) assay result from any respiratory specimen collected <72 hours prior to randomisation. During the study, this criterion was modified due to limitations in testing capacity to also allow a RT-PCR positive specimen that was collected ≥72 hours prior to randomisation if the site was unable to obtain a repeat sample and if the participant had progressive disease consistent with ongoing SARS-CoV-2 infection. Other inclusion criteria included agreeing not to participate in another COVID-19 treatment clinical trial through Day 29 and practicing heterosexual abstinence or using study-specified contraception through Day 29 for women of childbearing potential
Exclusion criteria	Exclusion criteria included having either an alanine aminotransferase (ALT) or an aspartate aminotransferase (AST) > 5 times the upper limit of the normal range; impaired renal function as determined by calculating an estimated glomerular filtration rate (eGFR), or need for haemodialysis or hemofiltration; allergy to study product; pregnancy or breast-feeding; and anticipated discharge from the hospital or transfer to another hospital within 72 hours of enrolment.
Intervention dosage (loading)	Remdesivir was administered intravenously as a 200 milligram loading dose on day 1.

Intervention dosage (maintenance)	A 100 milligram maintenance dose administered daily.
Intervention scheduled duration	Maintenance dose was given on days 2 through 10 or until hospital discharge or death.
Intervention actual duration	In the remdesivir arm, 208 received all 10 doses, 323 received <10 doses. In the placebo arm, 226 received all 10 doses, 291 received <10 doses.
Intervention route of administration	Intravenous
Comparator (where applicable)	A matching placebo was administered according to the same schedule and in the same volume as the active drug. A normal saline placebo was used at the European sites and at some non-European sites owing to a shortage of matching placebo; for these sites, the remdesivir and placebo infusions were masked with an opaque bag and tubing covers to maintain blinding.
Methods for population selection/allocation	Eligible patients were randomly assigned in a 1:1 ratio to receive either remdesivir or placebo. Randomisation was stratified by study site and disease severity at enrolment.
Methods of data analysis	The primary analysis was a stratified log-rank test of time to recovery with remdesivir as compared with placebo, with stratification by disease severity (the actual severity at baseline). For time-to-recovery and time-to-improvement analyses, data for patients who did not recover and data for patients who died were censored at day 29. Prespecified subgroups in these analyses were defined according to sex, baseline disease severity (according to stratification criteria and on the basis of the ordinal scale), age (18 to 39 years, 40 to 64 years, or ≥65 years), race, ethnic group, duration of symptoms before randomisation (measured as ≤10 days or >10 days, in quartiles, and as the median), site location, and presence of coexisting conditions. To assess the effect of disease severity on treatment benefit (recovery and mortality), post hoc analyses evaluated interactions of efficacy with baseline ordinal score (as a continuous variable). The primary outcome was initially a comparison of clinical status at day 15 on the eight category ordinal scale. However, the primary outcome was changed to a comparison of time to recovery by day 29 in response to evolving information, external to the trial, indicating that COVID-19 may have a more protracted course than previously anticipated. The change was proposed on March 22, 2020 (after 72 patients had been enrolled), by trial statisticians who were unaware of treatment assignments and had no knowledge of outcome data. The amendment was finalised on April 2, 2020, and

	the initial primary outcome was retained as the key secondary outcome. On April 27, 2020, the data and safety monitoring board reviewed efficacy results. Although this review was originally planned as an interim analysis, because of the rapid pace of enrolment, the review occurred after completion of enrolment while follow-up was still ongoing. At the time of the data and safety monitoring board report, which was based on data cut-off date of April 22, 2020, a total of 482 recoveries (exceeding the estimated number of recoveries needed for the trial) and 81 deaths had been entered in the database. At that time, the data and safety monitoring board recommended that the preliminary primary analysis report and mortality data from the closed safety report be provided to trial team members from the National Institute of Allergy and Infectious Diseases (NIAID). These results were subsequently made public. The treating physician could request to be made aware of the treatment assignment of patients who had not completed day 29 if clinically indicated (e.g., because of worsening clinical status), and patients originally in the placebo group could be given remdesivir.
Attrition/loss to follow-up	10 withdrew consent in the remdesivir arm and 14 withdrew consent in the placebo arm.
Source of funding	The trial was sponsored and primarily funded by the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD. This trial has been funded in part with federal funds from the NIAID and the National Cancer Institute, NIH, and by the Department of Defense, Defense Health Program. This trial has been supported in part by the NIAID of the NIH. The trial has also been funded in part by the governments of Denmark, Japan, Mexico, and Singapore. The trial site in South Korea received funding from the Seoul National University Hospital. Support for the London International Coordinating Centre was also provided by the United Kingdom Medical Research Council.
Study limitations (Author)	None mentioned.
Study limitations (Reviewer)	N/A
Other details	At baseline, 159 (15.0%) were categorised as having mild-to-moderate disease, and 903 (85.0%) were in the severe disease stratum. Severe disease was defined as participants meeting one or more of the following criteria: requiring invasive or non-invasive mechanical ventilation, requiring supplemental oxygen, an SpO2 ≤ 94% on room air, or tachypnoea (respiratory rate ≥ 24 breaths per

	minute). Mild / moderate disease was defined by a SpO2 > 94% and respiratory rate < 24 breaths per minute without supplemental oxygen requirement.

Study arms

Remdesivir (N = 541)

Placebo (N = 521)

Characteristics

Arm-level characteristics

Characteristic	Remdesivir (N = 541)	Placebo (N = 521)
Mean age (SD) (years) Mean (SD)	58.6 (14.6)	59.2 (15.4)
Male sex (%) Nominal	65.1	63.7
American Indian or Alaska Native No of events	n = 4 ; % = 1	n = 3 ; % = 1
Asian No of events	n = 79 ; % = 15	n = 56 ; % = 10
Black or African American No of events	n = 109 ; % = 21	n = 117 ; % = 22
White No of events	n = 279 ; % = 54	n = 287 ; % = 53
Hispanic or Latino No of events	n = 134 ; % = 26	n = 116 ; % = 21
Number of coexisting conditions: None No of events	n = 97 ; % = 19	n = 97 ; % = 18
Number of coexisting conditions: One No of events	n = 138 ; % = 26	n = 137 ; % = 25
Number of coexisting conditions: Two or more No of events	n = 296 ; % = 57	n = 283 ; % = 52
Type 2 diabetes No of events	n = 164 ; % = 31	n = 158 ; % = 29
Hypertension No of events	n = 269 ; % = 52	n = 264 ; % = 49
Obesity No of events	n = 242 ; % = 46	n = 234 ; % = 43

Outcomes

Study timepoints

- 14 day
- 28 day

Outcomes

Outcome	Remdesivir, 28 day, N = 541	Placebo, 28 day, N = 521
All cause mortality (number) No of events	n = 59 ; % = 11	n = 77 ; % = 15
All-cause mortality (High flow oxygen, NIV) No of events	n = 19 ; % = 4	n = 20 ; % = 4
All-cause mortality (invasive mechanical ventilation) No of events	n = 28 ; % = 5	n = 29 ; % = 6
All-cause mortality (Low flow oxygen at baseline) (No oxygen supplementation) No of events	n = 3/75 ; % = 4	n = 3/63 ; % = 4
Need for new mechanical ventilation or ECMO No of events	n = 52/402 ; % = 13	n = 82/364 ; % = 23
Need for new oxygen supplementation (high flow or NIV) No of events	n = 52/307 ; % = 17	n = 64/266 ; % = 24
Need for new oxygen supplementation (low flow) No of events	n = 27/75 ; % = 36	n = 28/63 ; % = 44
Clinical recovery by day 28 No of events	n = 399/541 ; % = 74	n = 352/521 ; % = 68

Outcome	Remdesivir, 28 day, N = 541	Placebo, 28 day, N = 521
Respiratory failure or ARDS No of events	n = 47/541; % = 9	n = 80/522 ; % = 15
Adverse events No of events	n = 273/541 ; % = 50	n = 295/522 ; % = 57
Serious adverse events No of events	n = 131/532 ; % = 25	n = 163/516 ; % = 32
Discontinuation due to adverse events No of events	n = 52/541 ; % = 10	n = 70/522 ; % = 13

Critical appraisal - Remdesivir - RoB

All cause mortality

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

All-cause mortality (High flow oxygen, NIV)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

All-cause mortality (invasive mechanical ventilation)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

All-cause mortality (Low flow oxygen at baseline) (No oxygen supplementation)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Need for new mechanical ventilation or ECMO

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Need for new oxygen supplementation (high flow or NIV)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Need for new oxygen supplementation (low flow)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low

Section	Question	Answer
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Clinical recovery by day 28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Respiratory failure or ARDS

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
interventions (effect of assignment to intervention)		
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Serious adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Discontinuation due to adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Goldman et al.

Bibliographic Reference	Goldman JD; Lye DCB; Hui DS; Marks KM; Bruno R; Montejano R; Spinner CD; Galli M; Ahn MY; Nahass RG; Chen YS; SenGupta D; Hyland RH; Osinusi AO; Cao H; Blair C; Wei X; Gaggar A; Brainard DM; Towner WJ; Muñoz J; Mullane KM; Marty FM; Tashima KT; Diaz G; Subramanian A; ; Remdesivir for 5 or 10 Days in Patients with Severe Covid-19.; The New England journal of medicine; vol. 383 (no. 19)

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04292899
Study start date	Mar-2021
Aim of the study	To evaluate the efficacy and safety of treatment with remdesivir for 5 or 10 days in patients with severe Covid-19 disease.
Country/geographical location	United States, Italy, Spain, Germany, Hong Kong, Singapore, South Korea, and Taiwan
Study setting	Hospital
Population description	Hospitalised patients who were at least 12 years of age who had SARS-CoV-2 infection confirmed by polymerase-chain-reaction assay within 4 days before randomisation.
Inclusion criteria	Eligible patients had radiographic evidence of pulmonary infiltrates and either had oxygen saturation of 94% or less while they were breathing ambient air or were receiving supplemental oxygen.
Exclusion criteria	• Patients receiving mechanical ventilation and extracorporeal membrane oxygenation (ECMO) at screening • Patients with signs of multiorgan failure. • Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels greater than 5 times the upper limit of the normal range or estimated creatinine clearance of less than 50 ml per minute (by the Cockcroft–Gault formula). • Patients receiving concurrent treatment (within 24 hours before the start of trial treatment) with other agents with putative activity against Covid-19.
Intervention dosage (loading)	200mg
Intervention dosage (maintenance)	100mg once daily
Intervention scheduled duration	Intervention = 5 days remdesivir

Intervention actual duration	5 days in 5 day group 9 days in 10 day group
Intervention route of administration	Intravenous treatment
Comparator (where applicable)	10 days remdesivir
Methods for population selection/allocation	Patients were randomly assigned in a 1:1 ratio using IWRS (Interactive web response systems) [information obtained from study protocol, Randomisation was not stratified.
Methods of data analysis	The prespecified primary analysis, performed after all patients completed 14 days in the trial, used the proportional odds model, including treatment as the independent variable and baseline clinical status as a continuous covariate. The conclusion would be that 10 days of treatment was superior to 5 days of treatment if the lower bound of the two-sided 95% confidence interval of the odds ratio (10 days to 5 days) on day 14 was greater than 1. For time-to-event end points (such as the time to clinical improvement, the time to recovery, and the time to modified recovery), the hazard ratio and its 95% confidence interval were estimated from a cause-specific proportional-hazards model that included treatment and baseline clinical status as covariates and treated death as the competing risk. For events associated with prespecified times (e.g., days 5, 7, 11, and 14), the difference in the proportion of patients with an event under evaluation (such as clinical improvement, recovery, and modified recovery) between treatment groups and its 95% confidence interval were estimated from the Mantel–Haenszel proportions, with adjustment according to baseline clinical status. For end points other than the primary end point, 95% confidence intervals have not been adjusted for multiplicity and should not be used to infer effects.
Attrition/loss to follow-up	172/200 people in the 5 day group completed the trial Of those who did not complete the 5-day course of treatment, reasons included hospital discharge (16 patients [8%]) and adverse events (9 [4%]). No patient in the 5-day group stopped treatment because of death. 86/197 people in the 10 day group completed the trial

	Of those who did not complete the 10-day course, reasons included hospital discharge (68 patients [35%]), adverse events (22 [11%]), and death (12 [6%]) Intention to treat analysis conducted
Source of funding	Funded by Gilead Sciences; GS-US-540-5773
Study limitations (Author)	Due to the context at the time of the trial, it seemed appropriate to allow for patients to be discharged from the hospital as soon as medically indicated, regardless of whether they had completed the full assigned course of treatment with remdesivir. As a result, only 44% of patients in the 10-day treatment group completed the full course of therapy. Patients who were not discharged were presumably those with more severe illness, which may account for the different rates of adverse events seen in the two groups. Another important limitation is that the authors do not have SARS-CoV-2 viral-load results during and after treatment, owing to the variability in local access to testing and practices across the global sites.
Study limitations (Reviewer)	The treatment groups were balanced in demographic characteristics but not in baseline disease characteristics. Greater proportions of patients in the 10-day group were in the two highest disease-severity groups.

Study arms

5 day (N = 200)

10 day (N = 197)

Characteristics

Arm-level characteristics

Characteristic	5 day (N = 200)	10 day (N = 197)
Age	61 (50 to 69)	62 (50 to 71)

Characteristic	5 day (N = 200)	10 day (N = 197)
Median (IQR)		
Male No of events	n = 120 ; % = 60	n = 133 ; % = 68
White No of events	n = 142 ; % = 71	n = 134 ; % = 70
White Sample size	n = 200	n = 192
Black No of events	n = 21 ; % = 10	n = 23 ; % = 12
Black Sample size	n = 200	n = 192
Asian No of events	n = 20 ; % = 10	n = 25 ; % = 13
Asian Sample size	n = 200	n = 192
Other No of events	n = 17 ; % = 8	n = 10 ; % = 5
Other Sample size	n = 200	n = 192
Receiving invasive mechanical ventilation or ECMO No of events	n = 4 ; % = 2	n = 9 ; % = 5
Receiving non-invasive ventilation or high-flow oxygen No of events	n = 49 ; % = 24	n = 60 ; % = 30
Receiving low-flow supplemental oxygen No of events	n = 113 ; % = 56	n = 107 ; % = 54
Not receiving supplemental oxygen but requiring medical care No of events	n = 34	n = 21 ; % = 11
Diabetes No of events	n = 47 ; % = 24	n = 43 ; % = 22

Characteristic	5 day (N = 200)	10 day (N = 197)
Hyperlipidaemia No of events	n = 40 ; % = 20	n = 49 ; % = 25
Hypertension No of events	n = 100 ; % = 50	n = 98 ; % = 50
Asthma No of events	n = 27 ; % = 14	n = 22 ; % = 11

Outcomes

Mortality

Outcome	5 day, , N = 200	10 day, , N = 197
Death at day 14 No of events	n = 16 ; % = 8	n = 21 ; % = 11

Adverse events

Outcome	5 day, , N = 200	10 day, , N = 197
Serious adverse events No of events	n = 42 ; % = 21	n = 68 ; % = 35
Adverse events No of events	n = 141 ; % = 70	n = 145 ; % = 74
Acute respiratory failure or ARDS No of events	n = 11 ; % = 5.5	n = 23 ; % = 11.68
Septic shock No of events	n = 2 ; % = 1	n = 5 ; % = 3
Discontinued due to adverse event No of events	n = 9 ; % = 4.5	n = 22 ; % = 19.8

Recovery

Outcome	5 day, , N = 200	10 day, , N = 197
Clinical recovery day 14 No of events	n = 129 ; % = 64	n = 106 ; % = 54

Outcome	5 day, , N = 200	10 day, , N = 197
Discharged from hospital No of events	n = 120 ; % = 60	n = 103; % = 52

Critical appraisal – Remdesivir – RoB

Death at day 14

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Greater proportions of patients in the 10-day group were in the two highest disease-severity groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low *(Since both arms of the study were treated with remdesivir it is unlikely that mortality outcome is impacted by deviations from intended intervention)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Some participants did not finish the regimen as they were discharged as soon as medically indicated)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(A large number of people discontinued treatment. More so in the control group [5 days]. ITT was used but no description of how missing data was handled)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Missing data and incomplete treatment for some participants)*
Overall bias and Directness	Overall Directness	Directly applicable

Serious adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Greater proportions of patients in the 10-day group were in the two highest disease-severity groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(A large number of people discontinued treatment. More so in the control group. ITT was used but no description of how missing data was handled)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Missing data and incomplete treatment for some participants. Knowledge of intervention allocation could influence this outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Greater proportions of patients in the 10-day group were in the two highest disease-severity groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(A large number of people discontinued treatment. More so in the control group. ITT was used but no description of how missing data was handled)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Missing data and incomplete treatment for some participants. Knowledge of intervention allocation could influence this outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Acute respiratory failure or ARDS

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Greater proportions of patients in the 10-day group were in the two highest disease-severity groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(A large number of people discontinued treatment. More so in the control group. ITT was used*

Section	Question	Answer
		but no description of how missing data was handled)
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Missing data and incomplete treatment for some participants. Knowledge of intervention allocation could influence this outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Septic shock

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Greater proportions of patients in the 10-day group were in the two highest disease-severity groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(A large number of people discontinued treatment. More so in the control group. ITT was used but no description of how missing data was handled)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Missing data and incomplete treatment for some participants. Knowledge of intervention allocation could influence this outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Discontinued due to adverse event

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Greater proportions of patients in the 10-day group were in the two highest disease-severity groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(A large number of people discontinued treatment. More so in the control group. ITT was used but no description of how missing data was handled)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Missing data and incomplete treatment for some participants. Knowledge of intervention allocation could influence this outcome)*

Section	Question	Answer
Overall bias and Directness	Overall Directness	Directly applicable

Clinical recovery day14

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Greater proportions of patients in the 10-day group were in the two highest disease-severity groups.)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(A large number of people discontinued treatment. More so in the control group. ITT was used but no description of how missing data was handled)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Missing data and incomplete treatment for some participants. Knowledge of intervention allocation could influence this outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Discharged from hospital

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Greater proportions of patients in*

Section	Question	Answer
		the 10-day group were in the two highest disease-severity groups.)
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(A large number of people discontinued treatment. More so in the control group. ITT was used but no description of how missing data was handled)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Higher levels of discontinuation due to adverse events in control arm. Could be influenced by knowledge of intervention)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Missing data and incomplete treatment for some participants. Knowledge of intervention allocation could influence this outcome)*
Overall bias and Directness	Overall Directness	Directly applicable

Lee, 2022

Bibliographic Reference	Lee TC; Murthy S; Del Corpo O; Senécal J; Butler-Laporte G; Sohani ZN; Brophy JM; McDonald EG; Remdesivir for the treatment of COVID-19: A systematic review and meta-analysis.; Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases; 2022

Study details

Study design	Systematic review and meta-analysis
Aims/ review questions	To evaluate the role of remdesivir on mortality in people hospitalised with COVID-19.

Search date	1 Jan 2020 to 21-Jan-2022
Country/ Geographical location	Global
Setting(s)	In hospital
Population description	People hospitalised with COVID-19
Exclusion criteria	Not reported
Searching methods	Searched PubMed from January 1st, 2020, to January 21, 2022, to identify randomised controlled trials comparing remdesivir to placebo or standard of care in all hospitalized adults. There were no language restrictions. The search syntax “remdesivir AND (randomized OR randomised) AND 2021-01-15[dp]:2022-01-21[dp]” was used. Two independent reviewers screened for eligibility. Studies were included if they recruited hospitalised adult patients and reported either all-cause mortality or provided sufficient data to calculate all-cause mortality. There were no exclusion criteria. During peer review, the search was repeated using the Cochrane Library, which yielded no additional trials.
Methods of data analysis	Analysis was stratified by the level of oxygen support. The authors started with a frequentist analysis, as this was expected to be the method understood by most readers and because it provides for a more direct comparison with other systematic reviews of treatments for Covid-19. A Restricted Maximum Likelihood Estimation (REML) random effects meta-analysis on the risk ratio (RR) scale was used to undertake the frequentist analysis using the metan [12] command in STATA version 17 (STATACorp, USA). During peer review, two sensitivity analyses were conducted. First, the authors repeated the analysis excluding any trials where we were unable to exactly categorise all patients into the WHO SOLIDARITY oxygen support strata. Second, the analysis was repeated excluding trials at high risk of bias. Next, to quantify the mortality benefit in absolute terms and to address clinically meaningful differences (*a priori* defined as the probability of achieving at least a 1% absolute mortality reduction), the authors conducted a Bayesian meta-analysis on the risk difference scale using R[13] and the bayesmeta package[14]. Vague proper non-informative priors were used: μ centered at 0 (standard deviation = 4), which corresponds to no effect; and heterogeneity τ assumed to be half-normal prior with a scale of 0.03 [8]. Figures of posterior density vs. absolute differences in mortality between remdesivir and control patients were generated, and they integrated the area under the curve to obtain the probability for any mortality benefit and for a benefit exceeding 1% respectively [8].
Risk of bias assessment	Authors use ROB-2 to assess RCTs in the systematic review~~ROB-2 criteria~~
Summary of findings	The RR for mortality comparing remdesivir versus control was 0.71 (95% confidence interval [CI] 0.42-1.22) in the patients who did not require supplemental oxygen; 0.83 (95%CI 0.73-0.95) for nonventilated patients

	requiring oxygen; and 1.19 (95%CI 0.98-1.44) for patients receiving mechanical ventilation.
Source of funding	Drs Lee, McDonald, and Brophy receive research salary support from the Fonds de Recherche Québec - Santé. Dr Butler-Laporte is supported by a scholarship from the Fonds de Recherche Québec - Santé and the Ministère de la Santé et des Services sociaux. The CATCO trial was funded by the Canadian Institutes of Health Research (CIHR). The funders had no influence on the conduct or content of this article.
Study limitations (Author)	There are limitations to this analysis, the principal one being that the standard of care for Covid-19 continues to evolve at a staggering pace. Earlier in the pandemic, trial participants were less likely to receive treatments now known to reduce adverse outcomes including steroids, monoclonal antibodies, immunomodulatory therapies, or therapeutic anticoagulation. Additionally, very few of the participants included in this analysis were vaccinated against Covid-19 and all results predate the delta and omicron variants. It is unlikely that there will be additional large randomized controlled trials of remdesivir in vaccinated patients or with newer variants remains and this makes inferences about the magnitude of benefit of remdesivir in these populations challenging. While we feel confident (moderately certain) about the inferences made for patients who require oxygen or mechanical ventilation, it is important to note that there were very few deaths in patients who did not require oxygen. A mortality benefit in this group presumably needs to be better delineated in the context of modern therapy and the baseline risk of the patient. A final limitation we wish to note is a small lack of granularity with respect to oxygen requirements for a handful of patients; however, in our sensitivity analyses which excluded those trials, there were only very small differences in the estimate of relative risk reduction. An individual patient meta-analysis could provide more precise results and transparent data reporting and while data sharing is welcomed, we recognize the complexities of conducting such a multinational study.

Study arms

Remdesivir (N = 4733)

Control (N = 4424)

Characteristics

Arm-level characteristics

Characteristic	Remdesivir (N = 4733)	Control (N = 4424)
Mechanical ventilation Number of patients across included studies that were classified as being on mechanical ventilation at baseline No of events	n = 520; % = 10.9	n= 515; % =11.6
Oxygen without mechanical ventilation Number of patients across included studies that were	n = 3034; % = 64.1	n= 2940; % = 66.4

Characteristic	Remdesivir (N = 4733)	Control (N = 4424)
classified as being on oxygen support at baseline, but not on mechanical ventilation No of events		
No oxygen Number of patients across included studies that were classified as not being on any oxygen support at baseline No of events	n = 1179; % = 24.9	n = 969; % = 21.9

Outcomes

Mortality by level of oxygen support across all studies included in SR

Outcome	Remdesivir, , N = 4733	Control, , N = 4424
Deaths among people on mechanical ventilation at baseline Number of mortality events among those treated with remdesivir (n=520) vs. those in control arm (n=515) No of events	n = 157 ; % = 30.2	n = 127 ; % = 24.7
Deaths among people on oxygen support at baseline Number of mortality events among those treated with remdesivir (n=3034) vs. those in control arm (n=2940) No of events	n = 346 ; % = 11.4	n = 405 ; % = 13.8
Deaths among people not on any oxygen support at baseline Number of mortality events among those treated with remdesivir (n=1179) vs. those in control arm (n=969) No of events	n = 24 ; % = 2	n = 27 ; % = 2.8

Included studies: Abd-Elsalam 2021, Ali 2022 (CATCO), Ader 2021 (DisCoVeRy), Beigel 2020 (ACTT-1), Mahajan 2021, Pan 2020 (WHO-SOLIDARITY interim results), Spinner 2020, Wang 2020. Patients classified in the Ader 2021 (DisCoVeRy) trial as having 'moderate' disease were grouped into the meta analysis for "people on oxygen support". Patients classified in the Ader 2021 (DisCoVeRy) trial as having 'severe' disease were grouped into the meta analysis for "people on mechanical ventilation". Patients in the Wang 2020 study were all included in the meta analysis for "people on oxygen support", even though n=3 patients were not receiving oxygen at baseline and n=1 patient was ventilated at baseline. Patients in the Spinner 2020 study were all included in the meta analysis for "people not on oxygen support at baseline" even though the study only reported their oxygen requirements at time of screening, not at time of first dose. Patients in the Abd-Elsalam 2021 study were included in the meta analysis for "people on oxygen support at baseline" because mechanical ventilation was a trial exclusion and oxygen saturation levels in both arms were below 90%.

Mortality in a subset of patients from Ali 2022 (CATCO)

Outcome	Remdesivir, , N = 579	Control, , N = 582
Deaths among people on mechanical ventilation at baseline Number of mortality events among those treated with remdesivir (n=52) vs. those in control arm (n=42) No of events	n = 19 ; % = 36.5	n = 16 ; % = 38.1
Deaths among people on oxygen support at baseline People treated with remdesivir (n=468) vs. those in control arm (n=498) No of events	n = 85 ; % = 18.2	n = 110 ; % = 22.1
Deaths among people not on any oxygen support at baseline People treated with remdesivir (n=59) vs. those in control arm (n=42) No of events	n = 5 ; % = 8.5	n = 7 ; % = 16.7

Authors of this systematic review reached out to the authors of the Ali 2022 (CATCO) RCT to extract data for the subset of patients in this study who do not overlap with patients included in the WHO-SOLIDARITY trial.

Mortality in a subset of patients from Ader 2021 (DisCoVeRy)

Outcome	Remdesivir, , N = 195	Control, , N = 197
Deaths among people with severe COVID-19 at baseline 'Severe disease' defined as high flow nasal oxygen, non-invasive, and invasive ventilationSample size: people treated with remdesivir (n=83) vs. those in control arm (n=86) No of events	n = 12 ; % = 14.5	n = 11 ; % = 12.8
Deaths among people with moderate COVID-19 at baseline 'Moderate disease' defined as no oxygen or oxygen by nasal prongs/mask. Sample size: people treated with remdesivir (n=112) vs. those in control arm (n=111) No of events	n = 4 ; % = 3.6	n = 9 ; % = 8.1

Authors of this systematic review reached out to the authors of the Ader 2021 (DisCoVeRy) RCT to extract data for the subset of patients in this study who do not overlap with patients included in the WHO-SOLIDARITY trial

Critical appraisal - GDT Crit App - ROBIS checklist
RoB for meta-analysis of mortality across all included studies

For the RoB of data from Ali 2022 [CATCO], click here for a complete assessment.

For the RoB of data from Ader 2022 [DisCoVeRy], click here for a complete assessment.

Section	Question	Answer
Study eligibility criteria	Did the review adhere to pre-defined objectives and eligibility criteria?	Yes
Study eligibility criteria	Were the eligibility criteria appropriate for the review question?	Yes
Study eligibility criteria	Were eligibility criteria unambiguous?	Yes
Study eligibility criteria	Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g. date, sample size, study quality, outcomes measured)?	Yes
Study eligibility criteria	Were any restrictions in eligibility criteria based on sources of information appropriate (e.g. publication status or format, language, availability of data)?	Yes
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?	No
Identification and selection of studies	Were methods additional to database searching used to identify relevant reports?	No
Identification and selection of studies	Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	No information
Identification and selection of studies	Were restrictions based on date, publication format, or language appropriate?	Yes
Identification and selection of studies	Were efforts made to minimise error in selection of studies?	No information
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Unclear
Data collection and study appraisal	Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	Yes
Data collection and study appraisal	Were all relevant study results collected for use in the synthesis?	Yes

Section	Question	Answer
Data collection and study appraisal	Was risk of bias (or methodological quality) formally assessed using appropriate criteria?	Yes
Data collection and study appraisal	Were efforts made to minimise error in risk of bias assessment?	Yes
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Did the synthesis include all studies that it should?	Yes
Synthesis and findings	Were all pre-defined analyses reported or departures explained?	Yes
Synthesis and findings	Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	Yes
Synthesis and findings	Was between-study variation (heterogeneity) minimal or addressed in the synthesis?	Yes
Synthesis and findings	Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Yes
Synthesis and findings	Were biases in primary studies minimal or addressed in the synthesis?	Yes
Synthesis and findings	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Low – *The narrow search approach presents some concerns but ultimately the review includes appropriate studies (the same studies found in our more extensive search)*
Overall study ratings	Applicability as a source of data	Partially applicable

Mahajan, 2021

Bibliographic Reference	Mahajan, Lakshmi; Singh, A P; Gifty; Clinical outcomes of using remdesivir in patients with moderate to severe COVID-19: A prospective randomised study.; Indian journal of anaesthesia; 2021; vol. 65 (no. suppl1); 41-s46

Study details

Study design	Randomised controlled trial (RCT)

Study start date	01-Jun-2020
Study end date	31-Dec-2020
Aim of the study	Evaluate improvement in clinical outcomes with remdesivir treatment for five days
Country/geographical location	India
Study setting	Hospital
Population description	People aged>=40-years old, in hospital with moderate to severe COVID-19 but not on mechanical ventilation
Inclusion criteria	Hospitalised patients who were between 18 and 60 years age group and had SARS-CoV-2 infection confirmed by polymerase-chain-reaction assay within the last 4 days
Exclusion criteria	Patients receiving mechanical ventilation or patients with multi organ failure were not included in the study. Serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels were estimated in all participants and those with levels greater than three times the upper limit of the normal range were excluded. In addition, patients were required to have a creatinine clearance above 40 ml per minute.
Intervention dosage (loading)	200mg
Intervention dosage (maintenance)	100mg
Intervention scheduled duration	Remdesivir group patients received IV 200 mg remdesivir on day 1, followed by 100 mg of remdesivir once daily for the subsequent four days
Intervention actual duration	Remdesivir group patients received IV 200 mg remdesivir on day 1, followed by 100 mg of remdesivir once daily for the subsequent four days
Intervention route of administration	IV
Comparator (where applicable)	Standard care: Drugs like corticosteroids and heparin were given as per SC protocol
Methods for population selection/allocation	Randomised consecutive patients
Methods of data analysis	SPSS
Attrition/loss to follow-up	N/A
Source of funding	Not stated
Study limitations (Author)	• All our study cases were of moderate to severe disease category; however, the disease is progressive and there

	can be an overlap of symptoms between categories and the definitions of ‘moderate’ and ‘severe’ category are variable. • We did not grade the adverse events. • We did not give placebo injection in the no-remdesivir group • Did not do blinding. • Single-centre study • Small sample size.
Study limitations (Reviewer)	• Very small sample size • Unblinded

Study arms

Remdesivir (N = 34)

Standard care (N = 36)

Characteristics

Study-level characteristics

Characteristic	**Study (N = 70)**
Age Mean (SD)	57.74 (13.1)
Gender % Male No of events	n = 48 ; % = 65.5
Diabetes No of events	n = 42 ; % = 60
Hypothyroidism No of events	n = 7 ; % = 10
Hyperlipidaemia No of events	n = 7 ; % = 10
Chronic kidney disease	n = 3 ; % = 4.3

Characteristic	Study (N = 70)
No of events	
Hypertension No of events	n = 32 ; % = 45.7

Arm-level characteristics

Characteristic	Remdesivir (N = 34)	Standard care (N = 36)
Receiving low-flow supplemental oxygen No of events	n = 27 ; % = 79.4	n = 26 ; % = 72.2
Receiving non-invasive ventilation or high-flow oxygen No of events	n = 7 ; % = 20.6	n = 10 ; % = 27.8
Duration of symptoms before involvement in trial (days) Mean (SD)	6.26 (2.49)	7.38 (0.99)

Outcomes

Remdesivir vs. standard care

Outcome	Remdesivir, , N = 34	Standard care, , N = 36
Did not require hospitalisation If a patient was discharged before or on day 10, it was recorded as not hospitalised No of events	n = 2 ; % = 5.9	n = 3 ; % = 8.3
Hospitalised, but did not require supplemental oxygen No of events	n = 0 ; % = 0	n = 0 ; % = 0
Hospitalised, required supplemental oxygen No of events	n = 4 ; % = 11.8	n = 6 ; % = 16.7
Required high-flow oxygen or non-invasive ventilation No of events	n = 19 ; % = 55.9	n = 22 ; % = 61.1
Required or received mechanical ventilation	n = 4 ; % = 11.8	n = 2 ; % = 5.6

Outcome	Remdesivir, , N = 34	Standard care, , N = 36
No of events		
Death No of events	n = 5 ; % = 14.7	n = 3 ; % = 8.3
Admission days [Length of hospital stay] Mean (SD)	11.55 (4.3)	12.38 (5.2)

Clinical status from day 12 to 24 on 6-point ordinal scale

Critical appraisal - Remdesivir - RoB

Progression to severe disease outcome 1 [Did not require hospitalisation]

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(1 participant analysed in a different group than was randomised to but analysis used was probably appropriate)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Some missing data not accounted for)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(This outcome is unlikely to be influenced by clinical judgement)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Missing data and some deviation from intervention)*
Overall bias and Directness	Overall Directness	Directly applicable

Progression to severe disease outcome 2 [Hospitalised, but did not require supplemental oxygen]

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(1 participant analysed in a different group than was randomised to but analysis used was probably appropriate)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Some missing data not accounted for)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(This outcome is unlikely to be influenced by clinical judgement)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Missing data and some deviation from intervention)*
Overall bias and Directness	Overall Directness	Directly applicable

Progression to severe disease outcome 3 [Hospitalised, required supplemental oxygen]

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(1 participant analysed in a different group than was randomised to but analysis used was probably appropriate)*
Domain 2b: Risk of bias due to deviations from the	Risk of bias judgement for deviations from the intended	Low

Section	Question	Answer
intended interventions (effect of adhering to intervention)	interventions (effect of adhering to intervention)	
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Some missing data not accounted for)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(This outcome is unlikely to be influenced by clinical judgement)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Missing data and some deviation from intervention)*
Overall bias and Directness	Overall Directness	Directly applicable

Progression to severe disease outcome 4 [Required high-flow oxygen or non-invasive ventilation]

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(1 participant analysed in a different group than was randomised to but analysis used was probably appropriate)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Some missing data not accounted for)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(This outcome is unlikely to be influenced by clinical judgement)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High *(Missing data and some deviation from intervention)*
Overall bias and Directness	Overall Directness	Directly applicable

Progression to severe disease outcome 5 [Required or received mechanical ventilation]

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(1 participant analysed in a different group than was randomised to but analysis used was probably appropriate)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Some missing data not accounted for)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(This outcome is unlikely to be influenced by clinical judgement)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Missing data and some deviation from intervention)*
Overall bias and Directness	Overall Directness	Directly applicable

Death

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear allocation concealment)*
Domain 2a: Risk of bias due to deviations from the	Risk of bias for deviations from the intended	Some concerns *(1 participant analysed in a*

Section	Question	Answer
intended interventions (effect of assignment to intervention)	interventions (effect of assignment to intervention)	*different group than was randomised to but analysis used was probably appropriate)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Some missing data not accounted for)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low *(This outcome is unlikely to be influenced by clinical judgement)*
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Missing data and some deviation from intervention)*
Overall bias and Directness	Overall Directness	Directly applicable

Admission days

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Some concerns *(Unclear allocation concealment)*
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Some concerns *(1 participant analysed in a different group than was randomised to but analysis used was probably appropriate)*
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Some concerns *(Some missing data not accounted for)*
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns *(Knowledge of treatment allocation could impact clinical judgement here)*

Section	Question	Answer
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	High *(Open label trial with subjective outcome, missing data and some deviation from intervention)*
Overall bias and Directness	Overall Directness	Directly applicable

WHO Solidarity Trial, 2022

Bibliographic Reference	WHO Solidarity Trial Consortium; Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses; The Lancet; 2022

Study details

Trial registration (if reported)	NCT04315948
Study start date	22-Mar-2020
Study end date	29-Jan-2021
Aim of the study	To obtain mortality data for remdesivir in patients hospitalised with COVID-19. This study also included hydroxychloroquine, and lopinavir with or without interferon, but that data is not relevant to this evidence review.
Country/geographical location	Albania, Argentina, Austria, Belgium, Brazil, Canada, Colombia, Egypt, Ethiopia, Finland, France, Georgia, Honduras, India, Indonesia, Iran, Ireland, Italy, Kuwait, Lebanon, Lithuania, Luxembourg, Malaysia, Mali, North Macedonia, Norway, Pakistan, Peru, Philippines, Portugal, Saudi Arabia, Spain, South Africa, Switzerland.
Population description	Hospital
Inclusion criteria	Eligible patients were 18 years of age or older, were hospitalised with a diagnosis of COVID-19, were not known to have received any trial drug, were not expected to be transferred elsewhere within 72 hours, and, in the physician’s view, had no contraindication to any trial drug (remdesivir, hydroxychloroquine, lopinavir, interferon).

Exclusion criteria	The protocol did not define contraindications to enrolment, but mentioned three possible contraindications (serious chronic liver or heart disease, or pregnancy)
Intervention dosage (loading)	200 mg remdesivir [Day 1]
Intervention dosage (maintenance)	100 mg remdesivir [Day 2-10]
Intervention scheduled duration	10 days
Intervention actual duration	10 days
Intervention route of administration	Intravenous
Comparator (where applicable)	Local standard care at the time of the study. Included corticosteroids, convalescent plasma and anti IL-6 medication. Treatment with corticosteroids, convalescent plasma, anti IL-6 medication was balanced between treatment and control arms.
Methods for population selection/allocation	Used open-label, unstratified randomisation. The study drugs were remdesivir, hydroxychloroquine, lopinavir (always given with ritonavir to slow hepatic clearance), and IFN-β1a (given with lopinavir until July 4, 2020). After receiving all data on a new patient and being told which study drugs were locally available (at least one had to be), the central computer assigned that patient, by unstratified randomisation in equal proportions, between the locally available options—i.e., an available study drug or control (no study drug). No placebos were used. All patients were, in addition to any study drugs, to receive the local usual standard of care. Assignment of a patient to no study drug when more than one study drug was locally available put that patient into the control group for each of the locally available drugs. Hence, there was partial overlap among the control groups. Each comparison between patients allocated to receive a study drug and its control was evenly randomised and unbiased, so in expectation both groups would be affected equally by differences between countries, hospitals, or time periods, and by variation in patient characteristics or management.
Methods of data analysis	All analyses were conducted according to the randomly assigned treatment, regardless of the actual treatment, excluding patients with a refuted COVID-19 diagnosis or consent not encrypted into the database. All entry data were recorded irrevocably before unstratified, computerised treatment assignment, yielding strict 1:1 randomisation with no foreknowledge of whether assignment would be to a particular drug or its controls. The protocol-specified primary analyses were of in-hospital mortality split by disease severity at entry. Severity was defined by ventilation and supplemental oxygen use recorded at entry, without distinguishing between low-flow and high-flow oxygen. Mortality rate ratios (RRs) or, equivalently, hazard ratios (HRs) and their p

	values were calculated from log-rank or Cox analyses, stratified by three age groups (<50 years, 50–69 years, and ≥70 years) and three respiratory support groups (none, oxygen only, and ventilated), yielding 3 x 3=9 strata. Mortality RRs describe only the proportional risk reductions, but the absolute risk reductions depend additionally on background risks. Graphs of mortality by time are from unstratified Kaplan-Meier methods, modified to assess in-hospital mortality. (Hence, the Kaplan-Meier denominators at each time include previously discharged patients. For example, if 99 of 100 patients were discharged alive before the last of them died, in-hospital mortality would be 1%, so at the time of that death the probability of not having died in hospital would be multiplied by 99/100.) If the stratified log-rank observed minus expected number of deaths is O − E with variance V, loge RR is calculated as (O − E) / V with variance 1 / V and a normal distribution. All CIs are 95%, with no allowance for multiple comparisons despite the dangers of unduly data-dependent emphasis on particular subgroups. Forest plots include χ2 statistics (based on [O − E]2 / V) to test for heterogeneity between RRs. In general, the more deaths in a stratum the larger is V and the smaller is 1/V, the variance of loge RR, so V is the weight that stratum gets.
Attrition/loss to follow-up	The risk on day N was calculated by first excluding patients with an outcome not reported or entry fewer than N days before dataset closure (or withdrawal of consent to follow-up or transfer elsewhere before day N). Then, the number of in-hospital deaths on day N was divided by the total number of patients in the hospital on day N or discharged alive before day N. This denominator (or risk set) was also used to calculate the contribution of day N to log-rank analyses and Cox analyses of in-hospital mortality. Denominators for the deaths on day 0, but not on later days, included patients with no follow-up reported (as deaths on day 0 would probably have been reported). 47 patients [23 in RDV arm and 24 in control arm] were excluded from the analysis because their COVID diagnosis was refuted or their consent was not encrypted in the study database; so follow-up censored in Kaplan-Meier at day 28.
Source of funding	WHO
Study limitations (Author)	Solidarity has several limitations. First, only simple information on respiratory support was collected at entry, and the reasons for

	needing oxygen were not recorded. Second, ventilation was more resource-limited in some countries or hospitals than others, and some patients who were not ventilated would have been ventilated had resources been available. This situation does not, however, invalidate the secondary analyses of ventilation or the composite outcome of death or ventilation (which is unaffected by any deaths that could have been prevented by ventilation). Moreover, heterogeneity between the collaborating countries and hospitals does not bias the comparison of study drug versus control, as all could give the allocated treatment and report the study outcomes reliably. Third, Solidarity recruitment preceded the delta and omicron variants (and widespread vaccination). For drugs such as remdesivir that act via internal non-structural proteins (NSPs), the emergence of these new viral variants might not materially affect drug efficacy. However, absolute effects on mortality might be smaller for lower-risk variants, or for patients whose risk during their current episode of hospitalisation for COVID-19 is reduced either by having previously been vaccinated, or by effective treatment during this episode with some other anti-viral drug(s), some effective immune-modulating drug(s), or good supportive care. Fourth, to maximise study size, controls did not receive placebo infusions, so the findings combine the pharmacological and non-pharmacological effects of allocation to daily remdesivir. Lastly, the chief limitation of Solidarity is study size. Worldwide, over 10,000 inpatients have been randomly assigned to receive either remdesivir or control, including some 8000 in Solidarity. Although substantial effects on mortality can now be excluded, it is difficult to demonstrate or refute moderate effects, especially if these are only in particular subgroups. If it had been possible to randomise another 10,000 patients, there would now be better evidence on how to treat the next 10 million.
Study limitations (Reviewer)	- Unblinded: may impact rates of initiating ventilation if patients and providers are aware of treatment allocation - Subgroups not separated by low vs. high-flow oxygen or NIV vs. IMV- as a result there may be heterogeneity within the subgroups in terms of response to remdesivir treatment
Other details	This study also included hydroxychloroquine, and lopinavir with or without interferon, but that data is not relevant to this evidence review and has not been extracted.

Study arms

Remdesivir (N = 4146)

Control (N = 4129)

Characteristics

Arm-level characteristics

Characteristic	Remdesivir (N = 4146)	Control (N = 4129)
Age <50 No of events	n = 1310 ; % = 32	n = 1326 ; % = 32
Age 50-69 No of events	n = 1920 ; % = 46	n = 1908 ; % = 46
Age >=70 No of events	n = 916 ; % = 22	n = 895 ; % = 22
No O2 at entry No of events	n = 869 ; % = 21	n = 861 ; % = 21
On O2 at entry No of events	n = 2918 ; % = 70	n = 2921 ; % = 71
Already ventilated at entry No of events	n = 359 ; % = 9	n = 347 ; % = 8
Europe or Canada No of events	n = 1649 ; % = 40	n = 1594 ; % = 39
Latin America No of events	n = 558 ; % = 13	n = 593 ; % = 14
Asia and Africa No of events	n = 1939 ; % = 47	n = 1942 ; % = 47
Male sex No of events	n = 2601 ; % = 63	n = 2639 ; % = 64
Female sex No of events	n = 1545 ; % = 37	n = 1490 ; % = 36
Diabetes No of events	n = 1129 ; % = 27	n = 1120 ; % = 27
Heart disease No of events	n = 929 ; % = 22	n = 935 ; % = 23
Chronic lung disease No of events	n = 284 ; % = 7	n = 281 ; % = 7

Characteristic	Remdesivir (N = 4146)	Control (N = 4129)
Asthma No of events	n = 247 ; % = 6	n = 242 ; % = 6
Chronic liver disease No of events	n = 57 ; % = 1	n = 72 ; % = 2

Outcomes

Outcomes

Outcome	Remdesivir, , N = 4146	Control, , N = 4129
All cause mortality In-hospital mortality (regardless of whether before or after day 28) No of events	n = 602 ; % = 14.5	n = 643 ; % = 15.6
All cause mortality - no oxygen at baseline In-hospital mortality among patients not receiving oxygen at baseline (n=869 in RDV arm, n=861 in control arm) No of events	n = 25 ; % = 2.9	n = 33 ; % = 3.8
All cause mortality - low-flow or high-flow oxygen at baseline In-hospital mortality among patients receiving oxygen at baseline (n=2918 in RDV arm, n=2921 in control arm) No of events	n = 426 ; % = 14.6	n = 476 ; % = 16.3
All cause mortality - ventilation [NIV or IMV] at baseline In-hospital mortality among patients ventilated at baseline (n=359 in RDV arm, n=347 in control arm) No of events	n = 151 ; % = 42.1	n = 134 ; % = 38.6
Progression to ventilation Need for new ventilation (NIV or IMV) among patients not ventilated at baseline [n=3787 in RDV arm, n=3782 in control arm] No of events	n = 535 ; % = 14.1	n = 593 ; % = 15.7
Discharge from hospital People discharged alive from hospital No of events	n = 3544 ; % = 85.5	n = 3486 ; % = 84.4

Critical appraisal - Remdesivir - RoB

All cause mortality

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low *(Although the study was not blinded, the risk of bias for mortality outcomes is low because knowledge of the intervention is unlikely to impact whether someone dies in hospital or not)*
Overall bias and Directness	Overall Directness	Directly applicable

Progression to ventilation

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from	Risk of bias judgement for deviations from the	Low

Section	Question	Answer
the intended interventions (effect of adhering to intervention)	intended interventions (effect of adhering to intervention)	
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Some concerns – outcome assessors were aware of intervention assignment
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(There is a moderate risk of bias for this outcome, due to the fact that the study was unblinded. It is possible that there are differences in the rates at which clinicians would initiate ventilation in patients due to knowledge of their assigned intervention.)*
Overall bias and Directness	Overall Directness	Directly applicable

Discharge from hospital

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Outcome assessor knowledge of intervention assignment could impact*

Section	Question	Answer
		likelihood of hospital discharge.)
Overall bias and Directness	Overall Directness	Directly applicable

Spinner et al.

Bibliographic Reference	Spinner CD; Gottlieb RL; Criner GJ; Arribas López JR; Cattelan AM; Soriano Viladomiu A; Ogbuagu O; Malhotra P; Mullane KM; Castagna A; Chai LYA; Roestenberg M; Tsang OTY; Bernasconi E; Le Turnier P; Chang SC; SenGupta D; Hyland RH; Osinusi AO; Cao H; Blair C; Wang H; Gaggar A; Brainard DM; McPhail MJ; Bhagani S; Ahn MY; Sanyal AJ; Huhn G; Marty FM; ; Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial.; JAMA; vol. 324 (no. 11)

Study details

Study design	Randomised controlled trial (RCT)
Trial registration (if reported)	NCT04292730
Study start date	15-Mar-2020
Study end date	18-Apr-2020
Aim of the study	To determine the efficacy of 5 or 10 days of remdesivir treatment compared with standard care on clinical status on day 11 after initiation of treatment.
Country/geographical location	France, Germany, Hong Kong, Italy, Netherlands, Korea, Singapore, Spain, Switzerland, Taiwan, UK, and US.
Study setting	Hospital
Population description	Hospitalised patients with confirmed severe acute COVID-19 and moderate COVID-19 pneumonia (pulmonary infiltrates and room-air oxygen saturation >94%).
Inclusion criteria	Patients must have met all of the following inclusion criteria to be eligible for participation in this study: 1. Willing and able to provide written informed consent (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 2. 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)

	3. SARS-CoV-2 infection confirmed by PCR ≤ 4 days before randomisation 4. Currently hospitalised and requiring medical care for COVID-19 5. SpO2 > 94% on room air at screening 6. Radiographic evidence of pulmonary infiltrates 7. Men and women of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception.
Exclusion criteria	Patients who met any of the following exclusion criteria were not enrolled in the study: 1. Participation in any other clinical trial of an experimental agent treatment for COVID-19 2. Concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 < 24 hours prior to study drug dosing Remdesivir. 3. Requiring mechanical ventilation at screening 4. ALT or AST > 5 x ULN 5. Creatinine clearance < 50 mL/min using the Cockcroft-Gault formula for participants ≥ 18 years of age and Schwartz Formula for participants < 18 years of age 6. Positive pregnancy test 7. Breastfeeding woman 8. Known hypersensitivity to the study drug, the metabolites, or formulation excipient
Intervention dosage (loading)	200 milligrams of remdesivir
Intervention dosage (maintenance)	100 milligrams of remdesivir on subsequent days.
Intervention actual duration	5-days or 10-days.
Intervention route of administration	Intravenous over 30 to 60 minutes.
Comparator (where applicable)	Standard care was not described.
Methods for population selection/allocation	Randomisation was not stratified. The randomisation list was created and validated by the interactive web response system (IWRS) vendor. A dummy randomisation list was provided in Microsoft Excel format to the biostatistician employed by the study

	sponsor for review. A separate list of sequential patient numbers within each treatment group was generated by the IWRS vendor. The randomisation had a block size of 6. Based on the treatment from the randomisation list, the IWRS provided the next sequential patient number to the site along with the treatment group assignment. The appropriate number of vials of open-label study drug were assigned to the patient. Sites did not have access to the randomisation list and could not know the sequence of treatments.
Methods of data analysis	The investigators calculated that 600 patients (200 in each group) would provide greater than 85% power to detect an odds ratio of 1.8 for each remdesivir group vs the standard care group using a 2-sided significance level of .05. The odds ratio of 1.8 was calculated based on proposed group sizes at the time of study conception and was not intended as a minimum clinically meaningful treatment effect, as no prior data were available on the distribution of clinical status categories over time in patients with moderate COVID-19. An odds ratio greater than 1 indicates changes in clinical status across all categories toward category 7 for the remdesivir groups vs the standard care group. All patients who were randomized and received at least 1 dose of remdesivir, or for the standard care group, had the day 1 visit, were assessed for efficacy and adverse events. For clinical status, the ordinal score was recorded as 1 on the day of death and all subsequent days; if a patient was discharged, the ordinal score was recorded as 7 on the day of discharge alive and all subsequent days unless the patient was re-hospitalized for COVID-19–related reasons; otherwise, the most recent assessment was used for missing values. They used SAS version 9.4 for all analyses. For the primary efficacy end point, each remdesivir group was compared with the standard care group at a 2-sided $\alpha = 0.025$ (Bonferroni). Proportional odds models were used with treatment as the independent variable; odds ratios and 95% CIs are presented. The assumption of proportional odds was tested using the score test, and supporting P values from the Wilcoxon rank sum test are provided if the proportional odds assumption was not met. Analyses including baseline clinical status as a covariate were also performed. For the secondary end point of proportion of patients with adverse events throughout the duration of the study, comparisons between each remdesivir group and the standard care group were performed using a Fisher exact test; point estimates of the group differences and corresponding 95% CIs were calculated. For the prespecified exploratory end points, death was considered the competing risk in these time-to-event analyses. Patients without the event of interest were censored on the day of the last non-missing ordinal scale assessment. All-cause mortality was estimated using the Kaplan-Meier product limit method with all available data. Each remdesivir group was

	compared with the standard care group using the log-rank test, and hazard ratios and 95% CIs were provided. Participants who did not die were censored on the last study day. Durations of oxygen therapy and hospitalisation were summarised and compared between groups using the Wilcoxon rank sum test.
Attrition/loss to follow-up	In the 10-day remdesivir arm, 8 withdrew consent. In the 5-day remdesivir arm, 11 withdrew consent and 1 was lost to follow-up. In the standard care arm, no equivalent data was provided.
Source of funding	Gilead Sciences
Study limitations (Author)	This study has several limitations. First, the original protocol was written when COVID-19 cases were largely confined to Asia and the clinical understanding of disease was limited to case series. This led to a change in the primary end point on the first day of study enrolment as it became clear that hospital discharge rates varied greatly across regions and the ordinal scale had become standard for interventional COVID-19 studies. Second, the study used an open-label design, which potentially led to biases in patient care and reporting of data. Third, because of the urgent circumstances in which the study was conducted, virologic outcomes such as effect of remdesivir on SARS-CoV-2 viral load were not assessed. Fourth, other laboratory parameters that may have aided in identifying additional predictors of outcomes were not routinely collected. Fifth, the ordinal scale used to evaluate outcomes was not ideal for detecting differences in patients with moderate COVID-19, especially for a clinical situation in which discharge decisions may be driven by factors other than clinical improvement.
Study limitations (Reviewer)	N/A

Study arms

10-day course of remdesivir (N = 193)

5-day course of remdesivir (N = 191)

Standard care (N = 200)

Characteristics

Arm-level characteristics

Characteristic	10-day course of remdesivir (N = 193)	5-day course of remdesivir (N = 191)	Standard care (N = 200)
median age (years) Nominal	56	58	57
Interquartile range (years) Range	45 to 66	48 to 66	45 to 66
Female (%) Nominal	39	40	38
White Nominal	107	109	112
White No of events	n = 107 ; % = 55	n = 109 ; % = 57	n = 112 ; % = 56
Black Nominal	37	35	27
Black No of events	n = 37 ; % = 19	n = 35 ; % = 18	n = 27 ; % = 14
Asian Nominal	31	34	37
Asian No of events	n = 31 ; % = 16	n = 34 ; % = 18	n = 37 ; % = 19
Other Nominal	13	8	17
Other No of events	n = 13 ; % = 7	n = 8 ; % = 4	n = 17 ; % = 9
Hispanic or Latino ethnicity Nominal	42	25	34

Characteristic	10-day course of remdesivir (N = 193)	5-day course of remdesivir (N = 191)	Standard care (N = 200)
Hispanic or Latino ethnicity No of events	n = 42 ; % = 22	n = 25	n = 34 ; % = 17
Body mass index, median (kg/m2) Nominal	28	27	27
Interquartile range (kg/m2) Range	25 to 32	24 to 30	24 to 31
Cardiovascular disease Nominal	111	111	107
Cardiovascular disease No of events	n = 111 ; % = 58	n = 111 ; % = 58	n = 107 ; % = 54
Hypertension Nominal	85	82	81
Hypertension No of events	n = 85 ; % = 44	n = 82 ; % = 43	n = 81 ; % = 41
Diabetes Nominal	85	71	76
Diabetes No of events	n = 85 ; % = 44	n = 71 ; % = 37	n = 76 ; % = 38
Asthma Nominal	31	22	28
Asthma No of events	n = 31 ; % = 16	n = 22 ; % = 12	n = 28 ; % = 14
Steroids Nominal	29	33	38
Steroids No of events	n = 29 ; % = 15	n = 33 ; % = 17	n = 38 ; % = 19
Hydroxychloroquine/chloroquine Nominal	22	16	89

Characteristic	10-day course of remdesivir (N = 193)	5-day course of remdesivir (N = 191)	Standard care (N = 200)
Hydroxychloroquine/chloroquine No of events	n = 22 ; % = 11	n = 16 ; % = 8	n = 89 ; % = 45
Lopinavir-ritonavir Nominal	11	10	43
Lopinavir-ritonavir No of events	n = 11 ; % = 6	n = 10 ; % = 5	n = 43 ; % = 22
Tocilizumab Nominal	1	1	10
Tocilizumab No of events	n = 1 ; % = 1	n = 1 ; % = 1	n = 10 ; % = 5
Azithromycin Nominal	41	35	62
Azithromycin No of events	n = 41 ; % = 21	n = 35 ; % = 18	n = 62 ; % = 31

Outcomes

Study timepoints

- 14 day
- 28 day

Outcomes

Outcome	10-day course of remdesivir, N = 193	5-day course of remdesivir, N = 191	5- and 10-day course of remdesivir, N=384	Standard care, N = 200
All cause mortality (number) No of events	n = 3/193 ; % =1.5	n = 2/191 ; % = 1	n = 5/384 ; % = 1.3	n = 4/200 ; % = 2

Outcome	10-day course of remdesivir, N = 193	5-day course of remdesivir, N = 191	5- and 10-day course of remdesivir, N=384	Standard care, N = 200
All-cause mortality (Low flow oxygen at baseline) No of events	-	-	n = 5/384 ; % = 1	n = 4/200 ; % = 2
Clinical recovery by day 28 No of events	n = 174/193 ; % = 90	n = 170/191 ; % = 89	-	n = 166/200 ; % = 83
Adverse events No of events	n = 113/193 ; % = 59	n = 98/191 ; % = 51	-	n = 93/200 ; % = 47
Serious adverse events No of events	n = 10/193 ; % = 5	n = 9/191 ; % = 5	-	n = 18/200 ; % = 9
Discontinuation due to adverse events No of events	n = 8/193 ; % = 4	n = 4/191 ; % = 4	-	n = 0/200 ; % = 0

Critical appraisal - Remdesivir - RoB

All cause mortality

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Concomitant interventions, incl. hydroxychloroquine/chloroquine, lopinavir-ritonavir, tocilizumab, and azithromycin, were not balanced between treatment and control arms. Given that the study wasn't blinded, there is a risk that treatment with concomitant interventions was greater in the control arm due to deviations from intended interventions)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Due to lack of blinding there are issues with concomitant medications (different in the standard care arm) and the recording of outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable

All-cause mortality (Low flow oxygen at baseline)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Concomitant interventions, incl. hydroxychloroquine/chloroquine, lopinavir-ritonavir, tocilizumab, and azithromycin, were not balanced between treatment and control arms. Given that the study wasn't blinded, there is a risk that treatment with concomitant interventions was greater in the control arm due to deviations from intended interventions)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Due to lack of blinding there are issues with concomitant medications (different in the standard care arm) and the recording of outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable

Clinical recovery by day 28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Concomitant interventions, incl. hydroxychloroquine/chloroquine, lopinavir-ritonavir, tocilizumab, and azithromycin, were not balanced between treatment and control arms. Given that the study wasn't blinded, there is a risk that treatment with concomitant interventions was greater in the control arm due to deviations from intended interventions.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Due to lack of blinding there are issues with concomitant medications (different in the standard care arm) and the recording of outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable

Adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Concomitant interventions, incl. hydroxychloroquine/chloroquine, lopinavir-ritonavir, tocilizumab, and azithromycin, were not balanced between treatment and control arms. Given that the study wasn't blinded, there is a risk that treatment with concomitant interventions was greater in the control arm due to deviations from intended interventions*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Due to lack of blinding there are issues with concomitant medications (different in the standard care arm) and the recording of outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable

Serious adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Concomitant interventions, incl. hydroxychloroquine/chloroquine, lopinavir-ritonavir, tocilizumab, and azithromycin, were not balanced between treatment and control arms. Given that the study wasn't blinded, there is a risk that treatment with concomitant interventions was greater in the control arm due to deviations from intended interventions*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Due to lack of blinding there are issues with concomitant medications (different in the standard care arm) and the recording of outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable

Discontinuation due to adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Some concerns *(Concomitant interventions, incl. hydroxychloroquine/chloroquine, lopinavir-ritonavir, tocilizumab, and azithromycin, were not balanced between treatment and control arms. Given that the study wasn't blinded, there is a risk that treatment with concomitant interventions was greater in the control arm due to deviations from intended interventions.)*
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Moderate *(Due to lack of blinding there are issues with concomitant medications (different in the standard care arm) and the recording of outcomes)*
Overall bias and Directness	Overall Directness	Directly applicable

Wang et al.

Bibliographic Reference	Wang Y; Zhang D; Du G; Du R; Zhao J; Jin Y; Fu S; Gao L; Cheng Z; Lu Q; Hu Y; Luo G; Wang K; Lu Y; Li H; Wang S; Ruan S; Yang C; Mei C; Wang Y; Ding D; Wu F; Tang X; Ye X; Ye Y; Liu B; Yang J; Yin W; Wang A; Fan G; Zhou F; Liu Z; Gu X; Xu J; Shang L; Zhang Y; Cao L; Guo T; Wan Y; Qin H; Jiang Y; Jaki T; Hayden FG; Horby PW; Cao B; Wang C; Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial.; Lancet (London, England); vol. 395 (no. 10236)

Study details

Study design	Randomised controlled trial (RCT)

Trial registration (if reported)	NCT04257656
Study start date	06-Feb-2020
Study end date	12-Mar-2020
Aim of the study	To assess the effectiveness and safety of intravenous remdesivir in adults (aged ≥18 years) admitted to hospital with severe COVID-19.
Country/geographical location	China
Population description	Adults (aged ≥18 years) admitted to hospital with severe COVID-19.
Inclusion criteria	Eligible patients were men and non-pregnant women with COVID-19 who were aged at least 18 years and were RT-PCR positive for SARS-CoV-2, had pneumonia confirmed by chest imaging, had oxygen saturation of 94% or lower on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and were within 12 days of symptom onset. Eligible patients 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.
Exclusion criteria	Exclusion criteria included pregnancy or breast feeding; hepatic cirrhosis; alanine aminotransferase or aspartate aminotransferase more than five times the upper limit of normal; known severe renal impairment (estimated glomerular filtration rate <30 mL/min per 1·73 m²) or receipt of continuous renal replacement therapy, haemodialysis, or peritoneal dialysis; possibility of transfer to a non-study hospital within 72 h; and enrolment into an investigational treatment study for COVID-19 in the 30 days before screening.
Intervention dosage (loading)	200 milligrams remdesivir.
Intervention dosage (maintenance)	100 milligrams on days 2–10
Intervention scheduled duration	10 days
Intervention actual duration	In the remdesivir arm, 5 participants received remdesivir for < 5 days. In the placebo arm, 2 received placebo for < 5 days.
Intervention route of administration	Intravenous
Comparator (where applicable)	Placebo

Methods for population selection/allocation	Eligible patients were randomly assigned (2:1) to either the remdesivir group or the placebo group. Randomisation was stratified according to the level of respiratory support as follows: (1) no oxygen support or oxygen support with nasal duct or mask; or (2) high-flow oxygen, non-invasive ventilation, invasive ventilation, or extracorporeal membrane oxygenation. The permuted block (30 patients per block) randomisation sequence, including stratification, was prepared by a statistician not involved in the trial using SAS software, version 9.4. Eligible patients were allocated to receive medication in individually numbered packs, according to the sequential order of the randomisation centre. Envelopes were prepared for emergency unmasking.
Methods of data analysis	The original design required a total of 325 events across both groups, which would provide 80% power under a one-sided type I error of 2·5% if the hazard ratio (HR) comparing remdesivir to placebo is 1·4, corresponding to a change in time to clinical improvement of 6 days assuming that time to clinical improvement is 21 days on placebo. One interim analysis using triangular boundaries and a 2:1 allocation ratio between remdesivir and placebo had been accounted for in the original design. Assuming an 80% event rate within 28 days across both groups and a dropout rate of 10% implies that about 453 patients should be recruited for this trial (151 on placebo and 302 on remdesivir). The possibility for an interim analysis after enrolment of about 240 patients was included in the design if requested by the independent data safety and monitoring board. The primary efficacy analysis was done on an intention-to-treat (ITT) basis with all randomly assigned patients. Time to clinical improvement was assessed after all patients had reached day 28; no clinical improvement at day 28 or death before day 28 were considered as right censored at day 28. Time to clinical improvement was portrayed by Kaplan-Meier plot and compared with a logrank test. The HR and 95% CI for clinical improvement and HR with 95% CI for clinical deterioration were calculated by Cox proportional hazards model. Other analyses include subgroup analyses for those receiving treatment 10 days or less vs more than 10 days after symptom onset, time to clinical deterioration (defined as one category increase or death), and for viral RNA load at entry. The differences in continuous variables between the groups was calculated using Hodges-Lehmann estimation. We present adverse event data on the patients' actual treatment exposure, coded using Medical Dictionary for Regulatory Activities. Statistical analyses were done using SAS software, version 9.4.
Attrition/loss to follow-up	In the remdesivir arm, 3 people did not start treatment. In the placebo arm, 1 person withdrew consent.

Source of funding	Gilead Sciences, Chinese Academy of Medical Sciences Emergency Project of COVID-19; Major Projects of National Science and Technology on New Drug Creation and Development; the National Key Research and Development Program of China; and the Beijing Science and Technology Project. This work was also supported by the China Evergrande Group, Jack Ma Foundation, Sino Biopharmaceutical Limited, Ping An Insurance (Group), and New Sunshine Charity Foundation. National Institutes of Health Research (NIHR), Wellcome Trust and the UK Department for International Development, the Bill & Melinda Gates Foundation.
Study limitations (Author)	Limitations of the study include insufficient power to detect assumed differences in clinical outcomes, initiation of treatment quite late in COVID-19, and the absence of data on infectious virus recovery or on possible emergence of reduced susceptibility to remdesivir. Of note, in non-human primates, the inhibitory effects of remdesivir on infectious SARS-CoV-2 recovery in bronchoalveolar lavages were much greater than in controls, but viral RNA detection in upper and lower respiratory tract specimens were not consistently decreased versus controls. Coronaviruses partially resistant to inhibition by remdesivir (about six-times increased EC50) have been obtained after serial in vitro passage, but these viruses remain susceptible to higher remdesivir concentrations and show impaired fitness. The frequent use of corticosteroids in this patient group might have promoted viral replication, as observed in SARS27 and MERS, although these studies only reported prolongation of the detection of viral RNA, not infectious virus. Furthermore, the investigators have no answer to whether longer treatment course and higher dose of remdesivir would be beneficial in patients with severe COVID-19.
Study limitations (Reviewer)	N/A

Study arms

Remdesivir (N = 158)

Placebo (N = 78)

Characteristics

Arm-level characteristics

Characteristic	Remdesivir (N = 158)	Placebo (N = 78)
median age (years) Nominal	66	64
Interquartile range (years) Range	57 to 73	53 to 70
Women (%) Nominal	44	35
Any comorbidities (number) Nominal	112 (71%)	55 (71%)
Hypertension Nominal	72 (46%)	30 (38%)
Diabetes Nominal	40 (25%)	16 (21%)
Coronary heart disease Nominal	15 (9%)	2 (3%)
Antibiotic (number) Nominal	142 (77%)	73 (81%)
Corticosteroids therapy (number) Nominal	102 (38%)	53 (40%)

Outcomes

Study timepoints

- 28 day

Outcomes

Outcome	Remdesivir, 28 day, N = 158	Placebo, 28 day, N = 78
All cause mortality (number) No of events	n = 22/158 ; % = 14	n = 10/78 ; % = 13
All-cause mortality (High flow oxygen, NIV	n = 11/29 ; % = 40	n = 3/10 ; % = 30

Outcome	Remdesivir, 28 day, N = 158	Placebo, 28 day, N = 78
No of events		
All-cause mortality (Low flow oxygen at baseline) (Low flow oxygen) No of events	n = 11/129 ; % = 9	n = 7/68 ; % = 10
Clinical recovery by day 28 No of events	n = 60/153 ; % = 39	n = 49/77 ; % = 64
Respiratory failure or ARDS No of events	n = 16/155 ; % = 10	n = 6/78 ; % = 8
Adverse events No of events	n = 102/155 ; % = 66	n = 50/78 ; % = 64
Serious adverse events No of events	n = 28/155 ; % = 18	n = 20/78 ; % = 26
Discontinuation due to adverse events No of events	n = 18/155 ; % = 12	n = 4/78 ; % = 5

Critical appraisal - Remdesivir - RoB

All-cause mortality

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

All-cause mortality (High flow oxygen, NIV

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

All-cause mortality (Low flow oxygen at baseline) (Low flow oxygen)

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low

Section	Question	Answer
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Clinical recovery by day 28

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Respiratory failure or ARDS

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low

Section	Question	Answer
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

Serious adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

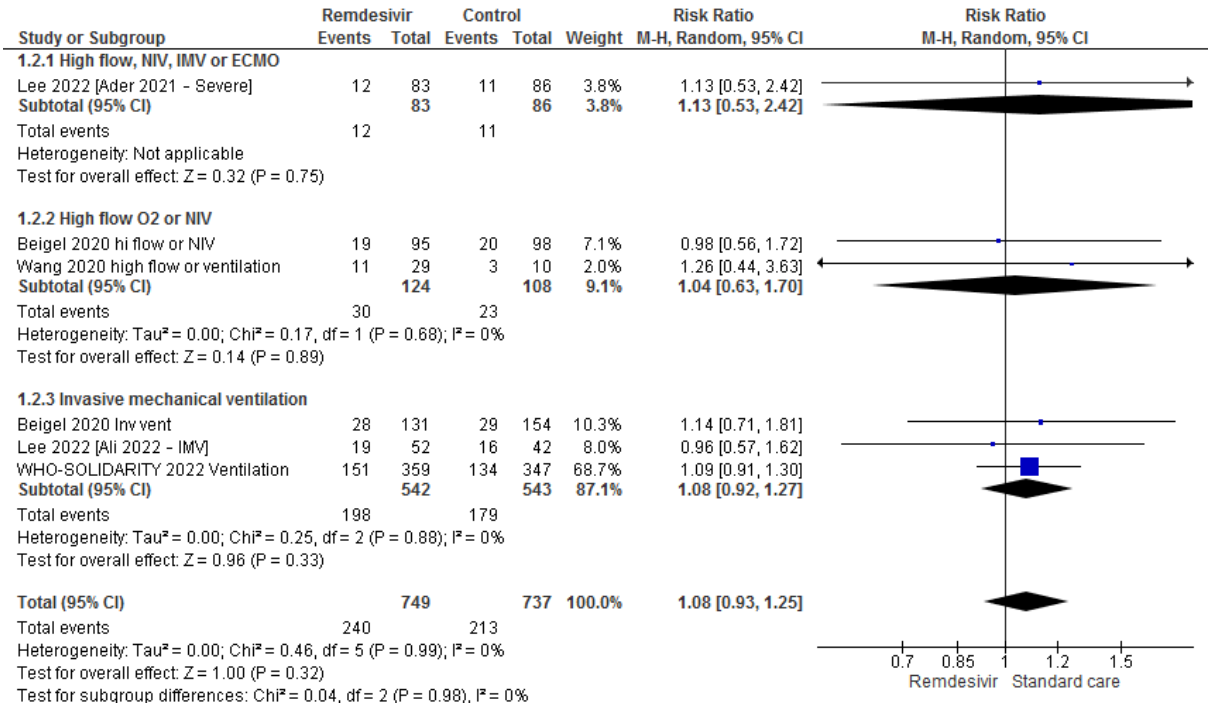
Discontinuation due to adverse events

Section	Question	Answer
Domain 1: Bias arising from the randomisation process	Risk of bias judgement for the randomisation process	Low
Domain 2a: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)	Risk of bias for deviations from the intended interventions (effect of assignment to intervention)	Low
Domain 2b: Risk of bias due to deviations from the intended interventions (effect of adhering to intervention)	Risk of bias judgement for deviations from the intended interventions (effect of adhering to intervention)	Low
Domain 3. Bias due to missing outcome data	Risk-of-bias judgement for missing outcome data	Low
Domain 4. Bias in measurement of the outcome	Risk-of-bias judgement for measurement of the outcome	Low
Domain 5. Bias in selection of the reported result	Risk-of-bias judgement for selection of the reported result	Low
Overall bias and Directness	Risk of bias judgement	Low
Overall bias and Directness	Overall Directness	Directly applicable

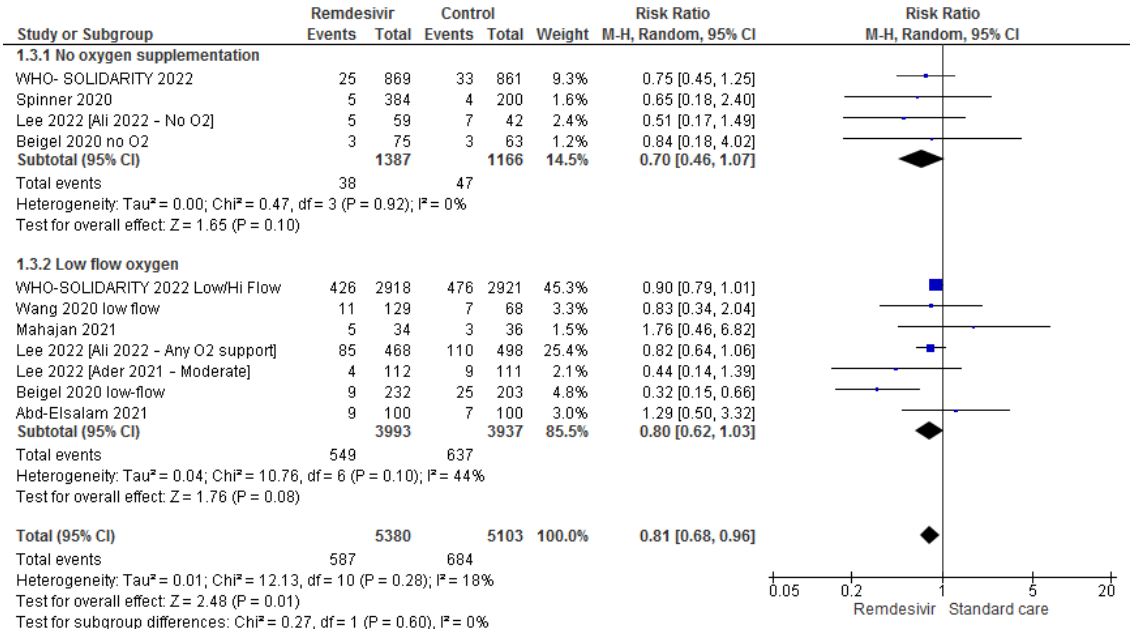
Appendix G: Forest Plots

Comparison 1: Remdesivir versus standard care/placebo

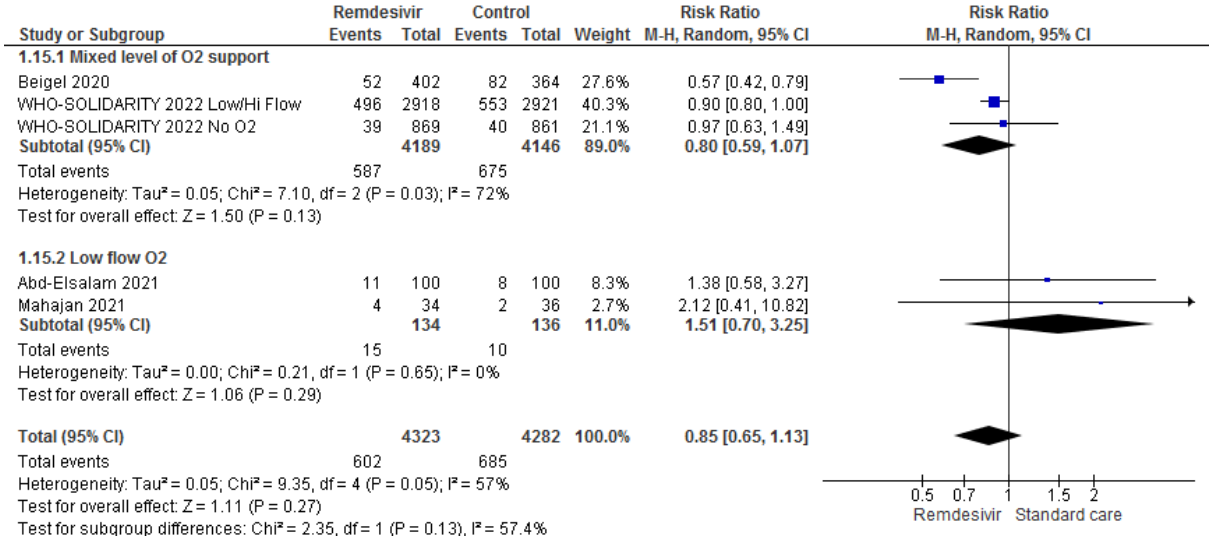
All-cause mortality (High flow oxygen, NIV or IMV at baseline



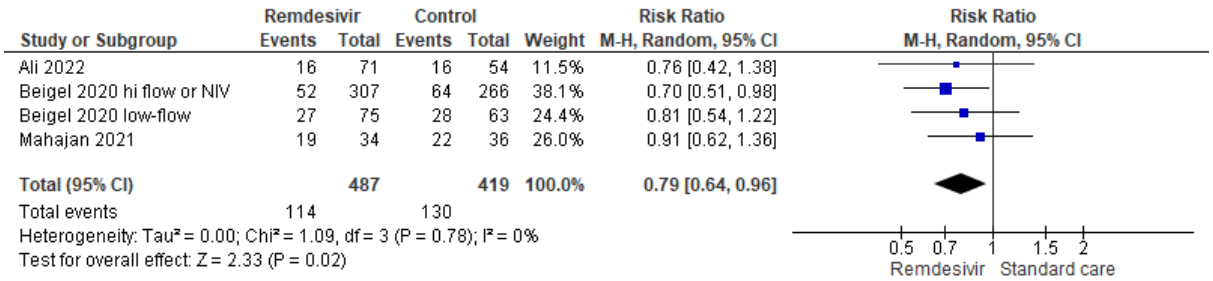
All-cause mortality (Low flow oxygen at baseline)



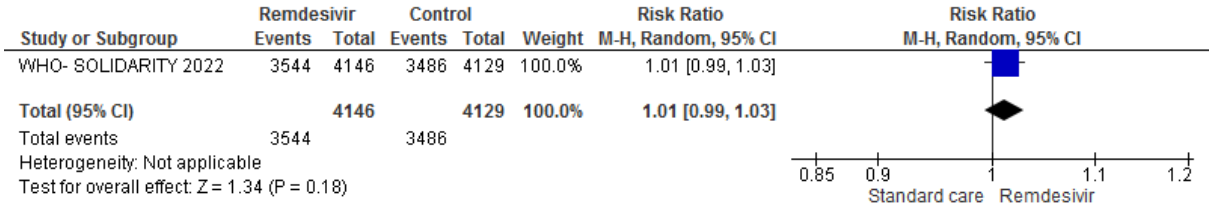
Need for invasive mechanical ventilation or ECMO



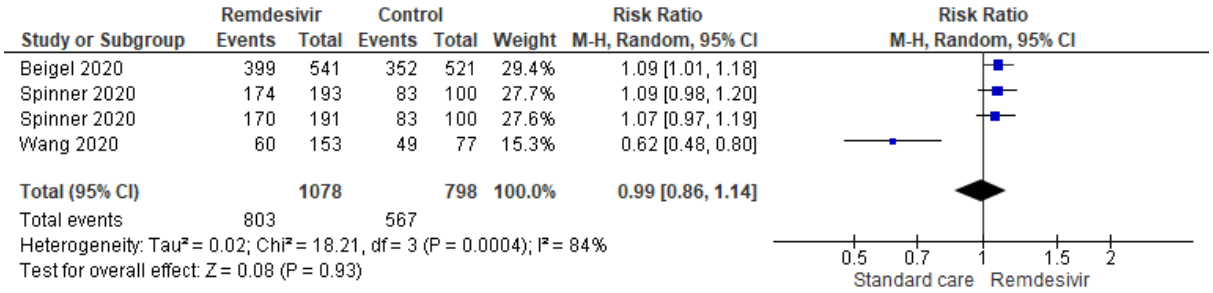
Need for oxygen supplementation



Discharge from hospital

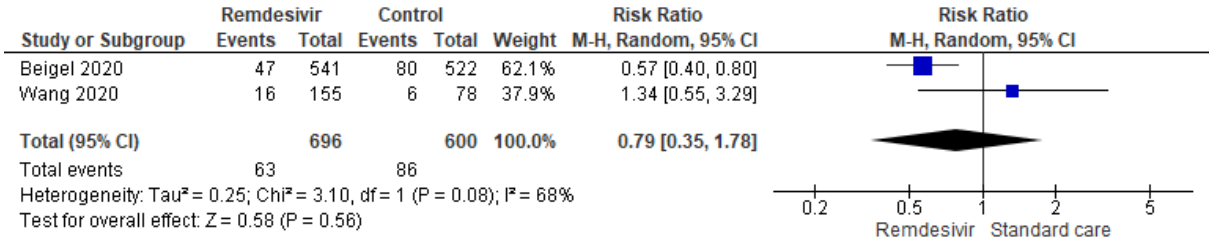


Clinical recovery by day 28

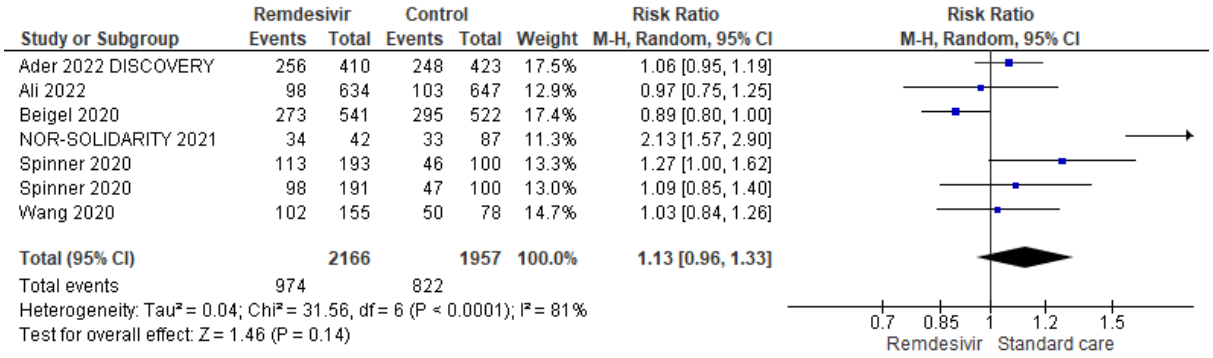


Note: the RR for clinical recovery by day 28 in the Spinner 2020 study is 1.09 [CI 95% 0.98, 1.20] for patients who were treated with remdesivir for 10 days, and 1.07 [CI 95% 0.97, 1.19] among patients treated with remdesivir for 5 days.

Respiratory failure or ARDS

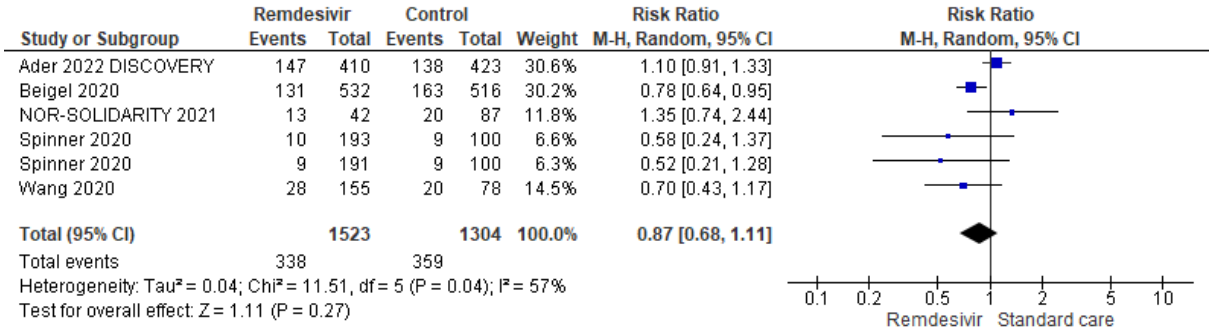


Adverse events



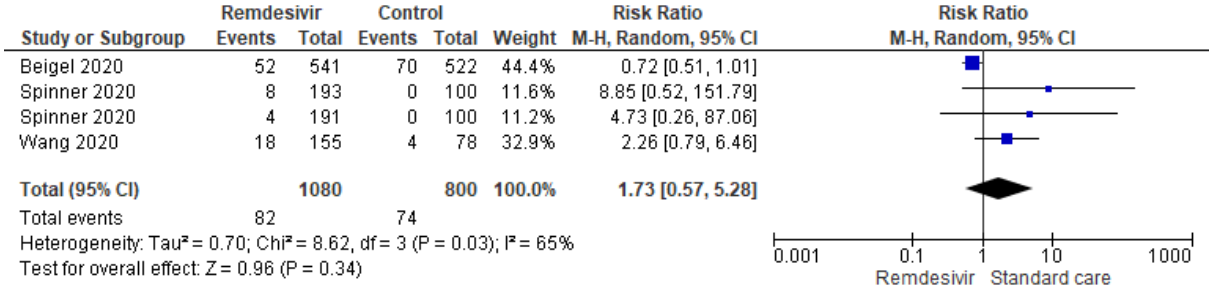
Note: the RR for adverse events in the Spinner 2020 study is 1.27 [CI 95% 1.00, 1.62] for patients who were treated with remdesivir for 10 days, and 1.09 [CI 95% 0.85, 1.40] among patients treated with remdesivir for 5 days.

Serious adverse events



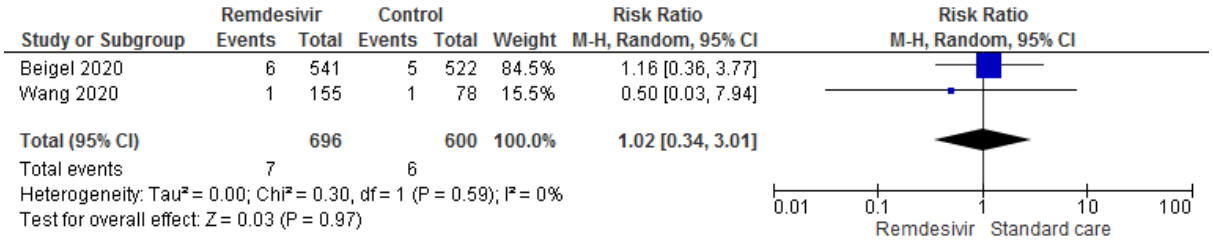
Note: the RR for serious adverse events in the Spinner 2020 study is 0.58 [CI 95% 0.24, 1.37] for patients who were treated with remdesivir for 10 days, and 0.52 [CI 95% 0.21, 1.28] among patients treated with remdesivir for 5 days.

Discontinuation due to adverse events

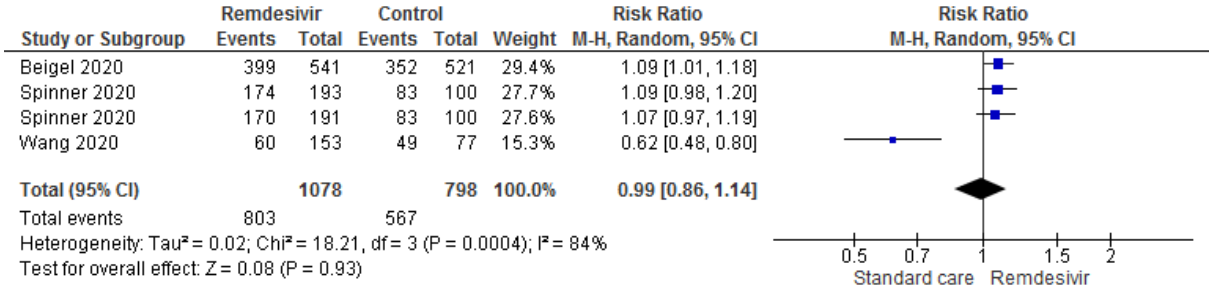


Note: the RR for discontinuation due to adverse events in the Spinner 2020 study is 8.85 [CI 95% 0.52, 151.79] for patients who were treated with remdesivir for 10 days, and 4.73 [CI 95% 0.26, 87.06] among patients treated with remdesivir for 5 days.

Septic shock

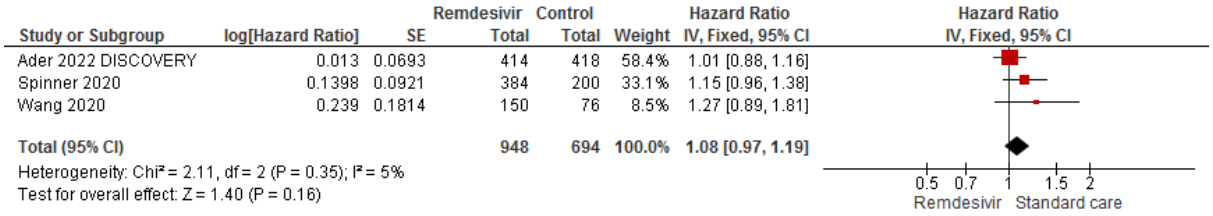


Clinical Recovery (by day 28)

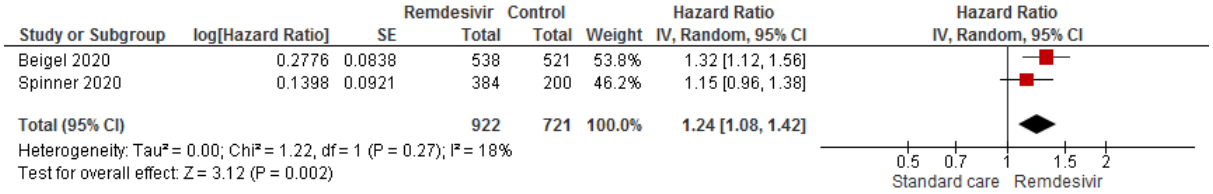


Note: the RR for clinical recovery by day 28 in the Spinner 2020 study is 1.09 [CI 95% 0.98, 1.20] for patients who were treated with remdesivir for 10 days, and 1.07 [CI 95% 0.97, 1.19] among patients treated with remdesivir for 5 days.

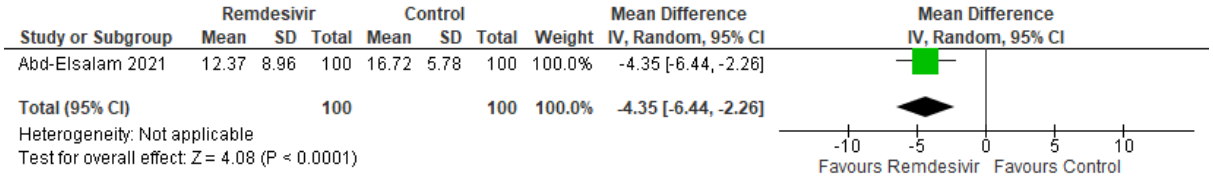
Time to improvement (2 points on scale)



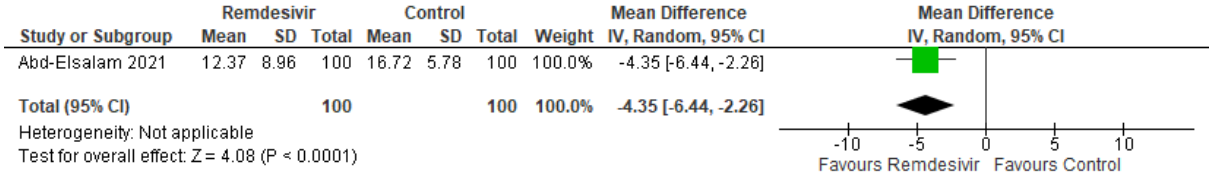
Time to recovery



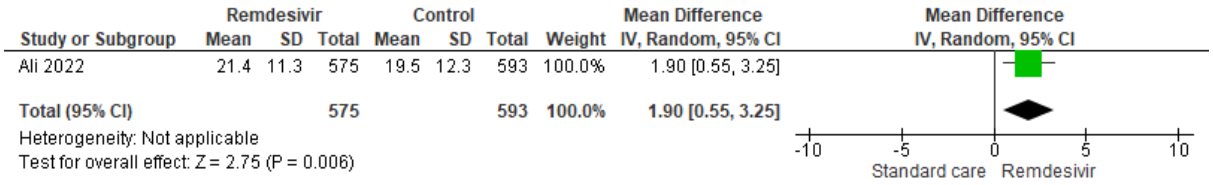
Duration of hospital stay



Oxygen-free days by day 28



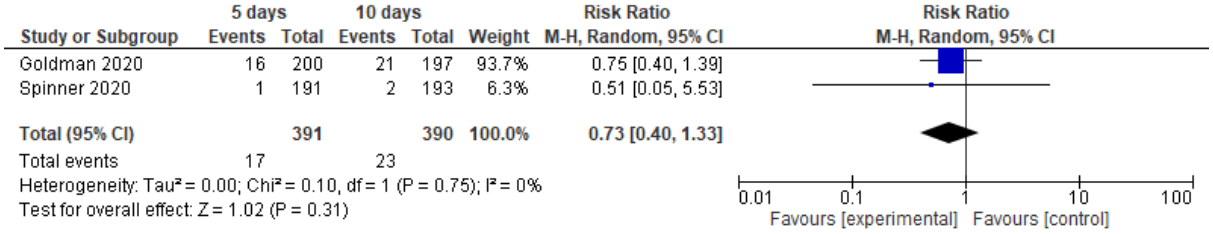
Ventilator-free days by day 28



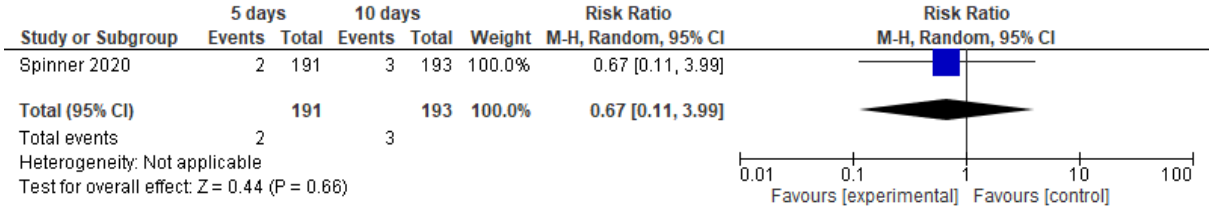
Comparison 2: Remdesivir for 5 days vs remdesivir for 10 days

Note that the below analyses have not been updated in this review

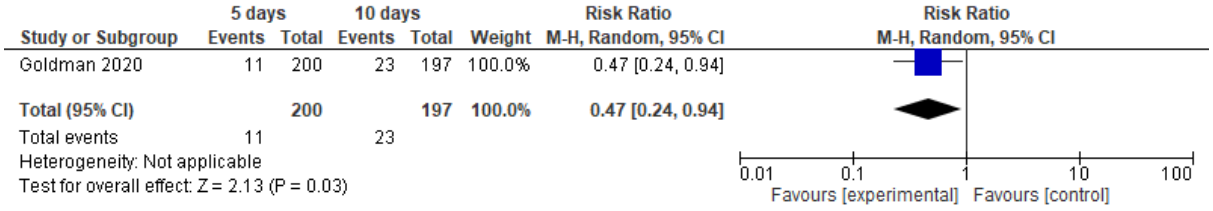
All-cause mortality (day 14)



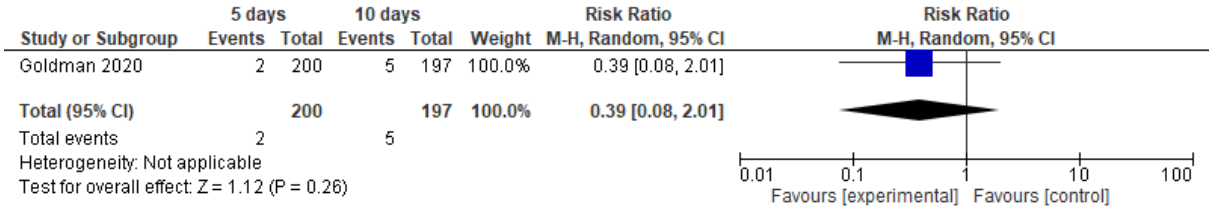
All-cause mortality (day 28)



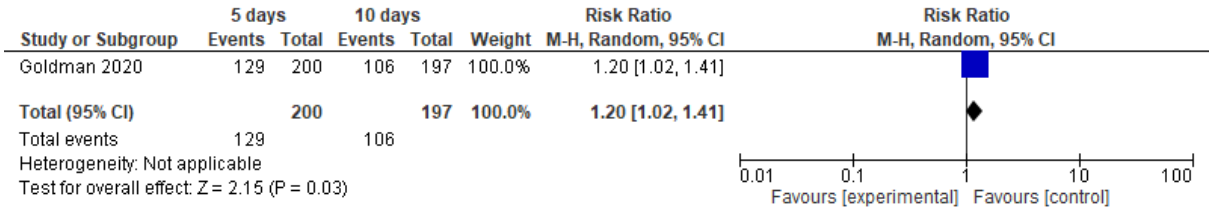
Acute respiratory failure or ARDS



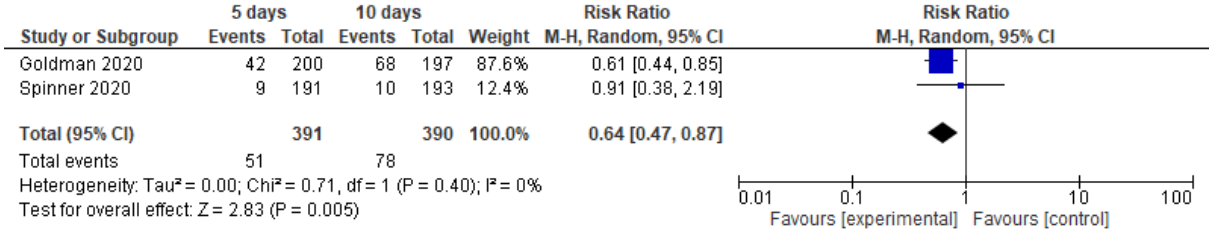
Septic shock



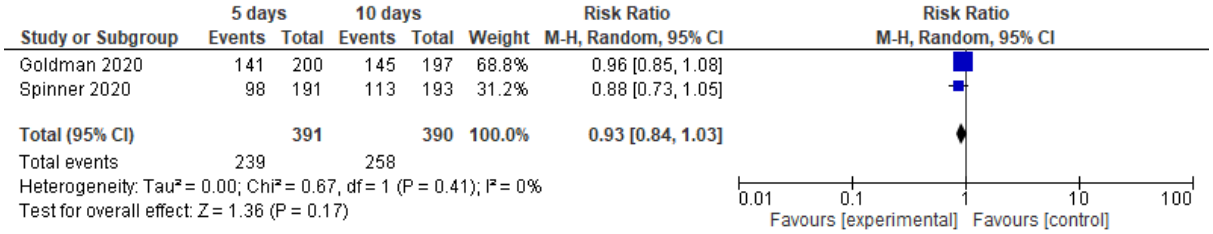
Clinical recovery (days 14)



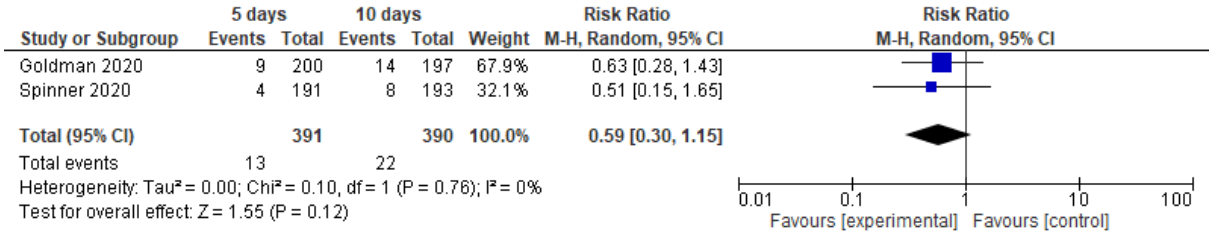
Serious adverse events



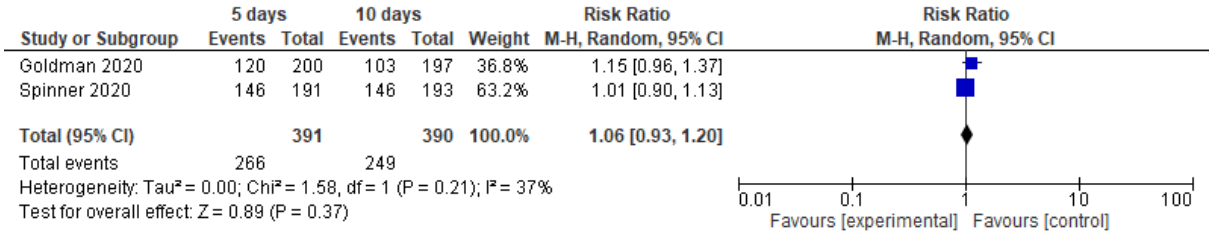
Adverse events



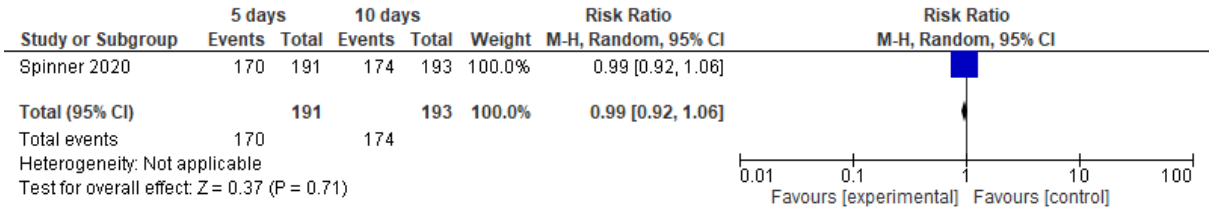
Discontinued due to adverse event



Discharged from hospital (day 14)



Discharged from hospital (day 28)



Appendix H: Studies overlapping with WHO-SOLIDARITY 2022

Study: Ader 2022 [DisCoVeRy]

Outcome: Mortality

Subgroup: Patients receiving no or low-flow oxygen at baseline [moderate COVID-19]

	Total No. RDV	Total No. Control	No. of events RDV	No. of events Control	RR
Published study data	253	251	15	15	-
Data extracted from Lee 2022 (excluding patients included in WHO-SOLIDARITY)	112	111	4	9	0.44 (0.14, 1.39)
Difference (Presumed overlap of study data with WHO-SOLIDARITY)	141	140	11	6	-

Study: Ader 2022 [DisCoVeRy]

Outcome: Mortality

Subgroup: Patients receiving IMV at baseline [Severe COVID-19]

	Total No. RDV	Total No. Control	No. of Events RDV	No. of Events Control	RR
Published Study data	161	167	19	22	-
Data extracted from Lee 2022 (excluding patients included in WHO-SOLIDARITY)	83	86	12	11	1.13 (0.53, 2.42)
Difference (Presumed overlap of study data with WHO-SOLIDARITY)	78	81	7	11	-

Study: Ali 2022 [CATCO]

Outcome: Mortality

Subgroup: Patients not receiving oxygen at baseline

	Total No. RDV	Total No. Control	No. of events RDV	No. of events Control	RR
Published study data	68	54	7	8	-
Data extracted from Lee 2022 (excluding patients included in WHO-SOLIDARITY)	59	42	5	7	0.51 (0.17, 1.49)
Difference (Presumed overlap of study data with WHO-SOLIDARITY)	9	12	2	1	-

Study: Ali 2022 [CATCO]

Outcome: Mortality

Subgroup: Patients receiving high or low-flow oxygen at baseline [oxygen therapy, high-flow nasal cannula, NIV]

	Total No. RDV	Total No. Control	No. of events RDV	No. of events Control	RR
Published study data	531	536	91	116	-
Data extracted from Lee 2022 (excluding patients included in WHO-SOLIDARITY)	468	498	85	110	0.82 (0.64, 1.06)
Difference (Presumed overlap of study data with WHO-SOLIDARITY)	63	38	6	6	-

Study: Ali 2022 [CATCO]

Outcome: Mortality

Subgroup: Patients receiving IMV at baseline

	Total No. RDV	Total No. Control	No. of events RDV	No. of events Control	RR
Published study data	56	52	19	21	-
Data extracted from Lee 2022 (excluding patients included in WHO-SOLIDARITY)	52	42	19	16	0.96 (0.57, 1.62)
Difference (Presumed overlap of study data with WHO-SOLIDARITY)	4	10	0	5	-

Appendix I: GRADE profiles

Remdesivir compared to placebo or standard care for COVID-19 in hospitalised people

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With placebo or standard care	With remdesivir	Relative effect (95% CI)	Risk with placebo or standard care	Risk difference with remdesivir
All-cause mortality (day 28; No oxygen or low flow oxygen)											
10483 (8 RCTs)	serious[a]	not serious	not serious[b]	not serious	none	Moderate	684/5103 (13.4%)	587/5380 (10.9%)	**RR 0.81** (0.68 to 0.96)	134 per 1,000	**25 fewer per 1,000** (from 43 fewer to 5 fewer)
All-cause mortality (day 28; High flow O2, NIV or IMV)											
1486 (6 RCTs)	serious[a]	not serious	not serious[b]	serious[c]	none	Low	213/737 (28.9%)	240/749 (32.0%)	**RR 1.08** (0.93 to 1.25)	289 per 1,000	**23 more per 1,000** (from 20 fewer to 72 more)
Need for new mechanical ventilation or ECMO											
8605 (4 RCTs)	serious[d]	not serious	not serious[b]	not serious	none	Moderate	685/4282 (16.0%)	602/4323 (13.9%)	**RR 0.85** (0.65 to 1.13)	160 per 1,000	**24 fewer per 1,000** (from 56 fewer to 21 more)
Serious adverse events											
2827 (5 RCTs)	serious[e]	serious[f]	not serious[b]	serious[c]	none	Very low	359/1304 (27.5%)	338/1523 (22.2%)	**RR 0.87** (0.68 to 1.11)	275 per 1,000	**36 fewer per 1,000** (from 88 fewer to 30 more)
Respiratory failure or ARDS											

Certainty assessment							Summary of findings				
1296 (2 RCTs)	not serious	serious[g]	not serious	serious[c]	none	Low	86/600 (14.3%)	63/696 (9.1%)	**RR 0.79** (0.35 to 1.78)	143 per 1,000	**30 fewer per 1,000** (from 93 fewer to 112 more)
Septic shock											
1296 (2 RCTs)	serious[e]	serious[f]	not serious	serious[c]	none	Very low	6/600 (1.0%)	7/696 (1.0%)	**RR 1.02** (0.34 to 3.01)	10 per 1,000	**0 fewer per 1,000** (from 7 fewer to 20 more)
Clinical recovery (day 28)											
1876 (3 RCTs)	serious[e]	serious[h]	not serious	serious[c]	none	Very low	567/798 (71.1%)	803/1078 (74.5%)	**RR 0.99** (0.86 to 1.14)	711 per 1,000	**7 fewer per 1,000** (from 99 fewer to 99 more)
Adverse events											
4123 (6 RCTs)	serious[e]	serious[i]	not serious[b]	serious[c]	none	Very low	822/1957 (42.0%)	974/2166 (45.0%)	**RR 1.13** (0.96 to 1.33)	420 per 1,000	**55 more per 1,000** (from 17 fewer to 139 more)
Time to improvement											
(3 RCTs)	serious[e]	not serious	not serious	serious[c]	none	Low			**HR 1.08** (0.97 to 1.19)	-	-
Discontinuation due to adverse events											
1880 (3 RCTs)	serious[e]	serious[g]	not serious	serious[c]	none	Very low	74/800 (9.3%)	82/1080 (7.6%)	**RR 1.73** (0.57 to 5.28)	93 per 1,000	**68 more per 1,000** (from 40 fewer to 396 more)
Discharge from hospital											
8275 (1 RCT)	serious[e]	not serious	not serious[b]	serious[c]	none	Low	3486/4129 (84.4%)	3544/4146 (85.5%)	**RR 1.01** (0.99 to 1.03)	844 per 1,000	**8 more per 1,000** (from 8 fewer to 25 more)

Certainty assessment							Summary of findings				
Time to recovery											
(2 RCTs)	serious[e]	not serious	not serious	not serious	none	Moderate	-	-	**HR 1.24** (1.08 to 1.42)	-	-
Duration of hospital stay											
200 (1 RCT)	serious[j]	not serious	serious[k]	serious[l]	none	Very low	100	100	-	The mean duration of hospital stay was 0	MD 4.35 lower (6.44 lower to 2.26 lower)
Oxygen free days at day 28											
1168 (1 RCT)	very serious[m]	not serious	not serious[b]	not serious	none	Low	593	575	-	The mean oxygen free days at day 28 was 0	MD 1.7 higher (0.46 higher to 2.94 higher)
Ventilator free days at day 28											
1168 (1 RCT)	very serious[m]	not serious	not serious[b]	not serious	none	Low	593	575	-	The mean ventilator free days at day 28 was 0	MD 1.9 higher (0.55 higher to 3.25 higher)

CI: confidence interval; **HR:** hazard ratio; **MD:** mean difference; **RR:** risk ratio

Explanations

a. Incomplete information to understand the overlap between studies
b. To note that these studies were conducted before vaccination for COVID-19 was rolled out
c. 95% CI crosses the line of no effect
d. Missing data in two studies. One study has a deviation from intended intervention for one participant.
e. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias
f. The magnitude of statistical heterogeneity was high, with I^2: 50%. May also be considered clinically heterogenous due to baseline severity differences.
g. The direction of the effect is not consistent between the included studies
h. The confidence interval of some of the studies do not overlap with those of most included studies/ the point estimate of some of the included studies.
i. The magnitude of statistical heterogeneity was high, with I^2: 81%.
j. Potential selective reporting

k. Corticosteroids were not included in standard care
l. n<300
m. Missing data unaccounted for; open label study and subjective outcome

Remdesivir for 5 days compared to remdesivir for 10 days for COVID-19 in hospital

Certainty assessment							Summary of findings				
							Study event rates (%)			Anticipated absolute effects	
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	With remdesivir for 10 days	With remdesivir for 5 days	Relative effect (95% CI)	Risk with remdesivir for 10 days	Risk difference with remdesivir for 5 days
All cause mortality (day 14)											
781 (2 RCTs)	not serious	not serious	not serious	serious[a]	none	Moderate	23/390 (5.9%)	17/391 (4.3%)	**RR 0.73** (0.40 to 1.33)	59 per 1,000	**16 fewer per 1,000** (from 35 fewer to 19 more)
All cause mortality (day 28)											
384 (1 RCT)	not serious	not serious	not serious	very serious[b]	none	Low	3/193 (1.6%)	2/191 (1.0%)	**RR 0.67** (0.11 to 3.99)	16 per 1,000	**5 fewer per 1,000** (from 14 fewer to 46 more)
Serious adverse events											
781 (2 RCTs)	serious[c]	not serious	not serious	not serious	none	Moderate	78/390 (20.0%)	51/391 (13.0%)	**RR 0.64** (0.47 to 0.87)	200 per 1,000	**72 fewer per 1,000** (from 106 fewer to 26 fewer)
Acute respiratory failure or ARDS											
397 (1 RCT)	not serious	not serious	not serious	very serious[b]	none	Low	23/197 (11.7%)	11/200 (5.5%)	**RR 0.47** (0.24 to 0.94)	117 per 1,000	**62 fewer per 1,000** (from 89 fewer to 7 fewer)
Septic shock											

Certainty assessment							Summary of findings				
397 (1 RCT)	serious[c]	not serious	not serious	very serious[b]	none	Very low	5/197 (2.5%)	2/200 (1.0%)	**RR 0.39** (0.08 to 2.01)	25 per 1,000	**15 fewer per 1,000** (from 23 fewer to 26 more)
Clinical recovery (day 14)											
397 (1 RCT)	serious[c]	not serious	not serious	serious[d]	none	Low	106/197 (53.8%)	129/200 (64.5%)	**RR 1.20** (1.02 to 1.41)	538 per 1,000	**108 more per 1,000** (from 11 more to 221 more)
Adverse events											
781 (2 RCTs)	serious[c]	not serious	not serious	not serious	none	Moderate	258/390 (66.2%)	239/391 (61.1%)	**RR 0.93** (0.84 to 1.03)	662 per 1,000	**46 fewer per 1,000** (from 106 fewer to 20 more)
Discontinued due to adverse event											
781 (2 RCTs)	serious[c]	not serious	not serious	serious[a]	none	Low	22/390 (5.6%)	13/391 (3.3%)	**RR 0.59** (0.30 to 1.15)	56 per 1,000	**23 fewer per 1,000** (from 39 fewer to 8 more)
Discharged from hospital (day 14)											
781 (2 RCTs)	serious[c]	not serious	not serious	not serious	none	Moderate	249/390 (63.8%)	266/391 (68.0%)	**RR 1.06** (0.93 to 1.20)	638 per 1,000	**38 more per 1,000** (from 45 fewer to 128 more)
Discharged from hospital (day 28)											
384 (1 RCT)	not serious	not serious	not serious	very serious[b]	none	Low	174/193 (90.2%)	170/191 (89.0%)	**RR 0.99** (0.92 to 1.06)	902 per 1,000	**9 fewer per 1,000** (from 72 fewer to 54 more)

CI: confidence interval; **RR:** risk ratio

Explanations

a. due to few events
b. Low number of patients, Only data from one study
c. Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias
d. Only data from one study