Supplementary Material*

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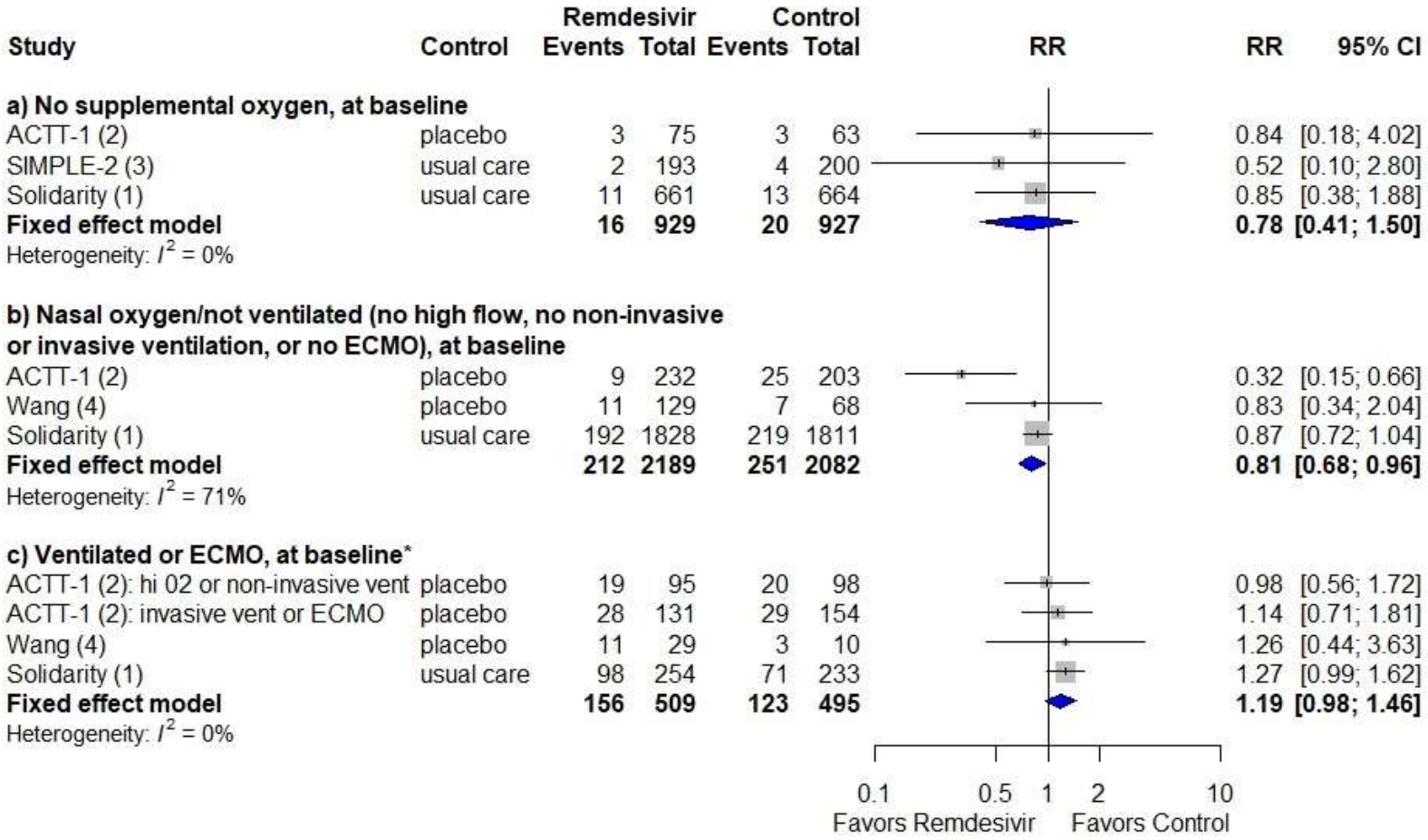
References

Item	Page
Supplement Figure 1a. Mortality results by initial respiratory status	2
Supplement Figure 1b. Need for ventilation/ECMO	3
Supplement Figure 2. Literature flow diagram	4
Supplement Table 1. Study characteristics of the included trials	5
Supplement Table 2. Summary of conclusions and updated findings for randomized trials of remdesivir	10
Supplement Table 3. Effect of remdesivir in randomized controlled studies	16
References	25

* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

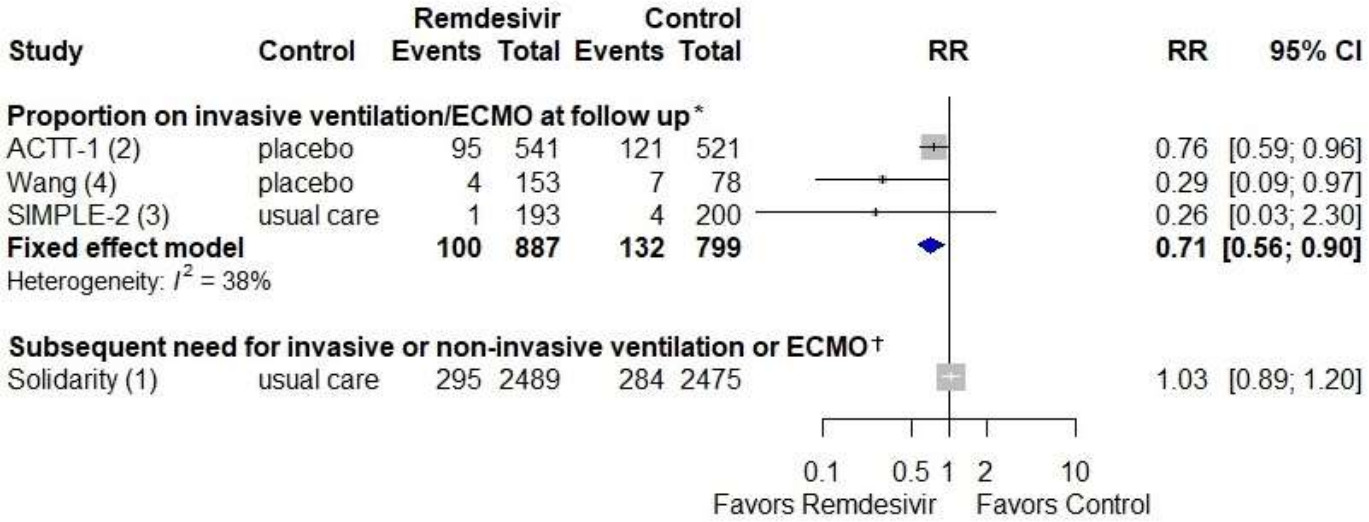
Supplement Figure 1a. Mortality Results by Initial Respiratory Status



CI=confidence interval; ECMO=extracorporeal membrane oxygenation; RR=risk ratio; blue diamond reflects pooled results from trials (listed above) that enrolled patients in the corresponding respiratory support subgroups.

* For Group C, Wang includes invasive ventilation or ECMO and Solidarity includes non-invasive or invasive ventilation or ECMO

Supplement Figure 1b. Need for ventilation/ECMO

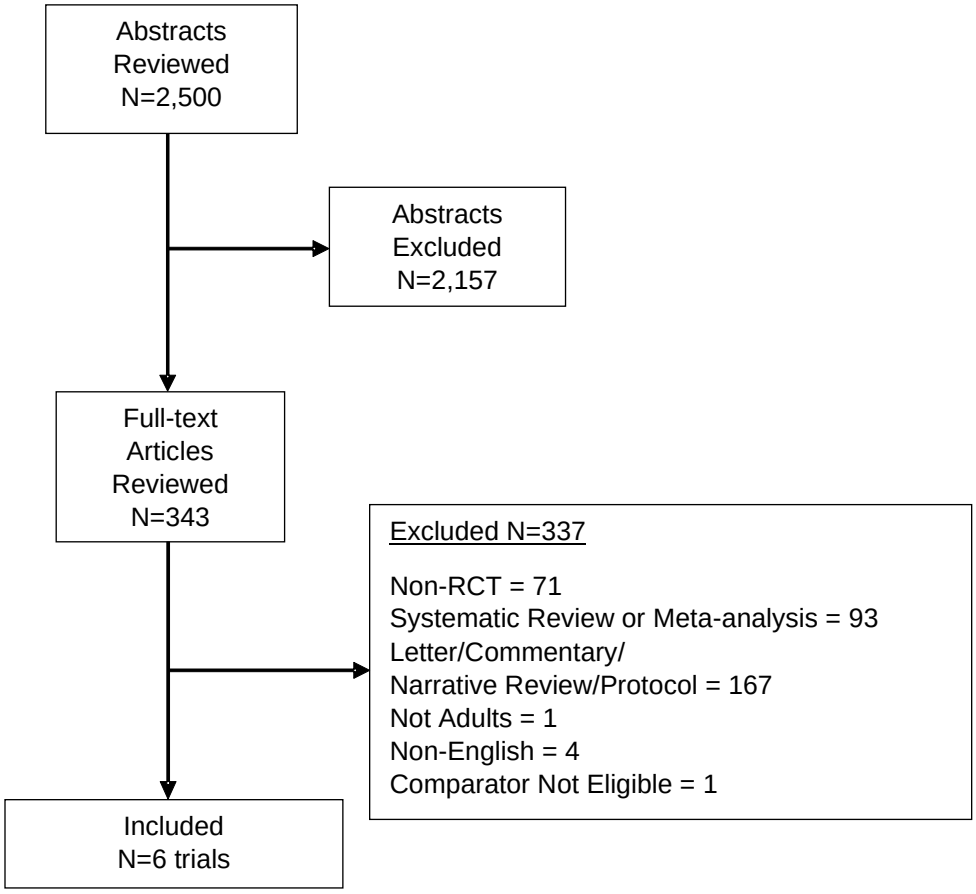


CI=confidence interval; ECMO=extracorporeal membrane oxygenation; RR=risk ratio

* For the pooled trials, defined as: proportion on invasive ventilation/ECMO (new vs continued from baseline) at follow up (ACTT-1 on day 15, Wang on day 14, and SIMPLE-2 on day 11).

† Unpooled Solidarity trial, defined as: subsequent need for ventilation in those not ventilated at baseline (through day 28)

Supplement Figure 2. Literature Flow Diagram



Supplement Table 1. Study Characteristics of the Included Trials

Author, Year Country **Funding** **Risk of Bias**	**Intervention** **Comparator** **Inclusion/exclusion criteria** **Study Period/Length of Follow-up**	**Demographics**
WHO Solidarity 2020[1] 30 countries: Europe (13), Canada, Latin America (5), Asia (9), Africa (2) Design: Open-label randomized trial Funding: No funders for main Solidarity trial Risk of Bias: Moderate	Intervention: Remdesivir, intravenous, (n=2750), 200 mg on day 0 followed by 100 mg on days 1-9 (treatment stopped at discharge or death) Comparator: No study drug (local standard of care) (n=2725) Inclusion criteria: ≥ 18 years, hospitalized with a diagnosis of COVID-19, not known to have received any study drug, without anticipated transfer elsewhere within 72 hours, no contraindication to any study drug (physician's view) Exclusion criteria: none reported **Study Period/Length of Follow-up:** 28 days (Note: mortality only during initial hospitalization; follow-up ceased at discharge)	**N=5475 randomized (5451 analyzed)** **Age (years):** <50: 35% 50-69: 47% 70+: 18% **Gender (male):** 63% **Race: NR** **Geographic Location** Europe or Canada: 26% Latin America: 18% Asia or Africa: 56% **Time from symptom onset to drug: NR** **Oxygen status on admission:** Percent on no oxygen: 24% Percent on oxygen: 67% Percent on ventilation: 9%
Beigel 2020[2] Adaptive Covid-19 Treatment Trial (ACTT-1) Multinational (60 sites and 13 subsites, 45 in the US) Design: RCT Funding: Primarily government, other	Intervention: Remdesivir (n=541) 200 mg on day 1 followed by 100 mg on days 2–10 (or until hospital discharge or death) in single daily infusions Comparator: Placebo (n=521) Inclusion criteria: 18 years or older and meeting one of the following criteria suggestive of lower respiratory tract infection at enrollment: radiographic infiltrates by imaging study, peripheral oxygen saturation (SpO2) ≤94% on room air, or requiring supplemental oxygen, mechanical ventilation, or ECMO; no limit to duration of symptoms prior	N=1062 **Age (years, mean):** 59 **Gender (male):** 64% **Race/Ethnicity:** White 53% Black/African American 21% Asian 13% Latino (of any race) 23% **Time from symptom onset to randomization** Overall, median [IQR] 9 days [6-12]

Author, Year Country Funding Risk of Bias	**Intervention Comparator Inclusion/exclusion criteria Study Period/Length of Follow-up**	**Demographics**
Risk of Bias: Low	to enrollment; laboratory-confirmed SARS-CoV-2 infection as determined by a positive RT-PCR assay result from any respiratory specimen collected <72 hours prior to randomization (during the study, this criterion was modified due to limitations in testing capacity to also allow a RT-PCR positive specimen that was collected ≥72 hours prior to randomization if the site was unable to obtain a repeat sample and if the participant had progressive disease consistent with ongoing SARS-CoV-2 infection) Exclusion criteria: ALT or AST >5 times the upper limit of the normal range, impaired renal function as determined by calculating an eGFR or need for hemodialysis or hemofiltration, allergy to study product, pregnancy or breast-feeding, and anticipated discharge from hospital or transfer to another hospital within 72 hours of enrollment **Study Period/Length of Follow-up:** 29 days	Remdesivir median [IQR] 9 days [6-12] Placebo median [IQR] 9 days [7-13] **Oxygen status on admission:** Percent on no oxygen 13% Percent on supplemental oxygen 41% Percent on non-invasive ventilation 18% Percent on invasive ventilation 27%
Spinner 2020[3] GS-US-540-5774 SIMPLE 2 105 sites in the US, France, Germany, Hong Kong, Italy, Republic of Korea, The Netherlands, Singapore, Spain, Switzerland, Taiwan and the United Kingdom Design: Randomized, open-label, multi-center Phase 3 clinical trial Funding: Industry Risk of Bias: Low	Intervention 1: Remdesivir, 5-day course (n=199) 200 mg on day 1 followed by 100 mg on days 2–5 in single daily infusions Intervention 2: Remdesivir, 10-day course (n=197) 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions Comparator: Standard care (n=200) Inclusion criteria: ≥ 18 years (at all sites), or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg (where permitted according to local law and approved by relevant review boards) currently hospitalized and requiring medical care for COVID-19; SARS-CoV-2 infection confirmed by PCR test ≤ 4 days before randomization; moderate COVID-19 pneumonia (peripheral capillary oxygen saturation (SpO_2)	**N=596 randomized (584 analyzed)** **Age (years, median):** 5-day group 58 10-day group 56 Standard care 57 **Gender (male):** 61% **Race:** White 58% Black 18% Asian 18% Other 7% Latino (of any race) 18% **Time from symptom onset to drug** Remdesivir 5-day median [IQR] 8 days [5-11] Remdesivir 10-day median [IQR] 8 days [5-11]

Author, Year Country Funding Risk of Bias	**Intervention Comparator Inclusion/exclusion criteria Study Period/Length of Follow-up**	**Demographics**
	>94% on room air radiographic evidence of pulmonary infiltrates) Exclusion criteria: Women who were pregnant or breast feeding infants, ALT or AST >5 times the upper limit of the normal range; creatinine clearance < 50 mL/min using the Cockcroft-Gault formula for participants ≥ 18 years of age and Schwartz Formula for participants < 18 years of age; mechanically ventilated at screening; concurrent treatment or planned concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2; participation in any other clinical trial of an experimental treatment for COVID-19 **Study Period/Length of Follow-up:** 11 days (primary outcome); final assessment on day 28	**Oxygen status on admission:** Percent on no oxygen: 84% Percent on supplemental oxygen: 15% Percent on non-invasive ventilation: NA Percent on invasive ventilation: NA
Wang 2020[4] China Design: RCT Funding: Government, other Risk of Bias: Low	Intervention: Remdesivir (n=158; 2:1 ratio) 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions Comparator: Placebo (n=79) Inclusion criteria: men and non-pregnant women with COVID-19, age at least 18 years, RT-PCR positive for SARS-CoV-2, pneumonia confirmed by chest imaging, oxygen saturation of 94% or lower on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, within 12 days of symptom onset Exclusion criteria: pregnancy or breast feeding; hepatic cirrhosis; ALT or AST >5 times the upper limit of the normal range; known severe renal impairment (estimated eGFR<30 mL/min per 1·73 m^2) or receipt of continuous renal replacement therapy, hemodialysis, or peritoneal dialysis; enrolment into an investigational treatment study for COVID-19 in the 30 days before screening	N=237 **Age (years, median):** Remdesivir 66 Placebo 64 **Gender (male):** Remdesivir 56% Placebo 65% **Race:** East Asian **Time from symptom onset to drug** Remdesivir median [IQR] 11 days [9-12] Placebo median [IQR] 10 days [9-12] **Oxygen status on admission:** Percent on no oxygen Remdesivir 0% Placebo 4% Percent on supplemental O_2

Author, Year Country Funding Risk of Bias	**Intervention Comparator Inclusion/exclusion criteria Study Period/Length of Follow-up**	**Demographics**
	Study Period/Length of Follow-up: 28 days	Remdesivir 82% Placebo 83% Percent on non-invasive ventilation Remdesivir 18% Placebo 12% Percent on invasive ventilation Remdesivir 0% Placebo 1%
Mahajan 2021[5] ** *India* ***Design: Open-label randomized trial ***Funding: No funders*** ***Risk of Bias: High***	***Intervention: Remdesivir, intravenous, (n=41) 200 mg on day 1 followed by 100 mg once daily on days 2-5. Both treatment groups continued supportive therapy*** ***Comparator: No study drug (local standard of care) (n=41)*** ***Inclusion criteria: 18 to 60 years of age hospitalized with a diagnosis of COVID-19 by PCR, radiographic evidence of pneumonia, respiratory rate >24/min, oxygen saturation ≤94%, creatine clearance >40 mL/min*** ***Exclusion criteria: receiving mechanical ventilation, multi organ failure, AST/ALT >3 times the upper limit of normal*** ***Study Period/Length of Follow-up: 24 days or until discharge or death***	***N=82 randomized (70 analyzed) Age (years): 58 Gender (male): 66% Race: NR Time from symptom onset to drug: mean 7 days Oxygen status on admission: Percent on no oxygen: 0% Percent on low-flow oxygen: 76% Percent on high-flow oxygen /non-invasive ventilation: 24% Percent on invasive mechanical ventilation: 0%***
Goldman 2020[6] GS-US-540-5773 SIMPLE 1 55 hospitals around the world, including sites in the US, Italy, Spain, Germany, Hong Kong,	Intervention 1: Remdesivir, 5-day course (n=200) 200 mg on day 1 followed by 100 mg on days 2–5 in single daily infusions Intervention 2: Remdesivir, 10-day course (n=197) 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions	N=397 **Age (years, median):** 5-day group 61 10-day group 62 **Gender (male):** 5-day group 60% 10-day group 68%

Author, Year Country **Funding** **Risk of Bias**	**Intervention** **Comparator** **Inclusion/exclusion criteria** **Study Period/Length of Follow-up**	**Demographics**
Singapore, South Korea, and Taiwan. Design: Randomized, open-label, multi-center Phase 3 clinical trial Funding: Industry Risk of Bias: Moderate	Inclusion criteria: patients ≥ 18 years (at all sites), or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg (where permitted according to local law) currently hospitalized with SARS-CoV-2 infection confirmed by PCR test ≤ 4 days before randomization; radiographic evidence of pulmonary infiltrates and peripheral capillary oxygen saturation (SpO2) ≤ 94% or requiring supplemental oxygen at screening Exclusion criteria: Pregnant or women who were breast feeding infants, ALT or AST >5 times the upper limit of the normal range, creatinine clearance < 50 mL/min using the Cockcroft-Gault formula for participants ≥ 18 years of age and Schwartz Formula for participants < 18 years of age; mechanically ventilated (including V-V ECMO) ≥ 5 days, or any duration of V-A ECMO; evidence of multiorgan failure; concurrent treatment with other agents with actual or possible direct acting antiviral activity against SARS-CoV-2 < 24 hours prior to study drug dosing; participant in any other clinical trial of an experimental treatment for COVID-19 **Study Period/Length of Follow-up:** 14 days (up to 30 days for adverse events)	**Race:** White 70% Black 11% Asian 11% Other 7% **Time from symptom onset to drug** Remdesivir 5-day median [IQR] 8 days [5-11] Remdesivir 10-day median [IQR] 9 days [6-12] **Oxygen status on admission:** Percent on no oxygen 14% Percent on supplemental oxygen 55% Percent on non-invasive ventilation 27% Percent on invasive ventilation 4%

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECMO = extracorporeal membrane oxygenation; eGFR = estimated glomerular filtration rate; IQR = interquartile range; RT-PCR = reverse transcription, polymerase-chain-reaction; SARS-CoV = Severe Acute Respiratory Syndrome Coronavirus-2 infection

* Indicates newly identified trial

Supplement Table 2. Summary of Conclusions and Updated Findings for Randomized Trials of Remdesivir

Comparison	Outcome	Conclusions from Last Report Version	New Trial Results/Analyses	Updated Conclusions
Remdesivir 10-day course versus control (placebo or standard of care) for any severity of COVID-19 4 trials (n=7171 randomized) (1,2,3,4)	Mortality	Remdesivir 10-day course probably results in little to no difference versus control (1,2,3,4) *Subgroup analyses (post-hoc), based on initial respiratory support:* • *Not requiring supplemental O_2;* may result in little to no difference versus control (1,2,3) • *Requiring supplemental O_2 but not ventilated;* may result in a moderate reduction versus control (1,2,4) • *Requiring ventilation/ECMO*;* may result in a moderate increase versus control (1,2,4)	No new evidence	No change in conclusions
	Proportion recovered†	Remdesivir 10-day course probably results in a moderate increase in percent recovered versus control (2,3,4)	No new evidence	No change in conclusions

Comparison	Outcome	Conclusions from Last Report Version	New Trial Results/Analyses	Updated Conclusions
	Proportion with clinical improvement‡	Remdesivir 10-day course may result in a moderate increase in percent with clinical improvement versus control (3,4)	No new evidence	No change in conclusions
	Hospital length of stay	No pooled analysis	No new evidence	No change in conclusions
	Time to recovery/ Clinical improvement	Remdesivir 10-day course may result in up to a large reduction in median time to recovery or a moderate reduction in time to clinical improvement versus control (2,3,4)	No new evidence	No change in conclusions
	Proportion on invasive ventilation/ECMO at follow-up	Remdesivir 10-day course may result in a small reduction versus control (2,3,4)	No new evidence	No change in conclusions
	Proportion with new need for ventilation	Remdesivir 10-day course probably results in little to no difference versus control (1)	No new evidence	No change in conclusions
	Serious adverse events	Remdesivir 10-day course probably results in a moderate reduction versus control (2,3,4)	No new evidence	No change in conclusions
Remdesivir 10-day course versus placebo	Mortality	Remdesivir 10-day course may result in a small reduction versus placebo (2,4)	No new evidence	No change in conclusions
2 trials, any severity COVID-19 (n=1299	Proportion recovered†	Remdesivir 10-day course probably results in a moderate increase versus placebo (2,4)	No new evidence	No change in conclusions

Comparison	Outcome	Conclusions from Last Report Version	New Trial Results/Analyses	Updated Conclusions
randomized) (2,4)	Proportion with clinical improvement‡	Remdesivir 10-day course may result in a moderate increase versus placebo (4)	No new evidence	No change in conclusions
	Hospital length of stay	Remdesivir 10-day course may result in a moderate reduction versus placebo (2,4)	No new evidence	No change in conclusions
	Time to recovery or clinical improvement	Remdesivir 10-day course may result in a moderate to large reduction versus placebo (2,4) *Subgroup analyses (prespecified):* (2) • Time to recovery did not vary by age, gender, symptom duration (≤10 days vs >10 days) or disease severity (mild/ moderate, or severe)	No new evidence	No change in conclusions
	Proportion on invasive ventilation/ECMO at follow-up	Remdesivir 10-day course may result in a moderate reduction versus placebo (2,4)	No new evidence	No change in conclusions
	Serious adverse events	Remdesivir 10-day course probably results in a moderate reduction versus placebo (2,4)	No new evidence	No change in conclusions
Remdesivir 10-day course versus standard of care, any	Mortality	Remdesivir 10-day course probably results in little to no difference versus SC (1,3)	No new evidence	No change in conclusions
	Proportion recovered†	Remdesivir 10-day course may result in a moderate	No new evidence	No change in conclusions

Comparison	Outcome	Conclusions from Last Report Version	New Trial Results/Analyses	Updated Conclusions
severity COVID-19		increase in percent recovered versus SC (3)		
2 trials (n=5872 randomized) (1,3)	Proportion with clinical improvement‡	Remdesivir 10-day course may result in a moderate increase in percent recovered versus SC (3)	No new evidence	No change in conclusions
	Hospital length of stay	The percentage of individuals hospitalized at days 7-14 did not differ between the remdesivir 10-day course and SC groups (1,3)	No new evidence	No change in conclusions
	Time to recovery or clinical improvement	Insufficient CoE (3)		
	Proportion on invasive ventilation/ECMO at follow-up	Remdesivir 10-day course may result in a small reduction versus SC (13)	No new evidence	No change in conclusions
	Proportion with new need for ventilation	Remdesivir 10-day course probably results in little to no difference versus control (1)	No new evidence	No change in conclusions
	Serious adverse events	Remdesivir 10-day course may result in a small reduction versus SC (3)	No new evidence	No change in conclusions
Remdesivir 5-day course versus standard of care	Mortality	Remdesivir 5-day course may result in a small reduction versus SC (3)	***1 new RCT (5), assessed as high risk of bias did not impact our conclusions*** **§**	No change in conclusions
2 trials (n=481	Proportion recovered†	Remdesivir 5-day course may result in a moderate increase versus SC (3)	No new evidence	No change in conclusions

Comparison	Outcome	Conclusions from Last Report Version	New Trial Results/Analyses	Updated Conclusions
randomized), moderate (3) **and severe COVID-19** (5)	Proportion with clinical improvement‡	Remdesivir 5-day course may result in a moderate increase versus SC (3)	No new evidence	No change in conclusions
	Hospital length of stay	The percentage of individuals hospitalized at day 11 and 14 did not differ between the remdesivir 5-day and SC groups (3)	No new evidence	No change in conclusions
	Time to recovery or clinical improvement	Remdesivir 5-day course may result in a small reduction versus SC (3)	***1 new RCT (5), assessed as high risk of bias did not impact our conclusions*** §	No change in conclusions
	Proportion on invasive ventilation/ECMO at follow-up	Remdesivir 5-day course may result in a small reduction versus SC (3)	No new evidence	No change in conclusions
	Proportion with new need for ventilation	NR	***Insufficient CoE, based on 1 new RCT (5) assessed as high risk of bias*** §	***Insufficient CoE (5)*** §
	Serious adverse events	Remdesivir 5-day course may result in a small reduction versus SC (3)	No new evidence	No change in conclusions
Remdesivir 5-day course versus Remdesivir 10-day course, moderate (3) **and severe** (6) **COVID-19 (excludes critical COVID-19) 2 trials**	Mortality	Remdesivir 5-day course may result in a small reduction versus 10-day course (3,6)	No new evidence	No change in conclusions
	Proportion recovered†	Remdesivir 5-day course may result in a moderate increase versus 10-day course (3,6)	No new evidence	No change in conclusions
	Proportion with clinical improvement‡	Remdesivir 5-day course may result in a moderate	No new evidence	No change in conclusions

Comparison	Outcome	Conclusions from Last Report Version	New Trial Results/Analyses	Updated Conclusions
(n=798 randomized)		increase versus 10-day course (3,6)		
	Hospital length of stay	The percentage of individuals hospitalized at day 11 and 14 did not differ between the remdesivir 5-day and 10-day course groups (3)	No new evidence	No change in conclusions
	Time to recovery or clinical improvement	Remdesivir 5-day course may result in a small reduction versus 10-day course (3,6)	No new evidence	No change in conclusions
	Proportion on invasive ventilation/ECMO at follow-up	Remdesivir 5-day course may result in a small reduction versus 10-day course (3,6)	No new evidence	No change in conclusions
	Serious adverse events	Remdesivir 5-day course may result in a moderate reduction versus 10-day course (3,6)	No new evidence	No change in conclusions

Abbreviations
COE=certainty of evidence; ECMO=extracorporeal membrane oxygenation; NR=not reported; SC=standard of care

* Includes some patients receiving Hi-flow oxygen and non-invasive ventilation
† Recovery was defined as discharge from the hospital or hospitalization for infection control purposes only (2) or discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care (3,4,6)]
‡ Clinical improvement was defined as a two-point reduction in patients' admission status on a 6-point ordinal scale (1= live discharge to 6=death), or live discharge from the hospital, whichever came first (4) or as an improvement of at least 2 points from baseline on 7-point ordinal scale (1=death to 7=discharged from hospital) (3,6)].
§ Indicates findings from newly identified trial

Supplement Table 3. Effect of Remdesivir in Randomized Controlled Studies

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
All-cause Mortality				
Remdesivir 10-day course versus placebo or standard of care; 4 trials (n=7142) (1,2,3,4)	11-29 days Any severity - No O_2 at baseline 25%; Receiving O_2 or ventilation (non-invasive and invasive) at baseline 75%	10.6% (384/3635) vs. 11.2% (394/3507) Pooled ARD -0.8 (-2.2 to 0.7)	Moderate ‡	Remdesivir 10-day course probably results in little to no difference in mortality versus placebo or standard care
Remdesivir 10-day course versus placebo; 2 trials (n=1298)	Beigel (ACTT-1) 2020 (2); 29 days Severe - No O_2 13%	10.9% (59/541) vs.14.8% (77/521) ARD -3.9% (-7.9 to 0.1)	Low §	Remdesivir 10-day course may result in a small reduction in mortality versus placebo; Range of ARDs -3.9% to 1.1%
	Wang 2020 (4); 28 days Severe - No O_2 1%	13.9% (22/158) vs. 12.8% (10/78) ARD 1.1% (-8.1 to 10.3)		
Remdesivir 10-day course versus standard of care; 2 trials (n=5844)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 11 days Moderate - No O_2 84%	1.0% (2/193) vs. 2.0% (4/200) ARD-1.0% (-3.4 to 1.4)	Moderate ‡	Remdesivir 10-day course probably results in little to no difference on mortality versus standard care; Range of ARDs -1.0% to -0.2%
	Solidarity 2020 (4); 28 days (*reported only during initial hospitalization; follow-up ceased after discharge*) Severe - No O_2 24%	11.0% (301/2743) vs. 11.2% (303/2708) ARD -0.2 (-1.9 to 1.5)		
Remdesivir 5-day course versus standard of care; 2 trials (n=461)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 11 days Moderate - No O_2 82%	0% (0/191) vs. 2.0% (4/200) ARD -2.0% (-4.2 to 0.2)	Low ‖	Remdesivir 5-day course may result in a small reduction versus SC
Bold indicates results from newly identified trial	***Mahajan 2021 (5); 24 days*** ***Severe - No O_2 0%***	***Per protocol (day 12 to 24)*** ***14.7% (5/34) vs. 8.3% (3/36)*** ***ARD 6.4% (-8.6 to 21.3)***		

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 5-day course versus Remdesivir 10-day course; 2 trials (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020 (6); 14 days Severe - No O_2 14%	8.0% (16/200) vs. 10.7% (21/197) ARD -2.7% (-8.4 to 3.1)	Low ¶	Remdesivir 5-day course of may result in a small reduction in mortality versus 10-day course; Range of ARDs -2.7% to -1.0%
	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 11 days Moderate - No O_2 86%	0% (0/191) vs. 1.0% (2/193) ARD -1.0% (-2.8 to 0.7)		
Proportion of patients recovered, defined as discharge from the hospital or hospitalization for infection control purposes only (5) or discharge from the hospital or hospitalized but not requiring supplemental oxygen or ongoing medical care (11-13)				
Remdesivir 10-day course versus placebo or standard of care; 3 trials (n=1682) (2,3,4)	28-29 days Any severity - No O_2 28%; Any O_2/Ventilation 72%	77.3% (683/884) vs. 71.6% (571/798) Pooled ARD 6.5% (2.4 to 10.7)	Moderate ‡	Remdesivir 10-day course probably results in a moderate increase in percent recovered versus placebo or standard care
Remdesivir 10-day course versus placebo; 2 trials (n=1289)	Beigel (ACTT-1) 2020 (2); 29 days Severe - No O_2 13%	73.8% (399/541) vs. 67.6% (352/521) ARD 6.2% (0.7 to 11.7)	Moderate ‡	Remdesivir 10-day course probably results in a moderate increase in percent recovered versus placebo; Range of ARDs 6.2% to 7.0%
	Wang 2020 (4); 28 days Severe - No O_2 1%	70.7% (106/150) vs. 63.6% (49/77) ARD 7.0% (-6.0 to 20.0)		
Remdesivir 10-day course versus standard of care; 1 trial (n=393)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 28 days Moderate - No O_2 84%	92.2% (178/193) vs. 85% (170/200) ARD 7.2% (1.0 to 13.5)	Low §	Remdesivir 10-day course may result in a moderate increase in percent recovered versus standard care
Remdesivir 5-day course versus standard of care; 1 trial (n=391)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 28 days Moderate - No O_2 82%	91.6% (175/191) vs. 85% (170/200) ARD 6.6% (0.3 to 12.9)	Low §	Remdesivir 5-day course may result in a moderate increase in percent recovered versus standard care

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 5-day course versus Remdesivir 10-day course; 2 trials (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020 (6); 14 days Severe - No O_2 14% Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 11 days Moderate - No O_2 86%	64.5% (129/200) vs. 53.8% (106/197) Baseline-adjusted ARD 6.3% (-2.8 to 15.4) 73.8% (141/191) vs. 68.4% (132/193) ARD 5.4% (-3.6 to 14.5)	Low ¶	Remdesivir 5-day course may result in a moderate increase in percent recovered versus 10-day course; Range of ARDs 5.4% to 6.3%
Clinical improvement, defined as a two-point reduction in patients' admission status on a 6-point ordinal scale (1= live discharge to 6=death), or live discharge from the hospital, whichever came first (4) as an improvement of at least 2 points from baseline on 7-point ordinal scale (1=death to 7=discharged from hospital) (3,6)				
Remdesivir 10-day course versus placebo (4) **or standard of care** (3)**;** 2 trials (n=629)	Wang 2020 (4); 28 days Severe - No O_2 1% Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 28 days Moderate - No O_2 84%	65.2% (103/158) vs. 57.7% (45/78) ARD 7.5% (-5.7 to 20.7) 90.2% (174/193) vs. 83% (166/200) ARD 7.2% (0.5 to 13.8)	Low §	Remdesivir 10-day course may result in a moderate increase in clinical improvement versus placebo or standard care Range of ARDs 7.2% to 7.5%
Remdesivir 5-day course versus standard of care; 1 trial (n=391)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 28 days Moderate - No O_2 82%	89.5% (171/191) vs. 83% (166/200) ARD 6.5% (-0.3 to 13.3)	Low §	Remdesivir 5-day course may result in a moderate increase in clinical improvement versus standard care
Remdesivir 5-day course versus Remdesivir 10-day course; 2 trials (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020 (6); 14 days Severe - No O_2 14% Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 11 days Moderate - No O_2 86%	64.5% (129/200) vs. 54.3% (107/197) Baseline-adjusted ARD 6.5% (-2.8 to 15.7) 70.2% (134/191) vs. 65.3% (126/193) ARD 4.9% (-4.5 to 14.2)	Low ¶	Remdesivir 5-day course may result in a moderate increase in clinical improvement versus 10-day course Range of ARDs 4.9% to 6.5%
Hospital Length of Stay (LOS), Days (Median IQR)				

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 10-day course versus placebo; 2 trials (n=1299)	Beigel (ACTT-1) 2020 (2); 29 days Severe - No O_2 13% Wang 2020 (4); 28 days Severe - No O_2 1%	*Initial hospitalization* 12 (6 to 28) vs. 17 (8 to 28) MD -5 days [95% CI, -7.7 to -2.3] 25 (16 to 38) vs. 24 (18 to 36) MD 0 days (-4.0 to 4.0)	Low **	Remdesivir 10-day course may result in a moderate reduction in median length of hospital stay versus placebo
Remdesivir 10-day course versus standard of care	Hospital LOS: NR Solidarity (1), Severe - No O_2 24%; No differences in percent hospitalized at 7 (69% vs. 59%) and 14 days (22% vs. 19%) SIMPLE-2 (3), Moderate - No O_2 84%: No differences in percent hospitalized at 11 (34% vs. 38%) and 14 days (23% vs. 31%).			
Remdesivir 5-day course versus standard of care	Hospital LOS: NR SIMPLE-2 (3), Moderate - No O_2 82%: No differences in percent hospitalized at 11 (30% vs. 38%) and 14 days (23% vs. 31%),			
Remdesivir 5-day course versus Remdesivir 10-day course	Hospital LOS: NR SIMPLE-2 (3), Moderate - No O_2 86%: No differences in percent hospitalized at 11 (30% vs. 34%) and 14 days (23% vs. 23%)			
Time to Recovery or Time to Clinical Improvement, Days, Median (IQR)				
Remdesivir 10-day course versus placebo or standard of care; 3 trials (n=1674) (2,3,4)	11-29 days Any severity - No O_2 28%; Any O_2/Ventilation 72%	Difference in medians ranged from -1 to 5 days)	Low ¶	Remdesivir 10-day course may result in an uncertain reduction in time to recovery in patients with moderate severity at day 11 and up to a large reduction in patients with severe disease at day 29 and a moderate reduction in median time to clinical improvement in patients with severe disease versus control
Remdesivir 10-day course versus placebo; 2 trials (n=1299)	Beigel (ACTT-1) 2020 (2); 29 days Severe - No O_2 13% *Recovery*	10 (95% CI 9 to 11) vs. 15 (95% CI 13 to 18); P<.001 Rate ratio 1.29 (1.12 to 1.49)	Low ††	Remdesivir 10-day course may result in large reduction in median time to recovery and a moderate reduction in

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
	Wang 2020 (4) 28 days Severe - No O_2 1% *Clinical Improvement*	21 (13 to 28) vs. 23 (18 to 36); HR 1.23 (0.87 to 1.75)		median time to clinical improvement versus placebo *(time to recovery did not vary by age, sex, symptom duration (≤10 days vs >10 days) or disease severity*) (2)
Remdesivir 10-day course versus standard of care; 1 trial (n=393)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 11 days Moderate - No O_2 84% *Recovery*	8 (4 to 13) vs. 7 (4 to 15); HR 1.11 (0.90 to 1.37)	Insufficient ‡‡	
Remdesivir 5-day course versus standard of care; 2 trials (n=461)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 11 days Moderate - No O_2 82%*Recovery*	6 (5 to 10) vs. 7 (4 to 15); HR 1.18 (0.96 to 1.45)	Low	Remdesivir 5-day course may result in a small reduction in median time to recovery versus standard care
Bold indicates results from newly identified trial	***Mahajan 2021; Day 10 through Day 20 Severe - No O_2 0% Recovery***	***Data NR Trialists noted patients in both groups "had an equal time to recovery (not defined) between 10 and 20 days."***		
Remdesivir 5-day course versus Remdesivir 10-day course; 2 trials (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020 (6); 14 days Severe - No O_2 14% *Recovery*	10 (6 to 18) vs. 11 (7 to not able to estimate); P NS HR 0.81 (0.64 to 1.04)	Low ¶	Remdesivir 5-day course may result in a small reduction in median time to recovery versus 10-day course
	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 11 days Moderate - No O_2 86% *Recovery*	6 (5 to 10) vs. 8 (4 to 13); HR NR		
Proportion on invasive ventilation/ECMO at follow up (Spinner on day 11, Wang on day 14 and ACTT-1 on day 15)				

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 10-day course versus placebo or standard of care; 3 trials (n=1686) (2,3,4)	11-15 days Any severity - No O_2 28%; Any O_2/Ventilation 72%	11.3% (100/887) vs. 16.5% (132/799) Pooled ARD -4.8% (-8.0 to -1.5)	Low §	Remdesivir 10-day course may result in a small reduction in proportion on invasive ventilation or ECMO at follow-up versus placebo or standard care
Remdesivir 10-day course versus placebo; 2 trials (n=1299)	Beigel (ACTT-1) 2020 (2) Severe - No O_2 13%	17.6% (95/541) vs. 23.2% (121/521) ARD -5.7% (-10.5 to -0.8)	Low §	Remdesivir 10-day course may result in a moderate reduction in proportion on invasive ventilation or ECMO at follow-up versus placebo
	Wang 2020 (4) Severe - No O_2 1%	2.6% (4/153) vs. 9.0% (7/78) ARD -6.4 (-13.2 to 0.5)		Range of ARDs -5.7% to -6.4%
Remdesivir 10-day course versus standard of care; 1 trial (n=393)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3) Moderate - No O_2 84%	0.5% (1/193) vs. 2.0% (4/200) ARD -1.5% (-3.7 to 0.7)	Low §	Remdesivir 10-day course may result in a small reduction in proportion on invasive ventilation or ECMO at follow-up versus standard care
Remdesivir 5-day course versus standard of care; 1 trial (n=391)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3) Moderate - No O_2 82%	0% (0/191) vs. 2.0% (4/200) ARD -2.0% (-4.2 to 0.2)	Low §	Remdesivir 5-day course may result in a small reduction in proportion on invasive ventilation or ECMO at follow-up versus standard care
Remdesivir 5-day course versus Remdesivir 10-day course; 2 trials (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020 (6) Severe - No O_2 14%	8.0% (16/200) vs. 16.8% (33/197) ARD -8.8% (-15.2 to -2.3)	Low §§	Remdesivir 5-day course may result in a small reduction in proportion on invasive l ventilation or ECMO versus 10-day course at follow-up Range of ARDs -8.8% to -0.5% (*Observed effects may vary based on the baseline disease severity of the enrolled patients in each trial, i.e. severe disease in SIMPLE-1 and moderate disease in SIMPLE-2)*
	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3) Moderate - No O_2 86%	0% (0/191) vs. 0.5% (1/193) ARD -0.5% (-1.9 to 0.9)		
Subsequent need for ventilation (invasive or non-invasive ventilation, or ECMO) in those not ventilated at baseline				

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 10-day course versus standard of care; 1 trial (n=4964) (1)	Follow-up through day 28 Severe - No O_2 24%	11.9% (295/2489) vs. 11.5% (284/2475) ARD 0.4% (-1.4 to 2.2)	Moderate ‡	Remdesivir 10-day course probably results in little to no difference in new need for ventilation versus standard care
Remdesivir 5-day course versus standard of care; 1 trial (n=70) (5) ***Bold indicates results from newly identified trial***	***Day 12 through Day 24 Severe - No O_2 0%***	***11.8% (4/34) vs. 5.6% (2/36) ARD 6.2% (-7.0 to 19.4)***	***Insufficient*** IIII	
Any Adverse Event (includes markers of COVID-19 progression and remdesivir toxicity)				
Remdesivir 10-day course versus placebo or standard of care; 3 trials (n=1674) (2,3,4)	11-29 days Any severity - No O_2 28%; Any O_2/Ventilation 72%	59.1% (520/880) vs. 58.7% (466/794) Pooled ARD -0.3 (-5.0 to 4.4)	Low §§	Remdesivir 10-day course may result in little to no difference in any adverse events versus control
Remdesivir 10-day course versus placebo; 2 trials (n=1281)	Beigel (ACTT-1) 2020 (2); 29 days Severe - No O_2 13% Wang 2020 (4); 28 days Severe - No O_2 1%	57.3% (305/532) vs. 62.6% (323/516) ARD -5.3% (-11.2 to 0.7) 65.8% (102/155) vs. 64.1% (50/78) ARD 1.7 (-11.3 to 14.7)	Low §	Remdesivir 10-day course may result in a small reduction in any adverse events versus placebo Range of ARDs -5.3% to 1.7%
Remdesivir 10-day course versus standard of care; 1 trial (n=393)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 11 days (Moderate - No O_2 84%	58.5% (113/193) vs. 47% (93/200) ARD 12.0% (2.2 to 21.9)	Low §	Remdesivir 10-day course may result in a moderate increase in any adverse events versus standard of care
Remdesivir 5-day course versus standard of care; 1 trial (n=391)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 11 days Moderate - No O_2 82%	51.3% (98/191) vs. 46.5% (93/200) ARD 4.8% (-5.1 to 14.7)	Low §	Remdesivir 5-day course may result in a small increase in any adverse events versus standard care

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 5-day course versus Remdesivir 10-day course; 2 trials (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020 (6); 14 days Severe - No O_2 14%	70.5% (141/200) vs. 73.6% (145/197) ARD -3.1% (-11.9 to 5.7)	Low ¶	Remdesivir 5-day course may result in a moderate reduction in any adverse events versus 10-day course Range of ARDs -7.2% to -3.1%
	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 11 days Moderate - No O_2 86%	51.3% (98/191) vs. 58.5% (113/193) ARD -7.2% (-17.2 to 2.7)		
Serious Adverse Events (includes markers of COVID-19 progression and remdesivir toxicity)				
Remdesivir 10-day course versus placebo or standard of care; 3 trials (n=1674) (2,3,4)	11-29 days Any severity - No O_2 28%; Any O_2/Ventilation 72%	19.2% (169/880) vs. 25.3% (201/794) Pooled ARD -6.3% (-10.2 to -2.4)	Moderate ‡	Remdesivir 10-day course probably results in a moderate reduction in serious adverse events versus control
Remdesivir 10-day course versus placebo; 2 trials (n=1299)	Beigel (ACTT-1) 2020 (2); 29 days Severe - No O_2 13%	24.6% (131/532) vs. 31.6% (163/516) ARD -7.0% (-12.4 to -1.5)	Moderate ‡	Remdesivir 10-day course probably results in a moderate reduction in serious adverse events versus placebo Range of ARDs -7.6% to -7.0%
	Wang 2020 (4); 28 days Severe - No O_2 1%	18.1% (28/155) vs. 25.6% (20/78) ARD -7.6 (-19.0 to 3.9)]		
Remdesivir 10-day course versus standard of care; 1 trial (n=393)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 11 days Moderate - No O_2 84%	5.2% (10/193) vs. 9.0% (18/200) ARD -3.8% (-8.9 to 1.2)	Low §	Remdesivir 10-day course may result in a small reduction in serious adverse events versus standard care
Remdesivir 5-day course versus standard of care; 1 trial (n=391)	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 11 days Moderate - No O_2 82%	4.7% (9/191) vs. 9.0% (18/200) ARD -4.3% (-9.3 to 0.7)	Low §	Remdesivir 5-day course may result in a small reduction in serious adverse events versus standard care

Comparison(s); Number of trials (number evaluated)	Study, Year (reference); Assessment timepoint; Disease severity, based on oxygen (O_2) status at admission	Absolute effect of Remdesivir versus Control (95% CI)	Certainty of Evidence	Summary
Remdesivir 5-day course versus Remdesivir 10-day course; 2 trials (n=781)	Goldman (GS-US-540-5773: SIMPLE-1) 2020 (6); 14 days Severe - No O_2 14%	21.0% (42/200) vs. 34.5% (68/197) ARD -13.5% (-22.2 to -4.8)	Low §§	Remdesivir 5-day course may result in a moderate reduction in serious adverse events versus 10-day course Range of ARDs 13.5% to 0.5% (*Observed effects may vary based on the baseline disease severity of the enrolled patients in each trial, i.e. severe disease in SIMPLE-1 and moderate disease in SIMPLE-2)*
	Spinner (GS-US-540-5774: SIMPLE-2) 2020 (3); 11 days Moderate - No O_2 86%	4.7% (9/191) vs. 5.2% (10/193) ARD -0.5% (-4.8 to 3.9)		

Abbreviations
ARD = Absolute risk difference; CI = Confidence intervals; HR=Hazard ratio; IQR = inter quartile range; MD=Mean difference; NR= Not reported; NS = Not statistically significant; RCT = Randomized controlled trial

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

† Thresholds for determining magnitude by outcome are as follow:
All-cause mortality: Little or No effect <1%; Small effect 1-2.9%; Moderate effect 3-4.9%; Large effect ≥5%
Recovery: Little or No effect <2%; Small effect 2-4.9%; Moderate effect 5-9.9%; Large effect ≥10%
Clinical Improvement: Little or No effect <2% Small effect 2-4.9%; Moderate effect 5-9.9%; Large effect ≥10%
Length of Stay: Little or No effect <1 day; Small effect ≥1-2 days; Moderate effect >2 to < 3 days; Large effect ≥3 days
Time to Recovery or Clinical Improvement: Little or No effect <1 day; Small effect ≥1-2 days; Moderate effect >2 to < 3 days; Large effect ≥3 days
Invasive ventilation or ECMO: Little or No effect <1%; Small effect 1-4.9%; Moderate effect 5-9.9%; Large effect ≥10%
Any adverse event: Little or No effect <2%; Small effect 2-4.9%; Moderate effect 5-19.9%; Large effect ≥20%
Severe adverse event: Little or No effect <1%; Small effect 1-4.9%; Moderate effect 5-9.9%; Large effect ≥10%

‡ Downgraded for imprecision
§ Downgraded two levels for imprecision (very wide CIs) and/or sparse data.
ǁ Downgraded two levels for imprecision (very wide CIs) and/or sparse data. The Mahajan trial (5), assessed as high risk of bias, did not impact the overall certainty of evidence or magnitude of effect
¶ Downgraded two levels for study limitations and imprecision (wide CIs)
** Downgraded two levels for imprecision and inconsistency
†† Downgraded two levels for difficulty in interpreting precision and inconsistency.

‡‡ Downgraded to insufficient for difficulty in interpreting results (HR not reported for 5-day vs.10 day) and higher median with 10-day vs standard of care but reduction in time to recovery favors 10-day based on HR
§§ Downgraded two levels for imprecision and inconsistency
ǁǁ Downgraded to insufficient for study limitations and imprecision (very wide CIs)

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