South African National Department of Health
Brief Report of Rapid Review
Component: COVID-19

TITLE: REMDESIVIR FOR COVID-19: EVIDENCE REVIEW OF THE CLINICAL BENEFIT AND HARM

Date: 15 DECEMBER 2020 *(fifth update of the initial 16 April 2020 rapid review report)*

Key findings

- We conducted a rapid review of available clinical evidence about use of remdesivir, with or without other medicines, for hospitalised patients with COVID-19.
- We identified a systematic review including five RCTs (n=7747) which includes the latest data from the SOLIDARITY randomised controlled trial (www.covid-nma.com).
- Remdesivir probably makes little or no difference to all-cause mortality at 14 to 28 days (relative risk (RR) 0.90 95% confidence interval (CI) 0.73 to 1.11, four trials, n = 7345, moderate certainty evidence due to imprecision).
- The SOLIDARITY trial reported that remdesivir compared to placebo had no effect on the need for ventilation in those not already ventilated at randomisation (295/2489 (11.9%) versus 284/2475 (11.5%) for remdesivir versus control respectively).
- Remdesivir is not associated with an increased risk of adverse events compared with placebo (RR 1.00 95% CI 0.87 to 1.15, 3 trials, n = 1894, low certainty evidence due to risk of bias in included trials and unexplained heterogeneity).
- We identified no reports on the use of remdesivir in children with COVID-19, although a clinical trial is planned in this group.

NEMLC THERAPEUTIC GUIDELINES SUB-COMMITTEE RECOMMENDATION:

	We recommend against the option and for the alternative (strong)	We suggest not to use the option or to use the alternative (conditional)	We suggest using either the option or the alternative (conditional)	We suggest using the option (conditional)	We recommend the option (strong)
Type of recommendation		X			

Recommendation: The NEMLC Subcommittee suggests that remdesivir not be recommended for treatment of hospitalised patients with COVID-19.

Rationale: Remdesivir has not demonstrated a significant effect on pre-specified clinically important outcomes such as mortality or need for ventilation. In addition, access to the medicine is limited and it remains expensive. Feasibility may be an issue as the medicine is not currently SAHPRA registered.

Level of Evidence: RCTs of low to moderate quality

Review indicator: New evidence of mortality/ hospitalisation benefit or other endpoints affecting resource utilisation

(Refer to appendix 4 for the evidence to decision framework)

Therapeutic Guidelines Sub-Committee for COVID-19: Marc Blockman, Karen Cohen, Renee De Waal, Andy Gray, Tamara Kredo, Gary Maartens, Jeremy Nel, Andy Parrish *(Chair),* Helen Rees, Gary Reubenson *(Vice-chair).*

Version	Date	Reviewer(s)	Recommendation and Rationale
First	16 April 2020	SM, RdW	Currently insufficient evidence to recommend remdesivir in treatment guidelines for COVID-19, except in a clinical trial setting.
Second	24 June 2020	SM, RdW	Remdesivir does not warrant preferential use over other alternative options. While evidence for the efficacy of remdesivir has improved it is still generally weak to moderate. The reduced time to improvement of severe disease may be desirable in the face of limited resources.
Third	29 September 2020	SM, RdW	Remdesivir does not warrant preferential use over other alternative options. While evidence for the efficacy of remdesivir has improved it is still generally weak to moderate. The reduced time to improvement of severe disease may be desirable in the face of limited resources.
Fourth	17 November 2020	SM, RdW	Remdesivir does not warrant preferential use over other alternative options. Remdesivir has not demonstrated a significant effect on mortality or need for ventilation.
Fifth	15 December 2020	SM, RdW	Remdesivir does not warrant preferential use over other alternative options. Remdesivir has not demonstrated a significant effect on mortality or need for ventilation.

BACKGROUND

SARS CoV-2, like other Coronaviruses, is an enveloped positive-stranded RNA virus.

Remdesivir is an inhibitor of the SARS-CoV-2 RNA-dependent RNA polymerase (RdRp), which is essential for viral replication.

Remdesivir has broad-spectrum activity against members of several virus families, including filoviruses (e.g., Ebola) and coronaviruses (e.g., SARS-CoV and Middle East respiratory syndrome coronavirus [MERS-CoV]) and has shown prophylactic and therapeutic efficacy in nonclinical models of these coronaviruses[1, 2, 3].

Remdesivir has also demonstrated activity against SARS-CoV-2 in vitro[4].

RESEARCH QUESTION: Should remdesivir be used for managing COVID-19 in hospitalised patients?

METHODS

We searched the Cochrane COVID-19 trials database and the Epistemonikos electronic databases on 4 September 2020 for RCTs and systematic reviews. Details of each search are provided in Appendix 1.

Search results were loaded onto the COVIDENCE systematic review management application. Duplicates were removed and screening of abstracts was conducted independently by the two reviewers. Conflicts were resolved by consensus and full text review was conducted by one reviewer. Additionally the living systematic reviews of RCTs on www.covid-nma.com were reviewed and included.

Subsequent to the 29 September rapid review, one of the included RCTS (Beigel et al, 2020)[8] for which only preliminary results had been published by September, published a final manuscript. The November 2020 rapid review included The Solidarity Trial interim results[6] in pre-print format, and this December update includes the published peer-reviewed article[7].

Eligibility criteria for review

Population: Patients with confirmed COVID-19, no restriction to age, but requiring hospitalisation.

Intervention: Remdesivir either alone or in combination with other medicines. No restriction on dose, frequency, or timing with respect to onset of symptoms/severity of disease.

Comparators: Any (standard of care/placebo or active comparator).

Outcomes: Mortality, duration of hospitalisation, proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab at chosen time-points post-diagnosis; time to negative SARS-CoV2 PCR on nasopharyngeal swab; progression to ICU admission; progression to mechanical ventilation; duration of ICU stay, adverse reactions and adverse events.

Study designs: Randomised controlled trials, and systematic reviews of randomised trials.

RESULTS

Table 1 summarises the main characteristics and outcomes of the included studies.
340 studies were imported for screening (including trials, systematic reviews and ongoing studies), and 91 duplicates removed. 249 studies were independently screened by two reviewers from which 181 were excluded as irrelevant.

One reviewer screened 68 full text studies for eligibility and inclusion in the review. Five references were deemed ineligible as they were in foreign languages. 25 references were systematic reviews, 11 of these were excluded as they

were conducted prior to any randomised trials being concluded for remdesivir, and a further 10 were excluded as they were published on non-peer-reviewed platforms. Thus, four systematic reviews were included, as well as the results of the NMA Living systematic review included in the original remdesivir rapid review.
A further 28 studies were flagged as ongoing.

11 studies cohort studies were identified and deemed ineligible for inclusion.

The WHO-initiated Solidarity trial [6,7] interim results were published on 3 December 2020. Remdesivir did not demonstrate any improvement in mortality at day 28 (Primary outcome measure) - Rate ratio, 0.95 (95% CI, 0.81 0.81 to 1.11) p=0.50 by log-rank test. It also had no appreciable effect on reduced initiation of ventilation in those not already ventilated. The numbers, study drug vs control, with ventilation initiated after randomization were: Remdesivir 295 vs 284 (11.9% vs 11.5%). The administration of remdesivir increased the percentage of patients remaining in hospital at day 7 (possibly because of the treatment duration), with no appreciable decrease in hospitalisation by day 21. . It is also important to note that in Solidarity, 47.8% and 47.6% of patients in the remdesivir and control arms respectively, received corticosteroids as part of their treatment.

Thus, five RCTs and five systematic reviews were included for outcomes purposes. The details of these studies are summarised in Table 1. Four RCTs compared remdesivir days of treatment against standard of care, whereas two compared remdesivir 5 days of treatment against 10 days.

The Cochrane supported living meta-analyses of these five RCTs[11] is included in appendix 2. This analysis has now also separated out Remdesivir versus standard of care (any duration) and Remdesivir 10 days versus Remdesivir 5 days treatment.

All-cause mortality at day 14 to day 28

- **Remdesivir 10 and 5 days compared to Standard Care/Placebo for Mild/Moderate/Severe/Critical COVID-19 (Four studies):**
  The included studies showed no statistically significant impact: RR 0.90 (95% CI 0.73 to 1.11)[11]. Four RCTs, 7345 patients.
- **Remdesivir 5 days compared to 10 days Moderate/Severe/Critical COVID-19 (Two studies)**
  The included studies showed no significant difference: RR 0.74 (95% CI 0.41 to 1.34)[11]. Two RCTs, 798 patients

Duration of hospitalisation

- **Remdesivir 10 days compared to Standard Care/Placebo for Mild/Moderate/Severe/Critical COVID-19**
  Wang et al[7] reported median duration of stay of 25 days (IQR 16 to 38) in the remdesivir group, and 24 (IQR 18 to 36) in the placebo group, but reported no significant difference in length of hospital stay. Spinner et al[9] did not quantify but stated there were no significant differences between the remdesivir and Standard of care groups. Beigel et al[8,] and Pan et al: not reported.
- **Remdesivir 5 days compared to 10 days Moderate/Severe/Critical COVID-19**
  Not reported

Proportion with negative SARS-CoV-2 PCR on nasopharyngeal swab

- **Remdesivir 10days compared to Standard Care/Placebo for Mild/Moderate/Severe/Critical COVID-19**
  This was only reported in one of the included RCTs as incidence of viral negative conversion by day 7:
  492 per 1.000 for the standard care group and 502 per 1.000 (374 to 679) in the remdesivir group (RR 1.02, 95% CI (0.76 to 1.38))[11].
- **Remdesivir 5 days compared to 10 days Moderate/Severe/Critical COVID-19**
  Not reported

Time to negative SARS-CoV2 PCR on nasopharyngeal swab

- **Remdesivir 10days compared to Standard Care/Placebo for Mild/Moderate/Severe/Critical COVID-19**
  Not reported.
- **Remdesivir 5 days compared to 10 days Moderate/Severe/Critical COVID-19**
  Not reported

Progression to ICU admission

- **Remdesivir 10 days compared to Standard Care/Placebo for Mild/Moderate/Severe/Critical COVID-19**
  Not reported.
- **Remdesivir 5 days compared to 10 days Moderate/Severe/Critical COVID-19**
  Not reported

Progression to mechanical ventilation

- **Remdesivir 10 days compared to Standard Care/Placebo for Mild/Moderate/Severe/Critical COVID-19**
  In the Solidarity Trial, Remdesivir did not reduce initiation of ventilation in those not already ventilated at randomisation (295/2743 versus 284/2708 for remdesivir versus control respectively). .
- **Remdesivir 5 days compared to 10 days Moderate/Severe/Critical COVID-19**
  Not reported

The Cochrane NMA Living meta-analysis[11] did not report on need for mechanical ventilation specifically, but did report the composite outcome of mechanical ventilation, additional organ support or death (WHO Progression score level 7 or above) at day 14 to 28

- **Remdesivir 10 days compared to Standard Care/Placebo for Mild/Moderate/Severe/Critical COVID-19**
  Based on 3 RCTs[2,8,9] and 1894 participants, the rate was lower in the remdesivir group (124 per 1000) versus 178 per 1000 in standard of care (RR 0.70 ; 95% CI 0.56 to 0.88)
- **Remdesivir 5 days compared to 10 days Moderate/Severe/Critical COVID-19**
  RR 0.58 (95% CI 0.40 to 0.85), based on 2 RCTs[9, 10] and 798 patients

Duration of ICU stay

- **Remdesivir 10days compared to Standard Care/Placebo for Mild/Moderate/Severe/Critical COVID-19**
  Not reported.
- **Remdesivir 5 days compared to 10 days Moderate/Severe/Critical COVID-19**
  Not reported

Adverse reactions and adverse events

- **Remdesivir 10 days compared to Standard Care/Placebo for Mild/Moderate/Severe/Critical COVID-19**
  RR 0.93 (95% CI 0.85 to 1.01). Two RCTs, 1894 patients.
- **Remdesivir 5 days compared to 10 days for Mild/Moderate/Severe/Critical COVID-19**
  RR 0.96 (95% CI 0.85 to 1.09), one RCTs, 402 patients.

Several trials are planned and ongoing – see Table 2.

CONCLUSION

The evidence base for remdesivir in hospitalised patients remains conflicting and inconsistent. Our rapid review included a high quality, up-to-date systematic review with five included trials. Remdesivir has not demonstrated a statistically significant effect on mortality or other clinically important benefits or harms. There has been limited reporting on progression to ICU care. The SOLIDARITY trial reported that remdesivir did not reduce the need for initiation of ventilation in those not already ventilated. The relative balance of benefits to cost, feasibility and equity underpin the decision not to suggest remdesivir use in the South African public sector context.

Reviewers: Shelley McGee (South African Medical Association), Renee De Waal (Centre for Infectious Disease Epidemiology and Research, University of Cape Town).

Declaration of interests: SM - employed by South African Medical Association that is sponsored by various pharmaceutical and device companies for CPD activities, exhibition at conferences and advertising in SAMJ; RdW - has no interests to declare.

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REFERENCES

1. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun 2020;11:222-222. https://www.ncbi.nlm.nih.gov/pubmed/31924756
2. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020;30:269-271. https://www.ncbi.nlm.nih.gov/pubmed/32020029
3. de Wit E, Feldmann F, Cronin J, et al. Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. Proc Natl Acad Sci U S A 2020;117:6771-6776. https://www.ncbi.nlm.nih.gov/pubmed/32054787
4. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, Shi Z, Hu Z, Zhong W, Xiao G. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020 Mar;30(3):269-271. doi: 10.1038/s41422-020-0282-0. Epub 2020 Feb 4.
5. United State Federal Drug Agency. Oct 2020. Full Prescribing Information – Velkury® (Remdesivir injection 100 mg/20 ml) Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/214787Orig1s000lbl.pdf. Accessed 30 October 2020.
6. Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results. WHO Solidarity trial consortium, Pan et al. 15 October 2020. medRxiv 2020.10.15.20209817; doi: https://doi.org/10.1101/2020.10.15.20209817
7. WHO Solidarity Trial Consortium, Pan H, Peto R, Henao-Restrepo AM, et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. N Engl J Med. 2020 Dec 2. doi: 10.1056/NEJMoa2023184. Epub ahead of print. PMID: 33264556.
8. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial [published correction appears in Lancet. 2020 May 30;395(10238):1694]. Lancet. 2020;395(10236):1569-1578. https://pubmed.ncbi.nlm.nih.gov/32423584/
9. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 — Final Report. . N Engl J Med 2020; 383:1813-1826. https://www.nejm.org/doi/full/10.1056/NEJMoa2007764
10. 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. doi:10.1001/jama.2020.16349
11. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 Days in Patients with Severe Covid-19 [published online ahead of print, 2020 May 27]. N Engl J Med. 2020;10.1056/NEJMoa2015301. https://pubmed.ncbi.nlm.nih.gov/32459919/
12. Living mapping and living network meta-analysis of COVID-19 studies: Remdesivir vs Standard care/Placebo. https://covid-nma.com/living_data/index.php

Table 1. Characteristics of included studies

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
Pan H et al 2020 [6] Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results Preprint of interim results PRIOR to Peer Review https://www.medrxiv.org/content/10.1101/2020.10.15.20209817v1 Note: This publication is a pre-print and has NOT been peer reviewed	Randomised controlled trial, phase 3, open-label	Adults ≥18 years recently hospitalised, or already in hospital, with definite COVID19 (mild to severe) n=2743 remdesivir n=2708 controls	• Local standard of care alone, OR local standard of care plus one of • Remdesivir (daily infusion for 10 days) • Chloroquine or hydroxychloroquine (two oral loading doses, then orally twice daily for 10 days) • Lopinavir with Ritonavir (orally twice daily for 14 days) • Lopinavir with Ritonavir (ditto) plus Interferon (daily injection for 6 days).	Mortality: Remdesivir vs its control (pre-planned analysis) RR=0.95 (95% CI 0.81-1.11; P=0.50), At 28 Days, mortality was 12.7% in the control group versus 12.5% in the Remdesivir group Initiation of ventilation and time to discharge: Remdesivir did not reduce initiation of ventilation in those not already ventilated at randomisation (295/2743 versus 284/2708 for remdesivir versus control respectively). Time to discharge was not appreciably changed in the remdesivir group versus the control group.
Spinner et al 2020 [9] Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19 (9) A Randomized Clinical Trial https://jamanetwork.com/journals/jama/fullarticle/2769871	Randomised controlled trial, phase 3, open-label	Hospitalised patients ≥12 years. Oxygen saturation on room air >94%. US, Europe, Asia (105 hospitals) n=197: 10-day course n=199: 5-day course n=200: standard of care (SoC)	Remdesivir IV 200 mg on Day 1, followed by 100 mg daily. Patients could be discharged before completing the course. A minority of patients received concomitant medications that included steroids, hydroxychloroquine/chloroquine, lopinavir/ritonavir, tocilizumab, and azithromycin. Steroid use was: 10-day group: 29/193(15%) 5-day group: 33/191 (17%) SoC: 38/200 (19%)	Original primary endpoint was hospital discharge by Day 14. This was amended during the study to distribution of clinical status (on a 7-point ordinal scale from death to hospital discharge) by Day 11. All-cause mortality (by Day 28): 10-day group: 2% (95% CI 0.0 to 3.6, p=0.72 versus SoC); 5-day group: 1% (95% CI 0.0 to 2.6, p=0.43 versus SoC); SoC group: 2% (95% CI 0.1 to 4.1) Duration of hospitalisation: Not reported, but authors state that there were no significant differences between remdesivir and SoC Duration of ICU admission or ventilation: Not reported, but very few patients progressed to invasive ventilation. Adverse reactions: 10-day group: 59% (12% more than Soc, 95% CI 1.6 to 21.8, p=0.02); 5-day group: 51% (4.8% more than Soc, 95% CI -5.2 to 14.7, p=0.36); SoC: 47%. Most common AEs: nausea, diarrhoea, headache, hypokalaemia.

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
				Primary endpoint: Better clinical status (versus SoC): 10-day group: not significantly different (p=0.18); 5-day group: odds ratio 1.65 (95% CI 1.09 to 2.48)
Goldman et al 2020 Remdesivir for 5 or 10 Days in Patients with Severe Covid-19(4) https://www.nejm.org/doi/full/10.1056/NEJMoa2015301?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed	Randomised open label phase 3 trial	Hospitalised patients >12 years of age with confirmed SARS-CoV-2 infection; radiographic evidence of pulmonary infiltrates; and oxygen saturation ≤94% or receiving supplemental oxygen. n = 200: 5-day course n = 197: 10-day course	Remdesivir 200 mg on day 1, followed by remdesivir 100 mg once daily for the subsequent 4 or 9 days. Primary outcome: day 14 clinical status on a 7-point ordinal scale	By day 14, a clinical improvement of ≥2 points occurred in 64% of patients in the 5-day group and in 54% in the 10-day group. After adjustment for baseline clinical status, Day 14 clinical status was similar between the two groups (P = 0.14).
Beigel et al. 2020 Remdesivir for the Treatment of Covid-19 — Final Report (8)https://www.nejm.org/doi/full/10.1056/NEJMoa2007764?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed 60 trial sites and 13 subsites in the United States (45 sites), Denmark (8), the United Kingdom (5), Greece (4), Germany (3), Korea (2), Mexico (2), Spain (2), Japan (1), and Singapore (1).	Double-blind, multi-centre randomized, placebo-controlled trial	Adults hospitalised with Covid-19 with lower respiratory tract involvement. n= 541 remdesivir n= 522 placebo At time of treatment initiation: 89% had severe disease. 127 did not require oxygen 421 required oxygen but no ventilation 197 were receiving non-invasive ventilation 272 were receiving invasive ventilation	IV Remdesivir 200-mg on day 1 followed by 100mg on days 2-10 or until discharge/death. Other treatment were allowed if the hospital had included them in a written policy. Other treatment received (if any) wasn't reported. Follow up of 29 days. *Primary outcome:* Time to recovery, defined by either discharge from the hospital (with or without need for home oxygen) or hospitalisation for infection-control purposes only (i.e.no need for oxygen or treatment). *Key secondary outcomes:* • Mortality at days 14 and 28 • Difference in clinical status defined by 8-category scale at day 15 • Grade 3 and 4 adverse events • Serious adverse events	The Kaplan–Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Serious adverse events were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%).
Wang et al (2020) Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial ([7]) https://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(20)31022-9.pdf	Double-blind, multi-centre randomised, placebo-controlled trial	Adults hospitalized with SARS-CoV-2 infection, with an interval from symptom onset to enrolment of ≤12 days, oxygen saturation of ≤94% or on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of ≤300 mm Hg	IV Remdesivir 200-mg on day 1 followed by 100mg on days 2 -10 Patients were permitted concomitant use of lopinavir–ritonavir, interferons, and corticosteroids. *Primary outcome:*	Recruitment was terminated early because of control of the epidemic in Wuhan (the intended sample size was ±450). 28-day mortality was similar between the two groups (22 [14%] died in the remdesivir group vs 10 (13%) in the placebo group; difference 1·1% [95% CI –8·1 to 10·3]).

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
10 hospitals in China were involved		Remdesivir group (n=158) Placebo group (n=78) *At time of treatment initiation:* 3 did not require oxygen 194 required oxygen but no ventilation 37 were receiving non-invasive ventilation 1 was receiving invasive ventilation	The primary endpoint was time to clinical improvement within 28 days. Clinical improvement was defined as a two-point reduction in patients' admission status on a six-point ordinal scale, or discharge from the hospital, whichever came first. *Secondary outcomes:* Proportions of patients in each category of the six-point scale at day 7, 14, and 28 after randomisation; all-cause mortality at day 28; frequency of invasive mechanical ventilation; duration of oxygen therapy; duration of hospital admission; and proportion of patients with nosocomial infection. *Safety outcomes* included treatment-emergent adverse events, serious adverse events, and premature discontinuations of study drug.	No significant differences were observed between the two groups in terms of length of mechanical ventilation, length of oxygen support, length of hospital stay, days from randomisation to discharge, days from randomisation to death and distribution of six-category scale at day 7, day 14, and day 28 . Adverse events were reported in 102 (66%) of 155 remdesivir recipients versus 50 (64%) of 78 placebo recipients. Remdesivir was stopped early due to adverse events in 18 (12%) patients versus 4 (5%) patients who stopped placebo early
Cochrane 2020 Rapid meta-analysis of Remdesivir versus placebo https://covid-nma.com/living_data/index.php	Meta-analysis of four studies against standard of care (Beigel et al 2020, Wang et al 2020 and Spinner et al and Pan et al 2020) as well as meta-analysis of 5 days versus 10 days of remdesivir (Goldman et al and Spinner et al)	As for RCTs	IV Remdesivir 200-mg on day 1 followed by 100mg on days 2 -10 IV Remdesivir on day one followed by 100 mg on days 2 to 5	See Appendix 2
Misra et al 2020 Efficacy of various treatment modalities for nCOV-2019: a systematic review and meta-analysis	Systematic review and Meta-analysis of two studies (Beigel et al 2020 and Wang et al 2020)	As for RCTs	IV Remdesivir 200-mg on day 1 followed by 100mg on days 2 -10	Remdesivir treatment over placebo was assessed in two RCTs. Compared to placebo group, Remdesivir was not associated with either all-cause mortality (RR 0.74; 95%CI 0.40 to 1.37), total adverse events (RR 0.91; 95%CI 0.79 to 1.05) or time to clinical recovery (SMD -0.78; 95%CI -2.05 to 0.50). However, a significant association was observed with better overall clinical recovery (RR 1.17; 95%CI 1.07 to 1.29) in Remdesivir group compared to placebo.
Yokoyama et al 2020.	Systematic review and Meta-analysis of four studies (Beigel et al 2020, Wang et al 2020, Goldman et al 2020 and Spinner et al 2020)	As for each RCT	IV Remdesivir 200-mg on day 1 followed by 100mg on days 2 -5 OR 2-10	The rate of clinical improvement was significantly higher in the 5-day remdesivir group and 10-day remdesivir group compared to standard care group (OR [95 % confidence interval [CI]] = 1.89 [1.40 to2.56], P < 0.001, OR [95 % CI] = 1.38 [1.15 to 1.66], P < 0.001, respectively).

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT	MAIN FINDINGS
				In addition, the rate of clinical improvement was significantly higher in the 5-day remdesivir group compared to the 10-day remdesivir group (OR [95 % confidence interval [CI]] = 1.37 [1.01 to 1.85], P = 0.041).
Siemieniuk et al 2020	Systematic review and Network Meta-analysis of two studies (Beigel et al 2020 and Wang et al 2020)	As for RCts	IV Remdesivir 200-mg on day 1 followed by 100mg on days 2 -10	Moderate certainty exists that remdesivir reduces both time to symptom resolution and duration of mechanical ventilation, but it remains uncertain whether remdesivir has any effect on mortality and other outcomes important to patients.
Jiang et al 2020 Effectiveness of remdesivir for the treatment of hospitalized Covid-19 persons: a network meta-analysis	Systematic review and Network Meta-analysis of four studies (Beigel et al 2020, Wang et al 2020, Goldman et al 2020 and Spinner et al 2020)	As for RCTs	IV Remdesivir 200-mg on day 1 followed by 100mg on days 2 -5 OR 2-10	Both 10-day and 5-day remdesivir regimens were associated with higher odds of clinical improvement [odds ratio (OR) of 10-day regimen: 1.35, 95% confidence interval (CI): 1.09 to1.67); OR of 5-day regimen: 1.81, CI: 1.32 to 2.45] and higher probabilities of clinical recovery [relative risk (RR) of 10-day regimen: 1.24, CI: 1.07 to1.43); RR of 5-day regimen: 1.47, CI: 1.16 – 1.87] compared with placebo.

Table 2. Characteristics of planned and ongoing studies

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT
SOLIDARITY trial https://www.ncbi.nlm.nih.gov/pubmed/32242116 **Note**: Interim Results published in The New England Journal of Medicine on 3 December 2020	Open-label randomized multi-country clinical trial	COVID-19 patients hospitalised with severe illness	Local standard of care alone, OR local standard of care plus one of • Remdesivir (daily infusion for 10 days) • Chloroquine or hydroxychloroquine (oral loading dose, then orally twice daily for 10 days) • Lopinavir + Ritonavir (orally twice daily for 10 days) • Lopinavir + Ritonavir (as above) plus Interferon (daily injection for 10 days).
Investigational Treatments for COVID-19 in Tertiary Care Hospital of Pakistan https://clinicaltrials.gov/ct2/show/NCT04492501	interventional retrospective case control, single centre based cohort study in Pak Emirates Military Hospital Rawalpindi (PEMH),	Inclusion Criteria: PCR positive confirmed COVID-19; Admitted in hospital Day of illness less than 14 days; no contraindications to invasive procedure or novel therapies	Procedure: Therapeutic Plasma exchange Biological: Convalescent Plasma Drug: Tocilizumab Drug: Remdesivir Biological: Mesenchymal stem cell therapy
A single-arm multicenter clinical trial to evaluate the safety and efficacy of Remdesivir in COVID-19 patients with progressive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) https://en.irct.ir/trial/46660	A single-arm, uncontrolled, open-label clinical trial to evaluate the safety and efficacy of Remdesivir in COVID-19 patients.	All confirmed COVID-19 patients who are still progressing despite receiving standard treatment. Exclusion criteria: Different treatment with national protocol, under mechanical ventilation and evidence of multiple organ failure.	Patients in the intervention group receive remdesivir (200 mg on the first day followed by 100 mg per day) in addition to the standard treatment
Multicenter, Retrospective Study of the Effects of Remdesivir in the Treatment of Severe Covid-19 Infections (REMDECO-19) Sponsor: Assistance Publique - Hôpitaux de Paris https://clinicaltrials.gov/ct2/show/NCT04365725	Retrospective cohort trial to assess the efficacy of remdesivir in hospitalised COVID-19 adults	200 COVID-19 patients hospitalized in several French hospitals	Compassionate use Remdesivir
Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Remdesivir (GS-5734™) in Participants From Birth to < 18 Years of Age With Coronavirus Disease 2019 (COVID-19) (CARAVAN) https://clinicaltrials.gov/ct2/show/NCT04431453	A Phase 2/3 Single-Arm, Open-Label Study	Following paediatric participants will be enrolled: • *Paediatric participants ≥28 days to <18 years old:* Cohort 1: ≥12 years to <18 years and weight ≥40 kg Cohort 2: ≥28 days to <18 years and weight ≥20 kg to <40 kg Cohort 3: ≥28 days to <18 years and weight ≥12 kg to <20 kg Cohort 4: ≥28 days to <18 years and weight ≥3 kg to <12 kg • *Term neonatal participants 0 days to <28 days old:* Cohort 5: ≥14 days to <28 days of age, gestational age >37 weeks and weight at screening ≥2.5 kg	Experimental: Remdesivir (RDV) Participants will receive RDV up to 10 days. The RDV dose administered in each cohort is as follows: Cohort 1: intravenous (IV) RDV 200 mg on Day 1 followed by IV RDV 100 mg daily Cohorts 2-5: IV RDV 5 mg/kg on Day 1 followed by IV RDV 2.5 mg/kg daily Cohorts 6-7: IV RDV at a dose to be determined based on RDV exposure data from Cohort 5

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT
		Cohort 6: 0 days to <14 days of age, gestational age >37 weeks and birth weight ≥2.5 kg • *Preterm neonates and infants 0 days to <56 days old:* Cohort 7: 0 days to <56 days of age, gestational age ≤37 weeks and birth weight ≥1.5 kg	
Study of Merimepodib in Combination With Remdesivir in Adult Patients With Advanced COVID-19 Sponsor: ViralClear Pharmaceuticals, Inc. https://clinicaltrials.gov/ct2/show/NCT04410354	This phase 2 randomized, double-blind, placebo-controlled study	Approximately 40 adult patients with advanced COVID-19 disease, who have a score of 3 or 4 on the National Institute of Allergy and Infectious Disease (NIAID) 8-point ordinal scale and at least one of the following: fever, cough, sore throat, malaise, headache, muscle pain, shortness of breath at rest or with exertion, confusion or symptoms of severe lower respiratory symptoms. Patients will be randomized 1:1 to receive oral administration of MMPD + remdesivir or placebo + remdesivir.	Drug: Merimepodib 400 mg (total daily dose of 1200 mg) for 10 days Other Name: VX-497 Drug: Remdesivir 200 mg loading dose on Day 0 followed by 100 mg daily dose for 4 days. If a subject does not demonstrate clinical improvement, 100 mg daily dose may be extended for up to 5 additional days (for a total of up to 10 days) Placebo Comparator: Placebo + remdesivir Drug: Matching Placebo 0 mg (total daily dose of 0 mg) for 10 days Drug: Remdesivir 200 mg loading dose on Day 0 followed by 100 mg daily dose for 4 days. If a subject does not demonstrate clinical improvement, 100 mg daily dose may be extended for up to 5 additional days (for a total of up to 10 days)
Study to Evaluate the Safety and Antiviral Activity of Remdesivir (GS-5734™) in Participants With Severe Coronavirus Disease (COVID-19) Sponsor: Gilead Sciences Information provided by (Responsible Party): Gilead Sciences https://clinicaltrials.gov/ct2/show/NCT04292899	Phase 3 Randomized Open-label Study Estimated completion: June 2020	Patients with severe COVID-19 disease and hospitalised. Aged ≥18 years (at all sites), or aged ≥12 and <18 years of age weighing ≥40 kg. Peripheral capillary oxygen saturation (SpO2) ≤94% or requiring supplemental oxygen at screening.	*There are four study arms.* In each remdesivir is the active, standard of care is the control. Experimental Study arms: **Part A:** Remdesivir (RDV), 5 Days (Not Mechanically Ventilated) Participants who are not mechanically ventilated will receive continued standard of care therapy together with RDV 200 mg on Day 1 followed by RDV 100 mg on Days 2, 3, 4, and 5. **Part A:** Remdesivir, 10 Days (Not Mechanically Ventilated) Participants who are not mechanically ventilated will receive continued standard of care therapy together with RDV 200 mg on Day 1 followed by RDV 100 mg on Days 2, 3, 4, 5, 6, 7, 8, 9, and 10. **Part B:** Remdesivir, 5 or 10 Days (Extension) Will enrol participants after enrolment to Part A is complete. Participants will receive continued standard of care therapy together with RDV 200 mg on Day 1 followed by RDV 100 mg on Days 2-10. **Part B**: Remdesivir 10 days (Mechanically Ventilated) Participants on mechanical ventilation will receive continued standard of care therapy together with RDV 200 mg on Day 1 followed by RDV 100 mg on Days 2-10
A Study to Evaluate the Efficacy and Safety of Remdesivir Plus Tocilizumab Compared With Remdesivir Plus Placebo in Hospitalized Participants With Severe COVID-19 Pneumonia (REMDACTA)	Phase III, Randomized, Double-Blind, Multicentre Study	Hospitalized with COVID-19 pneumonia confirmed per a positive polymerase chain reaction (PCR) of any specimen (e.g., respiratory, blood, urine, stool, and other bodily fluid) and evidenced by chest X-ray or CT scan.	Experimental: Remdesivir + Tocilizumab (RDV+TCZ) RDV loading dose followed by one infusion of TCZ on Day 1, and a once-daily maintenance dose of remdesivir from Days 2-10. Active Comparator: Remdesivir + Placebo (RDV+Placebo)

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT
Sponsor: Hoffmann-La Roche Collaborator: Gilead Sciences https://clinicaltrials.gov/ct2/show/NCT04409262		Requiring more than 6 L/min supplemental oxygen to maintain SpO2 > 93%.	Patients assigned to the RDV + placebo arm will receive an RDV loading dose followed by one infusion of TCZ-placebo on Day 1, and a once-daily maintenance dose of RDV from Days 2-10.
Adaptive COVID-19 Treatment Trial (ACTT) Sponsor: National Institute of Allergy and Infectious Diseases (NIAID) Information provided by (Responsible Party): National Institute of Allergy and Infectious Diseases (NIAID) https://clinicaltrials.gov/ct2/show/record/NCT04280705	Multicentre, Adaptive, blinded RCT Preliminary results of this study have already been published as per table 1. Final data collection date is set at April 1, 2023	Adults hospitalised with confirmed COVID-19 infection. Illness of any duration, and at least one of the following: Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), *OR* Clinical assessment (evidence of rales/crackles on exam) AND SpO2 < / = 94% on room air, *OR* Requiring supplemental oxygen, *OR* Requiring mechanical ventilation.	*Placebo* 200 mg of remdesivir placebo administered intravenously on Day 1, followed by a 100 mg once-daily maintenance dose of Remdesivir placebo for the duration of the hospitalization up to a 10 days total course. n=220. *Intervention: Other: Placebo* *Intervention: Drug: Remdesivir* 200 mg of Remdesivir administered intravenously on Day 1, followed by a 100 mg once-daily maintenance dose of Remdesivir for the duration of the hospitalization up to a 10 days total course. n=220.
Adaptive COVID-19 Treatment Trial 2 (ACTT-II) Sponsor: National Institute of Allergy and Infectious Diseases (NIAID) https://clinicaltrials.gov/ct2/show/NCT04401579	Adaptive randomized double-blind placebo-controlled trial Expected Completion date August 2023	Adults (>=18 years) admitted to a hospital with symptoms suggestive of COVID-19. Has laboratory-confirmed SARS-CoV-2 AND progressive disease suggestive of ongoing SARS-CoV-2 infection. Illness of any duration, and at least one of the following: Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR SpO2 < / = 94% on room air, OR Requiring supplemental oxygen, OR Requiring mechanical ventilation or ECMO.	*Experimental: Remdesivir plus Baricitinib* 200 mg remdesivir administered IV on Day 1, followed by a 100 mg/day maintenance dose while hospitalised for up to a 10-day total course and 4 mg (2 tablets of 2 mg) of Baricitinib administered orally daily for the duration of the hospitalization up to a 14-day total course. *Placebo Comparator: Remdesivir plus Placebo* 200 mg remdesivir administered IV on Day 1, followed by a 100 mg/day maintenance dose of Remdesivir while hospitalised for up to a 10-day total course and 4 mg (2 tablets of 2 mg) of baricitinib placebo administered orally daily for the duration of the hospitalisation up to a 14-day total course.
Adaptive COVID-19 Treatment Trial 3 (ACTT-3) Sponsor: National Institute of Allergy and Infectious Diseases (NIAID) https://clinicaltrials.gov/ct2/show/NCT04492475	This study is an adaptive randomized double-blind placebo-controlled trial to evaluate the safety and efficacy of novel therapeutic agents in hospitalized adults diagnosed with COVID-19.	Admitted to a hospital with symptoms suggestive of COVID-19. Has laboratory-confirmed SARS-CoV-2 infection as determined by polymerase chain reaction (PCR) or other commercial or public health assay in any respiratory specimen, as documented Illness of any duration, and at least one of the following: Radiographic infiltrates by imaging (chest x-ray, CT scan, etc.), OR SpO2 < / = 94% on room air, OR Requiring supplemental oxygen, OR Requiring mechanical ventilation.	*ACTT-3 will evaluate the combination of interferon beta-1a and remdesivir compared to remdesivir alone.*
The Efficacy of Different Anti-viral Drugs in COVID 19 Infected Patients Sponsor: Oslo University Hospital Information provided by (Responsible Party):	The WHO NOR-(Coronavirus infectious disease) COVID 19 multi-centre, adaptive,	Adult patients, Confirmed SARS-2-CoV-2 infection by PCR Admitted to the hospital ward or the ICU	*Drug: Hydroxychloroquine:* Orally (in ICU via gastrointestinal tubes) with 800 mg x 2 loading dose followed by 400 mg x 2 every day for a total of 10 days. *Drug: Remdesivir* Given intravenously 100 mg daily for the duration of the hospitalization and up to 10 days total course, with a loading dose of 200 mg at inclusion.

CITATION	STUDY DESIGN	POPULATION (N)	TREATMENT
Andreas Barratt-Due, Oslo University Hospital https://clinicaltrials.gov/ct2/show/NCT04321616	randomised, open clinical trial		*Other: Standard of Care* Supplied to all patients not receiving a drug intervention.
Expanded Access Treatment Protocol: Remdesivir (RDV; GS-5734) for the Treatment of SARS-CoV2 (CoV) Infection (COVID-19) Sponsor: Gilead Sciences https://clinicaltrials.gov/ct2/show/NCT04323761		Age ≥ 18 years or aged ≥ 12 and < 18 years of age weighing ≥ 40 kg Hospitalized with confirmed SARS-CoV2 by polymerase chain reaction (PCR) or known contact of confirmed case with syndrome consistent with coronavirus disease (COVID-19) with PCR pending'; Oxygen saturation (SpO2) ≤ 94% on room air or requiring supplemental oxygen at baseline; Alanine aminotransferase (ALT) < 5 x upper limit of normal (ULN) by local laboratory measure and/or ALT < 3 x ULN and bilirubin < 2 x ULN	Drug: Remdesivir Intravenous infusion administered over a 30 to 120 minute period
Trial of Treatments for COVID-19 in Hospitalized Adults (DisCoVeRy) Sponsor: Institut National de la Santé Et de la Recherche Médicale, France Information provided by (Responsible Party): Institut National de la Santé Et de la Recherche Médicale, France https://clinicaltrials.gov/ct2/show/NCT04315948	Multi-centre, adaptive, randomized, open clinical trial	Adult patients with laboratory-confirmed SARS-CoV-2 infection. Hospitalized patients with illness of any duration, and at least one of the following: Clinical assessment (evidence of rales/crackles on exam) AND SpO2 ≤ 94% on room air, OR Acute respiratory failure requiring mechanical ventilation and/or supplemental oxygen.	*Remdesivir:* 200 mg IV loading dose on Day 1, followed by a 100 mg once-daily IV maintenance dose for the duration of the hospitalisation up to a 10 days total course; n=620 *Lopinavir/ritonavir:* 400/100 mg administered every 12 h for 14 days in tablet form. Patients unable to take medications by mouth, the lopinavir/ritonavir will be administered as a 5-ml suspension every 12 h for 14 days via a pre-existing or newly placed nasogastric tube; n=620 *Experimental: Lopinavir/ritonavir plus Interferon ß-1a:* 400 lopinavir mg/100 mg ritonavir administered every 12 h for 14 days in tablet form. Patients unable to take medications by mouth, the lopinavir/ritonavir will be administered as a 5-ml suspension every 12 h for 14 days via a pre-existing or newly placed nasogastric tube; n=620. Interferon ß1a administered subcutaneously at the dose of 44 µg for a total of 3 doses in 6 days (day 1, day 3, day 6); n=620 *Experimental: Hydroxychloroquine:* Oral loading dose of 400 mg twice daily for one day followed by 400 mg/day for 9 days. The loading dose of hydroxychloroquine through a nasogastric tube will be increased to 600 mg twice a day for one day, followed by a maintenance dose of 400 mg/day for 9 days; n=620

Appendix 1: Search strategy (4 September 2020)

Cochrane COVID-19 Study Register 144 studies with 165 references remdesivir OR remdesevir
Epistemonikos (title:(Coronavirus* OR covid-19 OR covid19 OR 2019-ncov OR 2019ncov OR sars-cov-2 OR sars-cov2) OR abstract:(Coronavirus* OR covid-19 OR covid19 OR 2019-ncov OR 2019ncov OR sars-cov-2 OR sars-cov2)) AND (title:(remdesevir OR remdesivir) OR abstract:(remdesevir OR remdesivir)) **Output 175 records**
Cochrane Living Synthesis https://www.cochrane.org/news/cochrane-france-leads-collaborative-covid-19-living-evidence-project https://covid-nma.com/living_data/index.php

Appendix 2: Summary of findings of the Cochrane Living Meta-analysis: Remdesivir vs Placebo for Mild/ Moderate/Severe COVID-19

Patient or population: Mild/Moderate/Severe/Critical COVID-19
Setting: Wordwide
Intervention: Remdesivir
Comparison: Standard Care/Placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Standard Care/Placebo	Risk with Remdesivir				
Viral negative conversion D3	292 per 1.000	284 per 1.000 (178 to 450)	RR 0.97 (0.61 to 1.54)	196 (1 RCT) [b]	⨁◯◯◯ VERY LOW [c,d,e]	
Viral negative conversion D7	492 per 1.000	502 per 1.000 (374 to 679)	RR 1.02 (0.76 to 1.38)	196 (1 RCT) [b]	⨁◯◯◯ VERY LOW [c,d,f]	
Clinical improvement D7	345 per 1.000	366 per 1.000 (307 to 439)	RR 1.06 (0.89 to 1.27)	832 (2 RCTs) [g]	⨁⨁⨁◯ MODERATE [f]	
Clinical improvement D14-D28	759 per 1.000	805 per 1.000 (751 to 858)	RR 1.06 (0.99 to 1.13)	832 (2 RCTs) [g]	⨁⨁⨁◯ MODERATE [h]	
WHO progression score (level 6 or above) D7	451 per 1.000	419 per 1.000 (243 to 717)	RR 0.93 (0.54 to 1.59)	1298 (2 RCTs) [i]	⨁⨁◯◯ LOW [f,j]	
WHO progression score (level 6 or above) D14-D28	193 per 1.000	131 per 1.000 (106 to 164)	RR 0.68 (0.55 to 0.85)	1894 (3 RCTs) [k]	⨁⨁⨁◯ MODERATE [l]	
WHO progression score (level 7 or above) D7	359 per 1.000	251 per 1.000 (212 to 294)	RR 0.70 (0.59 to 0.82)	1298 (2 RCTs) [i]	⨁⨁⨁◯ MODERATE [h]	
WHO progression score level 7 or above D14-28	178 per 1.000	124 per 1.000 (100 to 156)	RR 0.70 (0.56 to 0.88)	1894 (3 RCTs) [k]	⨁⨁⨁⨁ HIGH	
All-cause mortality D7	63 per 1.000	43 per 1.000 (18 to 104)	RR 0.68 (0.28 to 1.64)	1298 (2 RCTs) [i]	⨁◯◯◯ VERY LOW [e,m]	
All-cause mortality D14-D28	112 per 1.000	101 per 1.000 (82 to 125)	RR 0.90 (0.73 to 1.11)	7345 (4 RCTs) [n]	⨁⨁⨁◯ MODERATE [f]	
Adverse events	583 per 1.000	542 per 1.000 (496 to 589)	RR 0.93 (0.85 to 1.01)	1894 (2 RCTs) [i]	⨁⨁⨁⨁ HIGH [o]	
Serious adverse events	40 per 1.000	24 per 1.000 (15 to 38)	RR 0.60 (0.38 to 0.96)	1894 (3 RCTs) [k]	⨁⨁⨁◯ MODERATE [o,p]	

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of 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
a. Last update: November 6, 2020
b. Wang Y, 2020
c. Risk of bias downgraded by 1 level: some concerns with missing data
d. Indirectness downgraded by 1 level: despite a multicentre design this is a single study from a single country, therefore results in this population might not be generalizable to other settings
e. Imprecision downgraded by 2 levels: due to very wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of events
f. Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm and low number of events
g. Spinner CD, 2020; Wang Y, 2020
h. Imprecision downgraded by 1 level: due to low number of events and/or participants
i. Wang Y, 2020; Beigel JH, 2020
j. Inconsistency downgraded by 1 level: I^2=77%
k. Beigel JH, 2020; Spinner CD, 2020; Wang Y, 2020
l. Risk of bias downgraded by 1 level: some concerns due to deviation from intended intervention and outcome measurement
m. Inconsistency downgraded by 1 level: I^2=53.1%
n. Spinner CD, 2020; SOLIDARITY (Remdesivir), 2020; Beigel JH, 2020; Wang Y, 2020
o. We presume that the adverse event rates, and the corresponding relative risks, are similar across diverse settings; therefore not downgraded for indirectness
p. Imprecision downgraded by 1 level: few events and a wide confidence intervalconsistent with the possibility of a benefit and the possibility of no effect.

Appendix 3: Forest plots for Cochrane Living Meta-analysis: Remdesivir 10 or 5 days vs Placebo for Moderate/Severe COVID-19

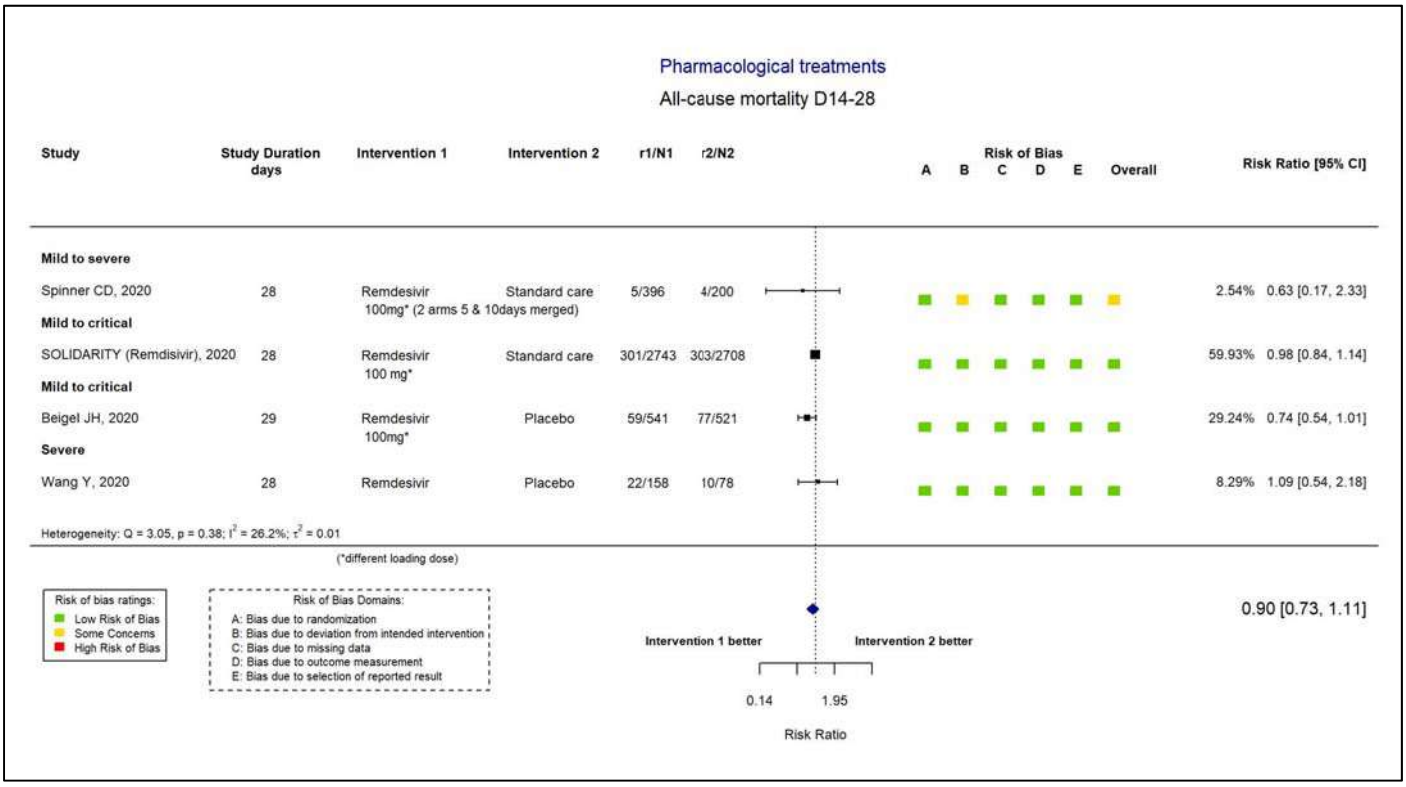

Figure 1: All-cause mortality, D14-28; Remdesivir 5 or 10 days versus standard of care

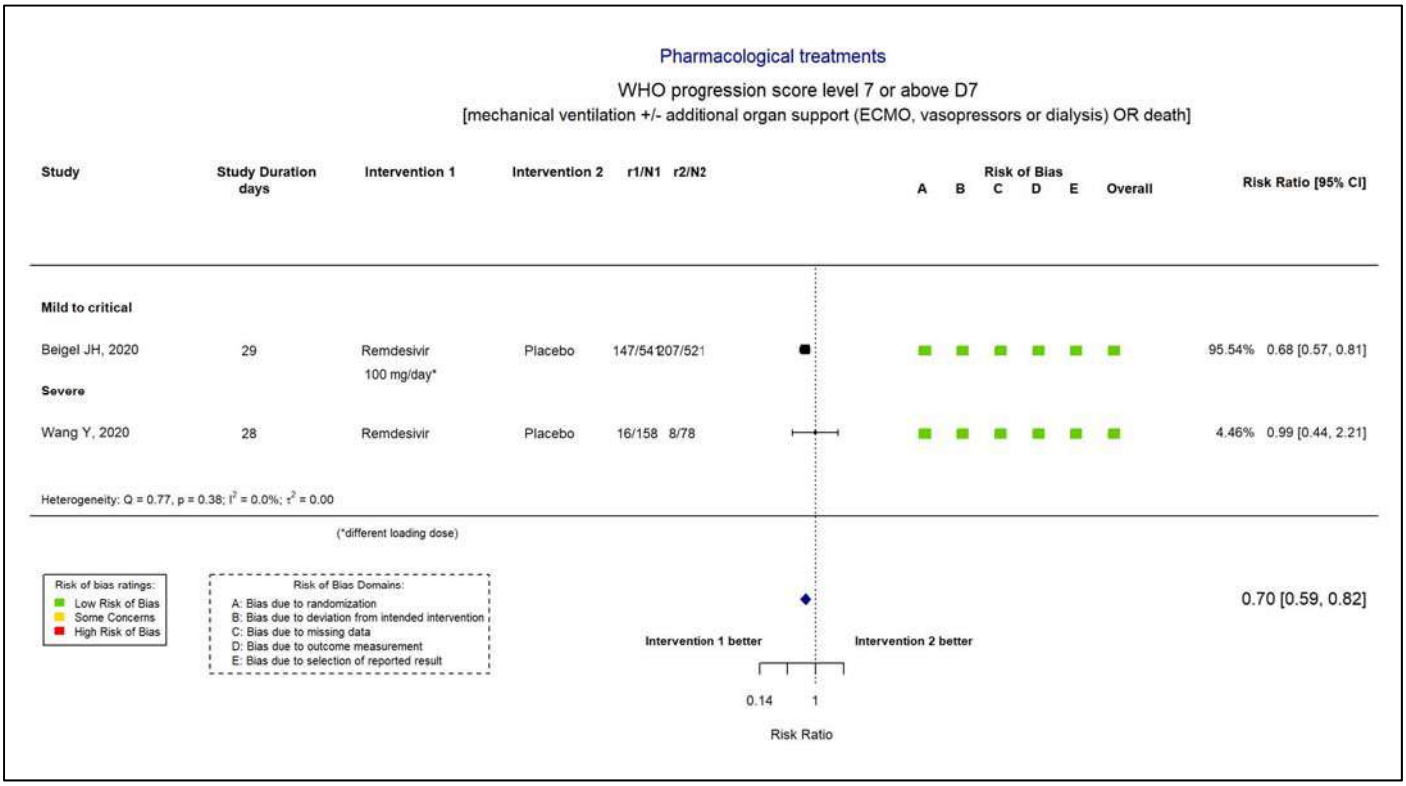

Figure 2: Progression to ventilation Remdesivir 5 or 10 days at D7

Appendix 4: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High: [ ] Moderate: [X] Low: [ ] Very low: [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Only four randomised trials have been published at this point and confidence intervals were relatively wide. One of these trials examined only 5 days versus 10 days of remdesivir and did not compare to standard of care. A fifth RCT has been published as interim results. Two trials were terminated early – one because of inability to recruit further patients, the other because further randomisation was considered unnecessary, so analyses are underpowered.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: [ ] Moderate: [ ] Small: [x] None: [ ]	All-cause mortality D14-28: RR 0.9 (0.73 to 1.11)) for the 10 days treatment. Given current limited resources, earlier discharge from hospital and less need for ventilators is desirable. However, the SOLIDARITY trial found no significant difference in need for ventilation or duration of hospital stay.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High: [ ] Moderate: [x] Low: [ ] Very low: [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	Adverse events were similar with remdesivir and placebo in the RCTs mentioned above.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: [ ] Moderate: [ ] Small: [ ] None: [x]	There does not seem to be any additional harms versus placebo.
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention: [x] Favours control: [ ] Intervention = Control *or* Uncertain: [ ]	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: [ ] No: [ ] Uncertain: [X]	Medicine is not SAHPRA registered, but enquiries can be made with the supplier regarding donation-access programme; or may be **accessed via Section 21**. Although emergency use authorisation only has been issued by the US FDA, the EMA has recommended conditional marketing authorisation, on the basis of a rolling review of the emergent evidence: https://www.ema.europa.eu/documents/smop-initial/chmp-summary-positive-opinion-veklury_en.pdf. The approved product information is accessible at: https://www.ema.europa.eu/en/documents/other/veklury-product-information-approved-chmp-25-june-2020-pending-endorsement-european-commission_en.pdf SAHPRA registration may be expedited due to the conditional EMA registration.
RESOURCE USE	**How large are the resource requirements?** More intensive: [X] Less intensive: [ ] Uncertain: [ ]	Price of medicines/treatment course: **Medicine** | **Price (ZAR)*** Remdesivir, IV, 200 mg loading dose, followed by 100 mg per day for 5-10 days (6 to 11 vials) | ***5 days***: 6375.60 to 14562.00 ***10 days***: 11688.60 to 26697.00 *The original manufacturer has licensed a number of Indian generic firms to make generic versions, and has included South Africa in the list of countries to which such products can be exported. Indicative costs for the generic versions, from potential South African

		supplier(s), is US$55 –US$150 per dose excluding VAT. At an exchange rate of R16.18, a vial would cost R1062.60–R2427.00. **Note:** Scale of volume procurement will affect the price. *Reference:* Email (29June2020) on file – Official quotation received by NDoH, Affordable Medicines Directorate. **Additional resources:** Safety monitoring (liver function tests). **Note:** The NEMLC Subcommittee acknowledges that economic evaluations of remdesivir have been done; one by the Clinton Health Access Initiative and another, the MOSAIC model (developed collaboratively by the University of Cape Town and the Medical Research Council). The economic evaluations show that remdesivir may reduce treatment costs because of reduction in length of hospitalisation. It is unclear whether those costs would be realised in the South African public sector setting however, especially given concerns regarding access.
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	Patients: No specific research surveying patients' value of this therapeutic agent is currently available. Healthcare workers likely consider the intervention to be acceptable.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [ ] Uncertain [X]	This would depend on the ability of hospitals to access the medicine via section 21.

Appendix 5: Updating of rapid report

Date	Signal	Rationale
9 December 2020	WHO SOLIDARITY RCT results printed in NEJM	The WHO SOLIDARITY RCT results reported in preprint format reported has recently been published peer-review format in the NEJM.