CoLab Network

Remdesivir for the Treatment of COVID-19 in the Inpatient Setting

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Key Messages

Remdesivir is fully or conditionally accepted to treat COVID-19 in many places around the world, including Canada.

We reviewed the current evidence on the potential benefits and harms of using remdesivir to treat COVID-19 in hospitalized patients in settings similar to Canada. We included 7 randomized controlled trials, with 4 studies being included in the WHO Solidarity trial. We conducted a separate analysis of the WHO Solidarity trial.

The pooled results from 3 studies suggest that remdesivir significantly reduces the need for mechanical ventilation compared to standard of care.

Findings suggest remdesivir may significantly reduce the need for intubation, but interpretation is limited as it was only reported in 1 study.

Findings suggest that remdesivir does not significantly reduce intensive care unit admissions, length of intensive care unit stay, or time to ventilation. Its impact on length of hospitalization, time to clinical improvement, and progression to high-flow oxygen is inconsistent.

The pooled results from 6 studies suggest that remdesivir significantly reduces the risk of death compared to standard of care. Alone, each individual randomized controlled trial showed no significant difference.

The incidence of serious adverse events and grade 3 or 4 adverse events does not appear to differ between remdesivir and standard of care. There are insufficient data to draw any conclusions on withdrawals due to adverse events and specific serious adverse events, including acute kidney injury, acute liver injury, and thrombocytopenia.

The studies were conducted before the emergence of the Omicron and Delta variants and before widespread vaccination. This may not fit well with the current epidemiology in Canada.

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Stakeholders:
One clinician with content expertise provided comments on this report.

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Abbreviations

AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ART	antiretroviral therapy
AST	aspartate aminotransferase
BMI	body mass index
CI	confidence interval
ECMO	extracorporeal membrane oxygen
ER	emergency room
HCQ	hydroxychloroquine
HR	hazard ratio
ICU	intensive care unit
INR	international normalized ratio
IQR	interquartile range
ITT	intention to treat
mITT	modified intention to treat
NCT	national clinical trial
NIPPV	noninvasive positive-pressure ventilation
NR	not reported
PHAC	Public Health Agency of Canada
PICOS	Population, Intervention, Comparator, Outcome, Study Design
PRESS	Peer Review of Electronic Search Strategies
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
REM	remdesivir
RIS	Research Information Services
ROB	risk of bias
RR	relative risk
RD	risk difference
SoC	standard of care

SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
VV-ECMO	venovenous extracorporeal membrane oxygenation
WDAE	withdrawal due to adverse event

Introduction and Rationale

Background and Rationale

Several drug treatments for COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are approved for use in Canada. Currently, the federal government, through the Public Health Agency of Canada (PHAC), is responsible for the procurement and allocation of the following drugs for COVID-19 that are in demand by federal, provincial, and territorial health care systems: nirmatrelvir-ritonavir (Paxlovid), remdesivir (Veklury), and tocilizumab (Actemra).

There is a need to gather postmarket drug information and evidence to explore options for procurement, allocation, and equitable distribution of COVID-19 drugs to facilitate future discussions regarding access to these drugs within Canadian health care systems. This report focuses on remdesivir (Veklury) for COVID-19 inpatient treatment. Table 1 outlines the approved indications for remdesivir in Canada.

CADTH conducted an evidence review on remdesivir for inpatient use, with a first publication in May 14, 2020, and updated in February 2021; refer to Remdesivir: Evidence Review and Appraisal (cadth.ca). The previous CADTH review included randomized controlled trials (RCTs) based on broad inclusion criteria in an era when the epidemiology and characteristics of COVID-19 were still not fully understood. It noted uncertainty in the benefits and harms of remdesivir for important outcomes such as mortality, and showed no differences between remdesivir and standard of care (SoC) for any outcomes in the interim analysis of the WHO Solidarity trial. In addition, at least 10 RCTs were ongoing at the time of this review. The current review provides more focused inclusion criteria and updated information.

Rationale
PHAC currently sources and distributes COVID-19 drugs for Canada's health care systems. Gathering postmarket evidence on their safety and efficacy is important to help determine fair access in the future.

Table 1

Approved Indications for Remdesivir (Veklury)

Approved use	Presentation and manufacturer	Administration
Remdesivir (Veklury)[a]		
For the treatment of COVID-19 in: • hospitalized adults and pediatric patients (at least 4 weeks of age and weighing at least 3 kg) with pneumonia requiring supplemental oxygen • nonhospitalized adults and pediatric patients (weighing at least 40 kg) with positive results of direct SARS-CoV-2 viral testing, and who are at high risk for progression to severe COVID-19, including hospitalization and death.	Powder for solution for infusion, 100 mg/vial (5 mg/mL when reconstituted) Gilead Sciences Canada, Inc.	Day 1: Single loading dose of 200 mg IV Day 2 onward: 100 mg given once daily IV • For hospitalized adults and adolescents with pneumonia requiring supplemental oxygen: The total duration of treatment should be at least 5 days and not more than 10 days. • For nonhospitalized adults who are at increased risk of progressing to severe COVID-19: Treatment should be initiated as soon as possible after diagnosis of symptomatic COVID-19 has been made, and within 7 days of symptom onset. The total duration of treatment should be 3 days.

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

[a] Source: Product monograph for Veklury, dated June 13, 2023.

Objectives

The objective is to evaluate the efficacy and safety of remdesivir for the treatment of COVID-19 in hospitalized adults and adolescents (inpatients).

Policy Questions

1. What new evidence on the effectiveness and safety of remdesivir in hospitalized patients is available since the publication of the previous CADTH report?
2. Which hospitalized patients are most likely to benefit from treatment with remdesivir?

Research Questions

This clinical review will address the previously cited policy questions by exploring the following research questions:

1. What is the efficacy of remdesivir in hospitalized patients with COVID-19?
2. What is the safety of remdesivir in hospitalized patients with COVID-19?
3. What are the characteristics of patients (e.g., comorbidities) associated with improved outcomes in the treatment of COVID-19 with remdesivir?
4. What are the characteristics of patients (e.g., comorbidities) that are associated with risk of adverse outcomes when treated with remdesivir?

Methods

Methods
We used a rapid systematic review approach, looking at randomized controlled trials. We selected studies for inclusion using criteria from the PICOS framework.

The research questions were addressed using a rapid systematic review approach. The review broadly followed the methods of the Cochrane Handbook for Systematic Reviews for Interventions[1] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist for systematic reviews.[2]

Literature Search Methods

An information specialist developed and conducted a literature search for clinical studies, using a peer-reviewed search strategy according to CADTH's PRESS Peer Review of Electronic Search Strategies checklist. The complete search strategy is presented in Appendix 1, which includes the syntax guide (Table 16).

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. The Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in EndNote. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the Population, Intervention, Comparator, Outcome, and Study Design (PICOS) framework and research questions. The main search concept was remdesivir. The US National Institutes of Health's ClinicalTrials.gov trials registry was also searched.

CADTH-developed search filters were applied to limit retrieval to RCTs or controlled clinical trials. Retrieval was not limited by publication date but was limited to the English or French language. Conference abstracts were excluded from the search results.

The initial search was completed on May 1, 2023. Regular alerts updated the database literature searches until June 19, 2023.

Eligibility Criteria

Studies that met the PICOS criteria were selected for inclusion (Table 2).

Table 2

Selection Criteria

Criteria	Description
Populations	Hospitalized adults and adolescents (aged 12 years to less than 18 years who weigh at least 40 kg) with COVID-19
Interventions	Remdesivir in addition to usual care (e.g., steroids, antibiotics, diuretics, oseltamivir)
Comparators	• Tocilizumab • Dexamethasone • Baricitinib • Usual care (e.g., steroids, antibiotics, diuretics, oseltamivir) • Placebo
Outcomes	Efficacy: • duration of hospitalization • ICU admission • length of ICU stay • progression to high-flow oxygen or NIPPV • progression to mechanical ventilation (invasive mechanical ventilation or ECMO/VV-ECMO) • need for intubation • time to clinical improvement (28 days) • time to progression to severe disease • time to receipt of mechanical ventilation Safety: • death (including survival, all-cause mortality) • SAEs • WDAEs • SAE – thrombocytopenia (low platelets) • SAE – acute liver injury • SAE – acute kidney injury

Criteria	Description
Study designs	Completed phase II or III RCTs or higher Exclusions: Nonrandomized studies, protocols for studies in progress or without results, terminated studies, registered studies in progress, editorials, letters, commentaries, conference abstracts, presentations, theses, preprints, duplicate studies, and studies not reported in English or French
Setting[a]	Studies with a similar health care system to Canada: Australia, Greece, Italy, Nordic countries (Denmark, Norway, Finland, Iceland, Sweden), Japan, Netherlands, New Zealand, Portugal, Spain, UK, US

ECMO = extracorporeal membrane oxygenation; ICU = intensive care unit; NIPPV = noninvasive positive-pressure ventilation; PHAC = Public Health Agency of Canada; RCT = randomized controlled trial; VV-ECMO = venovenous extracorporeal membrane oxygenation; WDAE = withdrawal due to adverse event.

[a] PHAC indicated preference for results from countries with similar health care systems and context for comparability, in particular countries with a decommodified health care system. Other countries included were high-income countries in the Organization for Economic Cooperation and Development (i.e., US, UK, Australia).

Population and Subgroups

Hospitalized adults and adolescents (aged 12 years to younger than 18 years, weighing at least 40 kg) with COVID-19 were included. Subgroups of interest were:

- patients who were immunocompromised
- patients by differing vaccination status
- patients by differing number of comorbidities
- Indigenous Peoples
- patients in underserved or equity-deserving groups (those who are unhoused, those with lower levels of education or income, rural and remote populations or those living in geographically disparate settings, racialized groups, and those who are refugees or new immigrants).

RCTs that enrolled mixed populations of both eligible and ineligible patients were included if separate data for the eligible population were reported, or if eligible patients accounted for at least 80% of the study population.

Intervention and Comparators

We included only RCTs in which remdesivir, in addition to usual care, was compared with any of the treatments listed below. We excluded studies in which remdesivir was given as background treatment and we could not separate out its effects. Some RCTs, for example, used remdesivir as part of the standard of care (SoC) for all patients along with other treatments such as supplemental oxygen, antibiotics, vasopressor support, peritoneal dialysis or hemodialysis, intravenous fluids, convalescent plasma, and dexamethasone. Comparators that were considered relevant for this review were:

- tocilizumab
- dexamethasone
- baricitinib
- usual care (e.g., steroids, antibiotics, diuretics, oseltamivir)
- placebo.

Outcomes Definition

For efficacy, we were interested in the following outcomes:

- duration of hospitalization
- intensive care unit (ICU) admission
- length of ICU stay
- progression to high-flow oxygen or noninvasive positive-pressure ventilation (NIPPV)
- progression to mechanical ventilation (invasive mechanical ventilation, or extracorporeal membrane oxygenation or venovenous extracorporeal membrane oxygenation [ECMO/VV-ECMO])
    - Generally, ECMO/VV-ECMO would be considered as a separate entity from mechanical ventilation. These outcomes were combined because ECMO is a relatively rare outcome, and reports often group mechanical ventilation and ECMO together.
- need for intubation
- time to clinical improvement (28 days)

- time to progression to severe disease
- time to receipt of mechanical ventilation.

For safety, we were interested in following outcomes:

- death (including survival and all-cause mortality)
- serious adverse events (SAEs)
- withdrawals due to adverse events (WDAEs)
- SAE – thrombocytopenia: a normal platelet count in adults ranges from 150,000 to 450,000 platelets per microlitre of blood; the severity of the thrombocytopenia is separated into mild (platelet counts between 101,000 and 140,000 per microlitre of blood), moderate (platelet counts between 51,000 and 100,000 per microlitre of blood), or severe (platelet counts between 51,000 and 21,000 per microlitre of blood)[3]
- SAE – acute liver injury: acute injury could be a named event or SAE, or some study-reported parameter involving alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), international normalized ratio (INR), total protein, or albumin
- SAE – acute kidney injury: for acute kidney (renal) injury, we extracted both what was reported as acute kidney injury, as well as creatinine clearance or definitions of injury. Creatinine clearance is often measured as millilitres per minute (mL/min) or millilitres per second (mL/s). Normal values are 97 mL/min to 137 mL/min (1.65 mL/s to 2.33 mL/s) for males and 88 mL/min to 128 mL/min (1.496 mL/s to 2.18 mL/s) for females.

Study Designs

Published randomized controlled studies that meet the previously described PICOS criteria were eligible for inclusion.

Study Selection Process

First, 2 independent reviewers applied the eligibility criteria to each title and abstract record identified in the literature search. All record conflicts were resolved through discussion and referring to a third reviewer. Then, at the second level eligibility screen, the eligibility criteria were applied to the full-text records by both reviewers independently, and a final decision about eligibility was made following the same consensus process used for the first level eligibility screen. The reviewers were not blinded to study authors or centre of publication prior to study selection. Study screening and assessment of eligibility were facilitated and standardized using the DistillerSR (Evidence Partners) software.

Quality Assessment

We applied the Cochrane Collaboration's Risk of Bias (ROB) tool (ROB version 1.0) to each of the included RCTs that reported at least one outcome of interest.[4] The ROB tool addresses 6 specific domains: sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other issues.

Each domain includes 1 or more specific entries in an ROB table, and a form was created in alignment with the Cochrane Collaboration's ROB template. The first part of the form involves describing what was reported to have happened in the study; the second part involves assigning a judgment relating to the ROB for that entry by answering a prespecified question about the adequacy of the study in relation to the entry, including a judgment of low, high, or unclear ROB.

For each unique RCT, we assessed the quality of the original primary publication with additional details sought from supporting literature (e.g., published protocol, ClinicalTrials.gov records), if necessary. Assessments were performed by 1 reviewer and verified by a second reviewer. Disagreements were resolved by consensus.

Publication bias was not assessed.

Clinical heterogeneity was assessed across studies by documenting and reviewing the following: variation in characteristics of study patients by type or severity of condition, demographics, and setting; variation in interventions in implementation (e.g., dose or intensity), components included, experience of practitioners, and nature of control (placebo, none, SoC); and variation in outcomes by measurement methods, event definition, cut points, and follow-up duration.

Generalizability of the study findings to the Canadian setting was evaluated based on a review of key demographic and clinical variables of the included studies, including age, sex, race or ethnicity, comorbidities, vaccination status, and COVID-19 variant. To evaluate the generalizability of the study results to the Canadian health care system today, we followed and applied the 4-step process suggested by Atkins et al.[5] to assess the generalizability of studies. In particular, in a PICOS statement we identified the key study characteristics to consider that could be collected and interpreted.

Data Extraction

Data were extracted by 1 reviewer using piloted and standardized data abstraction forms, and the extracted data were checked for accuracy by a second reviewer. Any disagreements were resolved by consensus.

The original, primary publication for each included RCT was used for data extraction, with supplementary data obtained from companion reports and ClinicalTrials.gov records when necessary to address the research questions. In situations where multiple publications for a unique RCT were available (e.g., supplemental online appendices, companion publications of specific outcomes, or populations from the original study), the most recently adjudicated data for each outcome were extracted, with preference given to published records.

The following data were extracted: basic characteristics, including publication year, study design, registration number, countries, study delivery time, funding resources, and COVID-19 variant; patient information, including eligibility criteria, sample size, sex, age, race,

immunocompromised status, vaccination status, belonging to underserved or equity-deserving groups, comorbidities, and time from symptom onset to hospitalization or emergency room (ER) visit; intervention characteristics, including name, duration, detailed description, and co-intervention; and definitions and results on outcomes of interest as listed previously.

For outcomes with multiple follow-up points, we recorded all of the time points.

Data Analyses and Synthesis

A descriptive summary of study selection, quality assessment, and study and patient characteristics is presented for each included RCT that reported at least 1 outcome of interest.

We used a random-effects model to synthesize the data for outcomes measured in 2 or more studies using similar definitions, even when high heterogeneity was indicated by large I^2 values. This was because we expected that clinical heterogeneity across studies may exist, such as different study designs, severity of disease, comorbidities, settings, and co-interventions. Due to limited information, we were not able to conduct any subgroup analysis of interest. We used RevMan Web to complete all analyses. As described at the end of the Results section, we conducted a sensitivity analysis wherein the data contributed by 4 RCTs with overlapping participants with the WHO Solidarity trial was replaced with data from the WHO Solidarity trial.

Results of Clinical Evaluation

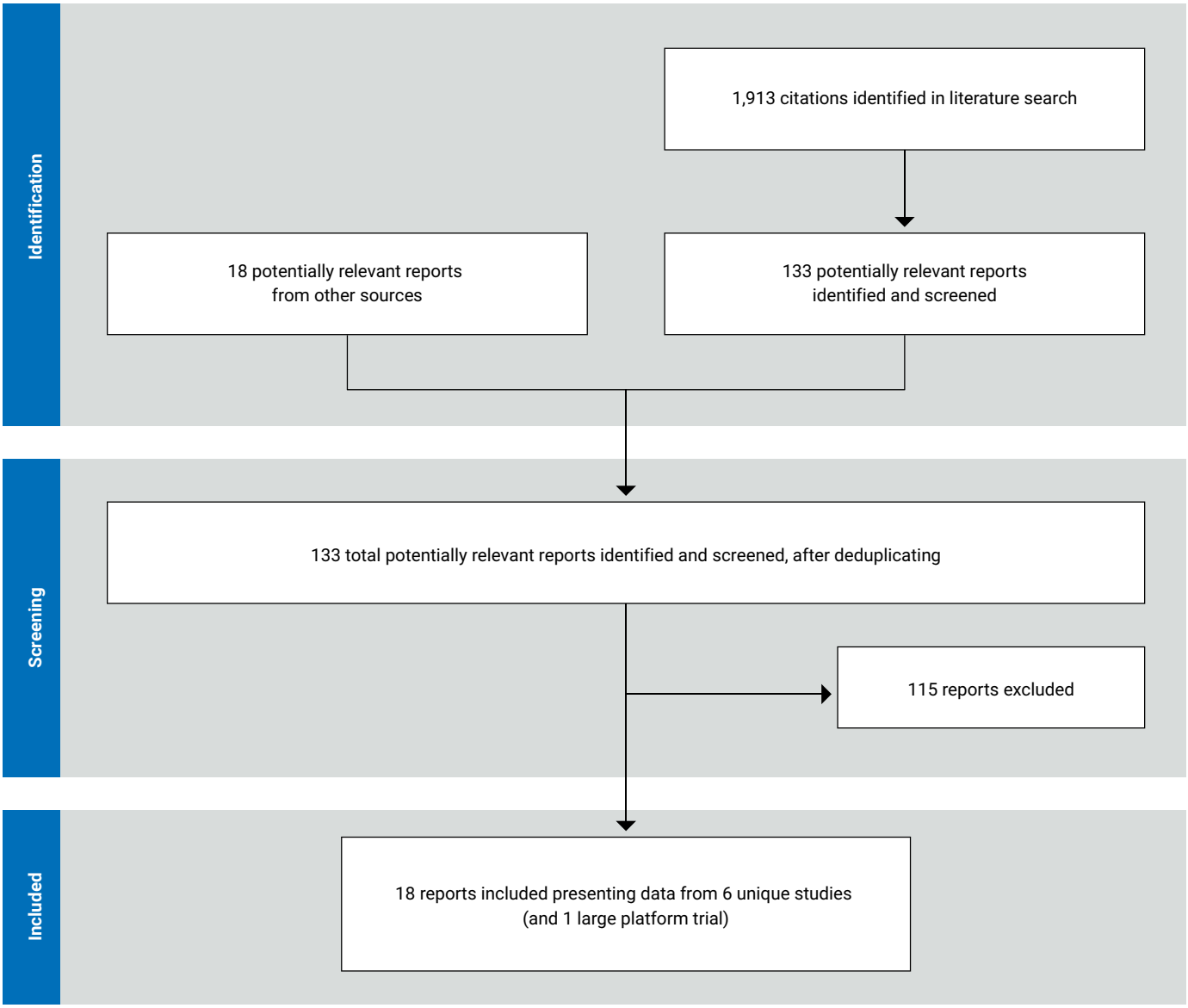
Selection of Primary Studies

Of the 1,913 citations identified in the literature search after removing duplicates, 133 reports were included for full-text screening. After retrieving and reviewing the full text against the eligibility criteria, 18 reports for 6 unique RCTs were included (Figure 1, Appendix 2). The 12 companion studies corresponding to each of the 6 unique RCTs are listed in Appendix 2, Table 17. The excluded studies are listed in Appendix 3, Table 18. It should be noted that the decision was made by CADTH to include the DisCoVeRy trial in the main analysis, as it was an add-on trial of the WHO Solidarity trial, although most patients were from France and only a few patients were from Portugal, the only country in the DisCoVeRy trial with a setting similar to the Canadian health care system.

Included Studies
Seven unique RCTs across 18 publications are included in the report. Each study compares remdesivir to the standard of care, with varying study designs and durations. We analyzed the WHO Solidarity trial separately.

Figure 1

PRISMA Flow Chart of Selected Reports



Study and Patient Characteristics of the Included Studies

The basic characteristics of the 6 included studies for this report are summarized in Table 3 and Table 4; we also provided more details of each study in Appendix 4 (Tables 19 to 24).

Four studies were 2-arm parallel study design trials comparing remdesivir (9 to 10 days) with SoC;[6-12] 1 was a 2-arm trial comparing remdesivir plus SoC versus placebo plus SoC,[13] and 1 was a 3-arm trial comparing remdesivir for 10 days and 5 days versus SoC.[14] All trials included adult patients and only 1 trial (Spinner, 2020[14]) included adolescent patients between the ages of 12 years and 18 years, weighing at least 40 kg. Five trials[6-9,12-14] considered short-term outcomes measured at 28 days or 29 days with additional follow-up measurements reported at 15 days in the ACTT-1 trial;[13] 11 days and 14 days in the GSD-US-540-5774 trial;[14] 2 days, 14 days, 21 days, and 60 days in the CATCO trial;[8] 7 days, 10 days, 14 days, 60 days, and 90 days in the NOR-Solidarity trial;[9] and 3 days, 5 days, 8 days, 11 days, 15 days, and 90 days in the DisCoVeRy trial.[12] Only 1 trial (SOLIDARITY Finland) was designed to capture long-term outcomes up to 1 year.[10]

None of the included trials reported information on any specific COVID-19 variant, but all of these trials were conducted pre-Omicron and pre-Delta. No study reported the exact variant among included patients, with only the CATCO trial indicating that recruitment extended well into Canada's third COVID-19 wave and the emergence of the Alpha variant.[8]

Regarding vaccination, only the DisCoVeRy trial[12] clearly reported that none of the patients had received a vaccine. However, based on the last recruitment dates among the other included studies, we may infer that all were conducted before noted waves of Omicron and Delta and before the widespread availability of vaccination.[15]

Key Point
The included studies were conducted before the emergence of the Omicron and Delta variants and before widespread vaccination. This may not fit well with the current epidemiology in Canada.

For the trial setting, 3 studies involved a single country, namely, Canada,[8] Norway,[9] and Finland,[10] and the latter 2 countries have a health care system similar to the system in Canada. Three studies involved multiple countries, 2 of which included a large proportion of patients from countries with a health care system like the system in Canada. The other study, the DisCoVeRy trial,[12] included patients from France, Belgium, Austria, Portugal, and Luxembourg, with only 36 of the 857 patients randomized being from Portugal, the only country listed in the PICOS framework (Table 2) as having a similar health care system to that of Canada.

Patients in 4 of the included trials either partially or completely overlap with those in the WHO Solidarity trial:[6,7]

- The SOLIDARITY Finland trial[10] is part of the WHO Solidarity trial, and all of the in-hospital (short-term) results were published as part of the international WHO Solidarity trial. The SOLIDARITY Finland trial reported long-term (1 year) results.
- The NOR-Solidarity trial[9] is an independent add-on study to the WHO Solidarity trial conducted in Norway that evaluated the effects of hydroxychloroquine and remdesivir compared with SoC in hospitalized patients with COVID-19, of which we are only interested in remdesivir compared with SoC. The NOR-Solidarity trial reported additional outcomes, including length of ICU stay, time to ventilation, ICU admission, SAEs, WDAEs, acute liver injury, acute kidney injury, and thrombocytopenia.
- The DisCoVeRy trial[12] was an add-on trial of the WHO Solidarity trial. It shared patients' baseline characteristics with the WHO Solidarity Consortium, as well as the dates of hospital discharge and eventual need for oxygen therapy either through standard device, high-flow device, noninvasive ventilation, mechanical ventilation, ECMO, or death. Among the patients included in the WHO Solidarity trial, 219 (8.0%) of 2,750 patients who were randomly assigned to receive remdesivir, and 221 (5.4%) of 4,088 patients randomly assigned to receive SoC, were shared by the DisCoVeRy trial. The DisCoVeRy trial was designed to further

Key Point
Four of the studies have a patient population that either partially or completely overlaps with patients in the WHO Solidarity trial. Most patients were from settings without a similar health care system and/or economy to Canada.

document clinical outcomes, virological kinetics, treatment pharmacokinetics, and related safety data. The preliminary analyses are reported here for remdesivir compared with SoC.

- The CATCO trial[8] was a substudy of the WHO Solidarity trial conducted in Canada, in which added data elements were collected to better understand the effects of specific drugs. Of the 1,282 patients in the CATCO trial, 951 were also included in the WHO Solidarity trial.

The results of these 4 eligible studies have been fully or partially reported in the consolidated results of the 30 or so countries in the WHO Solidarity trial. This is the large platform trial identified in Figure 1. The majority of patients in the WHO Solidarity trial were from settings in which the health care system was not similar to the system in Canada. As the policy question in this review is for Canada, the decision was made to use the 4 individual trials, 1 of which (the CATCO trial) only enrolled patients living in Canada, together with other studies with health care systems similar to the system in Canada for the analysis. Details on the WHO Solidarity trial are provided in the "WHO Solidarity Trial" section at the end of the Results section.

Table 3

Basic Characteristics of the Included Studies (I)

Characteristic	Beigel, 2020[13]	Spinner, 2020[14]	Ali, 2022[8]
Name and trial number	ACTT-1 NCT04280705	GSD-US-540-5774 NCT04292730	CATCO NCT04330690
Study time period	February 21, 2020, to April 19, 2020	March 15, 2020, to April 18, 2020	August 14, 2020, to April 1, 2021
Study design	Adaptive, double-blind RCT	Open-label RCT	Open-label RCT
Setting	US, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, and Singapore	France, Germany, Hong Kong, Italy, Korea, Netherlands, Singapore, Spain, Switzerland, Taiwan, UK, and US	Canada[a]

Characteristic	Beigel, 2020[13]	Spinner, 2020[14]	Ali, 2022[8]
Randomized, N	1,062	596	1,282 (951 were also included in WHO Solidarity)
Patients	Adult patients (aged ≥ 18 years) with COVID-19	Adult patients (aged ≥ 18 years) or adolescent patients (aged ≥ 12 years and < 18 years) weighing ≥ 40 kg	Adult patients with COVID-19
Treatment duration of remdesivir	10 days	10 days or 5 days	10 days Stopped if discharge occurred
Follow-up time points	15 days and 29 days	11 days, 14 days, and 28 days	7 days, 14 days, 21 days, 28 days, and 60 days (including after discharge)
Interventions	Group 1: Remdesivir Group 2: Placebo Both groups received SoC.	Group 1: Remdesivir 10 days Group 2: Remdesivir 5 days Group 3: SoC	Group 1: Remdesivir Group 2: SoC Both groups received SoC.
Outcomes of interest	• Duration of hospitalization • Time to clinical improvement • Progression to high-flow oxygen or NIPPV • Need for mechanical ventilation • Mortality • WDAEs • Grade 3 and 4 adverse events • SAEs • Acute liver injury • Acute kidney injury • Thrombocytopenia • Need for intubation	• Duration of hospitalization • Time to clinical improvement • Need for mechanical ventilation • Mortality • Grade 3 and 4 adverse event • SAEs • WDAEs • Acute liver injury • Acute kidney injury • Thrombocytopenia	• Duration of hospitalization • Progression to high-flow oxygen or NIPPV • Need for mechanical ventilation • Mortality • Acute liver injury • Acute kidney injury

NIPPV = noninvasive positive-pressure ventilation; RCT = randomized controlled trial; SAE = serious adverse event; SoC = standard of care; WDAE = withdrawal due to adverse event.

[a] Patients from this RCT partially or fully overlapped with patients from the WHO Solidarity trial.

Table 4

Basic Characteristics of the Included Studies (II)

Characteristic	Barratt-Due, 2021[9]	Nevalainen, 2022[10]	Ader, 2022[12]
Name and trial number	NOR-Solidarity NCT04321616	SOLIDARITY Finland NCT04978259	DisCoVeRy NCT04315948
Study time period	March 28, 2020, to October 4, 2020	July 23, 2020, to January 27, 2021	March 22, 2020, to January 21, 2021
Study design	Open-label RCT	Open-label RCT	Open-label RCT
Setting	Norway[a]	Finland[a]	France, Belgium, Austria, Portugal, Luxembourg (39 out of 48 sites in France)[a]
Randomized, N	185, with only 101 for eligible arms	208	857
Patients	Adult patients (aged ≥ 18 years) with COVID-19	Adult patients (aged ≥ 18 years) with COVID-19	Adult patients (aged ≥ 18 years) with COVID-19
Treatment duration of remdesivir	10 days All study treatments were discontinued at discharge.	10 days at maximum; the median duration of remdesivir treatment was 5 days (IQR, 4 days to 8 days).	10 days; treatment could be stopped after 5 days if the patient was discharged.
Follow-up time points	7 days, 10 days, 14 days, 28 days, 60 days, and 90 days (including after discharge)	In hospital and 1 year	3 days, 5 days, 8 days, 11 days, 15 days (plus or minus 2), 29 days (plus or minus 3), and 90 days if discharged
Interventions	Group 1: Remdesivir Group 2: SoC Both groups received SoC.	Group 1: Remdesivir Group 2: SoC Both groups received SoC.	Group 1: Remdesivir Group 2: SoC Both groups received SoC.
Outcomes of interest	• Length of ICU stay • Time to ventilation • ICU admission • Mortality • SAEs • WDAEs • Acute liver injury • Acute kidney injury • Thrombocytopenia	• Duration of hospitalization[b] • ICU admission[b] • Mortality	• Time to clinical improvement • Mortality • SAEs • Acute liver injury • Acute kidney injury • Thrombocytopenia

ICU = intensive care unit; IQR = interquartile range; RCT = randomized controlled trial; SAE = serious adverse event; SoC = standard of care; WDAE = withdrawal due to adverse event.

[a] Patients from this RCT partially or fully overlapped with patients from the WHO Solidarity trial.

The detailed characteristics of the patients in the 6 included studies for this report are provided in Table 5, Table 6, and Table 7.

Study Characteristics
Six studies included only adults (mean age 50 to 70 years). Five studies included information on race or ethnicity. Comorbidities varied among the studies.

The ACTT-1 trial[13] was a phase III, adaptive, double-blind, placebo-controlled trial of remdesivir compared with placebo in adult patients hospitalized with COVID-19. In addition, both groups received supportive care according to the SoC for the trial site hospital; detailed nonstudy drugs received included corticosteroids, convalescent plasma, nontrial IL-6 medication, nontrial interferon, and a nontrial antiviral. The study randomized 1,062 patients; 541 were randomized to remdesivir and 521 were randomized to placebo. The mean age of patients was 58.6 years (standard deviation [SD] = 14.6) in the remdesivir group and 59.2 years (SD = 15.4) in the placebo group; 35.6% were female and 64.4% were male. Overall, 53.3% were white, 21.3% were Black or African American, 12.7% were Asian, and 0.7% were American Indian or Alaska Native [wording from original source]. A total of 54.5% of patients had 2 or more coexisting conditions, including hypertension (50.2%), obesity (44.8%), and type 2 diabetes (30.3%).

The GS-US-540-5774 trial[14] was a manufacturer-conducted, open-label RCT that compared 5-day or 10-day remdesivir regimens with SoC in patients aged 12 years and older with moderate COVID-19. SoC was described as local SoC with no further details. Co-interventions were listed as being administered to some patients in all groups and included steroids, hydroxychloroquine, lopinavir-ritonavir, tocilizumab, and azithromycin. The mean age of patients was 58 years (interquartile range [IQR], 48 years to 66 years) in the 5-day remdesivir group, 56 years (IQR, 45 years to 66 years) in the 10-day remdesivir group, and 57 years (IQR, 45 years to 66 years) in the SoC group. Overall, 38.9% were female and 61.1% were male. More than half of the patients indicated their race as white (57.8%), followed by Asian (18.0%) and Black (17.5%), and 18% identified their ethnicity as Hispanic or Latino. Comorbidities included cardiovascular disease (56.3%), hypertension (42.5%), diabetes (39.7%), and asthma (13.9%).

The NOR-Solidarity, SOLIDARITY Finland, CATCO, and DisCoVeRy trials were 4 add-on, open-label randomized trials or substudies of the WHO Solidarity trial. All of the patients in the NOR-Solidarity and SOLIDARITY Finland trials were also included in the WHO Solidarity trial, while the CATCO and DisCoVeRy trials included some additional patients who were not in the WHO Solidarity trial. Similar to the WHO Solidarity trial, the NOR-Solidarity, SOLIDARITY Finland, and CATCO trials did not define SoC and only reported a list of co-interventions for some patients; only the DisCoVeRy trial indicated that corticosteroids and anticoagulants were added to the SoC: dexamethasone 6 mg once daily for 10 days or until discharge; dexamethasone 20 mg once daily for 5 days, followed by 10 mg once daily for 5 days for acute respiratory distress syndrome; and anticoagulation drugs administered according to local protocols for venous thromboembolism prophylaxis or therapy.

The NOR-Solidarity trial[9] was an open-label randomized trial conducted in Norway. The mean ages were 59.7 years (SD = 16.5) in the remdesivir group and 58.1 years (SD = 15.7) in the SoC group; overall, 27.3% were female and 72.7% were male. Race or ethnicity and the number of patients with comorbidities were not reported. In addition to smoking (43.9%), the most frequently reported comorbidities were hypertension (29.6%), obesity (23.0%), cardiac disease (19.8%), and diabetes (19.8%).

The SOLIDARITY Finland trial[10] was an open-label randomized trial conducted in Finland, in which 114 patients were randomized to remdesivir and 94 to SoC. The mean age was 57.2 years (SD = 13.5) in the remdesivir group and 59.7 years (SD = 13.2) in the SoC group; overall, 35.6% were female and 64.4% were male. Race or ethnicity was not reported. Also, the number of patients with comorbidities was not reported, but the most common comorbidity reported was diabetes (17.3%).

The CATCO trial,[8] conducted in Canada, was an open-label RCT in which 634 patients were randomized to remdesivir and 648 to SoC. The mean age of patients in the remdesivir group was 65 years (IQR, 53 years to 77 years) and 66 years (IQR, 54 years to 77 years)

in the SoC group; overall, 40.2% were female and 59.8% were male. The largest proportion of patients were white (40.9%), followed by South Asian (15.6%) and East Asian (6.3); 5.3% of patients were Indigenous or First Nations. The most commonly reported comorbidities were diabetes (36.1%), chronic cardiovascular disease (26.8%), chronic respiratory disease (13.9%), and asthma (10.9%).

The DisCoVeRy trial[12], an open-label RCT in which 414 patients were randomized to remdesivir and 418 to SoC, included patients from France, Belgium, Austria, Portugal, and Luxembourg, with most patients based in France. Only 4.2% of the patients were from Portugal, the sole country listed in the PICOS statement as having a health care system setting similar to the Canadian health care system. The median ages were 63 years (IQR, 55 years to 73 years) in the remdesivir group and 64 years (IQR, 55 years to 73 years) in the control group. Overall, 30% were female and 69.3% were white. The most commonly reported comorbidities were obesity (34.4%), chronic cardiac disease (27.8%), and diabetes (26.5%).

In summary, the 6 studies included adults (aged 18 years or older) with mean or median ages in the range of 50 years to 70 years; 1 study (Spinner, 2020 [GSD-US-540-5774])[14] included patients aged 12 years to 18 years, but the median age and IQR suggested very few patients were aged younger than 18 years. Five studies reported information on race or ethnicity, with only the CATCO trial[8] and ACTT-1 trial[13] including patients who are Indigenous, but no separate outcome data are available for Indigenous individuals. Comorbidities varied among these studies and only 2 studies (ACTT-1[13] and DisCoVeRy[12]) reported the number of comorbidities of the included patients. For specific comorbidities, the most frequent conditions were diabetes and hypertension in the ACTT-1 trial;[13] cardiovascular disease, hypertension, and diabetes in the GSD-US-540-5774 trial;[14] diabetes and heart disease in the WHO Solidarity trial; diabetes and chronic cardiovascular disease in the CATCO trial;[8] hypertension, smoking history, and obesity in the NOR-Solidarity trial;[9] diabetes in the SOLIDARITY Finland trial;[10] and obesity, diabetes, and smoking history in the DisCoVeRy trial.[12]

Table 5

Characteristics of Patients From the Included Studies (I)

Characteristic	Beigel, 2020 (ACTT-1)[13]		Spinner, 2020 (GSD-US-540-5774)[14]		
Treatment	Remdesivir[a]	Placebo[a]	Remdesivir 10 days[a]	Remdesivir 5 days[a]	SoC
Randomized patients, n	541	521	197[d]	199[d]	200[d]
Age, years	mean (SD)		median (IQR)		
	58.6 (14.6)	59.2 (15.4)	56 (45 to 66)	58 (48 to 66)	57 (45 to 66)
Sex, n (%)	Female: 189 (34.9) Male: 352 (65.1)	Female: 189 (36.3) Male: 322 (63.7)	Female: 75 (38.9) Male: 118 (61.1)	Female: 77 (40.3) Male: 114 (59.7)	Female: 75 (37.5) Male: 125 (62.5)
Race or ethnicity, n (%)	Race White: 279 (51.6) Black or African American: 109 (20.1) Asian: 79 (14.6) American Indian or Alaska native [wording from original source]: 4 (0.7) Native Hawaiian or Other Pacific Islander: 2 (0.4) Multi-racial: 2 (0.4) Unknown: 66 (12.2) Ethnicity Hispanic or Latino: 134 (24.8)	Race White: 287 (55.1) Black or African American: 117 (22.5) Asian: 56 (10.7) American Indian or Alaska native [wording from original source]: 3 (0.6) Native Hawaiian or Other Pacific Islander: 2 (0.4) Multi-racial: 1 (0.2) Unknown: 55 (10.6) Ethnicity Hispanic or Latino: 116 (22.3)	Race White: 107 (56.9)[e] Black: 37 (19.7)[e] Asian: 31 (16.5)[e] Other: 13 (6.9)[e] Ethnicity Hispanic or Latino: 42 (22.6)[f]	Race White: 109 (58.6)[e] Black: 35 (18.8)[e] Asian: 34 (18.3)[e] Other: 8 (4.3)[e] Ethnicity Hispanic or Latino: 25 (13.4)[f]	Race White: 112 (58.0)[e] Black: 27 (14.0)[e] Asian: 37 (19.2)[e] Other: 17 (8.8)[e] Ethnicity Hispanic or Latino: 34 (18.3)[f]
Immunocompromised patients, n (%)	NR	NR	NR	NR	NR
COVID-19 Variant	NR, but study conducted before emergence of Delta and Omicron variants		NR, but study conducted before emergence of Delta and Omicron variants		
Vaccination status	None (before vaccination era)		None (before vaccination era)		

Characteristic	Beigel, 2020 (ACTT-1)[13]		Spinner, 2020 (GSD-US-540-5774)[14]		
Underserved or equity-deserving groups, n(%)	NR	NR	NR	NR	NR
Number of patient comorbidities, n (%)	0: 97 (18.3)[b] 1: 138 (26)[b] ≥ 2: 296 (55.7)[b]	0: 97 (18.8)[b] 1: 137 (26.5)[b] ≥ 2: 283 (54.7)[b]	NR	NR	NR
Categories of comorbidities, n (%)	Type 2 diabetes: 164 (30.8)[c] Hypertension: 269 (50.6)[c] Obesity: 242 (45.6)[c]	Type 2 diabetes: 158 (30.4)[c] Hypertension: 264 (50.9)[c] Obesity: 234 (45.2)[c]	Cardiovascular disease: 111 (58)[d] Hypertension: 85 (44)[d] Diabetes: 85 (44)[d] Asthma: 31 (16)[d]	Cardiovascular disease: 111 (58)[d] Hypertension: 82 (43)[d] Diabetes: 71 (37)[d] Asthma: 22 (12)[d]	Cardiovascular disease: 107 (54)[d] Hypertension: 81 (41)d Diabetes: 76 (38)[d] Asthma: 28 (14)[d]
Time from symptom onset to hospitalization or ER, days	Median time (IQR) from symptom onset to randomization		Median duration (IQR) of symptoms before first dose of remdesivir		
	9 (6 to 12)	9 (7 to 13)	8 (5 to 11)	8 (5 to 11)	9 (6 to 11)

ER = emergency room; IQR = interquartile range; NR = not reported; SD = standard deviation; SoC = standard of care.

[a] Includes SoC.

[b] Data on comorbidities were missing for 11 patients and were incomplete for 3 patients; n = 1,048 (n = 531 in remdesivir and n = 517 in placebo).

[c] Data on comorbidities were missing for 11 patients and were incomplete for 3 patients; n = 1,051 (n = 532 in remdesivir and n = 519 in placebo) for diabetes and hypertension; n = 1,049 (n = 531 in remdesivir and n = 518 in placebo) for obesity.

[d] Only patients included in the primary analysis were considered; n = 584 (n = 193 in remdesivir, n = 191 in remdesivir 5, and n = 200 in SoC).

[e] Data on race were available for a subset of patients; n = 567 (n = 188 in remdesivir, n = 186 in remdesivir 5, and n = 193 in SoC).

[f] Data on ethnicity were available for a subset of patients; n = 559 (n = 186 in remdesivir, n = 187 in remdesivir 5, and n = 186 in SoC).

Table 6

Characteristics of Patients From the Included Studies (II)

Characteristic	Ali, 2022 (CATCO)[8]		Barratt-Due, 2021 (NOR-Solidarity)[9]	
Treatment	Remdesivir[a]	SoC	Remdesivir[a]	SoC
Randomized patients, n	634	648	43[d]	58[d]
Age, years	median (IQR)		mean (SD)	
	65 (53 to 77)	66 (54 to 77)	59.7 (16.5)	58.1 (15.7)
Sex, n (%)	Female: 260 (41.0) Male: 374 (59.0)	Female: 255 (39.4) Male: 393 (60.6)	Female: 13 (31.0) Male: 29 (69.0)	Female: 14 (24.6) Male: 43 (75.4)
Race/ethnicity, n (%)[b]	White: 269 (42.4) South Asian: 90 (14.2) East Asian: 40 (6.3) Indigenous or First Nations: 40 (6.3) Latin American: 23 (3.6) Arab: 22 (3.5) Black: 20 (3.2) West Asian: 8 (1.3) Other: 9 (1.4) Not available: 119 (18.8)	White: 255 (39.4) South Asian: 110 (17.0) East Asian: 42 (6.5) Indigenous or First Nations: 28 (4.3) Latin American: 21 (3.2) Arab: 24 (3.7) Black: 25 (3.9) West Asian: 12 (1.9) Other: 14 (2.2) Not available: 126 (19.5)	NR	NR
Immunocompromised patients, n (%)	NR	NR	NR	NR
COVID-19 variant	NR, but CATCO extended well into Canada's third COVID-19 wave and the emergence of the Alpha variant		NR, but same period as the WHO Solidarity trial; the recruitment preceded the Delta and Omicron variants	
Vaccination status	NR (enrolled patients before April 1, 2021)		None (before vaccination era)	
Underserved or equity-deserving groups, n (%)	NR	NR	NR	NR
Number of patient comorbidities, n (%)	NR	NR	NR	NR

Characteristic	Ali, 2022 (CATCO)[8]		Barratt-Due, 2021 (NOR-Solidarity)[9]	
Categories of comorbidities, n (%)	Diabetes: 155 (33.6)[c]	Diabetes: 188 (38.4)[c]	Ever smoking: 16 (39.0)[e]	Ever smoking: 27 (47.4)
	Chronic cardiovascular disease: 120 (26.0)[c]	Chronic cardiovascular disease: 135 (27.6)[c]	Hypertension: 15 (36.6)[e]	Hypertension: 14 (24.6)
	Chronic respiratory disease: 67 (14.5)[c]	Chronic respiratory disease: 65 (13.3)[c]	Obesity (BMI > 30 kg/m^2): 11 (28.9)[f]	Obesity (BMI > 30 kg/m^2): 9 (18.4)[f]
	Asthma: 49 (10.6)[c]	Asthma: 55 (11.2)[c]	Chronic cardiac disease: 6 (14.6)[e]	Chronic cardiac disease: 12 (21.1)
	Smoker: 23 (5.0)[c]	Smoker: 22(4.5)[c]	Diabetes: 9 (22.0)[e]	Diabetes: 9 (15.8)
	Chronic liver disease: 8 (1.7)[c]	Chronic liver disease: 19 (3.9)[c]	Chronic pulmonary disease: 4 (9.8)[e]	Chronic pulmonary disease: 3 (5.3)
	HIV positive: 1 (0.2)[c]	HIV positive: 1 (0.2)[c]		
Time from symptom onset to hospitalization or ER, days	Median time (IQR) from symptom onset to hospital admission, median (IQR)		Mean (SD) symptom duration before admission	
	6 (3 to 9)	6 (4 to 9)	7.5 (6.1)	7.2 (3.5)

ER = emergency room; IQR = interquartile range; NR = not reported; SD = standard deviation; SoC = standard of care.

[a] Includes SoC.

[b] Percentages add to more than 100% as multiple racial or ethnic groups may have been selected.

[c] Data on these comorbidities were available for a subset of patients; n = 951 (n = 461 in remdesivir and n = 490 in SoC).

[d] No postrandomization data for 2 patients and they were excluded from the analysis; n = 99 (n = 42 in remdesivir and n = 57 in SoC).

[e] Data on these comorbidities were missing for 1 patient; n = 98 (n = 41 in remdesivir and n = 57 in SoC).

[f] Data on obesity were missing for 12 patients; n = 87 (n = 38 in remdesivir and n = 49 in SoC).

Table 7

Characteristics of Patients From the Included Studies (III)

Characteristic	Nevalainen, 2022 (SOLIDARITY Finland)[10]		Ader, 2022 (DisCoVeRy)[12]	
Treatment	Remdesivir[a]	SoC	Remdesivir[a]	SoC
Randomized patients, n	114	94	414 (ITT); 406 (mITT)	418 (ITT); 418 (mITT)
Age, years	mean (SD)		median (IQR)	
	57.2 (13.5)	59.7 (13.2)	63 (55 to 73)	64 (54 to 72)
Sex, n (%)	Female: 40 (35.1) Male: 74 (64.9)	Female: 34 (36.2) Male: 60 (63.8)	Female: 123 (29.7) Male: 291 (70.3)	Female: 130 (31.1) Male: 288 (68.9)
Race or ethnicity, n (%)	NR	NR	White: 244 (67.8)[b] North African: 49 (13.6)[b] Sub-Saharan African: 30 (8.3)[b] Other: 37 (10.3)[b]	White: 255 (70.1)[b] North African: 61 (16.8)[b] Sub-Saharan African: 17 (4.7)[b] Other: 31 (8.5)[b]
Immunocompromised patients, n (%)	NR	NR	NR	NR
COVID-19 variant	NR, but same period as the WHO Solidarity trial; the recruitment preceded the Delta and Omicron variants		Before emergence of Delta and Omicron variants	
Vaccination status	NR (Enrolled patients before January 27, 2021, mostly before vaccination era)		No patient received vaccine	
Underserved or equity-deserving groups, n (%)	NR	NR	NR	NR
Number of patient comorbidities, n (%)	NR	NR	0: 109 (26.7)[c] 1: 142 (34.8)[c] 2: 97 (23.8)[c] > 2: 60 (14.7)[c]	0: 110 (26.4)[c] 1: 134 (32.2)[c] 2: 97 (23.3)[c] > 2: 75 (18.0)[c]

Characteristic	Nevalainen, 2022 (SOLIDARITY Finland)[10]		Ader, 2022 (DisCoVeRy)[12]	
Categories of comorbidities, n (%) n of N (%)[d]	Diabetes: 20 (17.5) Current smoking: 2 (1.8)	Diabetes: 16 (17.0) Current smoking: 4 (4.2)	Obesity: 138 of 402 (34.3) Chronic cardiac disease: 111 of 407 (27.3) Diabetes: 104 of 406 (25.6) Current or former smoker: 73 of 389 (18.8) Chronic pulmonary disease: 71 of 406 (17.5) Chronic kidney disease stage to III: 19 of 409 (4.6) Malignant hemopathy: 16 of 364 (4.4) Chronic neurological disorder including dementia: 18 of 406 (4.4) Autoinflammatory disease: 17 of 405 (4.2) Mild liver disease: 15 of 406 (3.7) Active malignant neoplasm: 13 of 406 (3.2) Transplantation: 2 of 406 (0.5) Asplenia: 1 of 406 (0.2) AIDS or HIV not on ART: 0 of 406 (0)	Obesity: 140 of 406 (34.5) Chronic cardiac disease: 118 of 416 (28.4) Diabetes: 113 of 412 (27.4) Current or former smoker: 68 of 396 (17.2) Chronic pulmonary disease: 75 of 411 (18.2) Chronic kidney disease stage I to III: 32 of 411 (7.8) Malignant hemopathy: 19 of 375 (5.1) Chronic neurological disorder including dementia: 16 of 416 (3.8) Autoinflammatory disease: 24 of 411 (5.8) Mild liver disease: 15 of 416 (3.6) Active malignant neoplasm: 15 of 416 (3.6) Transplantation: 9 of 416 (2.2) Asplenia: 3 of 415 (0.7) AIDS or HIV not on ART: 2 of 415 (0.5)
Time from symptom onset to hospitalization or ER (days)	NR		Median days from symptoms onset to random assignment	
	NR	NR	9.0 (7.0 to 11.0)	9.0 (7.0 to 12.0)

ART = antiretroviral therapy; BMI = body mass index; ER = emergency room; IQR = interquartile range; ITT = intention to treat; mITT = modified intention to treat; NR = not reported; SD = standard deviation; SoC = standard of care.

[a] Includes SoC.

[b] For Ader, 2022 (DisCoVeRy), data on ethnicity were available for a subset of patients; n = 724 (n = 360 in remdesivir and n = 364 in SoC).

[c] Data on the number of comorbidities were available for a subset of patients and no reason was provided; n = 824 (n = 408 in remdesivir and n = 416 in SoC).

[d] For Ader, 2022 (DisCoVeRy), the following numbers of patients had missing data for these variables: ethnicity (remdesivir: n = 54, control: n = 54); current smoking status (remdesivir: n = 26, control: n = 22); current or former smoking status (remdesivir: n = 25, control: n = 22); time from symptom onset to random assignment (remdesivir: n = 12, control: n = 8); obesity (remdesivir: n = 12, control: n = 4); autoinflammatory disease (remdesivir: n = 9, control: n = 2); AIDS or HIV not on ART (remdesivir: n = 8, control: n = 3); asplenia (remdesivir: n = 8, control: n = 3); mild liver disease (remdesivir: n = 8, control: n = 2); chronic neurological disorder including dementia (remdesivir: n = 8, control: n = 2); active malignant neoplasm (remdesivir: n = 8, control: n = 2); transplantation (remdesivir: n = 8, control: n = 2); chronic cardiac disease (remdesivir: n = 7, control: n = 2); chronic pulmonary disease (n = 9, remdesivir: n = 7, control: n = 2); chronic kidney disease stage I to III (n = 9, remdesivir: n = 7, control: n = 2); diabetes (n = 8, remdesivir: n = 6, control: n = 2).

Data Analysis and Synthesis

The results reported on the efficacy outcomes of interest in the RCTs, as well as additional results calculated based on these reported study results, are provided in Table 8. In Appendix 5, Table 25, the reported results are again provided, as well as the study authors' conclusions. Reported results were sufficient to pool data for some outcomes (namely, the need for mechanical ventilation).

Findings Suggest
Remdesivir does not significantly reduce ICU admissions, length of stay, or time to ventilation. Its impact on length of hospitalization, time to clinical improvement, and progression to high-flow oxygen is mixed.

Efficacy

Duration of hospitalization was reported in 3 studies. Beigel et al. (the ACTT-1 trial)[13] found that the initial length of hospital stay was statistically significantly shorter in the remdesivir group than in the placebo group, with a median difference of 5 days shorter, and a 95% confidence interval (CI) from 2.3 days to 7.7 days shorter. Spinner et al. (the GSD-US-540-5774 trial)[14] indicated no difference but did not report the data, and Ali et al. (the CATCO trial)[8] found a median difference of 0 days (IQR, −1 to 0) between remdesivir and SoC; when converted to means, there was no statistically significant difference between remdesivir and SoC with a mean difference (MD) of less than a day between the 2 groups, and a 95% CI from 2.75 days longer to 1.59 days shorter (MD = 0.66; 95% CI, −2.75 to 1.59).

Findings Suggest
Remdesivir significantly reduces the need for mechanical ventilation (reduction seen when pooling the results of 3 studies) and the need for intubation (only reported in 1 study) compared to standard of care.

ICU admission was reported in 1 study. Barratt-Due et al. (the NOR-Solidarity trial)[9] found no statistically significant difference between remdesivir and SoC in reducing ICU admissions, with less than a 1 percent difference in ICU admissions (risk difference [RD] = −0.3; 95% CI, −15.9 to 15.4) and an equal risk of ICU admission (relative risk [RR] = 0.99; 95% CI, 0.44 to 2.24).

Length of ICU stay was reported in the Barratt-Due et al. (NOR-Solidarity)[9] study. The data were reported in a cumulative probability plot, in which the duration of ICU stay in days was plotted against the cumulative proportion of patients experiencing this length of stay. The cumulative probability plots for the duration of ICU stay in days were similar for remdesivir and SoC. No statistical comparisons of the plots were made and the data were not provided with sufficient accuracy to provide effect estimates comparing remdesivir and SoC on ICU length of stay, to support the claim by the authors of no difference between the treatments. Again, there appears to be no substantial difference between remdesivir and SoC on the length of ICU stay.

Time to clinical improvement in days was reported in 3 studies using various measures based on the WHO 7-point ordinal scale: 1 = not hospitalized, no limitations on activities; 2 = not hospitalized, limitation on activities; 3 = hospitalized, not requiring supplemental oxygen; 4 = hospitalized, requiring supplemental oxygen; 5 = hospitalized, on noninvasive ventilation or high-flow oxygen devices; 6 = hospitalized, on invasive mechanical ventilation or ECMO; and 7 = death. In addition, the National Early Warning Score 2 (NEWS-2) was considered (i.e., aggregate score of respiration rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness or new confusion, and temperature). Beigel et al. (the ACTT-1 study)[13] reported time to recovery and time to clinical improvement, including a 1-category improvement on the WHO ordinal scale, a 2-category improvement on the WHO ordinal scale, and time to discharge or NEWS-2 less than or equal to 2 for 24 hours. The results showed patients in the remdesivir group had a statistically significantly shorter time to improvement of 1 category

(HR = 1.23; 95% CI, 1.08 to 1.41) or 2 categories (HR = 1.29; 95% CI, 1.12 to 1.48) on the ordinal scale from baseline than patients in the placebo group, and a shorter time to discharge or to a NEWS-2 of 2 or lower than those in the placebo group (HR = 1.27; 95% CI, 1.10 to 1.46). For the outcome of time to recovery through 29 days, a statistically significant shorter time to recovery of 5.3 days for remdesivir was found (MD = −5.33; 95% CI, −5.67 to −4.99). Time to recovery was defined as the first day on which the participant satisfied 1 of the following 3 categories from the ordinal scale: 1 = hospitalized, not requiring supplemental oxygen — no longer requires ongoing medical care; 2 = not hospitalized, limitation on activities and/or requiring home oxygen; or 3 = not hospitalized, no limitations on activities.

Spinner et al. (the GSD-US-540-5774 trial)[14] considered 5 outcomes related to time to improvement within 28 days, based on the WHO 7-point ordinal scale. This study considered the numbering of the WHO 7-point scale in reverse. The scores summarized here have been modified from their study to reflect the usual numbering system. They found that the difference between 10-day remdesivir and SoC was not statistically significant for time to clinical improvement (≥ 2 points on ordinal scale; HR = 1.16; 95% CI, 0.93 to 1.43); time to modified clinical improvement (≥ 1 point on ordinal scale; HR = 1.10; 95% CI, 0.90 to 1.36); time to recovery (ordinal score of 3 to 6 reduced to 1 to 2, or ordinal score of 2 reduced to 1 on the WHO ordinal scale; HR = 1.11; 95% CI, 0.90 to 1.37); and time to modified recovery (ordinal score of 4 to 6 reduced to 1 to 3, or ordinal score of 3 reduced to 1 to 2, or ordinal score of 2 reduced to 1 on the WHO ordinal scale; HR = 1.10; 95% CI, 0.90 to 1.36). Time to discontinuation of supplemental oxygen to room air (HR = 1.93; 95% CI, 1.11 to 3.36) was statistically significantly shorter for 10-day remdesivir than for SoC. The difference between 5-day remdesivir and SoC was not statistically significant for all of these outcomes.

Ader et al. (the DisCoVeRy trial)[12] considered 3 outcomes related to time to clinical improvement within 29 days based on the WHO 7-point ordinal scale, and found that the difference between

remdesivir and SoC was not statistically significant for days to improvement of 2 categories on the 7-point ordinal scale or hospital discharge (HR = 0.92; 95% CI, 0.79 to 1.08); days to NEWS-2 less than or equal to 2 or hospital discharge (HR = 1.03; 95% CI, 0.88 to 1.21); and days to hospital discharge (HR = 0.94; 95% CI, 0.80 to 1.11).

Time to ventilation was reported in 1 study. Barratt-Due et al. (the NOR-Solidarity trial)[9] found that there was no statistically significant difference between remdesivir and SoC in the time to receipt of mechanical ventilation (HR = 1.3; 95% CI, 0.5 to 3.4); (RR = 1.4; 95% CI, 0.4 to 5.8).

Progression to high-flow oxygen or NIPPV was reported in 2 studies. Beigel et al. (the ACTT-1 trial)[13] found that, among the 573 patients who were not receiving noninvasive ventilation, high-flow oxygen, invasive ventilation, or ECMO at baseline, the incidence of new noninvasive ventilation or high-flow oxygen use was statistically significantly lower in the remdesivir group than in the placebo group, by a difference of 7% (RD = −7.12%; 95% CI, −13.75 to −0.49) and a 30% RR reduction (RR = 0.70; 95% CI, 0.51 to 0.98). Ali et al. (the CATCO trial)[8] reported on the need for new oxygen — defined as being on oxygen on day 2 and no oxygen therapy on day 1 — in remdesivir versus SoC, and showed no statistically significant difference based on both the absolute RD (RD = −7.1%; 95% CI, −2.3 to 8.5) and the RR ratio (RR = 0.76; 95% CI, 0.42 to 1.38).

Need for mechanical ventilation (invasive mechanical ventilation or ECMO/VV-ECMO) was reported in 3 studies. Ali et al. (the CATCO trial)[8] reported new use of mechanical ventilation without identifying the follow-up time; we assumed it was up to 28 days, as other outcomes (e.g., mean oxygen-free and ventilator-free days) were reported at 28 days. A significant reduction of 7% in the new use of mechanical ventilation was found for remdesivir compared to SoC (RD = −7.0%; 95% CI, −10.6 to −3.4) with a 47% RR reduction (RR = 0.53; 95% CI, 0.38 to 0.75). Beigel et al. (the ACTT-1 trial)[13] reported new use of mechanical ventilation or ECMO at 29 days, and found a statistically significant reduction of 10% for remdesivir compared to SoC (RD = −9.59; 95% CI, −14.99 to −4.19) and an

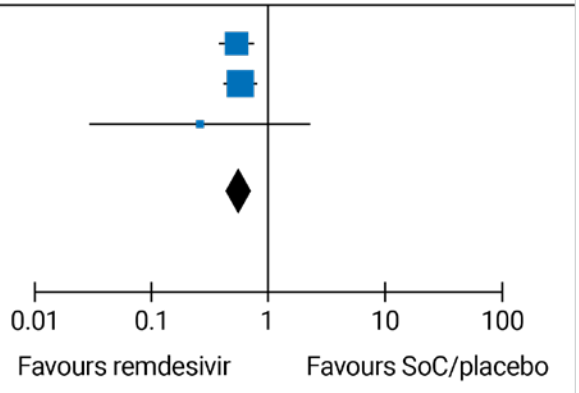
RR reduction of 43% (RR = 0.57; 95% CI, 0.42 to 0.79). Spinner et al. (the GSD-US-540-5774 trial)[14] reported 11-day, 14-day, and 28-day results on the number of patients who were newly hospitalized and required invasive mechanical ventilation or ECMO based on the second category on the 7-point ordinal scale. No statistically significant difference was found between remdesivir and SoC, in particular for the results at 28 days for the 10-day treatment duration with remdesivir, in which only 1 case occurred in the remdesivir group and 4 cases in the SoC group (RR = 0.26; 95% CI, 0.029 to 2.30). We combined the 28-day and 29-day results for these 3 studies, and found a statistically significant reduction in the need for mechanical ventilation or ECMO in the remdesivir group (10 days) compared with the SoC or placebo group (RR = 0.55; 95% CI, 0.44 to 0.69) (Figure 2).

Figure 2

Meta-Analysis of the Need for Mechanical Ventilation for Remdesivir Versus SoC or Placebo: Risk Ratio

Study or Subgroup	Remdesivir Events	Remdesivir Total	SoC/Placebo Events	SoC/Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Ali, 2022	46	575	89	593	46.5%	0.53 [0.38 , 0.75]
Beigel, 2020	52	402	82	364	52.4%	0.57 [0.42 , 0.79]
Spinner, 2020	1	193	4	200	1.1%	0.26 [0.03 , 2.30]
Total (95% CI)		**1170**		**1157**	**100.0%**	**0.55 [0.44, 0.69]**
Total events	99		175			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.56$, df = 2 (P = 0.75); $I^2 = 0\%$
Test for overall effect: Z = 5.10 (P < 0.00001)
Test for subgroup differences: Not applicable



CI = confidence interval; M-H = Mantel-Haenszel; SoC = standard of care.

Need for intubation was reported in 1 study. Beigel et al. (the ACTT-1 study)[13] summarized endotracheal intubations as respiratory failures at 29 days. A statistically significant reduction of 5.5% in the need for intubation was found for remdesivir compared to SoC (RD = −5.46%; 95% CI, −9.09 to 1.83) and a 43% RR reduction (RR = 0.57; 95% CI, 0.39 to 0.84).

Table 8

Results for Efficacy Outcomes of Interest

Reported results on outcomes of interest	Additional results calculated based on reported study results[a]
Duration of hospitalization (days)	
Beigel, 2020 (ACTT-1)[13]	
Duration of initial hospitalization, (follow-up 29 days), median (IQR) Remdesivir + SoC (n = 541): 12 (6 to 28) Placebo + SoC (n = 521): 17 (8 to 28) Difference of medians (95% CI): −5.0 (−7.7 to −2.3)	Length of hospitalization in days Remdesivir vs. placebo MD = −2.34; 95% CI, −4.22 to −0.46
Spinner, 2022 (GSD-US-540-5774)[14]	
No data available, narrative description.	NA
Ali, 2022 (CATCO)[8]	
Duration of hospital stay median (IQR) Remdesivir (n = 634): 10 (6 to 18) SoC (n = 647): 9 (6 to 17) Difference in medians: 0 (−1 to 0)	Length of hospitalization in days Remdesivir vs. SoC MD = 0.66; 95% CI, −2.75 to 1.59
Duration of hospital stay for survivors, median (IQR), n = 1,005[b] Remdesivir : 9 (6 to 17) SoC: 9 (6 to 16) Difference in medians: 0 (−1 to 0)	
Duration of hospital stay for nonsurvivors, median (IQR) n = 262[b] Remdesivir: 12 (5 to 20) SoC: 11 (6 to 20) Difference in medians: 0 (−2 to 2)	

Reported results on outcomes of interest	Additional results calculated based on reported study results[a]
Nevalainen, 2022 (SOLIDARITY Finland)[10]	
Reported duration of inpatient days as a baseline characteristic and not an outcome (n = 208) and after 1 year (n = 181), median (IQR) Baseline, n=208 Remdesivir (n = 114): 8 (6 to 11) SoC (n = 94): 8.5 (6 to 15) After 1 year, n=181 Remdesivir (n = 114): 8 (6 to 11) SoC (n = 94): 8 (6 to 14)	
ICU admission	
Barratt-Due, 2021 (NOR-Solidarity)[9]	
Admitted to ICU, % (95%CI)[c] Remdesivir + SoC (n = 42): 19.0 (95% CI, 9.2 to 32.6) SoC (n = 57): 19.3 (95% CI, 10.5 to 30.8) RD% = −0.3 (95% CI, −15.9 to 15.4)	ICU admission Remdesivir vs. SoC RR = 0.99; 95% CI, 0.44 to 2.24
Nevalainen, 2022 (SOLIDARITY Finland)[10]	
ICU treatment was reported as a characteristic of patients at baseline and at 1 year, n (%) Baseline, n=208 Remdesivir (n = 114): 12 (10.5%) SoC (n = 94): 11 (11.7%) After 1 year, n = 181 Remdesivir (n = 114): 10 (10.2%) SoC (n = 94): 10 (12.0%)	NC
Length of ICU stay	
Barratt-Due, 2021 (NOR-Solidarity)[9]	
Remdesivir (n = 42) was compared to SoC (n = 87). Results were reported as cumulative probability plots and the claim was made that for the duration of ICU stay, the plots showed no differences between the treatments.	The cumulative probability plots for the duration of ICU stay in days are similar for remdesivir and SoC. No statistical comparisons of the plots were made and the data were not provided with sufficient accuracy to provide effect estimates comparing remdesivir and SoC on ICU length of stay to support the claim by the authors of no difference between the treatments.

Reported results on outcomes of interest	Additional results calculated based on reported study results[a]
Time to clinical improvement	
Beigel, 2020 (ACTT-1)[13]	
Median time to recovery in days was defined as the first day on which the patient satisfied one of the following 3 categories from the ordinal scale: 1 = hospitalized, not requiring supplemental oxygen — no longer requires ongoing medical care; 2 = not hospitalized, limitation on activities and/or requiring home oxygen; and 3 = not hospitalized, no limitations on activities. Day 1 through Day 29, median (IQR) Remdesivir + SoC (n = 541) 10 (9 to 11) Placebo + SoC (n = 521) 15 (13 to 18) Median time to clinical improvement (95% CI) in days 1. Improvement of one category on ordinal scale Remdesivir + SoC (n = 541): 7.0 (95% CI, 6.0 to 8.0) Placebo + SoC (n = 521): 9.0 (95% CI, 8.0 to 11.0) HR = 1.23 (95% CI, 1.08 to 1.41) 2. Improvement of 2 categories on ordinal scale Remdesivir + SoC (n = 541): 11.0 (95% CI, 10.0 to 13.0) Placebo + SoC (n = 521): 14.0 (95% CI, 13.0 to 15.0) HR = 1.29 (95% CI, 1.12 to 1.48) 3. Discharge or NEWS-2 ≤ 2 for 24 hours Remdesivir + SoC (n = 541): 8.0 (95% CI, 7.0 to 9.0) Placebo + SoC (n = 521): 12.0 (95% CI, 10.0 to 15.0) HR = 1.27 (95% CI, 1.10 to 1.46)	Time to recovery in days Remdesivir vs. SoC (MD = −5.33; 95% CI, −5.67 to −4.99)

Reported results on outcomes of interest	Additional results calculated based on reported study results[a]
Spinner, 2022 (GSD-US-540-5774)[14]	
Categories of the WHO 7-point ordinal scale: 1 = death; 2 = hospitalized, requiring invasive mechanical ventilation or ECMO; 3 = hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 4 = hospitalized, requiring low-flow supplemental oxygen; 5 = hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (related or not to COVID-19); 6 = hospitalized, not requiring supplemental oxygen or ongoing medical care; and 7 = not hospitalized. 1. Time to clinical improvement (≥ 2-point improvement from baseline on the 7-point ordinal scale) in days, within 28 days[d] 10-day remdesivir (n = 193): 8 (4 to 14) 5-day remdesivir (n = 191): 6 (5 to 14) SoC (n = 200): 8 (5 to 22) 10-day vs .SoC: HR = 1.16 (95% CI, 0.93 to 1.43) 5-day vs. SoC: HR = 1.15 (95% CI, 0.93 to1.42) 2. Time to clinical improvement (≥ 1-point improvement from baseline on the 7-point ordinal scale) in days, within 28 days[d] 10-day remdesivir (n = 193): 7 (4 to 12) 5-day remdesivir (n = 191): 6 (4 to 9) SoC (n = 200): 7 (4 to 14) 10-day vs. SoC: HR = 1.10 (95% CI, 0.90 to 1.36) 5-day vs. SoC: HR = 1.19 (95% CI, 0.97 to 1.47) 3. Time to recovery (improvement from a baseline score of 2 to 5, to a score of 6 or 7; or from a baseline score of 6 to a score of 7) in days, within 28 days[d] 10-day remdesivir (n = 193): 8 (4 to 13) 5-day remdesivir (n = 191): 6 (5 to 10) SoC (n = 200): 7 (4 to 15) 10-day vs. SoC: HR = 1.11 (95% CI, 0.90 to 1.37) 5-day vs. SoC: HR = 1.18 (95% CI, 0.96 to 1.45)	NC

Reported results on outcomes of interest	Additional results calculated based on reported study results[a]
4. Time to modified recovery (improvement from a baseline score of 2 to 4 to a score of 5 to 7; improvement from a baseline score of 5 to a score of 6 to 7; or improvement from a baseline score of 6 to a score of 7) in days, within 28 days[d] 10-day remdesivir (n = 193): 7 (4 to 12) 5-day remdesivir (n = 191): 6 (4 to 9) SoC (n = 200): 7 (4 to 14) 10-day vs. SoC: HR = 1.10 (95% CI, 0.90 to 1.36) 5-day vs. SoC: HR = 1.19 (95% CI, 0.96 to 1.46) 5. Time to discontinuation of oxygen (to room air) in days, within 28 days[d] 10-day remdesivir (n = 193): 4 (2 to 6) 5-day remdesivir (n = 191): 5 (3 to 7) SoC (n = 200): 6 (4 to 14) 10-day vs. SoC: HR = 1.93 (95% CI, 1.11 to 3.36) 5-day vs. SoC: HR = 1.31 (95% CI, 0.79 to 2.18)	NC
Ader, 2022 (DisCoVeRy)[12]	
Categories of the WHO 7-point ordinal scale were: 1 = not hospitalized, no limitations on activities; 2 = not hospitalized, limitation on activities; 3 = hospitalized, not requiring supplemental oxygen; 4 = hospitalized, requiring supplemental oxygen; 5 = hospitalized, on noninvasive ventilation or high-flow oxygen devices; 6 = hospitalized, on invasive mechanical ventilation or ECMO; and 7 = death. 1. Days to improvement of 2 categories on the 7-point ordinal scale or hospital discharge in days, within 29 days Remdesivir (n = 414): 12 (8 to 24) SoC (n = 418): 11 (7 to 26) HR 0.92 (95% CI, 0.79 to 1.08) 2. Days to NEWS-2 ≤ 2 or hospital discharge in days, within 29 days Remdesivir (n = 414): 11 (7 to 24) SoC (n = 418): 11 (6 to 29) HR = 1.03 (95% CI, 0.88 to 1.21) 3. Days to hospital discharge in days, within 29 days Remdesivir (n = 414): 15 (10 to 29) SoC (n = 418): 13 (8 to 29) HR (95% CI): HR 0.94 (95% CI, 0.80 to 1.11)	NC

Reported results on outcomes of interest	Additional results calculated based on reported study results[a]
Time to ventilation	
Barratt-Due, 2021 (NOR-Solidarity)[9]	
Time to receipt of mechanical ventilation Remdesivir + SoC (n = 58) vs. SoC (n = 43): RR = 1.4 (95% CI, 0.4 to 5.8) HR = 1.3 (95% CI, 0.5 to 3.4)	NC
Progression to high-flow oxygen or NIPPV	
Beigel, 2020 (ACTT-1)[13]	
New use of new noninvasive ventilation or high-flow oxygen use during the study, day 29 Remdesivir + SoC (n = 307): 52 (17%; 95% CI, 13 to 22) Placebo + SoC (n = 266): 64 (24%; 95% CI, 19 to 30) RD% = −7 (95% CI, −14 to −1)	Progression to high-flow oxygen or NIPPV Remdesivir vs. SoC RR = 0.70; 95% CI, 0.51 to 0.98 RD% = −7.12; 95% CI, −13.75 to −0.49
Ali, 2022 (CATCO)[8]	
Need for new oxygen[e]; defined as being on oxygen on day 2 and no oxygen therapy on day 1 Remdesivir (n = 634): 16 (22.5%) SoC (n = 647): 16 (29.6%) RR = 0.76 (95% CI, 0.42 to 1.38) RD% = −7.1 (95%CI, −2.3 to 8.5)	NC
Need for mechanical ventilation (invasive mechanical ventilation or ECMO/VV-ECMO)	
Ali, 2022 (CATCO)[8]	
Need for new mechanical ventilation[c,e] (n = 1,168), defined as being on invasive ventilation from day 2 onward, but not on day 1 Remdesivir (n = 575): 46 (8.0%) SoC (n = 593): 89 (15.0%) RR = 0.53 (95% CI, 0.38 to 0.75) RD% = −7.0 (95% CI, −10.6 to −3.4)	NC
Beigel, 2020 (ACTT-1)[13]	
New use of mechanical ventilation or ECMO during study, day 29 Remdesivir + SoC (n = 402): 52 (13%, 95% CI, 10 to 17) Placebo + SoC (n = 364): 82 (23%, 95% CI, 19 to 27) Difference: −10 (95% CI, −15 to −4)	Need for mechanical ventilation Remdesivir vs. SoC RR = 0.57; 95% CI, 0.42 to 0.79 RD = −9.59; 95% CI, −14.99 to −4.19

Reported results on outcomes of interest	Additional results calculated based on reported study results[a]
Spinner, 2022 (GSD-US-540-5774)[14]	
Number of patients hospitalized requiring invasive mechanical ventilation or extracorporeal membrane oxygenation: second category on the 7-point ordinal scale (0 for all groups at baseline) Day 11 10-day remdesivir (n = 193): 1 (0.5%) 5-day remdesivir (n = 191): 0 (0%) SoC (n = 200): 4 (2%) Day 14 10-day remdesivir (n = 193): 1 (0.5%) 5-day remdesivir (n = 191): 0% SoC (n = 200): 5 (3%) Day 28 10-day remdesivir (n = 193): 1 (0.5%) 5-day remdesivir (n = 191): 0 (0%) SoC (n = 200): 4 (2%)	Need for mechanical ventilation, day 11 10-day remdesivir vs. SoC RR = 0.26; 95% CI, 0.029 to 2.30 Need for mechanical ventilation, day 11 5-day remdesivir vs. SoC RR = 0.12; 95% CI, 0.006 to 2.15 Need for mechanical ventilation, day 14 10-day remdesivir vs. SoC RR = 0.21; 95% CI, 0.024 to 1.76 Need for mechanical ventilation, day 14 5-day remdesivir vs. SoC RR = 0.095; 95% CI, 0.005 to 1.71 Need for mechanical ventilation, day 28 10-day remdesivir vs. SoC RR = 0.26; 95% CI, 0.029 to 2.30 Need for mechanical ventilation, day 28 5-day remdesivir vs. SoC RR = 0.12; 95% CI, 0.006 to 2.15
Need for intubation	
Beigel, 2020 (ACTT-1)[13]	
The combined number of subjects with respiratory failure or acute respiratory failure was 47 for remdesivir and 80 for placebo. Endotracheal intubations and serious adverse events (without a respiratory serious adverse event) were summarized as respiratory failures (Day 29) Remdesivir + SoC (n = 532): 39 (7.3%) Placebo + SoC (n = 516): 66 (12.8%)	Need for intubation Remdesivir vs. placebo RR = 0.57; 95% CI, 0.39 to 0.84 RD = −5.46%; 95% CI, −9.09 to 1.83

CI = confidence interval; ECMO = extracorporeal membrane oxygenation; HR = hazard ratio; ICU = intensive care unit; IQR = interquartile range; MD = mean difference; NA = not applicable; NC = no calculation; NEWS-2 = National Early Warning Score 2; NIPPV = noninvasive positive-pressure ventilation; OR = odds ratio; RD = risk difference; RR = relative risk; SoC = standard of care.

[a] Additional calculations based on the reported data were made to derive effect estimates and/or aid in identifying statistical significance.

[b] Number of patients in each arm not reported, only total number available.

[c] Unclear follow-up; we assumed 28 days, as it was related to hospitalization and the study is part of the WHO Solidarity trial.

[d] Estimates were from competing risk models and cause-specific proportional hazard models (with death as the competing risk).

[e] Unclear whether new oxygen was high-flow or not.

Safety

The results reported on the safety outcomes of interest in the RCTs, as well as additional results calculated based on these reported study results, are provided in Table 9. In Appendix 5, Table 26, the reported results are again provided, as well as the study authors' conclusions. Reported results were sufficient to pool data for some outcomes, namely: all-cause mortality, incidence of any SAEs, grade 3 or 4 AEs, SAE – acute kidney injury, and SAE – hepatobiliary disorders.

All-cause mortality was reported in all 6 studies. As outlined in the Methods section, we used the data from the 4 independent studies[8-10,12] of the WHO Solidarity trial, together with Beigel et al. (the ACTT-1 trial) and Spinner et al. (the GSD-US-540-5774 trial) in the analysis. Considering individual study results, mortality over the study period up to day 28 or 29 was lower in the remdesivir group compared to the SoC or placebo group, but not statistically significantly reduced, as the RR and 95% CI in Figure 3 illustrate. However, when these studies were combined in a meta-analysis, there was a statistically significant reduction in mortality for remdesivir compared to the SoC or placebo group, with a 20% RR reduction (RR = 0.81; 95% CI, 0.68 to 0.95) (Figure 3).

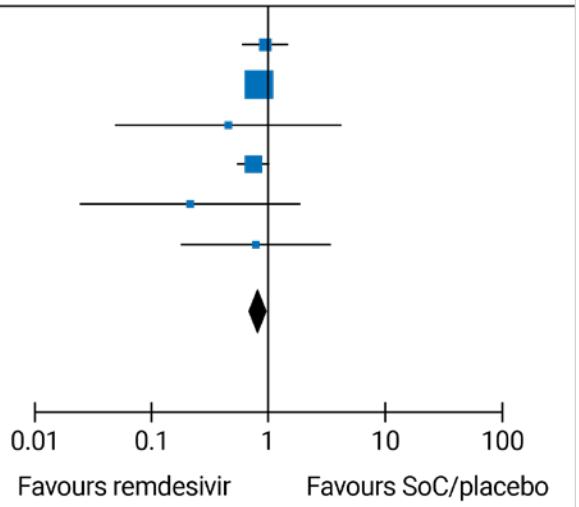
Key Finding
Combining the results of 6 RCTs showed that remdesivir significantly reduces the relative risk of death, despite each individual RCT showing no significant difference.

Figure 3

Meta-Analysis of All-Cause Mortality for Remdesivir Versus SoC or Placebo – Risk Ratio

Study or Subgroup	Remdesivir Events	Remdesivir Total	SoC/Placebo Events	SoC/Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Ader, 2022	34	414	37	418	13.6%	0.93 [0.59 , 1.45]
Ali, 2022	117	625	145	641	57.2%	0.83 [0.67 , 1.03]
Barratt-Due, 2021	1	42	3	57	0.5%	0.45 [0.05 , 4.20]
Beigel, 2020	59	541	77	521	26.8%	0.74 [0.54 , 1.01]
Nevalainen, 2022	1	103	4	88	0.6%	0.21 [0.02 , 1.88]
Spinner, 2020	3	193	4	200	1.2%	0.78 [0.18 , 3.43]
Total (95% CI)		**1918**		**1925**	**100.0%**	**0.81 [0.68 , 0.95]**
Total events	215		270			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.44$, df = 5 (P = 0.79); $I^2 = 0\%$
Test for overall effect: Z = 2.58 (P =0.010)
Test for subgroup differences: Not applicable



CI = confidence interval; M-H = Mantel-Haenszel; SoC = standard of care.

Any SAE up to 28 days or 29 days was reported in 4 studies. The studies by Ader et al. (the DisCoVeRy trial)[12] and Barratt-Due et al. (the NOR-Solidarity trial)[9] found a higher number of SAEs in the remdesivir group compared to the SoC or placebo group, but the increase was not statistically significant, as the RR and 95% CI in Figure 4 illustrate. The studies by Beigel et al. (the ACTT-1 trial)[13] and Spinner et al. (the GSD-US-540-5774 trial)[14] found a lower SAE incidence in the remdesivir group compared to the SoC or placebo group, with the former study identifying a statistically significant reduction (RR = 0.78; 95% CI, 0.64 to 0.95). When these studies were combined in a meta-analysis, there was no statistically significant difference between remdesivir and SoC or placebo (RR = 0.91; 95% CI, 0.68 to 1.21) (Figure 4).

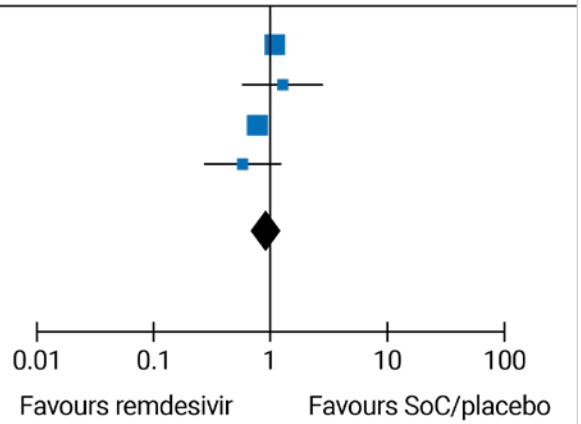
Key Finding
The incidence of serious adverse events and grade 3 or 4 adverse events does not appear to differ between remdesivir and standard of care.

Figure 4

Meta-Analysis of Any SAE for Remdesivir Versus SoC or Placebo – Risk Ratio

Study or Subgroup	Remdesivir Events	Remdesivir Total	SoC/Placebo Events	SoC/Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Ader, 2022	147	410	138	423	39.7%	1.10 [0.91 , 1.33]
Barratt-Due, 2021	8	42	13	87	10.0%	1.27 [0.57 , 2.84]
Beigel, 2020	131	532	163	516	39.2%	0.78 [0.64 , 0.95]
Spinner, 2020	10	193	18	200	11.1%	0.58 [0.27 , 1.22]
Total (95% CI)		**1177**		**1226**	**100.0%**	**0.91 [0.68 , 1.21]**
Total events	296		332			

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 8.36$, df = 3 (P = 0.04); $I^2 = 64\%$
Test for overall effect: Z = 0.67 (P =0.50)
Test for subgroup differences: Not applicable



CI = confidence interval; M-H = Mantel-Haenszel; SoC = standard of care.

Grade 3 or 4 AEs up to 28 days or 29 days were reported in 3 studies,[12-14] and all reported no statistically significant difference between remdesivir and SoC or placebo, as the RR and 95% CI in Figure 5 illustrate. Also, when these studies were combined, there was no statistically significant difference between remdesivir and SoC (RR = 0.92; 95% CI, 0.84 to 1.01) (Figure 5).

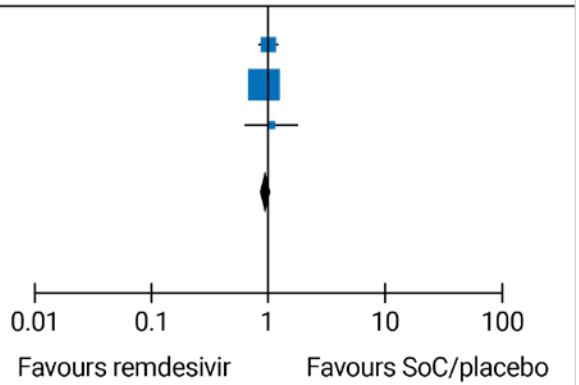
WDAEs were reported in 3 studies. Barratt-Due et al. (the NOR-Solidarity trial)[9] reported no occurrences of WDAEs for both study groups. Spinner et al. (the GSD-US-540-5774 trial)[14] reported 8 patients (4%) and 4 patients (2%) in the 10-day remdesivir and 5-day remdesivir groups, respectively, while for SoC, authors reported these as not applicable and an effect estimate could not be calculated. Beigel et al. (the ACTT-1 trial)[13] reported 52 patients (9.8%) in the remdesivir group and 70 patients (13.6%) in the placebo group, and although WDAEs were lower in the remdesivir group, the difference was not statistically significant (RR = 0.72; 95% CI, 0.51 to 1.01).

Figure 5

Meta-Analysis of Grade 3 or 4 AEs for Remdesivir Versus SoC or Placebo – Risk Ratio

Study or Subgroup	Remdesivir Events	Remdesivir Total	SoC/Placebo Events	SoC/Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Ader, 2022	143	410	150	423	25.9%	0.98 [0.82 , 1.18]
Beigel, 2020	273	532	295	516	70.9%	0.90 [0.80 , 1.00]
Spinner, 2020	24	193	24	200	3.1%	1.04 [0.61 , 1.76]
Total (95% CI)		**1135**		**1139**	**100.0%**	**0.92 [0.84, 1.01]**
Total events	440		469			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.91$, df = 2 (P = 0.63); $I^2 = 0\%$
Test for overall effect: Z = 1.67 (P = 0.10)
Test for subgroup differences: Not applicable



CI = confidence interval; M-H = Mantel-Haenszel; SoC = standard of care.

Acute kidney injury–related outcomes were reported in 4 studies. Ali et al. (the CATCO trial)[8] reported day 5 serum creatinine and new dialysis, and indicated that there was no difference in the number of patients requiring new dialysis (RR = 1.09; 95% CI, 0.54 to 2.19) and no difference in creatinine between remdesivir and SoC (MD = −0.92; 95% CI, −10.9 to 9.1). Spinner et al. (the GSD-US-540-5774 trial)[14] reported on different grades of creatinine clearance decrease up to 28 days, and no statistically significant difference was found between the 10-day remdesivir and SoC groups for: any grade (RR = 0.85; 95% CI, 0.61 to 1.19), grade 3 (RR = 0.81; 95% CI, 0.31 to 2.12), or grade 4 (RR = 0.42; 95% CI, 0.08 to 2.12). A similar result of no statistically significant difference was found for 5-day remdesivir versus SoC, except for the any grade category, in which a statistically significant difference was found between the 5-day remdesivir and SoC groups (RR = 0.49; 95% CI, 0.32 to 0.74). The previously mentioned outcomes in both studies were not defined as serious or nonserious in the original report. Beigel et al. (the ACTT-1 trial)[13] reported no statistically significant difference between remdesivir and placebo for acute kidney injury (RR = 0.56; 95% CI, 0.22 to 1.43), renal failure (RR = 0.39; 95% CI, 0.076 to 1.99), and glomerular filtration rate decrease (RR = 2.42; 95% CI, 0.47 to 12.44) under SAEs, and creatinine renal clearance decrease (RR = 0.65; 95% CI, 0.18 to 2.28) under nonserious AEs. Ader et al. (the DisCoVeRy trial)[12] reported acute kidney injury as one of the SAEs, and found no statistically significant difference between remdesivir and SoC (RR = 0.82; 95% CI, 0.39 to 1.74). Both Beigel et al. (the ACTT-1 trial) and Ader et al. (the DisCoVeRy trial) reported no statistically significant difference in acute kidney injury between remdesivir and SoC, and when these studies were combined, there was no statistically significant difference between remdesivir and SoC (RR = 0.71; 95% CI, 0.40 to 1.27) (Figure 6).

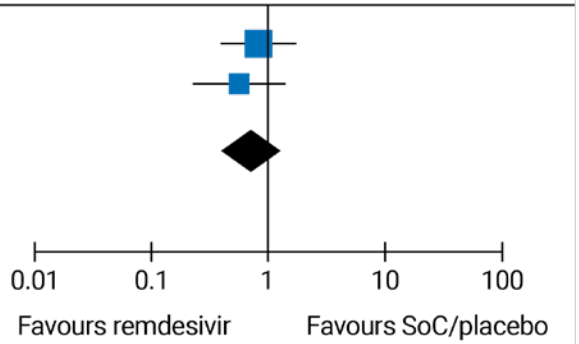
Key Finding
There are insufficient data to draw any conclusions on withdrawals due to adverse events and specific serious adverse events, including acute kidney injury, acute liver injury, and thrombocytopenia.

Figure 6

Meta-Analysis of Serious Acute Kidney Injury for Remdesivir Versus SoC or Placebo – Risk Ratio

Study or Subgroup	Remdesivir Events	Remdesivir Total	SoC/Placebo Events	SoC/Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Ader, 2022	12	406	15	418	60.5%	0.82 [0.39 , 1.74]
Beigel, 2020	7	532	12	516	39.5%	0.57 [0.22 , 1.43]
Total (95% CI)		**938**		**934**	**100.0%**	**0.71 [0.40, 1.27]**
Total events	19		27			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.38$, df = 1 (P = 0.54); $I^2 = 0\%$
Test for overall effect: Z = 1.16 (P = 0.25)
Test for subgroup differences: Not applicable



CI = confidence interval; M-H = Mantel-Haenszel; SoC = standard of care.

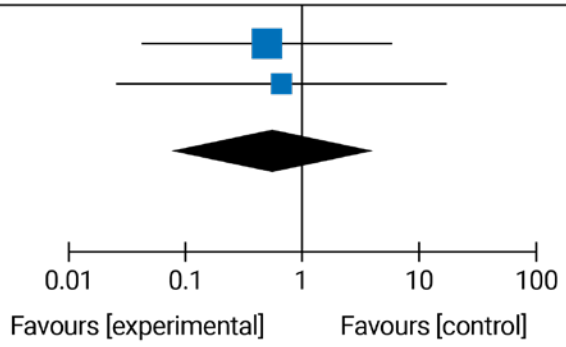
Acute liver injury–related outcomes were reported in 5 studies. Ali et al. (the CATCO trial)[8] reported new hepatic dysfunction, but it was not defined as an SAE in their report, and the authors found no differences in the incidence of hepatic dysfunction between the remdesivir and SoC groups (RR = 0.96, 95% CI, 0.72 to 1.26). Beigel et al. (the ACTT-1 trial)[13] found a statistically significant reduction in the number of patients with transaminase (AST or ALT) increase with remdesivir compared to placebo (RR = 0.56; 95% CI, 0.37 to 0.86), and found no statistically significant difference between remdesivir and placebo for the number of patients with a liver function test increase (RR = 0.97; 95% CI, 0.20 to 4.78) or hepatobiliary disorders (RR = 0.65; 95% CI, 0.11 to 3.85). The authors considered these nonserious AEs. Spinner et al. (the GSD-US-540-5774 trial)[14] reported ALT increase up to 28 days, and no statistically significant difference was found between the 10-day remdesivir and SoC groups for: any grade (RR = 0.83; 95% CI, 0.62 to 1.09), grade 3 (RR = 0.56; 95% CI, 0.21 to 1.48), or grade 4 (RR = 0.15; 95% CI, 0.01 to 2.85). Similarly, no statistically significant difference was found for AST: any grade (RR = 0.97; 95% CI, 0.72 to 1.31), grade 3 (RR = 0.35; 95% CI, 0.07 to 1.69), or grade 4 (RR = 0.09; 95% CI, 0.01 to 1.70). Barratt-Due et al. (the NOR-Solidarity trial)[9] reported hepatobiliary disorders (RR = 0.68; 95% CI, 0.028 to 16.40) and Ader et al. (the DisCoVeRy trial)[12] reported hepatobiliary disorders (cholangitis, hepatocellular injury, hepatorenal syndrome) (RR = 0.51; 95% CI, 0.047 to 5.66).
We combined the data for hepatobiliary disorders and found no statistically significant difference between remdesivir and SoC (RR = 0.57; 95% CI, 0.08 to 3.86) (Figure 7). We did not combine results from Beigel et al. (the ACTT-1 trial)[13] with others since the AE was reported as a nonserious AE, but we did include Ader et al. (the DisCoVeRy trial)[12] since it did not indicate whether this was a serious or nonserious AE.

Figure 7

Meta-Analysis of Hepatobiliary Disorders for Remdesivir Versus SoC or Placebo – Risk Ratio

Study or Subgroup	Remdesivir Events	Total	SoC Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Ader, 2022	1	406	2	418	63.8%	0.51 [0.05 , 5.66]
Barratt-Due, 2021	0	42	1	87	36.2%	0.68 [0.03 , 16.40]
Total (95% CI)		**448**		**505**	**100.0%**	**0.57 [0.08, 3.86]**
Total events	1		3			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 (P = 0.89); $I^2 = 0\%$
Test for overall effect: Z = 0.58 (P = 0.56)
Test for subgroup differences: Not applicable



CI = confidence interval; M-H = Mantel-Haenszel; SoC = standard of care.

Thrombocytopenia-related outcomes were reported in 4 studies. Ader et al. (the DisCoVeRy trial)[12] reported no thrombocytopenia with remdesivir and 1 patient in the SoC group, but this outcome was not defined as an SAE. Barratt-Due et al. (the NOR-Solidarity trial)[9] reported no cases of blood and lymphatic system disorders for both remdesivir and SoC, and these were not defined under SAEs. Spinner et al. (the GSD-US-540-5774 trial)[14] reported thrombocytopenia as an SAE and found 0 instances in all 3 groups (10-day remdesivir, 5-day remdesivir, and SoC). Beigel et al. (the ACTT-1 trial)[13] reported on platelet count decrease under nonserious AEs, with 6 patients (1.1%) and 2 patients (0.1%) in the remdesivir and placebo groups, respectively; platelet count decrease was greater in the remdesivir group, although the difference was not statistically significant (RR = 2.9; 95% CI, 0.59 to 14.35).

Table 9

Results for Safety Outcomes of Interest

Reported results on outcomes of interest	Additional results calculated based on reported study results[a]
Death	
Beigel, 2020 (ACTT-1)[13]	
1. Mortality through day 15, n (%) Remdesivir + SoC (n = 541): 35 (6.5%) Placebo + SoC (n = 532): 61 (11.5%) HR (95% CI): HR = 0.55 (95% CI, 0.36 to 0.83)	Death by day 29 Remdesivir vs. placebo RR = 0.74; 95% CI, 0.54 to 1.01
2. Mortality over the entire study period, by day 29, n (%) Remdesivir (n = 541): 59 (10.9%) SoC (n = 532): 77 (14.5%) HR = 0.73 (95% CI, 0.52 to 1.03)	

Reported results on outcomes of interest	Additional results calculated based on reported study results[a]
Spinner, 2022 (GSD-US-540-5774)[14]	
Death on 7-category scale, n (%) 1. Day 11 10-day remdesivir (n = 193): 2 (1%) 5-day remdesivir (n = 191): 0 (0%) SoC (n = 200): 4 (2%) 2. Day 14 10-day remdesivir (n = 193): 2 (1%) 5-day remdesivir (n = 191): 1 (1%) SoC (n = 200): 4 (2%) 3. Day 28 10-day remdesivir (n = 193): 3 (1.6%) 5-day remdesivir (n = 191): 2 (1%) SoC (n = 200): 4 (2%)	Death by day 28 10-day remdesivir vs. SoC RR = 0.78; 95% CI, 0.18 to 3.43 Death by day 28 5-day remdesivir vs. SoC RR 0.52; 95% CI, 0.097 to 2.83
Ali, 2022 (CATCO)[8]	
1. All-cause, in-hospital mortality, n = 1,267 (15 patients had missing hospital mortality and length of stay: 6 patients were still in hospital and 9 withdrew consent)[b] Remdesivir (n = 626): 117 (18.7%) SoC (n = 641): 145 (22.6%) RR = 0.83 (95% CI, 0.67 to 1.03) RD% = −3.9 (95% CI, −8.3 to 1.03) 2. Mortality by 60 days, n = 1,052 (230 patients withdrew consent or were lost to follow-up after discharge) Remdesivir (n = 512): 127 (24.8) SoC (n = 539): 152 (28.2) RR = 0.88 (95% CI, 0.72 to 1.07) RD% = −3.4 (95% CI, −8.8 to 1.9)	NC
Barratt-Due, 2021 (NOR-Solidarity)[9]	
1. Mortality during hospitalization, % (95% CI) Remdesivir + SoC (n = 42): 7.1 (1.8 to 17.5) SoC (n = 57): 7.0 (95% CI, 2.2 to 15.6) RR = 1.0 (95% CI, 0.2 to 4.6) HR = 1.0 (95% CI, 0.4 to 2.9) 2. Mortality at day 28, % (95% CI) Remdesivir + SoC (n = 42): 2.4 (95% CI, 0.1 to 10.1) SoC (n = 57): 5.3 (95% CI, 1.3 to 13.1) RD% = −2.9 (95% CI, −10.3 to 4.5) 3. Mortality at day 60, % (95% CI) Remdesivir +SoC (n = 42): 7.1 (95% CI, 1.8 to 17.5) SoC (n = 57): 5.3 (95% CI, 1.3 to 13.1) RD% = 1.9 (95% CI, −7.8 to 11.6)	Death by day 28 Remdesivir vs. SoC RR = 0.45; 95% CI, 0.049 to 4.20

Reported results on outcomes of interest	Additional results calculated based on reported study results[a]
Ader, 2022 (DisCoVeRy)[12]	
1. Death at day 15: 7-point ordinal scale, n (%)[c] Remdesivir (n = 414): 21 (5%) SoC (n = 418): 24 (6%) OR = 0.98 (95% CI, 0.77 to 1.25) 2. Death at day 29: 7-point ordinal scale Remdesivir (n = 414): 34 (8%) SoC (n = 418): 38 (9%) OR = 1.11 (95% CI, 0.87 to 1.42) 3. Death within 28 days Remdesivir (n = 414): 34 (8%) SoC (n = 418): 37 (9%) OR = 0.93 (95% CI, 0.57 to 1.52) 4. In-hospital death Remdesivir (n = 420): 33 SoC (n = 423): 38 Adjusted OR: OR = 0.84 (95% CI, 0.51 to 1.37) 5. Mortality at 3 months Remdesivir (n = 420): 43 SoC (n = 423): 49 Adjusted OR: OR = 0.87 (95% CI, 0.56 to 1.36).	Death by day 28 Remdesivir vs. SoC RR = 0.93; 95% CI, 0.59 to 1.45
Nevalainen, 2022 (SOLIDARITY Finland)[10]	
1. Mortality during hospitalization[b] Remdesivir (n = 103): 1 (0.9%) SoC (n = 88): 4 (4.3) 2. At 1 year, n = 181 Remdesivir (n = 103): 5 (4.4%) SoC (n = 88): 5 (5.3%) RR = 0.82 (95% CI, 0.25 to 2.76) RD% = −0.9 (95% CI, −7.9 to 5.3)	Death in hospital Remdesivir vs. SoC RR = 0.21; 95% CI, 0.024 to 1.88
SAEs and grade 3 or 4 AEs, total	
Beigel, 2020 (ACTT-1)[13]	
1. At least 1 SAE, 29 days, n (%) Remdesivir + SoC (n = 532): 131 (24.6%) Placebo + SoC (n = 516): 163 (31.6%) P = 0.010 2. Grade 3 and 4 AEs Remdesivir + SoC (n = 532): 273 (51.3%) Placebo + SoC (n = 516): 295 (57.2%) P = 0.058	SAEs, day 29 Remdesivir vs. placebo RR = 0.78; 95% CI, 0.64 to 0.95 Grade ≥ 3 AEs, day 29 Remdesivir vs. placebo RR = 0.79; 95% CI, 0.62 to 1.01

Reported results on outcomes of interest	Additional results calculated based on reported study results[a]
Spinner, 2022 (GSD-US-540-5774)[14]	
1. Any SAE, 28 days, n (%) 10-day remdesivir (n = 193): 10 (5%) 5-day remdesivir (n = 191): 9 (5%) SoC (n = 200): 18 (9%) 2. Any grade ≥ 3 AE 10-day remdesivir (n = 193): 24 (12%) 5-day remdesivir (n = 191): 20 (10%) SoC (n = 200): 24 (12%)	SAEs, day 28 10-day remdesivir vs. SoC RR = 0.58; 95% CI, 0.27 to 1.22 SAEs, day 28 5-day remdesivir vs. SoC RR = 0.52; 95% CI, 0.24 to 1.14 Grade ≥ 3 AEs, day 28 10-day remdesivir vs. SoC RR = 1.04; 95% CI, 0.57 to 1.90 Grade ≥ 3 AEs, day 28 5-day remdesivir vs. SoC RR = 0.87; 95% CI, 0.50 to 1.53)
Barratt-Due, 2021 (NOR-Solidarity)[9]	
Patients with serious AEs[d], 28 days, n (%) Remdesivir (n = 42): 8 (15.4%) SoC[e] (n = 87): 13 (14.9%)	SAEs, day 28 Remdesivir vs. SoC RR = 1.27; 95% CI, 0.57 to 2.84
Ader, 2022 (DisCoVeRy)[12]	
1. Any SAE, 29 days, n (%) Remdesivir (n = 410): 147 (35.9%) SoC (n = 423): 138 (32.6%) OR 1.77 (95% CI, 0.87 to 1.57) 2. Grade 3 or 4 AE Remdesivir (n = 410): 143 (34.9%) SoC (n = 423): 150 (36.2%) OR = 0.98 (95% CI, 0.73 to 1.32)	SAEs, day 29 Remdesivir vs. SoC RR = 1.10; 95% CI, 0.91 to 1.33 Grade ≥ 3 AEs, day 29 Remdesivir vs. SoC RR = 0.97; 95% CI, 0.73 to 1.30
Withdrawal of treatment due to AEs	
Barratt-Due, 2021 (NOR-Solidarity)[9]	
Withdrawal of treatment due to AEs Remdesivir + SoC (n = 42): 0 SoC[e] (n = 87): 0	WDAEs Remdesivir vs. SoC RR not estimable

Reported results on outcomes of interest	Additional results calculated based on reported study results[a]
Spinner, 2022 (GSD-US-540-5774)[14]	
Discontinuation of treatment because of AEs, N (%) 10-day remdesivir (n = 93): 8 (4%) 5-day remdesivir (n = 191): 4 (2%) SoC (n = 200): NR	Not estimable
Beigel, 2020 (ACTT-1)[13]	
Discontinued due to AEs or SAEs, other than death leading to treatment discontinuation, n (%) Remdesivir + SoC (n = 532): 52 (9.8%) Placebo + SoC (n = 516): 70 (13.6%)	WDAEs Remdesivir vs. SoC RR 0.72, 95% CI 0.51 to 1.01
SAE - acute kidney injury	
Ali, 2022 (CATCO)[8]	
Day 5 serum creatinine,[f] mean ± SD; median (IQR), n = 936[g] Remdesivir: 86.7 ± 78.0; 71 (IQR, 57 to 88.5) SoC: 87.7 ± 79.2; 69 (IQR, 57 to 87.5) MD = −0.92 (95% CI, −10.9 to 9.1) Median difference = −1 (95% CI, −4 to 2) New dialysis:[f] Defined as dialysis for those who were not on dialysis at baseline (16 patients were on dialysis on day 1 and were excluded), n (%) Remdesivir (n = 625): 16 (2.6%) SoC (n = 640): 15 (2.3%) RR = 1.09 (95% CI, 0.54 to 2.19) RD% = 0.2 (95% CI, −1.5 to 1.9)	NC

Reported results on outcomes of interest	Additional results calculated based on reported study results[a]
Spinner, 2022 (GSD-US-540-5774)[14]	
Creatinine clearance decrease,[f] n (%), up to 28 days 1. Any grade 10-day remdesivir (n = 176): 45 (26%) 5-day remdesivir (n = 178): 26 (15%) SoC (n = 183): 55 (30%) 2. Grade 3 (30 to < 60 mL/min or 30% to < 50% decrease from baseline) 10-day remdesivir (n = 176): 7 (4%) 5-day remdesivir (n = 178): 4 (2%) SoC (n = 183): 9 (5%) 3. Grade 4 (< 30 mL/min, ≥ 50% decrease from baseline, or dialysis needed) 10-day remdesivir (n = 176): 2 (1%) 5-day remdesivir (n = 178): 0 (0%) SoC (n = 183): 5 (3%)	Creatinine clearance decrease – any grade, day 28 10-day remdesivir vs. SoC RR = 0.85; 95% CI, 0.61 to 1.19 Creatinine clearance decrease – any grade, day 28 5-day remdesivir vs. SoC RR = 0.49; 95% CI, 0.32 to 0.74 Creatinine clearance decrease – grade 3, day 28 10-day remdesivir vs. SoC RR = 0.81; 95% CI, 0.31 to 2.12 Creatinine clearance decrease – grade 3, day 28 5-day remdesivir vs. SoC RR = 0.46; 95% CI, 0.14 to 1.46 Creatinine clearance decrease – grade 4, day 28 10-day remdesivir vs. SoC RR = 0.42; 95% CI, 0.082 to 2.12 Creatinine clearance decrease – grade 4, day 28 5-day remdesivir vs. SoC RR = 0.093; 95% CI, 0.005 to 1.68

Reported results on outcomes of interest	Additional results calculated based on reported study results[a]
Beigel, 2020 (ACTT-1)[13]	
Serious SAEs occurring in > 5 patients, n (%), 29 days 1. Acute kidney injury, under SAEs Remdesivir + SoC (n = 532): 7 (1.3%) Placebo + SoC (n = 516): 12 (2.3%) 2. Renal failure, under SAEs Remdesivir + SoC (n = 532): 2 (0.4%) Placebo + SoC (n = 516): 5 (1.0%) 3. Glomerular filtration rate decreased, under SAEs Remdesivir + SoC (n = 532): 5 (0.9%) Placebo + SoC (n = 516): 2 (0.4%) Nonserious AEs 4. Creatinine renal clearance decreased Remdesivir + SoC (n = 532): 4 (0.8%) Placebo + SoC (n = 516): 6 (1.2%) 5. Composite of glomerular filtration rate decreased, acute kidney injury, or renal failure Remdesivir + SoC (n = 532): 14 (2.6%) Placebo + SoC (n = 516): 17 (3.3%) 6. Composite of glomerular filtration rate decreased, acute kidney injury, blood creatinine increased, or creatinine renal clearance decreased Remdesivir + SoC (n = 532): 85 (16.0%) Placebo + SoC (n = 516): 105 (20.3%)	Acute kidney injury, day 29 Remdesivir vs. placebo RR = 0.56; 95% CI, 0.22 to 1.43 Renal failure, day 29 Remdesivir vs. placebo RR = 0.39; 95% CI, 0.076 to 1.99 Glomerular filtration rate decreased, day 29 Remdesivir vs. placebo RR = 2.42; 95% CI, 0.47 to 12.44 Creatinine renal clearance decreased, day 29 Remdesivir vs. placebo RR = 0.65; 95% CI, 0.18 to 2.28
Ader, 2022 (DisCoVeRy)[12]	
SAE – acute kidney injury[h], excluding acute renal failures defined based on the RIFLE classification; n (%), 29 days Remdesivir (n = 406): 12 (3%) SoC (n = 418): 15 (4%)	Acute kidney injury, day 29 Remdesivir vs. SoC RR = 0.82; 95% CI, 0.39 to 1.74
SAE - acute liver injury	
Ali, 2022 (CATCO)[8]	
New hepatic dysfunction[i], defined as acute liver function as clinically determined or ALT at day 5 more than twice ALT at day 1, n (%) Remdesivir (n = 625): 82 (13.1%) SoC (n = 642): 88 (13.7%) RR = 0.96 (95% CI, 0.72 to 1.26) RD% = −0.6 (95% CI, −4.4 to 3.1)	NC

Reported results on outcomes of interest	Additional results calculated based on reported study results[a]
Barratt-Due, 2021 (NOR-Solidarity)[9]	
SAE – hepatobiliary disorder Remdesivir + SoC (n = 42): 0 (0%) SoC[e] (n = 87): 1 (1.1%)	Hepatobiliary disorder, day 29 Remdesivir vs. SoC RR = 0.68; 95% CI, 0.028 to 16.40
Ader, 2022 (DisCoVeRy)[12]	
Hepatobiliary disorders, including 3 kinds: cholangitis, hepatocellular injury, and hepatorenal syndrome;[f] n (%) Remdesivir (n = 406): 1 (0%), hepatorenal syndrome SoC (n = 418): 2 (0%), 1 cholangitis and 1 hepatocellular injury	Hepatobiliary disorder Remdesivir vs. SoC RR = 0.51; 95% CI, 0.047 to 5.66
Spinner, 2022 (GSD-US-540-5774)[14]	
ALT increase, n (%), up to 28 days 1. Any grade 10-day remdesivir (n = 177): 57 (32%) 5-day remdesivir (n = 179): 61 (34%) SoC (n = 182): 71 (39%) 2. Grade 3 (> 5 to 10 times upper limit of normal) 10-day remdesivir (n = 177): 6 (3%) 5-day remdesivir (n = 179): 4 (2%) SoC (n = 182): 11 (6%) 3. Grade 4 (> 10 times upper limit of normal) 10-day remdesivir (n = 177): 0 (0%) 5-day remdesivir (n = 179): 0 (0%) SoC (n = 182): 3 (2%) Aspartate aminotransferase (AST) increase, n (%), up to 28 days 1. Any grade 10-day remdesivir (n = 175): 56 (32%) 5-day remdesivir (n = 177): 56 (32%) SoC (n = 182): 60 (33%) 2. Grade 3 (> 5 to 10 times upper limit of normal) 10-day remdesivir (n = 175): 2 (1%) 5-day remdesivir (n = 177): 3 (2%) SoC (n = 182): 6 (3%) 3. Grade 4 (> 10 times upper limit of normal) 10-day remdesivir (n = 175): 0 (0%) 5-day remdesivir (n = 177): 1 (1%) SoC (n = 182): 5 (3%)	ALT increase – any grade, day 28 10-day remdesivir vs. SoC RR = 0.83; 95% CI, 0.62 to 1.09 ALT increase – grade 3, day 28 10-day remdesivir vs. SoC RR = 0.56; 95% CI, 0.21 to 1.48 ALT increase – grade 4, day 28 10-day remdesivir vs. SoC RR = 0.15; 95% CI, 0.01 to 2.85 AST increase – any grade, day 28 10-day remdesivir vs. SoC RR = 0.97; 95% CI, 0.72 to 1.31 AST increase – grade 3, day 28 10-day remdesivir vs. SoC RR 0.35; 95% CI, 0.07 to 1.69 AST increase – grade 4, day 28 10-day remdesivir vs. SoC RR = 0.09; 95% CI, 0.01 to 1.70

Reported results on outcomes of interest	Additional results calculated based on reported study results[a]
Beigel, 2020 (ACTT-1)[13]	
1. The combined number of patients with transaminases increased,[j] AST increased, or ALT increased; n (%) Remdesivir + SoC (n = 532): 32 (6%) Placebo + SoC (n = 516): 55 (11%) 2. Liver function test increased[h] Remdesivir + SoC (n = 532): 3 (0.6%) Placebo + SoC (n = 516): 3 (0.6%) 3. Hepatobiliary disorders: hyperbilirubinemia[h] Remdesivir + SoC (n = 532): 2 (0.4%) Placebo + SoC (n = 516): 3 (0.6%)	Transaminases increase Remdesivir vs. placebo RR = 0.56; 95% CI, 0.37 to 0.86 Liver function test increase Remdesivir vs. placebo RR 0.97; 95% CI, 0.20 to 4.78 Hepatobiliary disorders Remdesivir vs. placebo RR 0.65; 95% CI, 0.11 to 3.85
SAE – thrombocytopenia	
Ader, 2022 (DisCoVeRy)[12]	
Thrombocytopenia, not defined under SAEs, n (%) Remdesivir (n = 406): 0 (0%) SoC (n = 418): 1 (0%)	Thrombocytopenia Remdesivir vs. SoC RR = 1.03; 95% CI, 0.065 to 16.37
Barratt-Due, 2021 (NOR-Solidarity)[9]	
Blood and lymphatic system disorders, not defined under SAEs, n (%) Remdesivir (n = 42): 0 (0%) SoC[e] (n = 87): 0 (0%)	Blood and lymphatic system disorders Remdesivir vs. SoC RR (95% CI): Not estimable
Spinner, 2022 (GSD-US-540-5774)[14]	
SAE – thrombocytopenia, n (%) 10-day remdesivir (n = 193): 0 (0%) 5-day remdesivir (n = 191): 0 (0%) SoC (n = 200): 0 (0%)	SAE – thrombocytopenia Remdesivir vs. SoC RR (95% CI): Not estimable
Beigel, 2020 (ACTT-1)[13]	
Platelet count decreased[k] Remdesivir + SoC (n = 532): 6 (1.1%) Placebo + SoC (n = 516): 2 (0.4%)	Platelet count Remdesivir vs. placebo RR = 2.91; 95% CI, 0.59 to 14.35

AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase; CI = confidence interval; HR = hazard ratio; IQR = interquartile range; MD = mean difference; NC = not calculated; NR = not reported; OR = odds ratio; RD = risk difference; RIFLE = Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; RR = relative risk; SAE = serious adverse event; SoC = standard of care; WDAE = withdrawal due to adverse event.

[a] Additional calculations based on the reported data were made to derive effect estimates and/or aid in identifying statistical significance.

[b] Unclear follow-up; we assumed 28 days, as it was related to hospitalization and the study is part of the WHO Solidarity trial.

[c] All analyses were adjusted for disease severity at randomization. Deaths for days 3, 5, 8, and 11 were also provided in this study.

[d] This study also provided the number of events, since a patient could have more than 1 event. These event numbers were 20 for SoC and 13 for remdesivir plus SoC.

[e] The SoC group is combination to 2 SoC groups considered in the study.

[f] Outcome was not defined as serious or nonserious in the study report.

[g] Number of patients in each group was not reported, only the total number available.

[h] There were different numbers on acute kidney injury (15 of 406 [4%] for remdesivir and 18 of 418 [4%] for SoC) in the supplementary file, but they were not defined as SAEs.

[i] Outcome not defined as SAE in the study report.

[j] Outcome was defined as nonserious AE occurring in 5 or more patients.

[k] Outcome considered under nonserious AEs.

Subgroup Analysis

Only 1 study reported a relevant subgroup analysis for an outcome of interest (Table 10). Beigel et al. (the ACTT-1 study)[13] reported subgroup analyses based on race or ethnicity for median time to recovery, which is related to time to clinical improvement. For patients who identified as white or "other," a statistically significant increase in the median time to recovery was found when patients were on placebo compared to patients on remdesivir (HR = 1.29; 95% CI, 1.06 to 1.57; and HR = 1.68; 95% CI, 1.10 to 2.58, respectively), but no statistically significant difference was found for those who identified as Asian or Black or African American (HR = 1.07; 95% CI, 0.73 to 1.58; and HR =1.25; 95% CI, 0.91 to 1.72, respectively). For those who identified as Hispanic or Latino, no statistically significant difference in the median time to recovery was found between placebo and remdesivir (HR = 1.28; 95% CI, 0.94 to 1.73), but in those who were not Hispanic or Latino, a statistically significant increase in the median time to recovery on placebo compared to remdesivir was found (HR = 1.31; 95% CI, 1.10 to 1.55).

Subgroup Analysis
Only 1 study reported a relevant subgroup analysis. The analysis was based on race and ethnic group for median time to recovery, which is related to time to clinical improvement.

Table 10

Subgroup Analysis Reported on Outcomes of Interest

Reported results on subgroups and outcomes of interest
Time to clinical improvement
Subgroup under underserved or equity-deserving groups
Beigel, 2020 (ACTT-1)[13]
Median time to recovery by treatment group within subgroups (95% CI)
Asian Remdesivir + SoC (n = 79): 11 (95% CI, 9 to15) Placebo + SoC (n = 56): 12 (95% CI, 9 to 15) HR = 1.07 (95% CI, 0.73 to 1.58)
Black or African American Remdesivir + SoC (n = 109): 10 (95% CI, 7 to 16) Placebo + SoC (n = 117): 15 (95% CI, 10 to 21) HR = 1.25 (95% CI, 0.91 to 1.72)
White Remdesivir + SoC (n = 279): 9 (95% CI, 8 to 12) Placebo + SoC (n = 287):15 (95% CI, 12 to 19) HR = 1.29 (95% CI, 1.06 to 1.57)
Other Remdesivir + SoC (n = 74): 9 (95% CI, 6 to 14) Placebo + SoC (n = 61): 24 (95% CI, 15.0 to NE) HR = 1.68 (95% CI, 1.10 to 2.58)
Hispanic or Latino Remdesivir + SoC (n = 134): 10 (95% CI, 7 to 14) Placebo + SoC (n = 116): 12.5 (95% CI, 9 to 22) HR 1.28 (95% CI, 0.94 to 1.73)
Not Hispanic or Latino Remdesivir + SoC (n = 516): 10 (95% CI, 8 to 12) Placebo + SoC (n = 373): 15 (95% CI, 13 to 18) HR = 1.31 (95% CI, 1.10 to 1.55)

CI = confidence interval; HR = hazard ratio; SoC = standard of care.

Summary of Critical Appraisal

We used the Cochrane ROB version 1.0 tool to assess the ROB of the included trials. The summary results can be found in Table 11, and the detailed judgments with justification can be found in Appendix 4, Tables 19 to 24.

Five studies used adequate and appropriate sequence generation processes and are at low ROB. In the NOR-Solidarity trial,[9] the randomization was computer generated; however, there were 2 RCTs with 2 separate control groups, and the allocation description did not clarify how the SoC was divided between the 2 active treatments. Some patients receiving SoC acted as controls for both active treatment groups, whereas some acted in 1 or the other, giving a partial overlap of the 2 control groups. In addition, the number of patients allocated to remdesivir (n = 46) and control (n = 34) were markedly different, even though an equal allocation ratio was followed; and for the analysis of AEs, the authors combined the 2 separate SoC groups, which broke the original randomization design.

All studies were at low ROB for allocation concealment based on the central randomization processes that were designed and implemented.

Five studies were at unclear ROB for blinding of participants and personnel since they were open-label RCTs, and this lack of blinding was a concern for some outcomes. Having objective outcomes will help mitigate, but not necessarily eliminate, the potential bias. Knowing a patient's allocated treatment may lead to performance bias in the way the patient is cared for in hospital and thus affect an outcome; for example, if a patient is not allocated to remdesivir, then they may be kept in hospital longer "just to be safe." This bias will vary by outcome, and so an unclear ROB was assigned. Detection bias resulting from a lack of blinding was less of a concern for assessing objective outcomes, and so a low ROB was assigned to the bias associated with blinding of outcome assessors. The study by Beigel et al. (ACTT-1)[13] was a double-blind RCT and was assigned a low

Risk of Bias Assessment
The 6 RCTs are all at a low risk of bias for 3 of 7 bias domains. For 5 RCTs, there is an unclear risk of bias for blinding of participants and personnel since they are open-label RCTs.

ROB for both blinding of participants and personnel, and blinding of outcome assessors.

Five studies were at low ROB for incomplete outcome data. The study by Spinner et al. (GSD-US-540-5774)[14] was deemed as having an unclear risk, because there was no reporting (reported as "not applicable" in the trial) of withdrawals or AEs in the standard care group, and all 200 patients were included in the analysis. Given that the analysis used the safety population, it is unclear as to whether there was complete follow-up in the control group or if there were patients who terminated early for reasons other than discharge.

Five studies were at low ROB for selective outcome reporting. The study by Spinner et al. (GSD-US-540-5774)[14] was classified as having an unclear risk, because the duration of hospitalization was 1 outcome of particular interest, but the authors described it as not being different between groups without reporting any data.

For other ROB, we did not find any other apparent sources of bias.

Table 11

ROB Assessment of Included Studies

Study	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Spinner (GS-US-540-5774)	Low	Low	Unclear	Low	Unclear	Unclear	Low
Beigel (ACTT-1)	Low	Low	Low	Low	Low	Low	Low
Ali (CATCO)	Low	Low	Unclear	Low	Low	Low	Low
Barratt-Due (NOR-Solidarity)	Unclear	Low	Unclear	Low	Low	Low	Low
Nevalainen (SOLIDARITY Finland)	Low	Low	Unclear	Low	Low	Low	Low
Ader (DisCoVeRy)	Low	Low	Unclear	Low	Low	Low	Low

ROB = risk of bias.

Note: Low = low ROB; high = high ROB; unclear = unclear ROB.

Generalizability

The elements characterizing the generalizability of these studies to Canada are summarized in terms of PICOS. For the population, 6 patient characteristics were identified a priori as important, and could be associated with differences in treatment outcomes, namely: age, sex, race or ethnicity, comorbidities, vaccination status, and COVID-19 variant. The average age in the 6 studies was approximately 60 years, and the percentage of female patients was below 40%, which is lower than expected in practice. For race and ethnicity, 4 of the studies provided race and/or ethnicity data, and a number of different groups were included, but in general, the majority of patients were white (with an average typically exceeding 50%). The study by Ali et al. (CATCO) included Indigenous or First Nations patients (5.3%), and the study by Beigel et al. (ACTT-1) included patients who identified as American Indian or Alaska Native [wording from original source] (0.7%). Several comorbidities were identified for 5 studies and no study reported on immunocompromised patients. The most important characteristics of concern regarding the generalizability of these studies to Canada today is the difference in vaccination status and the dominant COVID-19 variants at the time that the included studies were conducted. These studies were mostly planned and conducted before widespread vaccination programs were implemented, so the majority of patients were not vaccinated. Further, these studies were conducted before the emergence of the Omicron and Delta variants, and prior to the existence of any related subvariants of concern.

For the intervention and comparator, the remdesivir intervention was standardized and often in combination with SoC, but as a comparator, SoC can vary and was often unspecified. For outcomes, all studies reported on mortality and different follow-up times were considered, but the usual time period was 28 or 29 days, reflecting the most important efficacy and safety outcomes of treatment. Finally, for the setting, studies considered were restricted to those that had a health care system or economy similar to those in Canada.

Generalizability
The most concerning characteristics impacting generalizability include the difference in vaccination status, the dominant COVID-19 variant during the study periods, and the comparability of the standard of care.

WHO Solidarity Trial

As mentioned previously, patients in 4 of the included trials either partially or completely overlapped with those in the WHO Solidarity trial.[6,7] As such, it was excluded from the main analysis and reported on individually in the section that follows.

WHO Solidarity Trial
We excluded the trial from the main analysis, reporting on it individually. The trial included 405 hospitals, across 30 countries, with 4,169 patients randomized to the remdesivir treatment group.

Characteristics of the Study

The WHO Solidarity trial was a multicentre, open-label, adaptive RCT that compared remdesivir, hydroxychloroquine, lopinavir-ritonavir, or interferon beta-1a (combined with lopinavir-ritonavir until July 4, 2020) against their own control group, in hospitalized patients with a confirmed diagnosis of COVID-19. The study was conducted from March 2020 to January 2021. While there were 4 treatment groups, only the results of the remdesivir group are pertinent to this review. Since the trial was adaptive, treatment arms could be dropped and added accordingly. The trial included 405 hospitals across 30 countries. A total of 14,220 patients were included in the trial, with 8,320 patients assigned to remdesivir or its control group. More specifically, a total of 4,169 patients were randomized to the remdesivir treatment group and 4,151 patients were randomized to receive SoC according to local practices.[6,7] Treatment duration was for 9 days, and follow-up was 28 days. Further details on the study characteristics are provided in Table 12 and in Appendix 6, Table 27.

Table 12

Basic Characteristics of the WHO Solidarity Trial

Characteristic	WHO Solidarity Trial Consortium, 2022[6,7]
Name and trial number	WHO Solidarity NCT04315948
Study time period	March 22, 2020, to January 29, 2021
Study design	Open-label, adaptive RCT
Setting	Several countries in Europe, Latin America, Asia, and Africa, as well as Canada

Characteristic	WHO Solidarity Trial Consortium, 2022[6,7]
Randomized, N	14,220, with only 8,320 for eligible arms
Patients	Adult patients (aged ≥ 18 years) with COVID-19
Treatment duration of remdesivir	9 days
Follow-up time points	28 days
Interventions	Group 1: Remdesivir Group 2: SoC
Outcomes of interest	1. Need for mechanical ventilation 2. Mortality

RCT = randomized controlled trial; SoC = standard of care.

Characteristics of the Patients

Patients were recruited for this study worldwide. It is estimated that less than 40% of the patients were from settings in which the health care system was similar to Canada and considered relevant for this review. Co-interventions listed for some patients included corticosteroids, convalescent plasma, anti-IL-6 medication, nontrial interferon, and nontrial antiviral. The majority of patients were aged older than 50 years (68.2%). Overall, 36.7% were female and 63.3% were male. The most frequently reported comorbidities were diabetes (27.1%) and heart disease (22.5%). Table 13 provides further information on the characteristics of the patients enrolled in the remdesivir versus control groups of the WHO Solidarity trial.

Key Point
We estimate that less than 40% of the included patients were from a setting where the health care system and/or economy are similar to Canada.

Table 13

Characteristics of Patients From the WHO Solidarity Trial

Characteristic	WHO Solidarity Trial Consortium, 2022 (WHO Solidarity)[6,7]	
Treatment	Remdesivir[a]	SoC
Randomized patients, n	4,169[b]	4,151[b]
Age (years)	Range: n	
	< 50: 1,310 50 to 69: 1,920 ≥ 70: 916	< 50: 1,326 50 to 69: 1,908 ≥ 70: 895
Sex n (%)	Female: 1,545 (37.3) Male: 2,601 (62.7)	Female: 1,490 (36.1) Male: 2,639 (63.9)
Race or ethnicity, n (%)	NR	NR
Immunocompromised patients, n (%)	NR	NR
COVID-19 variant	NR, but recruitment preceded the Delta and Omicron variants	
Vaccination status	NR, but mostly in era before vaccination	
Underserved or equity-deserving groups, n (%)	NR	NR
Patients with comorbidities, n (%)	NR	NR
Categories of comorbidities, n (%)	Diabetes: 1,129 (27.2) Heart disease: 929 (22.4) Chronic lung disease: 284 (6.8) Asthma: 247 (6.0) Chronic liver disease: 57(1.4)	Diabetes: 1,120 (27.1) Heart disease: 935 (22.6) Chronic lung disease: 281 (6.8) Asthma: 242 (5.9) Chronic liver disease: 72 (1.7)
Time from symptom onset to hospitalization or ER (days)	NR	
	NR	NR

ER = emergency room; NR = not reported; SoC = standard of care.

[a] Includes SoC.

[b] Number of patients randomized; however, only 8,275 were included in the analysis, with 4,146 receiving remdesivir and 4,129 receiving SoC, which were the denominators of the 2 groups, respectively, for baseline characteristics.

Data Analysis and Synthesis

We assessed the sensitivity of the results when considering and incorporating the data from the large WHO Solidarity platform trial. The restriction of including only studies from countries that had a health care system similar to that of Canada markedly diminished the evidence base. The number of patients was reduced, the number of comparisons of outcomes was reduced, and the number of subgroups that could be considered was reduced. We incorporated an expanded body of evidence by evaluating the WHO Solidarity trial that, while satisfying the majority of our a priori eligibility criteria, was excluded from the main analysis, as it included patients that were not from countries that had a setting similar to Canada.

The results reported on the outcomes of interest in the WHO Solidarity trial are provided in Table 14 for efficacy and safety. Two such outcomes were identified: as an efficacy outcome, the need for mechanical ventilation; and as a safety outcome, all-cause mortality.

Need for mechanical ventilation (invasive mechanical ventilation or ECMO/VV-ECMO): The WHO Solidarity trial[6] reported initiation of ventilation in those not already ventilated at baseline. However, it was difficult to judge from the description if this included all types of mechanical ventilation, especially when it was indicated that disease severity at entry was not separated into high-flow and low-flow oxygen, or noninvasive and invasive ventilation. Results from the WHO Solidarity trial are in alignment with the main analysis. The combined data for the 3 studies with nonoverlapping patient populations from the main analysis (i.e., Ali et al.,[8] Beigel et al.,[13] and Spinner et al.[14]) identified a statistically significant reduction in the need for mechanical ventilation or ECMO at 28 or 29 days in the remdesivir group compared with the SoC or placebo group (RR = 0.55; 95% CI, 0.44 to 0.69) with a 45% RR reduction. The effect found in the WHO Solidarity trial was in the same direction, but only a 12% RR reduction was found that was borderline statistically significant (RR = 0.88; 95% CI, 0.77 to 1.00).

Key Finding
Similar to the main analysis, the WHO Solidarity trial found that remdesivir reduces the need for mechanical ventilation compared to standard of care. However, the significance was marginal.

All-cause mortality: In the WHO Solidarity trial, no statistically significant difference in all-cause mortality between remdesivir and SoC or placebo was identified, although it favoured a reduction with remdesivir (RR = 0.93; 95% CI, 0.84 to 1.03). When this trial result was combined with the Beigel et al. (ACTT-1)[13] and Spinner et al. (GSD-US-540-5774)[14] studies (the 2 other studies in which patient populations did not overlap with the WHO Solidarity trial), and the Ali et al. (CATCO)[8] study (including only the nonoverlapping patients), no statistically significant difference was found (RR = 0.92; 95% CI, 0.83 to 1.01) (Figure 8). This result was predominantly driven by the WHO Solidarity trial and was attenuated compared to the statistically significant effect reported for the main analysis (RR = 0.81; 95% CI, 0.68 to 0.95) (Figure 3).

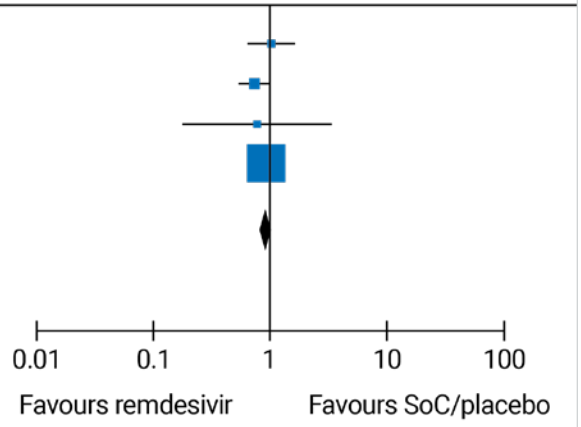
Key Finding
Unlike the main analysis, the WHO Solidarity trial found no significant difference in the relative risk of death between remdesivir and standard of care.

Figure 8

Meta-Analysis of All-Cause Mortality for Remdesivir Versus SoC or Placebo – Risk Ratio – Sensitivity Analysis With the WHO Solidarity Trial

Study or Subgroup	Remdesivir Events	Remdesivir Total	SoC/Placebo Events	SoC/Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Ali, 2022	31	170	27	153	4.2%	1.03 [0.65 , 1.65]
Beigel, 2020	59	541	77	521	9.0%	0.74 [0.54 , 1.01]
Spinner, 2020	3	193	4	200	0.4%	0.78 [0.18 , 3.43]
WHO Solidarity	602	4146	643	4129	86.4%	0.93 [0.84 , 1.03]
Total (95% CI)		**5050**		**5003**	**100.0%**	**0.92 [0.83 , 1.01]**
Total events	695		751			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.20$, df = 3 (P = 0.53); $I^2 = 0\%$
Test for overall effect: Z = 1.80 (P =0.07)
Test for subgroup differences: Not applicable



CI = confidence interval; M-H = Mantel=Haenszel; SoC = standard of care.

Table 14

WHO Solidarity Trial – Summary of Efficacy and Safety Outcomes of Interest

Reported results on the outcomes of interest
Need for mechanical ventilation (invasive mechanical ventilation or ECMO/VV-ECMO)
Initiation to ventilation in those not already ventilated at baseline,[a] n (%) Remdesivir: (n = 3,787): 535 (14.1%) SoC (n = 3,782): 593 (15.7%) RR = 0.88 (95% CI, 0.77 to 1.00) P = 0.04
Death
Death,[b] 28 days, n (%) Remdesivir (n = 3,787): 451 (11.9%) SoC (n = 3782): 509 (13.5%) RR = 0.86 (95% CI, 0.76 to 0.98)

ECMO = extracorporeal membrane oxygenation; VV-ECMO = venovenous extracorporeal membrane oxygenation; RR = relative risk; SoC = standard of care.

[a] Disease severity at entry did not separate high-flow from low-flow oxygen or noninvasive from invasive ventilation, and as a result, the type of ventilation was unclear (and thus not combined with other studies in a sensitivity analysis).

[b] Kaplan-Meier graphs to day 28 and mortality after day 28 (up to 150 days) for in-hospital mortality for remdesivir vs. control were reported by respiratory support at study entry (no oxygen; oxygen (low-flow or high-flow), but not ventilated; already ventilated).

ROB Assessment of WHO Solidarity Trial

The WHO Solidarity trial[6,7] was a platform trial that enrolled 454 hospitals in 35 countries, in 6 WHO regions, without stratification by region or country in the randomization process, and adequate sequence generation was considered to be unclear. It was assigned an unclear ROB for blinding of participants and personnel since it was an open-label RCT, and this lack of blinding is a concern for some outcomes. This trial was considered to be at high risk of selective outcome reporting by not reporting on AEs, although this was clearly identified in the methods of the study protocol. All other pertinent sources of bias were assessed to be at low ROB (Table 15). Details of these assessments can be found in Appendix 6, Table 27.

Risk of Bias Assessment
The WHO Solidarity trial is at low risk of bias for 4 of 7 bias domains. It has a high risk of bias in selective outcome reporting, and the risk of bias for the other 2 domains is unclear.

Table 15

ROB Assessment of the WHO Solidarity Trial

Study	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of bias
WHO Solidarity	Unclear	Low	Unclear	Low	Low	High	Low

ROB = risk of bias.

Discussion

Summary of Evidence

The aim of this rapid systematic review was twofold: to determine the efficacy for remdesivir in hospitalized patients with COVID-19, and to establish whether the use of remdesivir is safe in this setting. The project scope was informed by engaging with clinical experts and decision-makers and policy-makers to better understand the considerations for treatment with remdesivir in the inpatient setting and the potential health system impacts. A total of 18 publications met the final inclusion criteria, reporting findings from 6 RCTs and one large platform trial. The 6 RCTs compared the use of remdesivir to placebo or SoC, while the platform trial involved a number of active treatment comparisons (remdesivir, hydroxychloroquine, lopinavir-ritonavir, or interferon beta-1a with or without lopinavir-ritonavir) and a control arm of no trial intervention or local SoC. There were no other trials that compared remdesivir to an active treatment (i.e., tocilizumab, dexamethasone, or baricitinib) that met the eligibility criteria. All of the included studies broadly included adult inpatients with COVID-19. The Spinner et al. study[14] was the only trial to include adolescent patients between the ages of 12 and 18 years (weighing ≥ 40 kg).

Variants

The Omicron variant of SARS-CoV-2 was first identified in November 2021, and quickly surpassed Delta to become the predominant cause of COVID-19 globally. None of the included trials reported information related to any specific COVID-19 variant, and all were conducted and completed prior to the emergence of the Omicron variant, which limits their generalizability to the current health system context in Canada.[15] The CATCO trial did note that recruitment for the study extended well into Canada's third COVID-19 wave and overlapped with the emergence of the Alpha variant.[8] Data from the included RCTs are not reflective of the current health system status in Canada due to the timing of the recruitment and conduct of the studies, which do not overlap with the current SARS-CoV-2 variants of concern.

Variants and Vaccination
No study explicitly reported the exact variant of the included patients, but all trials were conducted before the emergence of the Omicron and Delta variants and before widespread vaccination.

Vaccination Status

Participants' vaccination status was not clearly reported, with the exception of the DisCoVeRy trial,[12] which stated that none of the patients were vaccinated. Based on the recruitment dates for all of the included studies, we may infer that all of the RCTs were conducted before the Omicron and Delta variants were materially prevalent and before the widespread availability of vaccination.[15] Data from the included RCTs are not reflective of the vaccination status of the current population in Canada.

Trial Setting

Three studies were conducted within a single country, including Canada,[8] Norway,[9] and Finland,[10] while 3 were multinational.[12,14] The DisCoVeRy trial[12] included patients from France, Belgium, Austria, Portugal, and Luxembourg, although more than 80% of the sites for the study were in France. The country with a health system most similar to Canada would be Portugal; however, less than 5% of study participants were from Portugal. The ACTT-1 and GSD-US-540-5774 studies recruited participants from multiple sites in the US, Denmark, UK, Greece, Germany, Korea, Mexico, Spain, Japan, Singapore, France, Hong Kong, Italy, Netherlands, Switzerland, and Taiwan. Within these settings, all studies were conducted in hospitalized patients with COVID-19.

Trial Setting
Three RCTs were conducted in a single country and 3 in multiple countries. The DisCoVeRy trial included patients in 5 countries, with only 4% being in a country with a similar health care system and/or economy to Canada.

Health Status of Included Participants

In the 6 included RCTs, patient comorbidities at baseline were not reported in 4 RCTs.[8-10,14] Approximately 55% of patients in the ACTT-1 trial and 40% of patients in the DisCoVeRy trial had 2 or more comorbidities. Of the comorbidities reported, diabetes; chronic cardiac, respiratory, or pulmonary disease; smoking status; and obesity were frequently reported, and often highest in the proportion of included patients. The health status of immunocompromised participants was not well reported. The DisCoVeRy trial reported proportions of patients at baseline with autoimmune disease (approximately 5%), hematological malignancies (approximately 4%), transplant recipients (< 2%), and those with active malignant neoplasms (approximately 5%), and both this trial and the CATCO trial reported inclusion of participants with HIV (< 0.5%).

Participant Health Status
Only 1 study reported on underserved or equity-deserving groups in a subgroup analysis. Only 2 studies reported on the number of comorbidities, and participants with a compromised immune system were not well reported.

The proportion of patients using supplemental oxygen, high-flow nasal oxygen, noninvasive ventilation, mechanical ventilation, or ECMO at baseline varied greatly within the included RCTs. Between 2% and 27% of patients may have already been on mechanical ventilation or ECMO at baseline, with the largest proportion being in the ACTT-1 study. This limits potential comparability to the GSD-US-540-5774 trial, in which patients were less severe at baseline and individuals on mechanical ventilation or ECMO at baseline were not eligible. In this RCT, more than 84% required no supplemental oxygen at study entry, and 15% required only low-flow oxygen. This study also had an imbalance of participants at baseline with the 10-day remdesivir group having a worse clinical status compared to the group who received 5 days of remdesivir treatment.

Only the ACTT-1 study reported details on underserved or equity-deserving groups in a subgroup analysis. The ACTT-1 study noted that “American Indian or Alaska Native” [wording from original source] patients were included (< 1% in both the remdesivir and placebo groups). The CATCO trial reported the proportion of Indigenous or First Nations patients in Canada within their baseline characteristics for the remdesivir (6.3%) and SoC (4.3%) arms. All RCTs were noted

to have higher proportions of male patients, and the highest proportion of participants identified as white. The DisCoVeRy trial reported a large proportion of enrolled participants from North Africa and Sub-Saharan Africa (approximately 25%). Ethnicity or race were not reported for patients enrolled in the NOR-Solidarity or SOLIDARITY Finland trials.

Co-interventions and SoC

The comparability of baseline care is difficult to elucidate for the included studies. Three of the included RCTs (the NOR-Solidarity, SOLIDARITY Finland, and CATCO trials) did not define their SoC in any detail and reported a limited list of co-interventions, which was not exhaustive for all included patients. Reported corticosteroid use also varied greatly. Only the DisCoVeRy trial reported use of corticosteroids, dexamethasone, and anticoagulants in the SoC protocol. Other RCTs noted that the SoC was left to the local site to administer, and while this may be more generalizable for real-world practice, it may limit the interpretation of the study results or the comparability to the Canadian setting specifically.

Standard of Care
Three RCTs did not define their standard of care and included a limited list of co-interventions. This makes comparability difficult.

Study Design and ROB

Five of the included RCTs were parallel, 2-arm designs of remdesivir for 10 days,[6,8-10,12,13] and 1 was a 3-arm parallel study comparing 5-day and 10-day durations of remdesivir to SoC.[14] Five RCTs were open-label designs and 1 RCT was double-blinded; however, none of the included studies were assessed to be at high ROB due to the blinding of participants, personnel, or outcome assessors. Within the included trials, short-term outcome measurement was generally at 28 or 29 days, with shorter or longer measurements reported at: 11 days and 14 days (GSD-US-540-5774);[14] 15 days (ACTT-1);[13] 2 days, 14 days, 21 days, and 60 days (CATCO);[8] 7 days, 10 days, 14 days, 60 days, and 90 days (NOR-Solidarity);[9] and 3 days, 5 days, 8 days, 11 days,15 days, and 90 days (DisCoVeRy).[12] Only 1 trial (SOLIDARITY Finland) was designed to capture long-term outcomes at 1 year.[10]
Three studies (the CATCO, NOR-Solidarity, and DisCoVeRy trials) specifically noted that they followed patients after hospital discharge.[8,9,12] Four studies[8-10,12] have been fully or partially reported in

Study Design and Bias
The key limitations across all studies include their open-label study design, the variation of disease severity among participants, and the lack of reported subgroup analysis.

1 international platform RCT, the WHO Solidarity trial.[6,7] The majority of patients in the WHO Solidarity trial (> 60%) were from settings in which the health care system was not similar to the system in Canada. These 4 studies, together with the other 2 studies[13,14] with health care systems similar to Canada, form the basis of the analysis in the review. These 4 studies were replaced in the analysis with the WHO Solidarity trial as a sensitivity analysis.

The most important limitation across the included RCTs was related to their open-label design, the varying disease severity of the included participants, and not reporting sufficient subgroup data to permit an exhaustive exploration into many of the populations of interest in this review. In ROB assessments, most trials were rated as having low ROB for all domains. The GS-US-540-5774 trial was rated as being at high risk for selective outcome reporting and unclear for incomplete outcome data. Reviewers reported insufficient details regarding the duration of hospitalization across groups. The NOR-Solidarity trial was assessed to have a high ROB for the adequate sequence generation domain as the randomization processes were considered simple and there were concerns regarding the allocation ratio of participants for this small trial (49 versus 34 patients). The original randomization was broken for the reporting of AE outcomes, which was a concern.

Interpretation of Clinical Results

Efficacy

What Is the Efficacy of Remdesivir in Hospitalized Patients With COVID-19?

Remdesivir may reduce the need for mechanical ventilation or ECMO and the need for intubation for remdesivir compared to SoC, the latter of which was only reported in 1 study. There is insufficient or inconsistent evidence regarding the other a priori selected efficacy outcomes of remdesivir in hospitalized patients with COVID-19, based on the clinical outcomes investigated in this review. Remdesivir may reduce the time to clinical improvement for hospitalized patients compared to patients who receive SoC;

Efficacy
The evidence is insufficient or mixed on the efficacy of remdesivir in hospitalized patients with COVID-19 for most outcomes. It may reduce the need for mechanical ventilation and intubation compared to standard of care.

however, variations in the outcome definitions and reporting limited the pooling and interpretation of these data.

Duration of hospitalization: In the Beigel et al. (ACTT-1) study,[13] the initial length of hospital stay was statistically significantly shorter in the remdesivir group compared to the placebo control group (12 days versus 17 days), while the Spinner et al. (GSD-US-540-5774)[14] and Ali et al. (CATCO) studies[8] reported finding no statistically significant difference between remdesivir and SoC. For Spinner et al. (GSD-US-540-5774), this result was reported descriptively, which limited our knowledge of the exact duration of hospitalization in each group and our ability to combine the data with other studies.

ICU admission, length of ICU stay, and time to ventilation: The Barratt-Due et al. (NOR-Solidarity) study[9] was the only study reporting ICU admission, length of ICU stay, and time to ventilation, and did not find sufficient evidence of remdesivir in statistically significantly reducing the rate of ICU admission or the length of ICU stay, or increasing the time to receipt of mechanical ventilation compared to SoC. This study included a separate RCT of hydroxychloroquine versus SoC, and we only used the data for remdesivir versus its SoC control. However, we judged the randomization as being at high ROB, as the allocation description in the text did not clarify how the SoC was split between the 2 active treatment comparisons; further, some patients receiving SoC acted as controls for both active treatment groups. In addition, the number of patients allocated to remdesivir and control were quite unequal (49 versus 34), although the study reported that equal allocation of patients was followed.

Time to clinical improvement: Various measures were used for time to clinical improvement. All were based on the WHO 7-point ordinal scale: 1 = not hospitalized, no limitations on activities; 2 = not hospitalized, limitation on activities; 3 = hospitalized, not requiring supplemental oxygen; 4 = hospitalized, requiring supplemental oxygen; 5 = hospitalized, on noninvasive ventilation or high-flow oxygen devices; 6 = hospitalized, on invasive mechanical ventilation

or ECMO; and 7 = death. As well, NEWS-2 was also considered (i.e., aggregate score of respiration rate, oxygen saturation, systolic blood pressure, pulse rate, level of consciousness or new confusion, and temperature). The Beigel et al. (ACTT-1) study[13] reported time to recovery and time to clinical improvement, including a 1-category improvement on the WHO ordinal scale, a 2-category improvement on the WHO ordinal scale, and time to discharge or NEWS-2 less than or equal to 2 for 24 hours. The results showed patients in the remdesivir group had a statistically significantly shorter time to improvement of 1 category (HR = 1.23; 95% CI, 1.08 to 1.41) or 2 categories (HR = 1.29; 95% CI, 1.12 to 1.48) on the ordinal scale from baseline than patients in the placebo group, and a statistically significantly shorter time to discharge or to a NEWS-2 of 2 or lower than those in the placebo group (HR = 1.27; 95% CI, 1.10 to 1.46).

The Spinner et al. (GSD-US-540-5774) study[14] considered 5 outcomes related to time to improvement within 28 days based on the WHO 7-point ordinal scale, and found that the difference between 10-day remdesivir and SoC was not statistically significant for: time to clinical improvement (≥ 2 points on ordinal scale) (HR = 1.16; 95% CI, 0.93 to 1.43); time to modified clinical improvement (≥ 1 point on ordinal scale) (HR = 1.10; 95% CI, 0.90 to 1.36); time to recovery (ordinal score of 3 to 6 reduced to 1 to 2 or ordinal score of 2 reduced to 1 on the WHO ordinal scale) (HR = 1.11; 95% CI, 0.90 to 1.37); and time to modified recovery (ordinal score of 4 to 6 reduced to 1 to 3, or ordinal score of 3 reduced to 1 to 2, or ordinal score of 2 reduced to 1 on the WHO ordinal scale) (HR = 1.10; 95% CI, 0.90 to 1.36). Time to discontinuation of supplemental oxygen to room air (HR = 1.93; 95% CI, 1.11 to 3.36) was statistically significantly shorter for 10-day remdesivir than for SoC. The difference between 5-day remdesivir and SoC was not statistically significant for all of these outcomes.

The Ader et al. (DisCoVeRy) study[12] considered 3 outcomes related to time to clinical improvement within 29 days based on the WHO 7-point ordinal scale, and found that the difference between remdesivir and SoC was not statistically significant for: days to improvement of 2 categories on the 7-point ordinal scale or hospital

discharge (HR = 0.92; 95% CI, 0.79 to 1.08); days to NEWS-2 less than or equal to 2 or hospital discharge (HR = 1.03; 95% CI, 0.88 to 1.21); and days to hospital discharge (HR = 0.94; 95% CI, 0.80 to 1.11).

Progression to high-flow oxygen or NIPPV: The Beigel et al. (ACTT-1) study[13] found the incidence of new noninvasive ventilation or high-flow oxygen use was statistically significantly lower in the remdesivir group than in the placebo group (7% difference between remdesivir and placebo) (95% CI, 1% to 14%), while the Ali et al. (CATCO) study[8] showed no statistically significant difference on the need for new oxygen in remdesivir versus SoC. These conflicting findings could be partially related to the different definitions, which was clearly stated in the ACTT-1 trial, while in the CATCO trial it was only reported as new oxygen and unclear as to whether it was high-flow or not.

Need for mechanical ventilation (invasive mechanical ventilation or ECMO/VV-ECMO): The Ali et al. (CATCO) study[8] found a modest but significant reduction in the new use of mechanical ventilation in remdesivir compared to SoC. The Beigel et al. (ACTT-1) study[13] found a statistically significant reduction in new use of mechanical ventilation or ECMO at 29 days in remdesivir compared to placebo. The Spinner et al. (GSD-US-540-5774) study[14] found no statistically significant difference between remdesivir and SoC on the number of patients who were newly hospitalized that required invasive mechanical ventilation or ECMO based on the second category of the 7-point WHO ordinal scale at 28 days. We combined the 28-day and 29-day results for these 3 studies, and found a statistically significant reduction in the need for mechanical ventilation or ECMO in the remdesivir group compared with SoC or placebo group (RR = 0.55; 95% CI, 0.44 to 0.69). Of the 3 studies that informed the need for mechanical ventilation, 2 studies[8,13] (Ali et al. and Beigel et al.) were at low ROB in general, and together contributed nearly 99% of the weight to the overall estimate; the other study[14] had unclear ROB for blinding, selective outcome reporting, and incomplete outcome data, but its contribution to the overall estimate was very small. In this case, there was low ROB associated with the need for mechanical ventilation effect estimate. In addition, the WHO Solidarity trial

reported initiation of ventilation, and the results suggested that remdesivir had a small statistically significant effect against progression to ventilation compared to SoC (RR = 0.88; 95% CI, 0.77 to 1.00; P = 0.04). However, it was difficult to judge from the description if these were all mechanical ventilation. We were uncertain about the ROB due to randomization of this study, as it was not stratified by country, although one could expect that the pandemic condition would vary by location.

Need for intubation: The Beigel et al. (ACTT-1) study[13] summarized endotracheal intubations as respiratory failures at 29 days. A statistically significant reduction was found for remdesivir compared to placebo (RR = 0.57; 95% CI, 0.39 to 0.84). These data, together with a lower incidence of new oxygen use among patients, suggest that treatment with remdesivir may have prevented the progression to more severe respiratory disease.

Safety

What Is the Safety of Remdesivir in Hospitalized Patients With COVID-19?

Although the individual included studies in this review did not find statistically significant differences in mortality, the pooled RR resulted in a statistically significant reduction in death from any cause for patients taking remdesivir when compared to SoC. It is likely that the reduction in mortality would be considered clinically important. The results for mortality were not robust to the sensitivity analysis involving the WHO Solidarity trial[6,7] and were not statistically significant.

There is no statistically significant difference in the total number of SAEs, Grade 3 or 4 AEs, WDAEs, or acute liver or kidney disease for hospitalized patients with COVID-19 taking remdesivir, when compared with SoC. The only study reporting thrombocytopenia did not have any cases documented in any study arm.

Safety
The reduction in death seen from remdesivir is likely considered clinically important. The incidence of serious adverse events and grade 3 or 4 adverse events did not differ between remdesivir and standard of care.

All-cause mortality: All of the included trials reported this outcome. Based on the main analysis for the data from independent add-on studies[8-10,12] of the WHO Solidarity trial, with Ader et al. (the DisCoVeRy trial), Ali et al. (the CATCO trial), Beigel et al. (the ACTT-1 trial), Barratt-Due et al. (the NOR-Solidarity trial), Nevalainen et al. (the SOLIDARITY Finland trial), and Spinner et al. (the GSD-US-540-5774 trial), there is a statistically significant reduction in mortality for remdesivir compared to SoC or placebo (RR = 0.81; 95% CI, 0.68 to 0.95), although no statistically significant reduction was found in each single study. Three of these studies[8,12,13] were all low-risk, and together contributed more than 97% of the weight to the overall estimate. The Spinner et al. study[14] again had an overall unclear ROB but contributed very little to the overall estimate. There is low ROB associated with the estimate of all-cause mortality. For a sensitivity analysis, the 4 independent add-on studies of the WHO Solidarity trial were replaced with the WHO Solidarity trial to avoid double-counting the data for the same patients. The combined results were not statistically significant (RR = 0.92; 95% CI, 0.83 to 1.01).

Any SAE and grade 3 or 4 AE: The Ader et al. (DisCoVeRy)[12] and Barratt-Due et al. (NOR-Solidarity) studies[9] found a higher number of SAEs in the remdesivir group compared to the SoC group (although these were not statistically significantly increased), while the Beigel et al. (ACTT-1)[13] and Spinner et al. (GSD-US-540-5774) studies[14] found a lower SAE incidence in the remdesivir group compared to the SoC or placebo group, with the former study identifying a statistically significant reduction. After combining the 4 studies in a meta-analysis, there was no statistically significant difference between remdesivir and SoC or placebo (RR = 0.91; 95% CI, 0.68 to 1.21). Similarly, the meta-analysis data on grade 3 or 4 AEs from the Ader et al. (DisCoVeRy), Beigel et al. (ACTT-1), and Spinner et al. (GSD-US-540-5774) studies were not statistically significant different between remdesivir and SoC or placebo (RR = 0.88; 95% CI, 0.73 to 1.05).

WDAEs: The Barratt-Due et al. (NOR-Solidarity) study[9] reported no cases of WDAEs for both the remdesivir and SoC groups. The Spinner et al. (GSD-US-540-5774) study[14] reported 8 cases (4%) and 4 cases (2%) in the 10-day remdesivir and 5-day remdesivir groups, respectively; for SoC, the authors reported this as not applicable. The Beigel et al. (ACTT-1) study[13] reported lower WDAEs in the remdesivir group than in the placebo group, but the difference was not statistically significant (RR = 0.72; 95% CI, 0.51 to 1.01). Spinner et al. (the GSD-US-540-5774 trial) reported this as not applicable for SoC. We could not combine any of these data to make the result more precise.

Acute kidney injury: The Beigel et al. (ACTT-1)[13] and Ader et al. (DisCoVeRy) studies[12] reported acute kidney injury as 1 of the SAEs, and both reported no statistically significant difference between remdesivir and SoC orplacebo, which was the same result when the studies were combined in a meta-analysis (RR = 0.70; 95% CI, 0.39 to 1.27).

Acute liver injury: Ali et al. (the CATCO trial)[8] found no differences in the incidence of hepatic dysfunction between the remdesivir and SoC groups, although this outcome was not defined as an SAE in their report. Spinner et al. (the GSD-US-540-5774 trial)[14] reported ALT increase and AST increase up to 28 days, and no statistically significant difference was found between the 10-day remdesivir and SoC groups. Barratt-Due et al. (the NOR-Solidarity trial)[9] and Ader et al. (the DisCoVeRy trial)[12] reported hepatobiliary disorders. The combined data found no statistically significant difference between remdesivir and SoC for hepatobiliary disorders.

Thrombocytopenia: Only the Spinner et al. (GSD-US-540-5774) study[14] reported thrombocytopenia as an SAE and found no cases for the 5-day remdesivir, 10-day remdesivir, or SoC groups.

Subgroups

What are the characteristics of patients (e.g., comorbidities) associated with improved outcomes in the treatment of COVID-19 with remdesivir?

What are the characteristics of patients (e.g., comorbidities) that are associated with risk of adverse outcomes when treated with remdesivir?

We were not able to conduct any subgroup analyses based on groups identified a priori for vaccination status, underserved or equity-deserving groups, number of comorbidities, and Indigenous patients, because of the limited aggregate data reported in the included studies.

Subgroups
Subgroup analysis was not feasible because of insufficient data.

Strengths and Limitations of the Systematic Review

Strengths

We designed, implemented, and conducted a systematic review and meta-analysis following the best practices as outlined in the Cochrane Handbook of Systematic Reviews of Interventions. The literature search was updated in order to include RCTs published to June 19, 2023. The systematic review was specific to the Canadian context. To ensure that the data were not double-counted, we separated the analyses into a main analysis of individual trials and a subanalysis that excluded the extension trials from the WHO Solidarity trial.

Strengths
This review reported on studies specific to the Canadian context; to ensure data were not double counted, 2 separate analyses were done to separate the WHO Solidarity trial from the 4 component trials.

Limitations

The main limitation of this report is the lack of identified clinical evidence for some of the key populations of interest, and the varying clinical end point definitions, which limited the analyses that could be conducted. We only included published data, which may exclude information available in preprints or grey literature. Although we conducted comprehensive searches for evidence, the number of primary studies eligible for inclusion was low. Without comparative evidence of remdesivir versus SoC or placebo for many clinical end points, and no head-to-head trials identified, we could not address corresponding research questions on efficacy and safety.

Limitations
There are 2 main limitations to the studies included in this review: the lack of clinical evidence for some of the key populations of interest, and varying definitions of the clinical end points.

Conclusions and Implications for Decision- or Policy-Making

Implications
Remdesivir is likely safe and may be effective in reducing the need for mechanical ventilation in hospitalized patients with COVID-19 infection, but further evidence is needed.

To determine the efficacy, effectiveness, and safety of remdesivir in hospitalized patients with COVID 19, a systematic review of controlled clinical trials was undertaken. This review was undertaken to update a previous report by CADTH, and the PICOS was modified to provide more relevant evidence for decision- or policy-making for the Canadian health care system. Six RCTs and 1 large platform trial were included in the current review. Due to overlap in the study participants, evidence reported in the platform trial was considered separately from that reported in the other included studies. Due to the rapid format for this systematic review, no evidence grading was conducted to formally assess the trustworthiness of the reported effects. All of these trials were conducted before the emergence of the Omicron and Delta variants, and before widespread vaccination, and may not be generalizable to the current context in Canada.

The volume of evidence available to assess the efficacy and safety of remdesivir in hospital has increased slightly for the RCTs since the last CADTH report, which previously considered 4 RCTs and 1 platform trial,[7,13,14,16,17] and identified several studies in progress. Three of the previously identified trials (the ACTT-1, WHO Solidarity, and GS-US-540-5774 trials)[6,7,13,14] met the eligibility criteria for the current review, and the remaining 2 trials were excluded. The RCT by Wang et al.[17] was excluded, as it was conducted in a setting that was out of scope, and a manufacturer-conducted trial (GS-US-540-5773)[16] was excluded as it compared different durations of remdesivir and did not include any currently eligible comparator (duration of administration of remdesivir was considered out of scope). Several of the trials identified as having preliminary results or being in progress by the previous CADTH review (e.g., the DisCoVeRy, CATCO, and WHO Solidarity trials) are also now published and included in the current review. With the newly identified studies, statistical pooling for some outcome measures was feasible and appropriate, where previously only a descriptive summary of results

was possible. No data were available to form conclusions regarding any populations of interest, including Indigenous Peoples or those who are considered to be in underserved or equity-deserving groups. Although we endeavoured to include study data relevant to the Canadian health system or economy, some of the included trials and the WHO Solidarity trial utilized multicentre and multinational designs that include settings not comparable to Canadian contexts. The results from these trials, in context with their individual strengths and limitations, are likely to provide the most relevant currently available evidence to inform decision- and policy-making for the Canadian health care system.

What Is the Efficacy or Effectiveness of Remdesivir in Hospitalized Patients With COVID-19?

Data were available for all efficacy outcomes of interest, except time to progression to severe disease; however, the only outcome with sufficient evidence for pooling was progression to invasive mechanical ventilation (or ECMO). No observational or real-world evidence was sought in the current rapid systematic review. Although many of the studies were designed and conducted to be pragmatic, the research environment imposed as part of the study implementation could limit conclusions related specifically to the effectiveness of remdesivir in inpatient settings.

No firm conclusions can be made pertaining to the effect of remdesivir on time to clinical improvement, as the outcomes were reported inconsistently using different definitions across and within the included studies. As a result of this variation, no pooling or combination of results was feasible or appropriate. The individual trials reported conflicting results for the direction of effect, or no differences. In the only subgroup data available within the included studies, data from the ACTT-1 study provided time to clinical improvement for a number of variations of improvement.

Our meta-analysis of 3 RCTs found that remdesivir may reduce the risk for progression to invasive mechanical ventilation or ECMO at 28 days. No subgroup data were available and sensitivity analysis

with the WHO Solidarity trial was not feasible. The reported effect from the study was consistent, in that results showed a reduction in risk, albeit less in magnitude and without statistical significance. There were no additional data across studies to investigate these differences based on severity of COVID-19 at baseline or other key variables, and so it is difficult to form any firm conclusions regarding the effect of remdesivir on the risk for progression to mechanical ventilation or ECMO; however, we may consider this as an important potential benefit that may have considerable resource implications for the health system.

There are conflicting results in the included trials regarding the effect of remdesivir on duration of hospitalization, and so no conclusions can be made. There are insufficient data to form any conclusions regarding the effect of remdesivir on progression to high-flow nasal oxygen or noninvasive ventilation, ICU admission, length of ICU stay, time to ventilation, or need for intubation.

What Is the Safety of Remdesivir in Hospitalized Patients With COVID-19?

Data for safety were available for all RCTs. Meta-analyses for the safety outcomes of interest were conducted for all-cause mortality, SAEs, grade 3 or 4 AEs, and for both acute kidney and liver injuries. Based on the pooled evidence for 3,843 patients in 6 trials, remdesivir administered to hospitalized patients reduced the RR for all-cause mortality by 20%. Although no formal assessment of clinical importance or trustworthiness of these findings was completed (i.e., using GRADE), this could be interpreted as a clinically significant reduction in death. No data were available in any trial to permit consideration for subgroups and the results were not corroborated in the sensitivity analyses involving the WHO Solidarity trial, but the direction of the effect is the same. No observational evidence was collected as part of this rapid systematic review, and so these results for mortality were not formally compared against any reported real-world evidence for remdesivir.

The pooled results found no difference in the total number of patients who experienced any SAEs or grade 3 or 4 AEs, acute kidney injury, acute liver injury, or hepatobiliary disorders, when remdesivir was compared to placebo or SoC. Data were insufficient to form any firm conclusions regarding WDAEs. Although the scope of this review did not specifically consider tolerability or nonsevere AEs specifically, remdesivir did appear to be well tolerated, and we may conclude from the limited data presented in 3 trials that WDAEs were unlikely to differ. Thrombocytopenia was very uncommon and only 1 outcome was documented in the SoC group in 1 trial, and 3 trials reported no events in any patient. Based on these limited data, we may conclude that it is more likely than not that use of remdesivir for hospitalized patients does not generally lead to more SAEs compared to standard care.

Which Hospitalized Patients Are Most Likely to Benefit From Treatment With Remdesivir?

Patient health status plays a pivotal role in COVID-19 treatment because this may influence both antiviral selection and any health outcome effects. There was insufficient evidence to consider whether any reported effects varied by age or number of comorbidities. Results from the current review do not adequately consider individuals potentially at the highest risk for severe outcomes due to COVID-19, as the studies did not report data sufficiently for people who were immunocompromised, or who had a health status or age that placed them at higher risk. Although we included considerations for age, sex, gender, and Indigenous Peoples, alongside other underserved or equity-deserving groups in hospitalized individuals with COVID-19, the study data reported were insufficient for any pooled analyses in any of these subgroups of interest.

What Other Considerations Are There for Decision- or Policy-Making Related to Inpatient Treatment With Remdesivir?

As the included studies were conducted before the identification and spread of the Omicron and Delta variants of SARS-CoV-2 — or any subvariants of concern — and before any pervasive vaccination programs were implemented, conclusions considered for the Canadian health care system must consider these limitations. SoC has also evolved as our clinical knowledge and experience has improved, and so therapeutic decision-making and SoCs in Canada are likely different now and more targeted to individual patient decision-making, compared to when these trials were conducted in 2021 or earlier. This limits the generalizability of this evidence to our current health care context.

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Authors

Clinical Review

George A. Wells acted as the principal investigator by developing and leading the approach and providing research oversight, and contributed to validation and interpretation of the results as well as drafting and finalizing the report.

Xiaoqin Wang contributed by screening studies; extracting data; analyzing and interpreting results, figures, and tables; and drafting and finalizing the report.

Joan Peterson contributed by screening studies, extracting and verifying data, assessing risk of bias, drafting tables, and drafting and revising the report.

Zemin Bai contributed by screening studies, extracting and verifying data, informing statistical approaches, and revising the report.

Shannon Kelly contributed to the conceptualization and design of the approach, provided research oversight, interpreted results, and drafted and finalized the report.

Melissa Brouwers contributed to the choice of topic, question refinement, protocol, interpretation of the data, and review and refinement of the report.

Research Information Science

Hannah Loshak designed and executed the literature search strategy, monitored search alerts, prepared the search methods section and appendix, managed referencing of the report, and provided final approval of the version of the report submitted for publication.

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Conflicts of Interest

George A. Wells disclosed the following:

Payment as Advisor or Consultant

Thermedical: Ablation system and catheter needle 2021

VBI Vaccines Inc.: Coronavirus Vaccine 2020. Design and Analysis advice for preparation of FDA submission.

Other

VBI Vaccines Inc.: Coronavirus Vaccine 2020. Data Safety Monitoring Board – Member.

Emily Reynen disclosed the following:

LifeArc Charities UK: Co-investigator (member) for *Nebulized Furosemide for Pulmonary Inflammation in Intubated, Mechanically Ventilated Patients With COVID-19 – a Phase 2/3 Study*

TELUS Health Solutions Inc.: Provided a comprehensive HTA report and a drug formulary listing recommendation for TELUS Health formularies (member)

Ontario Committee to Evaluate Drugs: Committee member

No other conflicts of interest were declared.

For more information on CoLab and its work visit **colab.cadth.ca**

Canada's Drug and Health Technology Agency

CoLab Network

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About CADTH: CADTH is a not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs and medical devices in our health care system.

About CoLab: CoLab is a pan-Canadian network of experts in applied research, scientific methods, and data analysis. CoLab members work with CADTH's Post-Market Drug Evaluation Program to produce credible and timely evidence on post-market drug safety and effectiveness.

Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Overview

Interface: Ovid

Databases

- MEDLINE All (1946 to present)
- Embase (1974 to present)

Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: May 1, 2023

Alerts: Monthly search update provided prior to project completion

Search filters applied: randomized controlled trials; controlled clinical trials

Limits

- Language limit: English- and French-language
- Conference abstracts: excluded

Table 16

Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires terms to be adjacent to each other within # number of words (in any order)
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Keyword heading word
.dq	Candidate term word (Embase)
.pt	Publication type
.rn	Registry number
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multidatabase Strategy

1 (remdesivir* or Veklury* or Redyx* or gs-5734 or gs5734 or gs-465124 or gs465124 or gs-829143 or gs829143 or 3QKI37EEHE).ti,ab,kf,ot,hw,nm,rn.

2 exp Covid-19/ or SARS-CoV-2/

3 (coronavirus/ or betacoronavirus/ or coronavirus infections/) and (disease outbreaks/ or epidemics/ or pandemics/)

4 (nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARS-COV2 or SARSCOV-2 or SARSCOV2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2).ti,ab,kf,nm,ox,rx,px.

5 ((new or novel or "19" or "2019" or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).ti,ab,kf,ot.

6 ((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kf,ot.

7 ((Wuhan or Hubei) adj5 pneumonia).ti,ab,kf,ot.

8 or/2-7

9 1 and 8

10 9 use medall

11 *remdesivir/ or (remdesivir* or Veklury* or Redyx* or gs-5734 or gs5734 or gs-465124 or gs465124 or gs-829143 or gs829143).ti,ab,kf,dq.

12 exp Coronavirus disease 2019/

13 sars-related coronavirus/ or SARS coronavirus/

14 (coronavirinae/ or betacoronavirus/ or coronavirus infection/) and (epidemic/ or pandemic/)

15 (nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARSCOV-2 or SARS-COV2 or SARSCOV2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Corona Virus 2).ti,ab,kf,hw,ot.

16 ((new or novel or "19" or "2019" or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).ti,ab,kf,hw,ot.

17 ((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,ab,kf,ot.

18 ((Wuhan or Hubei) adj5 pneumonia).ti,ab,kf,ot.

19 or/12-18

20 11 and 19

21 20 use oemezd
22 (conference abstract or conference review).pt.
23 21 not 22
24 10 or 23
25 (Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Equivalence Trial or Clinical Trial, Phase III).pt.
26 Randomized Controlled Trial/
27 exp Randomized Controlled Trials as Topic/
28 "Randomized Controlled Trial (topic)"/
29 Controlled Clinical Trial/
30 exp Controlled Clinical Trials as Topic/
31 "Controlled Clinical Trial (topic)"/
32 Randomization/
33 Random Allocation/
34 Double-Blind Method/
35 Double Blind Procedure/
36 Double-Blind Studies/
37 Single-Blind Method/
38 Single Blind Procedure/
39 Single-Blind Studies/
40 Placebos/
41 Placebo/
42 Control Groups/
43 Control Group/
44 (random* or sham or placebo*).ti,ab,hw,kf.
45 ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
46 ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf.
47 (control* adj3 (study or studies or trial* or group*)).ti,ab,kf.
48 (Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf.
49 allocated.ti,ab,hw.
50 ((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf.
51 ((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf.

52 (pragmatic study or pragmatic studies).ti,ab,hw,kf.
53 ((pragmatic or practical) adj3 trial*).ti,ab,hw,kf.
54 ((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf.
55 (phase adj3 (III or "3") adj3 (study or studies or trial*)).ti,hw,kf.
56 or/25-55
57 24 and 56
58 remove duplicates from 57
59 limit 58 to (english or french)

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

Search results: 17 studies found for: remdesivir | "COVID-19" | Completed Studies

Appendix 2: List of Included Studies

Note that this appendix has not been copy-edited.

Table 17

Included Studies

Study	Citation
ACTT-1	Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med*. 2020;383(19):1813-1826. **[Main report]**
	Jen HH, Chang WJ, Lin TY, et al. Evaluating Clinical Efficacy of Antiviral Therapy for COVID-19: A Surrogate Endpoint Approach. *Infect Dis Ther*. 2021;10(2):815-825.
	Colombo CJ, Colombo RE, Maves RC, et al. Performance Analysis of the National Early Warning Score and Modified Early Warning Score in the Adaptive COVID-19 Treatment Trial Cohort. *Crit Care Explor*. 2021;3(7):e0474.
	Thiede JM, Gress AR, Libby SD, et al. Immune Profiling to Determine Early Disease Trajectories Associated With Coronavirus Disease 2019 Mortality Rate: A Substudy from the ACTT-1 Trial. *J Infect Dis*. 2021;223(8):1339-1344.
	Fintzi J, Bonnett T, Sweeney DA, et al. Deconstructing the Treatment Effect of Remdesivir in the Adaptive Coronavirus Disease 2019 (COVID-19) Treatment Trial-1: Implications for Critical Care Resource Utilization. *Clin Infect Dis*. 2022;74:2209-2217.
	Paules CI, Gallagher SK, Rapaka RR, et al. Remdesivir for the Prevention of Invasive Mechanical Ventilation or Death in Coronavirus Disease 2019 (COVID-19): A Post Hoc Analysis of the Adaptive COVID-19 Treatment Trial-1 Cohort Data. *Clin Infect Dis*. 2022;74(7):1260-1264.
GS-US-540-5774	Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. *JAMA*. 2020;324(11):1048-1057.
WHO Solidarity	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. *Lancet*. 2022;399(1033):1941-1953. **[Main report]**
	Pan H, Peto R, Henao-Restrepo AM, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. *N Engl J Med*. 2021;384(6):497-511.

Study	Citation
CATCO	Ali K, Azher T, Baqi M, et al. Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: a randomized controlled trial. *CMAJ*. 2022;194(7):E242-E251.**[Main report]**
	Ali K, Azher T, Baqi M, et al. Remdesivir for the treatment of patients in hospital with COVID-19 in Canada: A randomized controlled trial. [French]. *CMAJ*. 2022;194(20):E713-E723.
	Lau VI, Fowler R, Pinto R, et al. Cost-effectiveness of remdesivir plus usual care versus usual care alone for hospitalized patients with COVID-19: an economic evaluation as part of the Canadian Treatments for COVID-19 (CATCO) randomized clinical trial. *CMAJ Open*. 2022;10(3):E807-E817.
DisCoVeRy	Ader F, Bouscambert-Duchamp M, Hites M, et al. 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. *Lancet Infect Dis*. 2022;22(2):209-221.**[Main report]**
	Lingas G, Neant N, Gaymard A, et al Effect of remdesivir on viral dynamics in COVID-19 hospitalized patients: a modelling analysis of the randomized, controlled, open-label DisCoVeRy trial. *J Antimicrob Chemother*. 2022;77(5):1404-1412.
	Ader F, Bouscambert-Duchamp M, Hites M, Peiffer-Smadja N, Mentre F, Burdet C. Final results of the DisCoVeRy trial of remdesivir for patients admitted to hospital with COVID-19. *Lancet Infec Dis*. 2022;22(6):764-765.
NOR-Solidarity	Barratt-Due A, Olsen IC, Nezvalova-Henriksen K, et al. Evaluation of the Effects of Remdesivir and Hydroxychloroquine on Viral Clearance in COVID-19 : A Randomized Trial. *Ann Intern Med*. 2021;174(9):1261-1269. **[Main report]**
	Lerum TV, Maltzahn NN, Aukrust P, et al. Persistent pulmonary pathology after COVID-19 is associated with high viral load, weak antibody response, and high levels of matrix metalloproteinase-9. *Sci Rep*. 2021;11(1):23205.
SOLIDARITY Finland	Nevalainen OPO, Horstia S, Laakkonen S, et al. Effect of remdesivir post hospitalization for COVID-19 infection from the randomized SOLIDARITY Finland trial. *Nat Commun*. 2022;13(1):6152.

Appendix 3: List of Excluded Studies

Note that this appendix has not been copy-edited.

Table 18

Excluded Studies

Reason for exclusion	Citation
Wrong population	Brown SM, Katz MJ, Ginde AA, et al. Consistent Effects of Early Remdesivir on Symptoms and Disease Progression Across At-Risk Outpatient Subgroups: Treatment Effect Heterogeneity in PINETREE Study. *Infect Dis Ther*. 2023;12(4):1189-1203.
	Pan DZ, Odorizzi PM, Schoenichen A, et al. Remdesivir improves biomarkers associated with disease severity in COVID-19 patients treated in an outpatient setting. *Commun Med* (London). 2023;3(1):2.
	Mazzitelli M, Trunfio M, Sasset L, et al. Risk of hospitalization and sequelae in patients with COVID-19 treated with 3-day early remdesivir vs. controls in the vaccine and Omicron era: A real-life cohort study. *J Med Virol*. 2023;95(3):e28660.
	Piccicacco N, Zeitler K, Ing A, et al. Real-world effectiveness of early remdesivir and sotrovimab in the highest-risk COVID-19 outpatients during the Omicron surge. *J Antimicrob Chemother*. 2022;77(10):2693-2700.
	Gottlieb RL, Vaca CE, Paredes R, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. *N Engl J Med*. 2022;386(4):305-315.
	Del Borgo C, Garattini S, Bortignon C, et al. Effectiveness, Tolerability and Prescribing Choice of Antiviral Molecules Molnupiravir, Remdesivir and Nirmatrelvir/r: A Real-World Comparison in the First Ten Months of Use. *Viruses*. 2023;15(4):21.
	Pinargote-Celorio H, Otero-Rodriguez S, Gonzalez-de-la-Aleja P, et al. Mild SARS-CoV-2 infection in vulnerable patients: implementation of a clinical pathway for early treatment. *Enferm Infecc Microbiol Clin*. 2023;30:S2529-993X(23)00090-4.
	Mikulska M, Testi D, Russo C, et al. Outcome of early treatment of SARS-CoV-2 infection in patients with haematological disorders. *Br J Haematol*. 2023;201(4):628-639.
	Tiseo G, Barbieri C, Galfo V, et al. Efficacy and Safety of Nirmatrelvir/Ritonavir, Molnupiravir, and Remdesivir in a Real-World Cohort of Outpatients with COVID-19 at High Risk of Progression: The PISA Outpatient Clinic Experience. *Infect Dis Ther*. 2023;12(1):257-271.
	Colaneri M, Pieri TC, Roda S, et al. Assessing the Efficacy of Early Therapies against SARS-CoV-2 in Hematological Patients: A Real-Life Study from a COVID-19 Referral Centre in Northern Italy. *J Clin Med*. 2022;11(24):7452.
	Solera JT, Arbol BG, Bahinskaya I, Marks N, Humar A, Kumar D. Short-course early outpatient remdesivir prevents severe disease due to COVID-19 in organ transplant recipients during the omicron BA.2 wave. *Am J Transplant*. 2023;23(1):78-83.
	Manciulli T, Spinicci M, Rossetti B, et al. Safety and Efficacy of Outpatient Treatments for COVID-19: Real-Life Data from a Regionwide Cohort of High-Risk Patients in Tuscany, Italy (the FEDERATE Cohort). *Viruses*. 2023;15(2):438.

Reason for exclusion	Citation
Wrong intervention	Brown SM, Peltan I, Kumar N, et al. Hydroxychloroquine versus azithromycin for hospitalized patients with COVID-19: Results of a randomized, active comparator trial. *Ann Am Thorac Soc*. 2021;18(4):590-597.
	Temesgen Z, Kelley CF, Cerasoli F, et al. C reactive protein utilisation, a biomarker for early COVID-19 treatment, improves lenzilumab efficacy: results from the randomised phase 3 'LIVE-AIR' trial. *Thorax*. 2022;06:06.
	I-SPY COVID Consortium. Report of the first 7 agents in the I-SPY COVID trial: a phase 2, open label, adaptive platform randomised controlled trial. *EClinicalMedicine*. 2023;58:101889.
	Shah T, McCarthy M, Nasir I, et al. Colchicine and high-intensity rosuvastatin in the treatment of non-critically ill patients hospitalised with COVID-19: a randomised clinical trial. *BMJ Open*. 2023;13(2): e067910.
	Jain MK, De Lemos JA, McGuire DK, et al. Atovaquone for treatment of COVID-19: A prospective randomized, double-blind, placebo-controlled clinical trial. *Front Pharmacol*. 2022;13:1020123.
	DiNubile MJ, Parra S, Salomo AC, Levinson SL. Adjunctive Recombinant Human Plasma Gelsolin for Severe Coronavirus Disease 2019 Pneumonia. *Open Forum Infect Dis*. 2022;9(8):ofac357.
	Fintzi J, Bonnett T, Tebas P, et al. Unraveling the Treatment Effect of Baricitinib on Clinical Progression and Resource Utilization in Hospitalized COVID-19 Patients: Secondary Analysis of the Adaptive COVID-19 Treatment Randomized Trial-2. *Open Forum Infect Dis*. 2022;9(7):ofac219.
	Coutre SE, Barnett C, Osiyemi O, et al. Ibrutinib for Hospitalized Adults With Severe Coronavirus Disease 2019 Infection: Results of the Randomized, Double-Blind, Placebo-Controlled iNSPIRE Study. *Open Forum Infect Dis*. 2022;9(5):ofac104.
	Roshon M, Lemos-Filho L, Cherevka H, Goldberg L, Salottolo K, Bar-Or D. A Randomized Controlled Trial to Evaluate the Safety and Efficacy of a Novel Inhaled Biologic Therapeutic in Adults with Respiratory Distress Secondary to COVID-19 Infection. *Infect Dis Ther*. 2022;11(1):595-605.
	Temesgen Z, Burger CD, Baker J, et al. Lenzilumab Efficacy and Safety in Newly Hospitalized Covid-19 Subjects: Results from the Live-Air Phase 3 Randomized Double-Blind Placebo-Controlled Trial. *medRxiv*. 2021; 2021.05.01.21256470. [non–peer-reviewed preprint]
	Wolfe CR, Tomashek KM, Patterson TF, et al. Baricitinib versus dexamethasone for adults hospitalised with COVID-19 (ACTT-4): a randomised, double-blind, double placebo-controlled trial. *Lancet Respir Med*. 2022;10(9):888-899.
	Barkauskas C, Mylonakis E, Poulakou G, et al. Efficacy and Safety of Ensovibep for Adults Hospitalized With COVID-19 : A Randomized Controlled Trial. *Ann Intern Med*. 2022;175(9):1266-1274.
	ACTIV-3–Therapeutics for Inpatients with COVID-19 (TICO) Study Group. Tixagevimab-cilgavimab for treatment of patients hospitalised with COVID-19: a randomised, double-blind, phase 3 trial. L*ancet Respir Med*. 2022;10(10):972-984.
	Nickols NG, Mi Z, DeMatt E, et al. Effect of Androgen Suppression on Clinical Outcomes in Hospitalized Men With COVID-19: The HITCH Randomized Clinical Trial. *JAMA Netw Ope*n. 2022;5(4):e227852.
	ITAC (INSIGHT 013) Study Group. Hyperimmune immunoglobulin for hospitalised patients with COVID-19 (ITAC): a double-blind, placebo-controlled, phase 3, randomised trial. *Lancet*. 2022;399(10324):530-540.
	Ortigoza MB, Yoon H, Goldfeld KS, et al. Efficacy and Safety of COVID-19 Convalescent Plasma in Hospitalized Patients: A Randomized Clinical Trial. *JAMA Intern Med*. 2022;182(2):115-126.
	Lundgren JD, Grund B, Barkauskas CE, et al. Responses to a Neutralizing Monoclonal Antibody for Hospitalized Patients With COVID-19 According to Baseline Antibody and Antigen Levels : A Randomized Controlled Trial. *Ann Intern Med*. 2022;175(2):234-243.

Reason for exclusion	Citation
Wrong intervention	Temesgen Z, Burger CD, Baker J, et al. Lenzilumab in hospitalised patients with COVID-19 pneumonia (LIVE-AIR): a phase 3, randomised, placebo-controlled trial. *Lancet Respir Med*. 2022;10(3):237-246.
	Branch-Elliman W, Ferguson R, Doros G, et al. Subcutaneous sarilumab for the treatment of hospitalized patients with moderate to severe COVID19 disease: A pragmatic, embedded randomized clinical trial. *PLoS One*. 2022;17(2):e0263591.
	Perlin DS, Neil GA, Anderson C, et al. Randomized, double-blind, controlled trial of human anti-LIGHT monoclonal antibody in COVID-19 acute respiratory distress syndrome. *J Clin Invest*. 2022;132(3):e153173.
	Kalil AC, Mehta AK, Patterson TF, et al. Efficacy of interferon beta-1a plus remdesivir compared with remdesivir alone in hospitalised adults with COVID-19: a double-bind, randomised, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2021;9(12):1365-1376.
	Menichetti F, Popoli P, Puopolo M, et al. Effect of High-Titer Convalescent Plasma on Progression to Severe Respiratory Failure or Death in Hospitalized Patients With COVID-19 Pneumonia: A Randomized Clinical Trial. *JAMA Netw Open*. 2021;4(11):e2136246.
	Rosas IO, Diaz G, Gottlieb RL, et al. Tocilizumab and remdesivir in hospitalized patients with severe COVID-19 pneumonia: a randomized clinical trial. *Intensive Care Med*. 2021;47(11):1258-1270.
	Marconi VC, Ramanan AV, de Bono S, et al. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. *Lancet Respir Me*d. 2021;9(12):1407-1418.
	Ader F, Peiffer-Smadja N, Poissy J, et al. An open-label randomized controlled trial of the effect of lopinavir/ritonavir, lopinavir/ritonavir plus IFN-beta-1a and hydroxychloroquine in hospitalized patients with COVID-19. *Clin Microbiol Infect*. 2021;27(12):1826-1837.
	Lundgren JD, Grund B, Barkauskas CE, et al. A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. *N Engl J Me*d. 2021;384(10):905-914.
	Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. *N Engl J Med*. 2021;384(9):795-807.
	Mazzotta V, Cozzi Lepri A, Colavita F, et al. Viral load decrease in SARS-CoV-2 BA.1 and BA.2 Omicron sublineages infection after treatment with monoclonal antibodies and direct antiviral agents. *J Med Virol*. 2023;95(1):e28186.
	Cacho J, Nicolas D, Bodro M, et al. Use of remdesivir in kidney transplant recipients with SARS-CoV-2 Omicron infection. *Kidney Int*. 2022;102(4):917-921.
	Kilcoyne A, Jordan E, Zhou A, et al. Clinical and economic benefits of lenzilumab plus standard of care compared with standard of care alone for the treatment of hospitalized patients with COVID-19 in the United States from the hospital perspective. *J Med Econ*. 2022;25(1):160-171.
	Bertuccio P, Degli Antoni M, Minisci D, et al. The impact of early therapies for COVID-19 on death, hospitalization and persisting symptoms: a retrospective study. *Infection*. 2023;6:1-12
	Green ACA, Curtis HJ, Higgins R, et al. Trends, variation, and clinical characteristics of recipients of antiviral drugs and neutralising monoclonal antibodies for covid-19 in community settings: retrospective, descriptive cohort study of 23.4 million people in OpenSAFELY. *BMJ Med*. 2023;2(1):e000276.
	Scotto R, Buonomo AR, Iuliano A, et al. Remdesivir Alone or in Combination with Monoclonal Antibodies as an Early Treatment to Prevent Severe COVID-19 in Patients with Mild/Moderate Disease at High Risk of Progression: A Single Centre, Real-Life Study. *Vaccines (Basel)*. 2023;11(2):200.
	Lasagna A, Albi G, Figini S, et al. Long-COVID in Patients with Cancer Previously Treated with Early Anti-SARS-CoV-2 Therapies in an Out-of-Hospital Setting: A Single-Center Experience. *Cancers (Basel)*. 2023;15(4):1269.

Reason for exclusion	Citation
Wrong intervention	Raad II, Hachem R, Masayuki N, et al. International multicenter study comparing COVID-19 in patients with cancer to patients without cancer: Impact of risk factors and treatment modalities on survivorship. *eLife*. 2023;12:e81127. Biscarini S, Villa S, Genovese C, et al. Safety Profile and Outcomes of Early COVID-19 Treatments in Immunocompromised Patients: A Single-Centre Cohort Study. *Biomedicines*. 2022;10(8):2002. Jia X, Cao S, Lee AS, et al. Anti-nucleocapsid antibody levels and pulmonary comorbid conditions are linked to post-COVID-19 syndrome. *JCI Insight*. 2022;7(13):e156713. Hall VG, Al-Alahmadi G, Solera JT, et al. Outcomes of SARS-CoV-2 Infection in Unvaccinated Compared With Vaccinated Solid Organ Transplant Recipients: A Propensity Matched Cohort Study. *Transplantation*. 2022;106(8):1622-1628.
Wrong setting	Hadadi A, Ajam A, Montazeri M, et al. Effects of Remdesivir on in-Hospital and Late Outcomes of Patients With Confirmed or Clinically Suspected COVID-19: A Propensity Score-Matched Study. *Acta Medica Iranica*. 2022;60(7):407-412. Popescu C, Andrei AI, Ciresa A, Sturza F, Duna F, Popescu GA. Early Use of Remdesivir in Obese Male Patients with Covid-19 Can Improve the Prognosis. *Farmacia*. 2022;70(1):76-80. Taghavi, M. R., Tavanaei Tamanaei, T., Oghazian, M. B., Tavana, E., Mollazadeh, S., Niloofar, P., Oghazian, S., Hoseinzadeh, A., Hesari, A., Ansari Mohseni, M., Rezaei, S., Haresabadi, M. Effectiveness of Fortified Garlic Extract Oral Capsules as Adjuvant Therapy in Hospitalized Patients with Coronavirus Disease 2019: A Triple-Blind Randomized Controlled Clinical Trial. *Curr Ther Res Clin Exp*. 2023;98:100699. Bansode S, Singh PK, Tellis M, et al. A Comprehensive Molecular and Clinical Investigation of Approved Anti-HCV Drugs Repurposing against SARS-CoV-2 Infection: A Glaring Gap between Benchside and Bedside Medicine. *Vaccines (Basel)*. 2023;11(3):515. Galal MW, Ahmed M, Shao Y, et al. The Use of Mebendazole in COVID-19 Patients: An Observational Retrospective Single Center Study. *Adv Virol*. 2022;2022:3014686. Amoushahi A, Moazam E, Tabatabaei AR, et al. Efficacy and Safety of Inhalation of Nebulized Ethanol in COVID-19 Treatment: A Randomized Clinical Trial. Cureus. 2022;14(12):e32218. Mortaz E, Jamaati H, Dezfuli NK, et al. Changes in PD-1- and CTLA-4-bearing blood lymphocytes in ICU COVID-19 patients treated with Favipiravir/Kaletra or Dexamethasone/Remdesivir: a pilot study. *Iran J Allergy Asthma Immunol*. 2023;22(1):99-109. Kasiri H, Ghazaiean M, Rouhani N, Naderi-Behdani F, Ghazaeian M, Ghodssi-Ghassemabadi R. The effects of colchicine on hospitalized COVID-19 patients: A randomized, double-blind, placebo-controlled clinical trial. *J Investig Med*. 2023;71(2):124-131. Tam AR, Zhang RR, Lung KC, et al. Early Treatment of High-Risk Hospitalized Coronavirus Disease 2019 (COVID-19) Patients With a Combination of Interferon Beta-1b and Remdesivir: A Phase 2 Open-label Randomized Controlled Trial. *Clin Infect Dis*. 2023;76(3):e216-e226. Mousapour P, Hamidi Farahani R, Mosaed R, Asgari A, Hazrati E. Efficacy and safety of acetylcysteine for the prevention of liver injury in COVID-19 intensive care unit patients under treatment with remdesivir. *Gastroenterol Hepatol Bed Bench*. 2022;15(3):241-248. Mohiuddin Chowdhury ATM, Kamal A, Abbas KU, et al. Efficacy and Outcome of Remdesivir and Tocilizumab Combination Against Dexamethasone for the Treatment of Severe COVID-19: A Randomized Controlled Trial. *Front Pharmacol*. 2022;13:690726. Panda PK, Singh BO, Moirangthem B, et al. Antiviral Combination Clinically Better Than Standard Therapy in Severe but Not in Non-Severe COVID-19. *Clin Pharmacol*. 2021;13:185-195.

Reason for exclusion	Citation
Wrong setting	Gupta S, Dixit PK, Ghana P, et al. Open-label randomized control trial of hydroxychloroquine in patients with moderate to severe coronavirus disease 2019 infection. *Med J Armed Forces India*. 2021;77(Suppl 2):S305-S311. Mahajan L, Singh AP, Gifty. Clinical outcomes of using remdesivir in patients with moderate to severe COVID-19: A prospective randomised study. *Indian J Anaesth*. 2021;65(Suppl 1):S41-S46. Aryan H, Farahani RH, Chamanara M, et al. Evaluation of the efficacy of oral nano-silymarin formulation in hospitalized patients with COVID-19: A double-blind placebo-controlled clinical trial. *Phytother Res*. 2022;36(10):3924-3931. Essai CATCO (Canadian Treatments for COVID-19); pour le Réseau de recherche clinique de l'Association pour la microbiologie médicale et l'infectiologie Canada (AMMI Canada) le Groupe canadien de recherche en soins intensifs (CCCTG). Remdésivir chez les patients hospitalisés pour la COVID-19 au Canada: essai clinique randomisé et contrôlé. *CMAJ*. 2022;194(20):E713-E723. Guzman-Esquivel J, Galvan-Salazar HR, Guzman-Solorzano HP, et al. Efficacy of the use of mefenamic acid combined with standard medical care vs. standard medical care alone for the treatment of COVID-19: A randomized double-blind placebo-controlled trial. *Int J Mol Med*. 2022;49(3):29. Shohan M, Nashibi R, Mahmoudian-Sani MR, et al. The therapeutic efficacy of quercetin in combination with antiviral drugs in hospitalized COVID-19 patients: A randomized controlled trial. *Eur J Pharmacol*. 2022;914:174615. Fakharian A, Barati S, Mirenayat M, et al. Evaluation of adalimumab effects in managing severe cases of COVID-19: A randomized controlled trial. *Int Immunopharmacol*. 2021;99:107961. Martin-Onraet A, Barrientos-Flores C, Vilar-Compte D, Perez-Jimenez C, Alatorre-Fernandez P. Use of remdesivir for COVID-19 in patients with hematologic cancer. *Clin Exp Med*. 2022;12:1-8. Hajimoradi M, Sharif Kashani B, Dastan F, et al. Remdesivir associated sinus bradycardia in patients with COVID-19: A prospective longitudinal study. *Front Pharmacol*. 2022;13:1107198. Rajme-Lopez S, Martinez-Guerra BA, Zalapa-Soto J, et al. Early Outpatient Treatment With Remdesivir in Patients at High Risk for Severe COVID-19: A Prospective Cohort Study. *Open Forum Infect Dis*. 2022;9(10):ofac502. Aksak-Was BJ, Chober D, Serwin K, et al. Remdesivir Reduces Mortality in Hemato-Oncology Patients with COVID-19. *J Inflamm Res*. 2022;15:4907-4920. Kim T, Joo DH, Lee SW, Lee J, Lee SJ, Kang J. Real-World Efficacy of Regdanvimab on Clinical Outcomes in Patients with Mild to Moderate COVID-19. *J Clin Med*. 2022;11(5):1412. Gupta V, Ingawale S, Bhondve A, et al. Clinical Study of Use of Remdesivir and Tocilizumab in Severely Ill COVID-19 Patients. *J Assoc Physicians India*. 2021;69(7):14-19. Elec AD, Oltean M, Goldis P, et al. COVID-19 after kidney transplantation: Early outcomes and renal function following antiviral treatment. *Int J Infect Dis*. 2021;104:426-432.
Wrong study design	Fintzi J, Bonnett T, Sweeney DA, et al. Deconstructing the Treatment Effect of Remdesivir in the Adaptive Coronavirus Disease 2019 (COVID-19) Treatment Trial-1: Implications for Critical Care Resource Utilization. *Clin Infect Dis*. 2022;74(12):2209-2217. Department of Error: Remdesivir and 3 other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses. *Lancet*. 2022;400(10362).

Reason for exclusion	Citation
Wrong study design	Ohsfeldt R, Kelton K, Klein T, et al. Cost-Effectiveness of Baricitinib Compared With Standard of Care: A Modeling Study in Hospitalized Patients With COVID-19 in the United States. *Clin Ther*. 2021;43(11):1877-1893.e4.
	Bauer RN, Teterina A, Shivram H, et al. Prognostic value of severe acute respiratory syndrome coronavirus-2 viral load and antibodies in patients hospitalized with COVID-19. *Clin Transl Sci*. 2023;16(6):1049-1062.
	Pilgram L, Appel KS, Ruethrich MM, et al. Use and effectiveness of remdesivir for the treatment of patients with covid-19 using data from the Lean European Open Survey on SARS-CoV-2 infected patients (LEOSS): a multicentre cohort study. *Infection*. 2023;51(4):1033-1049.
	Potter GE, Bonnett T, Rubenstein K, et al. Temporal Improvements in COVID-19 Outcomes for Hospitalized Adults: A Post Hoc Observational Study of Remdesivir Group Participants in the Adaptive COVID-19 Treatment Trial. *Ann Intern Med*. 2022;175(12):1716-1727.
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Reason for exclusion	Citation
Wrong study design	Gutierrez R, Mendez-Figueroa H, Biebighauser JG, Bhalwal A, Pineles BL, Chauhan SP. Remdesivir use in pregnancy during the SARS-CoV-2 pandemic. *J Matern Fetal Neonatal Med*. 2022;35(25):9445-9451.
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Appendix 4: Detailed Characteristics and ROB for Included Studies

Note that this appendix has not been copy-edited.

Table 19

Beigel, 2020 (ACTT-1) – Study Characteristics and ROB

Study details	Description
Characteristics	
Methods	Adaptive phase III, double-blind, placebo-controlled, multicentre RCT 1:1 randomization stratified by study site and disease severity at enrolment **Time period:** February 21, 2020, to April 19, 2020 **Trial registration:** NCT04280705

Participants	1,062 adult patients (≥ 18 years) with COVID-19
	Inclusion criteria:
	• ≥ 18 years old
	• Laboratory-confirmed SARS-CoV-2 infection by RT-PCR < 72 hours prior to randomization or ≥ 72 hours prior to randomization if unable to obtain sample or if patient had progressive disease consistent with SARS-CoV-2
	• Agreement to not participate in another COVID-19 clinical trial through day 29
	• Symptoms of any duration and at least one of the following (suggestive of lower respiratory tract infection):
	  • Radiographic infiltrates by imaging
	  • O2 saturation ≤ 94% on room air or requiring supplemental oxygen, mechanical ventilation, or ECMO
	Exclusion criteria:
	• Pregnant or breastfeeding
	• AST or ALT > 5 times ULN
	• eGFR < 30 mL/min (including patients receiving hemodialysis or hemofiltration)
	• Anticipated discharge from the hospital or transfer to another hospital that is not a study site within 72 hours
	• Allergy to study medication

Study details	Description	
Interventions	**Intervention 1 (n = 541):** Remdesivir 200 mg given as an IV infusion on day 1 then 100 mg daily given as an IV infusion on days 2 to 10 or until hospital discharge or death **Intervention 2 (n = 521):** Matching placebo given as an IV infusion on day 1 then as an IV infusion on days 2 to 10. A placebo of normal saline of equal volume was given at the European sites and some non-European sites due to a shortage of matching placebo supplies. **Both groups get:** Supportive care according to the standard of care for the trial site hospital. Details of selected nonstudy drugs received are reported in Table S2 of the original study, including *Corticosteroids, Convalescent plasma, Anti-IL-6 medication, Non-trial interferon, Non-trial antiviral*.	
Outcomes	**Primary:** Time to recovery **Key secondary** outcome • Clinical status on an eight-point ordinal scale on day 15 **Other secondary outcomes** • Time to improvement of one or 2 categories from the baseline clinical status ordinal scale • Clinical status as assessed on the ordinal scale at days 3, 5, 8, 11,15, 22, and 29 • Mean change in status on the ordinal scale from day 1 to days 3, 5, 8, 11, 15, 22, and 29 • Time to discharge or NEWS-2 of ≤ 2 (maintained for 24 hours), whichever occurred first • Change in NEWS from day 1 to days 3, 5, 8, 11,15, 22, and 29 • Days of supplemental oxygen, with noninvasive ventilation or high-flow oxygen, and with invasive ventilation of ECMO up to day 29 • Incidence and duration of new oxygen use, of non- invasive ventilation or high-flow oxygen, and of invasive ventilation or ECMO up to day 29 • Number of days of hospitalization up to day 29 • Mortality at 14 and 28 days after enrolment • Grade 3 and 4 adverse events and serious adverse events • Discontinuation or temporary suspension of infusions • Changes in assessed laboratory values over time.	
Country and setting	73 study locations from 10 countries: US, Denmark, the UK, Greece, Germany, Korea, Mexico, Spain, Japan, and Singapore	
Funding source from industry	Gilead Sciences provided remdesivir for use in this trial but did not provide any financial support	
Risk of bias		
Adequate sequence generation	Low	"Eligible patients were randomly assigned in a 1:1 ratio to receive either remdesivir or placebo. Randomization was stratified by study site and disease severity at enrollment." Based on protocol/supplement, randomization was performed using a web-based Internet Data Entry System, Advantage eClinical. (page 1814)

Study details	Description	
Allocation concealment	Low	"Eligible patients were randomly assigned in a 1:1 ratio to receive either remdesivir or placebo. Randomization was stratified by study site and disease severity at enrollment." Based on protocol/supplement, randomization was performed using a web-based Internet Data Entry System, Advantage eClinical. (page 1814)
Blinding of participants and personnel	Low	"double-blind": "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." Appropriate method of blinding described. (page 1814)
Blinding of outcome assessors	Low	"double blind": "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." Appropriate method of blinding described. It is likely all study personnel were blinded. (page 1814)
Incomplete outcome data Loss to follow-up/missing data	Low	There were 24 of 541 patients (4.4%) receiving remdesivir and 13 of 521 patients (2.5%) receiving placebo who did not complete the study. These numbers include patients who did not receive the study treatment as well as those who were withdrawn for various reasons.
Selective outcome reporting	Low	Comprehensive reporting of pre specified outcomes in the manuscript and supplement.
Other sources of bias	Low	None apparent

Table 20

Spinner, 2020 (GSD-US-540-5774) – Study Characteristics and ROB

Study details	Description
Characteristics	
Methods	Randomized (1:1:1), open-label, phase 3, multicentre trial; randomization unstratified **Time period:** March 15, 2020, to April 18, 2020 **Trial registration:** 04292730
Participants	**N Randomized:** 596 **Inclusion Criteria:** • Currently hospitalized and requiring medical care for COVID-19 • Aged ≥ 18 years (at all sites), or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg (where permitted according to law and institutional review board [IRB] or independent ethics committee) • Willing and able to provide written informed consent (patients ≥ 18 years of age) or assent (legal guardian patient ≥ 12 and < 18 years of age) • SARS-CoV-2 infection confirmed by PCR ≤ 4 days before randomization • SpO2 > 94% on room air at screening • Radiographic evidence of pulmonary infiltrates • Men and women of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception. **Exclusion Criteria:** • Participation in any other clinical trial of an experimental drug treatment for COVID-19 • 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 (RDV; GS-5734™) • Requiring mechanical ventilation at screening • ALT or AST > 5 x ULN • Creatinine clearance < 50 mL/min using the Cockcroft-Gault formula for patients ≥ 18 years of age and Schwartz Formula for patients < 18 years of age • Positive pregnancy test or breastfeeding • Known hypersensitivity to the study drug, the metabolites, or formulation
Interventions	**Intervention 1:** Remdesivir 10 days (n = 197) 200 mg of remdesivir intravenously on day 1, followed by 100 mg of remdesivir once daily for the subsequent 9 days, infused over 30 to 60 minutes. **Intervention 2:** Remdesivir 5 days (n = 199) 200 mg of remdesivir intravenously on day 1, followed by 100 mg of remdesivir once daily for the subsequent 4 days, infused over 30 to 60 minutes. **Intervention 3:** Standard of Care Local standard of care. No details provided. **Co-interventions:** steroids, hydroxychloroquine, lopinavir-ritonavir, tocilizumab, and azithromycin, were all listed as being administered to some patients in all groups

Study details	Description	
Outcomes	**Primary Outcome:** • Clinical status on day 11 on a 7-point ordinal scale ranging from death (category 1) to discharged (category 7) **Secondary Outcomes:** • Key secondary end point: proportion of patients with adverse events throughout the duration of the study. • Prespecified exploratory outcomes were: (1) time to recovery (improvement from a baseline score of 2 to 5 to a score of or 7 or from a baseline score of 6 to a score of 7); (2) time to modified recovery (improvement from a baseline score of 2 to 4 to a score of 5 to 7, improvement from a baseline score of 5 to a score of 6-7, or improvement from a baseline score of 6 to a score of 7); (3) time to clinical improvement (≥ 2-point improvement from baseline on the 7-point ordinal scale);(4) time to 1-point or larger improvement; and (5) time to discontinuation of any oxygen support. The proportion of patients with these outcomes was also assessed on days 5, 7, and 11. • Other exploratory outcomes were duration of hospitalization, duration of different modes of respiratory support, and all-cause mortality.	
Country and setting	105 hospitals in the US, Europe, and Asia (France, Germany, Hong Kong, Italy, Korea, Netherlands, Singapore, Spain, Switzerland, Taiwan, UK, US)	
Funding source from industry	This study was sponsored by Gilead Sciences.	
Risk of bias		
Adequate sequence generation	Low	"Randomization was not stratified. The randomization list was created and validated by the interactive web response system (IWRS) vendor. A dummy randomization list was provided in Microsoft Excel format to the biostatistician employed by the study sponsor for review." (page 1049) Low ROB for randomization but the lack of stratification in a multicentre study is a concern.
Allocation concealment	Low	"A separate list of sequential patient numbers within each treatment group was generated by the IWRS vendor. The randomization had a block size of 6. Based on the treatment from the randomization 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 randomization list and could not know the sequence of treatments." (page 1049) The web-based platform indicates central randomization.
Blinding of participants and personnel	Unclear	"Treatment was open label because the sponsor had an insufficient number of placebo containing vials to support this trial." All outcomes of interest were objective, but performance and attrition bias could still be operating and affect some outcomes.
Blinding of outcome assessors	Low	"Treatment was open label because the sponsor had an insufficient number of placebo containing vials to support this trial." From the Supplement/Protocol it was noted: "Blinding of treatment assignments or data will not be performed in this study." All outcomes of interest were objective, so detection bias is less of a concern and lack of blinding did not likely influence assessment of the outcomes.

Study details	Description	
Incomplete outcome data Loss to follow-up/missing data	Unclear	If discharge and death are not considered as missing, then the percentages of missing patients in the treatment groups were 21 of 197 (11%) and 11 of 199 (6%). Excluding discharge and death, which are outcomes, the completion rate at 10 days was 172 of 197 (87.3%) and at 5 days was 180 of 199 (90.5%). There was no reporting of withdrawals or adverse events in the standard care group and all 200 patients were included in the analysis. Given that the analysis used the safety population it is unclear as to whether there was complete follow-up in the control group or if there were patients who terminated early for reasons other than discharge.
Selective outcome reporting	Unclear	Duration of hospitalization is one of the outcomes of interest. Authors only narratively reported it as no difference between groups without providing any data.
Other sources of bias	Low	None apparent

Table 21

Ali, 2022 (CATCO) – Study Characteristics and ROB

Study details	Description
Characteristics	
Methods	A pragmatic, multicentre open-label randomized (1:1) controlled trial. Randomization was unstratified. **Time period:** August 14, 2020, to April 1, 2021 **Trial registration:** NCT04330690
Participants	**N Randomized:** 1,282 (951 were also included in Solidarity) **Inclusion criteria:** • Adults admitted to participating hospitals with laboratory-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
Interventions	**Intervention 1:** N = 634 Remdesivir + standard of care. IV 200 mg on day 0 and 100 mg on days 1 through 9 or until hospital discharge or death. **Intervention 2:** N = 648 SoC available at the time. **Co-interventions:** All other care decisions were left to the treating physicians, including dexamethasone or tocilizumab or both for eligible patients. Baseline corticosteroid use, which was the standard of care for inpatients on oxygen, was similar across both groups.
Outcomes	**Primary:** • In-hospital mortality **Secondary:** • New need for mechanical ventilation (for those not ventilated at baseline) • Length of stay • Clinical severity of illness on days 3, 5, 8, 11, 15, 29 and 60 (including after discharge) according to the WHO Ordinal Scale • Oxygen-free and ventilator-free days at day 28 from time of randomization • Safety outcomes of special interest, including new hepatic dysfunction and new need for renal replacement therapy
Country and setting	Canada – 52 Canadian hospitals
Funding source from industry	Not industry sponsored. Funded by Canadian Institute of Health Research.

Study details	Description	
Risk of bias		
Adequate sequence generation	Low	"We performed randomization through the global Solidarity trial until Jan. 29, 2021, and then in Canada until Apr. 1, 2021, through a Web-based server after Solidarity ceased randomization to remdesivir." (page E243)
Allocation concealment	Low	Web-based server denotes central randomization.
Blinding of participants and personnel	Unclear	All outcomes of interest were objective, but performance and attrition bias could still be operating and affect some outcome. Lack of blinding does not seem to be a high-risk issue, but unclear risk.
Blinding of outcome assessors	Low	All outcomes of interest were objective, so detection bias is less of a concern and lack of blinding did not likely influence assessment.
Incomplete outcome data Loss to follow-up/missing data	Low	For remdesivir 14 of 634 randomized (2.2%) patients either did not receive or did not complete the intervention. For controls, 3 of 647 (0.5%) withdrew consent. All of these patients with the exception of one control were included in the analysis. (calculated from flow chart Figure 1 in published paper)
Selective outcome reporting	Low	Prespecified outcomes are reported in the results.
Other sources of bias	Low	None apparent

Table 22

Barratt-Due, 2021 (NOR-Solidarity) – Study Characteristics and ROB

Study details	Description
Characteristics	
Methods	An independent, add-on, open-label, randomized (1:1:1) controlled trial to the WHO Solidarity study. Randomization was unstratified. **Time period:** March 28, 2020 to October 4, 2020 **Trial registration:** NCT04321616
Participants	**N Randomized:** 185, with only 101 for eligible arms **Inclusion criteria:** Adults (≥ 18 years) with SARS-CoV-2 infection confirmed by PCR who were admitted to the hospital ward or intensive care unit (ICU) with no anticipated transfer to a nonstudy hospital within 72 hours of inclusion. **Exclusion criteria:** • acute occurrence of a comorbid condition in a 7-day period before inclusion • known intolerance to study drugs • participation in a potentially confounding trial • concomitant medications interfering with the study drugs
Interventions	**Treatment 1:** N = 43 Remdesivir +standard of care. IV 200 mg on day 1, then 100 mg daily up to 9 days **Treatment 2:** N = 58 Standard of care – undefined. **Co-interventions:** Some patients received steroids, other immunomodulatory drugs, ACE inhibitors 2 Angiotensin II receptor blockers.
Outcomes	**Primary:** • all-cause, in-hospital mortality **Secondary:** • receipt of invasive mechanical ventilation • time to first receipt and duration of mechanical ventilation • receipt and duration of treatment at an ICU • occurrence of suspected unexpected serious adverse reaction
Country and setting	Norway – 23 Norwegian hospitals
Funding source from industry	No industry funding. Primary funding source - National Clinical Therapy Research in the Specialist Health Services, Norway

Study details	Description	
Risk of bias		
Adequate sequence generation	Unclear	Randomization was computer generated. The randomization lists were not stratified or blocked; thus, the randomization can be regarded as simple. There are 2 RCTs with 2 separate control groups, however, the allocation description in text does not clarify how the SoC is split between the 2 active treatments. Some patients receiving SoC act as controls for both active treatment groups, whereas some act in one or the other, giving a partial overlap of the 2 control groups. In addition, the number of patients allocated to remdesivir and control are quite unequal (49 vs. 34). For AE outcomes, authors combined the 2 control groups, which broke the original randomization as there were 2 separate trials.
Allocation concealment	Low	Web based platform denotes central randomization.
Blinding of participants and personnel	Unclear	Open-label without a placebo control. All outcomes of interest were objective, but performance and attrition bias could still be operating and affect some outcome. Lack of blinding does not seem to be a high-risk issue, but unclear risk.
Blinding of outcome assessors	Low	"Despite being a randomized controlled trial with blinded analyses of all relevant data, it did not include a placebo group" (page 8 in published paper) Reported outcomes were objective. Detection bias likely not an issue. Lack of blinding is low ROB.
Incomplete outcome data Loss to follow-up/missing data	Low	5 of 58 (8.6%) randomized remdesivir patients and 5 of 43 (11.6%) control patients did not complete 3 months of follow-up. (excluding death, calculated from the flow chart Figure 1 in published paper)
Selective outcome reporting	Low	Prespecified outcomes in the methods section are reported in the results.
Other sources of bias	Low	None apparent

Table 23

Nevalainen, 2022 (SOLIDARITY Finland) – Study Characteristics and ROB

Study details	Description
Characteristics	
Methods	A pragmatic, parallel 1:1 randomized open-label multicentre trial. Randomization was unstratified **Time period:** July 23, 2020, to January 27, 2021 **Trial registration:** NCT04978259
Participants	**N Randomized:** 208 **Inclusion criteria:** • patients ≥18 years of age with a PCR-confirmed diagnosis of COVID-19 requiring hospitalization **Exclusion criteria:** • had an estimated life expectancy of <3 months • another acute severe condition during the past week • liver enzyme levels more than 5 times the upper reference limit • severe kidney failure • pregnant or breastfeeding • participated in another trial
Interventions	**Treatment 1:** N = 114 Remdesivir + standard of care. Remdesivir was started on either the day of hospital admission or the first or second full day of hospitalization or later. 200 mg was administered intravenously on the first day and 100 mg per day until discharge or for a maximum duration of 10 days **Treatment 2:** N = 94 Standard of care (undefined) **Co-interventions:** 69.4% and 76.6% received dexamethasone
Outcomes	**Primary:** • long-term recovery (analyses were also stratified by the need of oxygen therapy at randomization) and symptoms **Secondary:** • to assess exertional dyspnea, and the EQ-5D-5L and the visual analogue scale (VAS) scale to measure mobility, self-care, usual daily activities, general pain/discomfort, anxiety/depression, and an overall impression of health (Supplementary) • recorded in-hospital deaths in the Castor system and obtained subsequent death dates up to March 2022 from the Digital and Population Data Services Agency (Helsinki, Finland).
Country and setting	Finland – 11 Finnish hospitals

Study details	Description	
Funding source from industry	Not industry funded. The Academy of Finland (335527; KAOT), Foundation of the Finnish Anti-Tuberculosis Association (KAOT), Helsinki University Hospital (TYH2022330; KAOT), Päivikki and Sakari Sohlberg Foundation (KAOT), Sigrid Jusélius Foundation (KAOT), TampereTuberculosis Foundation (J.R. and KAOT), and TampereUniversity Hospital State Research Funding (9AC085; J.R.) funded this study. WHO provided the study drug (remdesivir), donated by Gilead Sciences. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and the decision to submit the manuscript for publication.	
Risk of bias		
Adequate sequence generation	Low	"We randomized patients (and collected data) using web-based Castor EDC software" (page 4 of published paper). Computer based randomization.
Allocation concealment	Low	Web-based platform denotes central randomization.
Blinding of participants and personnel	Unclear	"open-label multicenter trial comparing the local standard of care (SoC) and SoC with intravenous remdesivir" (page 4 of published paper). Outcomes of interest are objective. However, performance and attrition bias may be operating and affect some outcomes, and so in general ROB is unclear.
Blinding of outcome assessors	Low	Outcomes of interest are objective, and detection bias is likely not an issue and outcome assessment not likely to be affected by lack of blinding.
Incomplete outcome data Loss to follow-up/missing data	Low	For the mortality analysis 13 of 114 patients (11.4%) receiving remdesivir and 6 of 94 patients (6.4%) receiving standard care did not complete follow-up. Of these patients 8 and 4 were unable to be contacted. Mortality data were collected, however, from Digital and Population Data Services Agency and would not rely on patient contact. (calculated from Figure 1 in published paper)
Selective outcome reporting	Low	All patients and short-term outcomes are in the WHO solidarity study. This study mainly focused on long-term outcomes.
Other sources of bias	Low	None apparent. "The SOLIDARITY Finland recruited patients to the remdesivir trial until the WHO halted the trial"

Table 24

Ader, 2022 (DisCoVeRy) – Study Characteristics and ROB

Study details	Description
Characteristics	
Methods	A phase III, open-label, adaptive, multicentre, randomized (1:1), controlled trial Stratified on severity of disease and on European administrative region **Time period:** March 22, 2020, to January 21, 2021 **Trial registration:** NCT04315948
Participants	**N Randomized:** 857 **Inclusion criteria:** • aged 18 years or older, admitted to hospital with laboratory-confirmed SARS-CoV-2 infection and illness of any duration with at least one of the following: clinical assessment (evidence of rales or crackles on examination) and oxygen saturation (SpO2) of 94% or less on room air; or requirement of supplemental oxygen, high-flow oxygen devices, noninvasive ventilation, or mechanical ventilation **Exclusion criteria:** • had liver enzymes (alanine aminotransferase or aspartate aminotransferase) more than 5 times the upper limit of normal • a stage 4 severe chronic kidney disease or requiring dialysis (estimated glomerular filtration rate less than 30 mL/min) • transfer within 72 h to another hospital that was not a study site was anticipated • pregnant of breastfeeding • had contraindication to any study medication including allergy • treated with one of the evaluated antiviral drugs in the past 29 days • used ribavirin either in the past 29 days or concomitantly to random assignment
Interventions	**Treatment 1: N = 429** Remdesivir + standard of care. Remdesivir administered intravenously at a loading dose of 200 mg on day 1 followed by a 100 mg, 1-h infusion once daily for a total duration of 10 days. Cessation was allowed after 5 days if the patients was discharged from the hospital. Median duration of treatment was 9 days (IQR 5–10). **Treatment 2: N = 428** **Co-interventions:** Corticosteroids and anticoagulants were added to the standard of care: dexamethasone 6 mg once daily for 10 days or until discharge; dexamethasone 20 mg once daily for 5 days, followed by 10 mg once daily for 5 days for acute respiratory distress syndrome; anticoagulation were administered according to local protocols for venous thromboembolism prophylaxis or therapy. Other supportive treatments, such as immunomodulatory agents, were allowed in all groups and left to the investigator's discretion.

Study details	Description	
Outcomes	**Primary:** • clinical status at day 15 as measured on the seven-point ordinal scale of the WHO Master Protocol **Secondary:** • clinical status and change from baseline of the clinical status at days 3, 5, 8, 11, and 29 • time to an improvement of one and 2 categories as measured on the seven-point ordinal scale or hospital discharge until day 29 • change from baseline of the National Early Warning Score 2 (NEWS-2) at days 3, 5, 8, 11, 15, and 29 • time to NEWS-2 of 2 or lower or hospital discharge until day 29 • time to hospital discharge until day 29 and duration of hospitalization • time to new mechanical ventilation, ECMO, or death until day 29 • oxygenation and ventilator-free days until day 29 • in-hospital mortality and mortality at days 28 and 90 • the cumulative incidence of any grade 3 or 4 adverse events or of any serious adverse event and the grade changes in the biological and inflammatory patterns of patients over time	
Country and setting	France 48 sites (39 centres), Belgium (3 sites), Austria (3 sites), Portugal (2 sites), and Luxembourg (one site)	
Funding source from industry	No industry funding. Received funding from European Union's Horizon 2020 research and innovation programme (Europe); Austrian Group Medical Tumor (Austria); Belgian Health Care Knowledge Centre (Belgium); Fonds Erasme-COVID-Université Libre de Bruxelles (Belgium). REACTing, a French multidisciplinary collaborative network working on emerging infectious diseases (France); Ministry of Health (France); Domaine d'intérêt majeur One Health Île-de-France (France); European Regional Development Fund (Luxembourg); Ministry of Health (Portugal); Agency for Clinical Research and Biomedical Innovation (Portugal).	
Risk of bias		
Adequate sequence generation	Low	"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 severity of disease at inclusion and on European administrative region" (page 211 of published paper)
Allocation concealment	Low	"Randomisation was done in the electronic case report form to ensure appropriate allocation concealment" (page 211 of published paper)
Blinding of participants and personnel	Unclear	"Allocated treatment was not masked to participants nor study investigator." (page 211 of published paper). Although outcomes are objective, lack of blinding may lead to risk of performance and attrition bias that could affect some outcomes.
Blinding of outcome assessors	Low	Outcomes of interest are objective, and detection bias unlikely to affect outcomes.

Study details	Description	
Incomplete outcome data Loss to follow-up/missing data	Low	406 of 429 (94.6%) and 418 of 428 (97.7%) received at least one dose of intervention. No other information on how many complete the study. (calculated from flow chart Figure 1 in published paper)
Selective outcome reporting	Low	Prespecified outcomes in the methods section are reported in the results.
Other sources of bias	Low	None apparent. (Note: Trial was stopped early. The decision was endorsed by the DisCoVeRy steering committee on January 19, 2021, with subsequent cessation of patient recruitment on January 21, 2021.)

Appendix 5: Reported Results on Outcomes of Interest With Conclusions From Authors of Included Studies

Note that this appendix has not been copy-edited.

In Table 25, the reported results on the efficacy outcomes of interest from the randomized controlled trial are presented as in Table 8. In addition, concluding comments by the study investigators are provided as reported in the RCT. This provides a summary of the perspective of the investigators on the results of their study. However, even though the RCT report has been peer-reviewed, caution in reading these comments must be exercised since investigators may have overinterpreted the associations and causality of their results.

Table 25

Reported Results on Efficacy Outcomes of Interest With Study Authors' Conclusion

Reported results on outcomes of interest	Authors' conclusion
Duration of hospitalization (days)	
Beigel, 2020 (ACTT-1)[13]	
Duration of initial hospitalization, (follow-up 29 days), median (IQR) Remdesivir + SoC (n = 541): 12 (6 to 28) Placebo + SoC (n = 521): 17 (8 to 28) Difference of medians (95% CI): −5.0 (−7.7 to −2.3)	"The initial length of hospital stay was shorter in the remdesivir group than in the placebo group (median, 12 days vs. 17 days)" (page 1820)
Spinner, 2022 (GSD-US-540-5774)[14]	
No data available, narrative description.	"There were no significant differences between the remdesivir and SoC groups in duration of oxygen therapy or hospitalization." (page 1053)

Reported results on outcomes of interest	Authors' conclusion
Ali, 2022 (CATCO)[8]	
Duration of hospital stay median (IQR) Remdesivir (n = 634): 10 (6 to 18) SoC (n = 647): 9 (6 to 17) Difference in medians: 0 (−1 to 0) Duration of hospital stay for survivors, median (IQR), n = 1,005[b] Remdesivir : 9 (6 to 17) SoC: 9 (6 to 16) Difference in medians: 0 (−1 to 0) Duration of hospital stay for nonsurvivors, median (IQR) n = 262[b] Remdesivir: 12 (5 to 20) SoC: 11 (6 to 20) Difference in medians: 0 (−2 to 2)	"Duration of hospital stay was not different between the 2 groups, and we observed no difference in duration of hospital stay for survivors." (page E246)
Nevalainen, 2022 (SOLIDARITY Finland)[10]	
Reported duration of inpatient days as a baseline characteristic and not an outcome (n = 208) and after 1 year (n = 181), median (IQR) Baseline, n = 208 Remdesivir (n = 114): 8 (6 to 11) SoC (n = 94): 8.5 (6 to 15) After 1 year, n = 181 Remdesivir (n = 114): 8 (6 to 11) SoC (n = 94): 8 (6 to 14)	Not analyzed as an outcome. No interpretation.
ICU admission	
Barratt-Due, 2021 (NOR-Solidarity)[9]	
Admitted to ICU, % (95% CI)[c] Remdesivir + SoC (n = 42): 19.0 (95% CI, 9.2 to 32.6) SoC (n = 57): 19.3 (95% CI, 10.5 to 30.8) RD% = −0.3 (95% CI, −15.9 to 15.4)	"We found no effects of remdesivir or HCQ on the rate of ICU admission." (page 5)

Reported results on outcomes of interest	Authors' conclusion
Nevalainen, 2022 (SOLIDARITY Finland)[10]	
ICU treatment was reported as a characteristic of patients at baseline and at 1 year, n (%) Baseline, n = 208 Remdesivir (n = 114): 12 (10.5%) SoC (n = 94): 11 (11.7%) After 1 year, n = 181 Remdesivir (n = 114): 10 (10.2%) SoC (n = 94): 10 (12.0%)	Not analyzed as an outcome. No interpretation.
Length of ICU stay	
Barratt-Due, 2021 (NOR-Solidarity)[9]	
Remdesivir (n = 42) was compared to SoC (n = 87). Results were reported as cumulative probability plots and the claim was made that for the duration of ICU stay, the plots showed no differences between the treatments.	"Duration of ICU stay and…showed no differences between the treatments." (page 6)

Reported results on outcomes of interest	Authors' conclusion
Time to clinical improvement	
Beigel, 2020 (ACTT-1)[13]	
Median time to recovery in days was defined as the first day on which the patient satisfied one of the following 3 categories from the ordinal scale: 1 = hospitalized, not requiring supplemental oxygen — no longer requires ongoing medical care; 2 = not hospitalized, limitation on activities and/or requiring home oxygen; and 3 = not hospitalized, no limitations on activities. Day 1 through Day 29, median (IQR) Remdesivir + SoC (n = 541) 10 (9 to 11) Placebo + SoC (n = 521) 15 (13 to 18) Median time to clinical improvement (95% CI) in days. 1. Improvement of one category on ordinal scale Remdesivir + SoC (n = 541): 7.0 (95% CI, 6.0 to 8.0) Placebo + SoC (n = 521): 9.0 (95% CI, 8.0 to 11.0) HR = 1.23 (95% CI, 1.08 to 1.41) 2. Improvement of 2 categories on ordinal scale Remdesivir + SoC (n = 541): 11.0 (95% CI, 10.0 to 13.0) Placebo + SoC (n = 521): 14.0 (95% CI, 13.0 to 15.0) HR = 1.29 (95% CI, 1.12 to 1.48) 3. Discharge or NEWS-2 ≤ 2 for 24 hours Remdesivir + SoC (n = 541): 8.0 (95% CI, 7.0 to 9.0) Placebo + SoC (n = 521): 12.0 (95% CI, 10.0 to 15.0) HR = 1.27 (95% CI, 1.10 to 1.46)	"Patients in the remdesivir group had a shorter time to improvement of one or of 2 categories on the ordinal scale from baseline than patients in the placebo group." (page 1820) "Patients in the remdesivir group had a shorter time to discharge or to a National Early Warning Score of 2 or lower than those in the placebo group." (page 1820)

Reported results on outcomes of interest	Authors' conclusion
Spinner, 2022 (GSD-US-540-5774)[14]	
Categories of the WHO 7-point ordinal scale: 1 = death; 2 = hospitalized, requiring invasive mechanical ventilation or ECMO; 3 = hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 4 = hospitalized, requiring low-flow supplemental oxygen; 5 = hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (related or not to COVID-19); 6 = hospitalized, not requiring supplemental oxygen or ongoing medical care; and 7 = not hospitalized. 1. Time to clinical improvement (≥ 2-point improvement from baseline on the 7-point ordinal scale) in days, within 28 days[d] 10-day remdesivir (n = 193): 8 (4 to 14) 5-day remdesivir (n = 191): 6 (5 to 14) SoC (n = 200): 8 (5 to 22) 10-day vs .SoC: HR = 1.16 (95% CI, 0.93 to 1.43) 5-day vs. SoC: HR = 1.15 (95% CI, 0.93 to1.42) 2. Time to clinical improvement (≥ 1-point improvement from baseline on the 7-point ordinal scale) in days, within 28 day[sd] 10-day remdesivir (n = 193): 7 (4 to 12) 5-day remdesivir (n = 191): 6 (4 to 9) SoC (n = 200): 7 (4 to 14) 10-day vs. SoC: HR = 1.10 (95% CI, 0.90 to 1.36) 5-day vs. SoC: HR = 1.19 (95% CI, 0.97 to 1.47) 3. Time to recovery (improvement from a baseline score of 2 to 5, to a score of 6 or 7; or from a baseline score of 6 to a score of 7) in days, within 28 days[d] 10-day remdesivir (n = 193): 8 (4 to 13) 5-day remdesivir (n = 191): 6 (5 to 10) SoC (n = 200): 7 (4 to 15) 10-day vs. SoC: HR = 1.11 (95% CI, 0.90 to 1.37) 5-day vs. SoC: HR = 1.18 (95% CI, 0.96 to 1.45)	"There were no significant differences between the 5-day or 10-day remdesivir groups and standard care for any of the exploratory end points—time to 2-point or greater improvement in clinical status, time to 1-point or greater improvement in clinical status, time to recovery, time to modified recovery, and time to discontinuation of oxygen support" (page 1053)

Reported results on outcomes of interest	Authors' conclusion
4. Time to modified recovery (improvement from a baseline score of 2 to 4 to a score of 5 to 7; improvement from a baseline score of 5 to a score of 6 to 7; or improvement from a baseline score of 6 to a score of 7) in days, within 28 days[d] 10-day remdesivir (n = 193): 7 (4 to 12) 5-day remdesivir (n = 191): 6 (4 to 9) SoC (n = 200): 7 (4 to 14) 10-day vs. SoC: HR = 1.10 (95% CI, 0.90 to 1.36) 5-day vs. SoC: HR = 1.19 (95% CI, 0.96 to 1.46) 5. Time to discontinuation of oxygen (to room air) in days, within 28 days[d] 10-day remdesivir (n = 193): 4 (2 to 6) 5-day remdesivir (n = 191): 5 (3 to 7) SoC (n = 200): 6 (4 to 14) 10-day vs. SoC: HR = 1.93 (95% CI, 1.11 to 3.36) 5-day vs. SoC: HR = 1.31 (95% CI, 0.79 to 2.18)	
Ader, 2022 (DisCoVeRy)[12]	
Categories of the WHO 7-point ordinal scale were: 1 = not hospitalized, no limitations on activities; 2 = not hospitalized, limitation on activities; 3 = hospitalized, not requiring supplemental oxygen; 4 = hospitalized, requiring supplemental oxygen; 5 = hospitalized, on noninvasive ventilation or high-flow oxygen devices; 6 = hospitalized, on invasive mechanical ventilation or ECMO; and 7 = death. 1. Days to improvement of 2 categories on the 7-point ordinal scale or hospital discharge in days, within 29 days Remdesivir (n = 414): 12 (8 to 24) SoC (n = 418): 11 (7 to 26) HR 0.92 (95% CI, 0.79 to 1.08) 2. Days to NEWS-2 ≤ 2 or hospital discharge in days, within 29 days Remdesivir (n = 414): 11 (7 to 24) SoC (n = 418): 11 (6 to 29) HR = 1.03 (95% CI, 0.88 to 1.21) 3. Days to hospital discharge in days, within 29 days Remdesivir (n = 414): 15 (10 to 29) SoC (n = 418): 13 (8 to 29) HR (95% CI): HR 0.94 (95% CI, 0.80 to 1.11)	No significant difference between the groups was observed for these outcomes. "In this randomised controlled trial, the use of remdesivir for the treatment of hospitalised patients with COVID-19 was not associated with clinical improvement at day 15 or day 29" (page 219 from ref 12)

Reported results on outcomes of interest	Authors' conclusion
Time to ventilation	
Barratt-Due, 2021 (NOR-Solidarity)[9]	
Time to receipt of mechanical ventilation Remdesivir + SoC (n = 58) vs. SoC (n = 43): RR = 1.4 (95% CI, 0.4 to 5.8) HR = 1.3 (95% CI, 0.5 to 3.4)	"We found no effects of remdesivir on … and the time to receipt of mechanical ventilation." (pages 5-6)
Progression to high-flow oxygen or NIPPV	
Beigel, 2020 (ACTT-1)[13]	
New use of new noninvasive ventilation or high-flow oxygen use during the study, day 29 Remdesivir + SoC (n = 307): 52 (17%; 95% CI, 13 to 22) Placebo + SoC (n = 266): 64 (24%; 95% CI, 19 to 30) RD% = −7 (95% CI, −14 to −1)	"Among the 573 patients who were not receiving noninvasive ventilation, high-flow oxygen, invasive ventilation, or ECMO at baseline, the incidence of new noninvasive ventilation or high-flow oxygen use was lower in the remdesivir group than in the placebo group" (page 1820)
Ali, 2022 (CATCO)[8]	
Need for new oxygen[e]; defined as being on oxygen on day 2 and no oxygen therapy on day 1 Remdesivir (n = 634): 16 (22.5%) SoC (n = 647): 16 (29.6%) RR = 0.76 (95% CI, 0.42 to 1.38) RD% = −7.1 (95% CI, −2.3 to 8.5)	No interpretation
Need for mechanical ventilation (invasive mechanical ventilation or ECMO/VV-ECMO)	
Ali, 2022 (CATCO)[8]	
Need for new mechanical ventilation[c,e] (n = 1,168), defined as being on invasive ventilation from day 2 onward, but not on day 1 Remdesivir (n = 575): 46 (8.0%) SoC (n = 593): 89 (15.0%) RR = 0.53 (95% CI, 0.38 to 0.75) RD% = −7.0 (95% CI, −10.6 to −3.4)	"The benefit of treatment was most apparent for preventing the need for mechanical ventilation, suggesting probable added value for patients with less severe disease to avoid progression during hospital stay." (page E247)
Beigel, 2020 (ACTT-1)[13]	
New use of mechanical ventilation or ECMO during study, day 29 Remdesivir + SoC (n = 402): 52 (13%, 95% CI, 10 to 17) Placebo + SoC (n = 364): 82 (23%, 95% CI, 19 to 27) Difference: −10 (95% CI, −15 to −4)	"The incidence of new mechanical ventilation or ECMO use among the 766 patients who were not receiving these interventions at enrollment was lower in the remdesivir group than in the placebo group." (page 1820)

Reported results on outcomes of interest	Authors' conclusion
Spinner, 2022 (GSD-US-540-5774)[14]	
Number of patients hospitalized requiring invasive mechanical ventilation or extracorporeal membrane oxygenation: second category on the 7-point ordinal scale (0 for all groups at baseline) Day 11 10-day remdesivir (n = 193): 1 (0.5%) 5-day remdesivir (n = 191): 0 (0%) SoC (n = 200): 4 (2%) Day 14 10-day remdesivir (n = 193): 1 (0.5%) 5 -day remdesivir (n = 191): 0% SoC (n = 200): 5 (3%) Day 28 10-day remdesivir (n = 193): 1 (0.5%) 5-day remdesivir (n = 191): 0 (0%) SoC (n = 200): 4 (2%)	No specific interpretation on this. The overall conclusion on the distribution of the 7-point ordinal scale was "Among patients with moderate COVID-19, those randomized to a 10-day course of remdesivir did not have a statistically significant difference in clinical status compared with standard care at 11 days after initiation of treatment. Patients randomized to a 5-day course of remdesivir had a statistically significant difference in clinical status compared with standard care, but the difference was of uncertain clinical importance" (page 1056)
Need for intubation	
Beigel, 2020 (ACTT-1)[13]	
The combined number of subjects with respiratory failure or acute respiratory failure was 47 for remdesivir and 80 for placebo. Endotracheal intubations and serious adverse events (without a respiratory serious adverse event) were summarized as respiratory failures (Day 29) Remdesivir + SoC (n = 532): 39 (7.3%) Placebo + SoC (n = 516): 66 (12.8%)	"Our data also suggest that treatment with remdesivir may have prevented the progression to more severe respiratory disease, as shown by the lower proportion of serious adverse events due to respiratory failure among patients in the remdesivir group, as well as a lower incidence of new oxygen use among patients who were not receiving oxygen at enrollment and a lower proportion of patients needing higher levels of respiratory support during the study." (page 1821)

CI = confidence interval; ECMO = extracorporeal membrane oxygenation; HR = hazard ratio; ICU = intensive care unit; IQR = interquartile range; MD = mean difference; NA = not applicable; NEWS-2 = National Early Warning Score 2; NIPPV = noninvasive positive-pressure ventilation; OR = odds ratio; RD = risk difference; RR = relative risk; SoC = standard of care.

[a] Additional calculations based on the reported data were made to derive effect estimates and/or aid in identifying statistical significance.

[b] Number of patients in each arm were not reported, only total number available.

[c] Unclear follow-up, we assumed 28 days, as it was related to hospitalization and study is part of the WHO Solidarity trial.

[d] Estimates were from competing risk models and cause-specific proportional hazard models (with death as the competing risk).

[e] Unclear whether new oxygen was high-flow or not.

In Table 26, the reported results on the safety outcomes of interest from the randomized controlled trial are presented as in Table 9. In addition, concluding comments by the study investigators are provided as reported in the RCT. This provides a summary of the perspective of the investigators on the results of their study. However, even though the RCT report has been peer-reviewed, caution in reading these comments must be exercised since investigators may have overinterpreted the associations and causality of their results.

Table 26

Reported Results on Safety Outcomes of Interest With Study Authors' Conclusion

Reported results on outcomes of interest	Authors' conclusion
Death	
Beigel, 2020 (ACTT-1)[13]	
1. Mortality through day 15, n (%) Remdesivir + SoC (n = 541): 35 (6.5%) Placebo + SoC (n = 532): 61 (11.5%) HR (95% CI): HR = 0.55 (95% CI, 0.36 to 0.83) 2. Mortality over the entire study period, by day 29, n (%) Remdesivir (n = 541): 59 (10.9%) SoC (n = 532): 77 (14.5%) HR = 0.73 (95% CI, 0.52 to 1.03)	"The between group differences in mortality varied considerably according to baseline severity. However, the interaction tests suggest greater benefit (with respect to recovery and mortality) in lower ordinal score categories (7-point ordinal scale). This should not be interpreted as conclusively showing a lack of efficacy in higher ordinal score categories." (page 1820)
Spinner, 2022 (GSD-US-540-5774)[14]	
Death on 7-category scale, n (%) 1. Day 11 10-day remdesivir (n = 193): 2 (1%) 5-day remdesivir (n = 191): 0 (0%) SoC (n = 200): 4 (2%) 2. Day 14 10-day remdesivir (n = 193): 2 (1%) 5-day remdesivir (n = 191): 1 (1%) SoC (n = 200): 4 (2%) 3. Day 28 10-day remdesivir (n = 193): 3 (1.6%) 5-day remdesivir (n = 191): 2 (1%) SoC (n = 200): 4 (2%)	"All 9 deaths through day 28 occurred in patients aged 64 years or older, and none was attributed to remdesivir treatment." (page 1054)

Reported results on outcomes of interest	Authors' conclusion
Ali, 2022 (CATCO)[8]	
1. All-cause, in-hospital mortality, n = 1,267 (15 patients had missing hospital mortality and length of stay: 6 patients were still in hospital and 9 withdrew consent)[b] Remdesivir (n = 626): 117 (18.7%) SoC (n = 641): 145 (22.6%) RR = 0.83 (95% CI, 0.67 to 1.03) RD% = −3.9 (95% CI, −8.3 to 1.03) 2. Mortality by 60 days, n = 1,052 (230 patients withdrew consent or were lost to follow-up after discharge) Remdesivir (n = 512): 127 (24.8) SoC (n = 539): 152 (28.2) RR = 0.88 (95% CI, 0.72 to 1.07) RD% = −3.4 (95% CI, −8.8 to 1.9)	"Among 1,282 patients admitted with COVID-19 to 52 hospitals in Canada, in-hospital mortality of patients treated with remdesivir was lower than that of control patients. Small, regional trials are at high risk of being underpowered to detect modest, but important, treatment effects, and international collaboration is fundamental. This trial found that in Canadian patients in hospital with COVID- 19, remdesivir, in combination with standard care, improved secondary outcomes of need for mechanical ventilation in patients not ventilated at entry, compared with standard care alone, while being underpowered to detect a difference in mortality. Understanding which patient populations would have the largest benefit should be the focus of future meta-analyses." (page E247)
Barratt-Due, 2021 (NOR-Solidarity)[9]	
1. Mortality during hospitalization, % (95% CI) Remdesivir + SoC (n = 42): 7.1 (1.8 to 17.5) SoC (n = 57): 7.0 (95% CI, 2.2 to 15.6) RR = 1.0 (95% CI, 0.2 to 4.6) HR = 1.0 (95% CI, 0.4 to 2.9) 2. Mortality at day 28, % (95% CI) Remdesivir + SoC (n = 42): 2.4 (95% CI, 0.1 to 10.1) SoC (n = 57): 5.3 (95% CI, 1.3 to 13.1) RD% = −2.9 (95% CI, −10.3 to 4.5) 3. Mortality at day 60, % (95% CI) Remdesivir +SoC (n = 42): 7.1 (95% CI, 1.8 to 17.5) SoC (n = 57): 5.3 (95% CI, 1.3 to 13.1) RD% = 1.9 (95% CI, −7.8 to 11.6)	"Neither remdesivir nor HCQ had any effect on mortality, the need for mechanical ventilation, or duration of hospital stay" (pages 6 to 7)

Reported results on outcomes of interest	Authors' conclusion
Ader, 2022 (DisCoVeRy)[12]	
1. Death at day 15: 7-point ordinal scale, n (%)c Remdesivir (n = 414): 21 (5%) SoC (n = 418): 24 (6%) OR = 0.98 (95% CI, 0.77 to 1.25) 2. Death at day 29: 7-point ordinal scale Remdesivir (n = 414): 34 (8%) SoC (n = 418): 38 (9%) OR = 1.11 (95% CI, 0.87 to 1.42) 3. Death within 28 days Remdesivir (n = 414): 34 (8%) SoC (n = 418): 37 (9%) OR = 0.93 (95% CI, 0.57 to 1.52) 4. In-hospital death Remdesivir (n = 420): 33 SoC (n = 423): 38 Adjusted OR: OR = 0.84 (95% CI, 0.51 to 1.37) 5. Mortality at 3 months Remdesivir (n = 420): 43 SoC (n = 423): 49 Adjusted OR: OR = 0.87 (95% CI, 0.56 to 1.36)	"In this randomised controlled trial, the use of remdesivir for the treatment of hospitalised patients with COVID-19 was not associated with clinical improvement at day 15 or day 29, nor with a reduction in mortality." (page 219 in ref 12) "Remdesivir did not have a significant effect on in-hospital mortality nor on mortality at 3 months." (page 764 in ref 11)
Nevalainen, 2022 (SOLIDARITY Finland)[10]	
1. Mortality during hospitalization[b] Remdesivir (n = 103): 1 (0.9%) SoC (n = 88): 4 (4.3) 2. At 1 year, n = 181 Remdesivir (n = 103): 5 (4.4%) SoC (n = 88): 5 (5.3%) RR = 0.82 (95% CI, 0.25 to 2.76) RD% = −0.9 (95% CI, −7.9 to 5.3)	No comparison interpretation between groups. "Patients experienced much lower in-hospital mortality rates in Finland (2.4%) than in the global trial (15.0%) and were therefore a potentially more suitable patient population (likely earlier phase of the disease) for an antiviral drug." (page 3)
SAEs and grade 3 or 4 AEs, total	
Beigel, 2020 (ACTT-1)[13]	
1. At least 1 SAE, 29 days, n (%) Remdesivir + SoC (n = 532): 131 (24.6%) Placebo + SoC (n = 516): 163 (31.6%) P = 0.010 2. Grade 3 and 4 AEs Remdesivir + SoC (n = 532): 273 (51.3%) Placebo + SoC (n = 516): 295 (57.2%) P = 0.058	No specific interpretation for these data.

Reported results on outcomes of interest	Authors' conclusion
Spinner, 2022 (GSD-US-540-5774)[14]	
1. Any SAE, 28 days, n (%) 10-day remdesivir (n = 193): 10 (5%) 5-day remdesivir (n = 191): 9 (5%) SoC (n = 200): 18 (9%) 2. Any grade ≥ 3 AE 10-day remdesivir (n = 193): 24 (12%) 5-day remdesivir (n = 191): 20 (10%) SoC (n = 200): 24 (12%)	"…the rates of grade 3 or higher adverse events and serious adverse events were not higher in the 10-day remdesivir group than in the 5-day remdesivir and standard care groups."(page 1055)
Barratt-Due, 2021 (NOR-Solidarity)[9]	
Patients with serious AEs[d], 28 days, n (%) Remdesivir (n = 42): 8 (15.4%) SoCe (n = 87): 13 (14.9%)	"Most other serious adverse events were related to respiratory failure and interpreted as attributable to disease Progression." (page 6) No interpretation for comparison.
Ader, 2022 (DisCoVeRy)[12]	
1. Any SAE, 29 days, n (%) Remdesivir (n = 410): 147 (35.9%) SoC (n = 423): 138 (32.6%) OR 1.77 (95% CI, 0.87 to 1.57) 2. Grade 3 or 4 AE Remdesivir (n = 410): 143 (34.9%) SoC (n = 423): 150 (36.2%) OR = 0.98 (95% CI, 0.73 to 1.32)	"Among the 833 patients included in the safety analysis, no significant difference was evidenced in the occurrence of grade 3–4 adverse events nor of serious adverse events." (page 764 of ref 11)
Withdrawal of treatment due to AEs	
Barratt-Due, 2021 (NOR-Solidarity)[9]	
Withdrawal of treatment due to AEs Remdesivir + SoC (n = 42): 0 SoCe (n = 87): 0	No interpretation. 0 events in both groups
Spinner, 2022 (GSD-US-540-5774)[14]	
Discontinuation of treatment because of AEs, N (%) 10-day remdesivir (n = 93): 8 (4%) 5-day remdesivir (n = 191): 4 (2%) SoC (n = 200): NR	No interpretation

Reported results on outcomes of interest	Authors' conclusion
Beigel, 2020 (ACTT-1)[13]	
Discontinued due to AEs or SAEs, other than death leading to treatment discontinuation, n (%) Remdesivir + SoC (n = 532): 52 (9.8%) Placebo + SoC (n = 516): 70 (13.6%)	No interpretation
SAE – acute kidney injury	
Ali, 2022 (CATCO)[8]	
Day 5 serum creatinine[f], mean ± SD; median (IQR), n = 936[g] Remdesivir: 86.7 ± 78.0; 71 (IQR, 57 to 88.5) SoC: 87.7 ± 79.2; 69 (IQR, 57 to 87.5) MD = −0.92 (95% CI, −10.9 to 9.1) Median difference = −1 (95% CI, −4 to 2) New dialysis[f]: Defined as dialysis for those who were not on dialysis at baseline (16 patients were on dialysis on day 1 and were excluded), n (%) Remdesivir (n = 625): 16 (2.6%) SoC (n = 640): 15 (2.3%) RR = 1.09 (95% CI, 0.54 to 2.19) RD% = 0.2 (95% CI, −1.5 to 1.9)	"There was no difference in safety events of new dialysis, change in creatinine, or new hepatic dysfunction between the 2 groups." (page E242)
Spinner, 2022 (GSD-US-540-5774)[14]	
Creatinine clearance decrease[f], n (%), up to 28 days 1. Any grade 10-day remdesivir (n = 176): 45 (26%) 5-day remdesivir (n = 178): 26 (15%) SoC (n = 183): 55 (30%) 2. Grade 3 (30 to < 60 mL/min or 30% to < 50% decrease from baseline) 10-day remdesivir (n = 176): 7 (4%) 5-day remdesivir (n = 178): 4 (2%) SoC (n = 183): 9 (5%) 3. Grade 4 (< 30 mL/min, ≥ 50% decrease from baseline, or dialysis needed) 10-day remdesivir (n = 176): 2 (1%) 5-day remdesivir (n = 178): 0 (0%) SoC (n = 183): 5 (3%)	No specific interpretation for these outcomes. "Adverse events were experienced by 51% of patients in the 5-day remdesivir group, 59% in the 10-day remdesivir group, and 47% in the standard care group. The difference in proportions between the 5-day remdesivir group and standard care was not statistically significant (4.8%; 95% CI, −5.2% to 14.7%; P = .36), but the difference between the 10-day remdesivir group and standard care was significant (12.0%; 95% CI, 1.6% to 21.8%; P = .02)." (page 1054)

Reported results on outcomes of interest	Authors' conclusion
Beigel, 2020 (ACTT-1)[13]	
Serious SAEs occurring in > 5 patients, n (%), 29 days 1. Acute kidney Injury, under SAEs Remdesivir + SoC (n = 532): 7 (1.3%) Placebo + SoC (n = 516): 12 (2.3%) 2. Renal failure, under SAEs Remdesivir + SoC (n = 532): 2 (0.4%) Placebo + SoC (n = 516): 5 (1.0%) 3. Glomerular filtration rate decreased, under SAEs Remdesivir + SoC (n = 532): 5 (0.9%) Placebo + SoC (n = 516): 2 (0.4%) Nonserious AEs 4. Creatinine renal clearance decreased Remdesivir + SoC (n = 532): 4 (0.8%) Placebo + SoC (n = 516): 6 (1.2%) 5. Composite of glomerular filtration rate decreased, acute kidney injury, or renal failure Remdesivir + SoC (n = 532): 14 (2.6%) Placebo + SoC (n = 516): 17 (3.3%) 6. Composite of glomerular filtration rate decreased, acute kidney injury, blood creatinine increased, or creatinine renal clearance decreased Remdesivir + SoC (n = 532): 85 (16.0%) Placebo + SoC (n = 516): 105 (20.3%)	No interpretation for the specific SAE. "The most common nonserious adverse events occurring in at least 5% of all patients included decreased glomerular filtration rate, decreased hemoglobin level, decreased lymphocyte count, respiratory failure, anemia, pyrexia, hyperglycemia, increased blood creatinine level, and increased blood glucose level. The incidence of these adverse events was generally similar in the remdesivir and placebo groups." (page 1821)
Ader, 2022 (DisCoVeRy)[12]	
SAE – acute kidney injury[h], excluding acute renal failures defined based on the RIFLE classification; n (%), 29 days Remdesivir (n = 406): 12 (3%) SoC (n = 418): 15 (4%)	No specific interpretation for this outcome.
SAE – acute liver injury	
Ali, 2022 (CATCO)[8]	
New hepatic dysfunction[i], defined as acute liver function as clinically determined or ALT at day 5 more than twice ALT at day 1, n (%) Remdesivir (n = 625): 82 (13.1%) SoC (n = 642): 88 (13.7%) RR = 0.96 (95% CI, 0.72 to 1.26) RD% = −0.6 (95% CI, −4.4 to 3.1)	"There were no differences in secondary safety outcomes between intervention groups in serum creatinine on day 5, incidence of new dialysis or incidence of hepatic dysfunction." (page E246)

Reported results on outcomes of interest	Authors' conclusion
Barratt-Due, 2021 (NOR-Solidarity)[9]	
SAE – hepatobiliary disorder Remdesivir +SoC (n = 42): 0 (0%) SoCe (n = 87): 1 (1.1%)	No interpretation
Ader, 2022 (DisCoVeRy)[12]	
Hepatobiliary disorders, including 3 kinds: cholangitis, hepatocellular injury, and hepatorenal syndrome[f]; n (%) Remdesivir (n = 406): 1 (0%), hepatorenal syndrome SoC (n = 418): 2 (0%), 1 cholangitis and 1 hepatocellular injury	No interpretation
Spinner, 2022 (GSD-US-540-5774)[14]	
ALT increase, n (%), up to 28 days 1. Any grade 10-day remdesivir (n = 177): 57 (32%) 5-day remdesivir (n = 179): 61 (34%) SoC (n = 182): 71 (39%) 2. Grade 3 (> 5 to 10 times upper limit of normal) 10-day remdesivir (n = 177): 6 (3%) 5-day remdesivir (n = 179): 4 (2%) SoC (n = 182): 11 (6%) 3. Grade 4 (> 10 times upper limit of normal) 10-day remdesivir (n = 177): 0 (0%) 5-day remdesivir (n = 179): 0 (0%) SoC (n = 182): 3 (2%) Aspartate aminotransferase (AST) increase, n (%), up to 28 days 1. Any grade 10-day remdesivir (n = 175): 56 (32%) 5-day remdesivir (n = 177): 56 (32%) SoC (n = 182): 60 (33%) 2. Grade 3 (> 5 to 10 times upper limit of normal) 10-day remdesivir (n = 175): 2 (1%) 5-day remdesivir (n = 177): 3 (2%) SoC (n = 182): 6 (3%) 3. Grade 4 (> 10 times upper limit of normal) 10-day remdesivir (n = 175): 0 (0%) 5-day remdesivir (n = 177): 1 (1%) SoC (n = 182): 5 (3%)	Interpretation is available only for total AEs and SAEs, and not for the individual events. For total SAE: "Serious adverse events were less common in the remdesivir groups (5% in both 5-day and 10-day groups) than in the standard care group (9%), differences of −4.3% (95% CI, −9.7% to 0.9%; P = .11) for the 5-day remdesivir group vs standard care and −3.8% (95% CI, −9.3% to 1.4%; P = .17) for the 10-day remdesivir group vs standard care." (page 1054)

Reported results on outcomes of interest	Authors' conclusion
Beigel, 2020 (ACTT-1)[13]	
1. The combined number of patients with transaminases increased[j], AST increased, or ALT increased; n (%) Remdesivir + SoC (n = 532): 32 (6%) Placebo + SoC (n = 516): 55 (11%) 2. Liver function test increased[h] Remdesivir + SoC (n = 532): 3 (0.6%) Placebo + SoC (n = 516): 3 (0.6%) 3. Hepatobiliary disorders: hyperbilirubinemia[h] Remdesivir + SoC (n = 532): 2 (0.4%) Placebo + SoC (n = 516): 3 (0.6%)	No interpretation for these outcomes. Relevant conclusions are for most common nonserious adverse events "The most common nonserious adverse events occurring in at least 5% of all patients included decreased glomerular filtration rate, decreased hemoglobin level, decreased lymphocyte count, respiratory failure, anemia, pyrexia, hyperglycemia, increased blood creatinine level, and increased blood glucose level. The incidence of these adverse events was generally similar in the remdesivir and placebo groups." (page 1821)
SAE – thrombocytopenia	
Ader, 2022 (DisCoVeRy)[12]	
Thrombocytopenia, not defined under SAEs, n (%) Remdesivir (n = 406): 0 (0%) SoC (n = 418): 1 (0%)	No interpretation
Barratt-Due, 2021 (NOR-Solidarity)[9]	
Blood and lymphatic system disorders, not defined under SAEs, n (%) Remdesivir (n = 42): 0 (0%) SoC[e] (n = 87): 0 (0%)	No interpretation, 0 events for both groups
Spinner, 2022 (GSD-US-540-5774)[14]	
SAE – thrombocytopenia, n (%) 10-day remdesivir (n = 193): 0 (0%) 5-day remdesivir (n = 191): 0 (0%) SoC (n = 200): 0 (0%)	No interpretation, 0 events for both groups
Beigel, 2020 (ACTT-1)[13]	
Platelet count decreased[k] Remdesivir + SoC (n = 532): 6 (1.1%) Placebo + SoC (n = 516): 2 (0.4%)	No interpretation.

AE = adverse event; ALT = alanine transaminase; AST = aspartate aminotransferase: CI = confidence interval; HR = hazard ratio; IQR = interquartile range; MD = mean difference; OR = odds ratio; RD = risk difference; RR = relative risk; SAE = serious adverse event; SoC = standard of care; WDAE = withdrawal due to adverse event; RIFLE = Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease; NC = not calculated; NR = not reported.

[a] Additional calculations based on the reported data were made to derive effect estimates and/or aid in identifying statistical significance.

[b] Unclear follow-up, we assumed 28 days, as it was related to hospitalization and study is part of the WHO Solidarity trial.

[c] All analyses were adjusted for disease severity at randomization. Deaths for days 3, 5, 8, and 11 were also provided in this study.

d This study also provided the number of events, since a patient could have more than 1 event. These event numbers were 20 for SoC and 13 for remdesivir + SoC.

[e] The SoC group is combination to 2 SoC groups considered in the study.

[f] Outcome was not defined as serious or nonserious in the study report.

[g] Number of patients in each group were not reported, only the total number available.

[h] There were different numbers on acute kidney injury (15 of 406 [4%] for remdesivir and 18 of 418 [4%] for SoC) in the supplementary file, but they were not defined as SAEs.

[i] Outcome not defined as SAE in the study report.

[j] Outcome was defined as nonserious adverse event occurring in 5 or more patients.

[k] Outcome considered under nonserious AEs.

Appendix 6: Detailed Characteristics and ROB for the WHO Solidarity Trial

Note that this appendix has not been copy-edited.

Table 27

WHO Solidarity Trial Consortium, 2022 (WHO Solidarity) – Study Characteristics and ROB

Study characteristics	Description
Methods	Simple, international, open-label, randomized trial (1:1). Randomization was unstratified **Time period:** March 22, 2021, to January 29, 2021 **Trial registration:** NCT04315948
Participants	**N randomized:** 8,320 **Inclusion:** Contraindication to any locally available study drug. **Exclusion Criteria:** • Protocol did not define exclusion criteria, but mentioned 3 possible contraindications to enrolment - serious chronic liver or heart disease, or pregnancy.
Interventions	**Intervention 1:** Remdesivir intravenous infusion, 200 mg on day 0 and 100 mg on days 1–9 **Intervention 2:** Local standard of care. (Undefined) **Co-interventions:** Investigators reported the percentage of use of selected nonstudy drugs in each groups. These drugs included: corticosteroids (most common), convalescent plasma, anti-IL-6 medication, nontrial interferon, and nontrial antiviral.
Outcomes	**Primary outcome:** • In-hospital mortality, subdivided by disease severity. **Secondary outcomes:** • Progression to ventilation if not already ventilated, and time to discharge from hospital. • Cause-specific mortality was not a primary or secondary outcome, although cardiac-related deaths are analysed in the appendix. • Composite analyses of ventilation or death in those not ventilated at entry.
Country and setting	WHO in collaboration with national co-ordinators and principal investigators in 35 countries (in Europe, Canada, Latin America, Asia, and Africa)
Funding source from industry	Gilead Science donated remdesivir, but had no role in other aspects of research.

Risk of bias		
Bias	**Judgement**	**Support for judgement**
Adequate sequence generation	Unclear	Randomization through computerized system - low risk. From published paper "For each drug, all patient characteristics were reasonably well balanced between the study drug and control groups" (page 1946) Lack of stratification by countries may still be a concern.
Allocation concealment	Low	Central randomization
Blinding of participants and personnel	Unclear	Although outcomes are objective, lack of blinding may lead to risk of performance and attrition bias that could affect some outcomes.
Blinding of outcome assessors	Low	Data analysis was blinded. Assessment of outcomes such as mortality and ventilation are objective so although study was open-label, the ROB is low.
Incomplete outcome data Loss to follow-up/ missing data	Low	"Of 4077 such patients allocated remdesivir, 3892 (95.5%) were taking remdesivir halfway through the scheduled treatment period, compared with 73 (1.8%) of 4057 such patients allocated compared to control." (page 1946)
Selective outcome reporting	High	All outcomes specified in the protocol are reported in the results. However, in the protocol under schedule of assessment they state under Schedule of Assessments "Report any serious and unexpected adverse reactions to study website" There was no reporting of adverse events which would be expected in an intervention study therefore judged high ROB.
Other sources of bias	Low	None apparent