EUnetHTA Joint Action 3 WP4

Rapid Collaborative Review

REMDESIVIR FOR THE TREATMENT OF HOSPITALISED PATIENTS WITH COVID-19

Update 1

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The content of this update 1 of the Rapid Collaborative Review Report represents a consolidated view based on the consensus within the Authoring Team; it cannot be considered to reflect the views of the European Network for Health Technology Assessment (EUnetHTA), EUnetHTA's participating institutions, the European Commission and/or the Consumers, Health, Agriculture and Food Executive Agency or any other body of the European Union. The European Commission and the Agency do not accept any responsibility for use that may be made of the information it contains.

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For further information on the work distribution and further contributors, please see Appendix 5.

Conflict of interest

All authors, co-authors and dedicated reviewers involved in the production of this assessment have declared they have no conflicts of interest in relation to the technology and comparator(s) assessed according to the EUnetHTA declaration of interest (DOI) form. Conflict of Interest was evaluated following the EUnetHTA Procedure Guidance for handling DOI form (https://eunethta.eu/doi).

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LIST OF ABBREVIATIONS

AE	Adverse Events
ARDS	Acute Respiratory Distress Syndrome
CDSR	Cochrane Database of Systematic Reviews
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CMA	Conditional Marketing Authorization
COVID-19	Coronavirus Disease 2019
CSR	Clinical Study Reports
DOI	Declaration of Interest
DR	Dedicated Reviewers
ECDC	European Centre for Disease Prevention and Control
ECMO	Extracorporeal membrane oxygenation
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
EUnetHTA	European Network of Health Technology Assessment
EuroMOMO	European Mortality Monitoring
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HRQoL	Health-related quality of life
HTA	Health Technology Assessment
HTAi	Health Technology Assessment international
MAH	Marketing Authorisation Holder
MD	Mean Difference
MEDLINE	Medical Literature Analysis and Retrieval System Online
MERS-CoV	Middle East respiratory syndrome coronavirus
PaO2/FiO_2	Ratio of arterial partial pressure of oxygen to fraction of inspired oxygen
PICO	Population, intervention, control, outcome
PTRCR	Pharmaceutical Rapid Collaborative Review
RCT	Randomised Control Trials
REA	Relative Effectiveness Assessment
RoB	Risk of Bias
RR	Relative Risk
SAE	Serious Adverse Events
SARS-CoV	Severe Acute Respiratory Syndrome Coronavirus
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SD	Standard Deviation
SLR	Systematic Literature Review
SMD	Standardised mean difference
SOFA	Sequential organ failure assessment
SpO_2	Oxygen saturation
SR	Systematic reviews
WHO	World Health Organization
WP4	Work Package 4

1 INTRODUCTION

In 2020, EUnetHTA prioritized its activities around Coronavirus disease 2019 (COVID-19) to respond to the public health emergency.

In terms of COVID-19 products, EUnetHTA is producing 'Rapid Collaborative Reviews' for diagnostic testing as well as for therapeutic treatments and 'Rolling Collaborative Reviews' for therapeutic treatments. These are evidence-based reports with a timely synthesis of available evidence on the comparative effectiveness and safety of health technologies (diagnostic, therapeutic, etc.) for the management of the current pandemic, with continuous updates as research evolves[1].

Following the original Rapid Collaborative Review - PTRCR15, published in September 2020 [1], evidence gaps were identified, such as the need for adequately powered RCTs with clinically relevant outcomes, including all-cause mortality, the additional need for and duration of mechanical ventilation, additional need for and duration of supplemental oxygen and duration of hospitalisation. The subsequent publication of results from two RCTs, including the final report of the ACTT-1 trial [2] and the preliminary report of the WHO SOLIDARITY trial [3], as well as data from two living clinical guidelines [4-6], are used to summarise the most recent evidence to further support the local production of national/regional HTA reports.

1.1 Overview of the disease or health condition: COVID-19

As of November 30, 2020, across the European Union/European Economic Area (EU/EEA) and the United Kingdom (UK) there has been a further increase in COVID-19 infections and the current situation represents a major threat to public health. The impact in terms of pressure on healthcare services and mortality has become increasingly evident [7].

As of 06 December 2020, 13 972 781 cases and 347 088 deaths have been reported in the EU/EEA and the UK [8]. Pooled data from 18 countries for week 48 show that there were 1.8 patients per 100 000 population in ICU due to COVID-19, which is 82% of the peak ICU occupancy observed during the pandemic. Pooled weekly ICU admissions based on data from 13 countries were 2.2 new admissions per 100 000, which is 59% of the peak rate to date. Hospital and/or ICU occupancy and/or new admissions due to COVID-19 were high (at least 25% of the peak level during the pandemic) or had increased compared to the previous week in 29 countries. The 14-day COVID-19 death rate for the EU/EEA and the UK, based on data collected by ECDC from official national sources from 31 countries, was 104.6 (country range: 2.8–286.6) per million population[2].

1.1.1 Clinical symptoms and disease severity

Adults with COVID-19 can be grouped into the following severity of illness categories, although the criteria in each category may overlap or vary across guidelines and clinical trials [5]. Clinical symptoms and COVID-19 severity of illness categories are presented in Table 1.1

[1] https://eunethta.eu/services/COVID-19/

[2] https://covid19-country-overviews.ecdc.europa.eu/

Table 1.1. COVID-19 severity of illness categories

WHO definitions of disease severity for COVID-19	NIH COVID-19 Treatment Guidelines (last update October 9, 2020)
***Non-severe COVID-19**:* Defined as absence of any signs of severe or critical COVID-19.	***Asymptomatic or Presymptomatic Infection**:* Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test or an antigen test), but who have no symptoms that are consistent with COVID-19.
	***Mild Illness**:* Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhoea, loss of taste and smell) but who do not have shortness of breath, dyspnoea, or abnormal chest imaging.
	***Moderate Illness**:* Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO_2) ≥94% on room air at sea level.
***Severe COVID-19**:* Defined by any of: - Oxygen saturation <90% on room air[a] - Respiratory rate >30 breaths per minute in adults and children >5years old, ≥60 breaths/min in children <2 months old, ≥50 in children 2-11 months old, and ≥40 in children 1-5 years old - Signs of severe respiratory distress (accessory muscle use, inability to complete full sentences, and, in children, very severe chest wall indrawing, grunting, central cyanosis, or presence of any other general danger signs).	***Severe Illness**:* Individuals who have SpO_2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, respiratory frequency >30 breaths per minute, or lung infiltrates >50%.
***Critical COVID-19**:* Defined by the criteria for acute respiratory distress syndrome (ARDS), sepsis, septic shock, or other conditions that would normally require the provision of life sustaining therapies such as mechanical ventilation (invasive or non-invasive) or vasopressor therapy.	***Critical Illness**:* Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.

Source: [4-6]
[a] Caution: The panel noted that the oxygen saturation threshold of 90% to define severe COVID-19 was arbitrary and should be interpreted cautiously when used for determining which patients should be offered systemic corticosteroids. For example, clinicians must use their judgment to determine whether a low oxygen saturation is a sign of severity or is normal for a given patient with chronic lung disease. Similarly, a saturation >90-94% on room air may be abnormal if the clinician suspects that this number is on a downward trend. Generally, if there is any doubt, the panel suggested erring on the side of considering the illness as severe.
Abbreviations: ARDS=acute respiratory distress syndrome; SARS-CoV-2=Severe Acute Respiratory Syndrome Coronavirus 2; SpO_2=oxygen saturation; PaO2/FiO_2=ratio of arterial partial pressure of oxygen to fraction of inspired oxygen.

Patients admitted to hospital with COVID-19 typically report symptoms onset three to five days after exposure (fatigue, chills), progressing to fever and dry cough 48 hours later. Transition to severe disease with hypoxaemia can occur five to seven days into the symptomatic illness, about 8-14 days after original exposure [9]. Recently, the 4C Mortality Score has been developed and validated, categorising patients as being at low, intermediate, high, or very high risk of death, to directly inform clinical decision making, and can be used to stratify patients admitted to hospital with COVID-19 into different management groups [10].

1.2 Current clinical management

Pharmacological treatment options for COVID-19 are limited and there are trials underway to assess the efficacy of available medicines to manage the disease. EUnetHTA Rolling Collaborative Reviews present the comparative data on effectiveness and safety of potential therapies for COVID-19, and are updated on a monthly basis [11].

Standard of care, as previously described [1] can vary according to country and currently is guided by disease severity. For severe disease, standard of care is based on supportive treatment including supplemental oxygen, thromboprophylaxis and management of comorbidities and nosocomial

complications, including empiric antimicrobial therapy if indicated. In critically ill patients, it includes ventilatory support (i.e., invasive mechanical ventilation, extracorporeal membrane oxygenation (ECMO)), hemodynamic and organ support, as well as other interventions aimed at the prevention and management of complications.

Currently, two pharmaceuticals are approved for treatment of COVID-19 hospitalized patients: remdesivir and dexamethasone. Remdesivir (Veklury), received a conditional marketing authorisation in EU in July 2020, for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen [12]. On October 22, 2020 the U.S. Food and Drug Administration approved remdesivir for use in adult and paediatric patients 12 years of age and older and weighing at least 40 kilograms (about 88 pounds) for the treatment of COVID-19 requiring hospitalization.

Dexamethasone use is endorsed by EMA in adults and adolescents (from 12 years of age and weighing at least 40 kg) who require supplemental oxygen therapy. Dexamethasone can be taken by mouth or given as an injection or infusion (drip) into a vein. In all cases, the recommended dose in adults and adolescents is 6 milligrams once a day for up to 10 days. Companies that market dexamethasone medicines can request this new use to be added to their product's license by submitting an application to national medicines agencies or to EMA [13, 14].

1.2.1 Treatment management with corticosteroids and remdesivir according the WHO and US NIH clinical guidelines

WHO living guidance

The new WHO living guidance on corticosteroids for COVID-19 was published [4, 6, 15]. The WHO panel made two recommendations: a strong recommendation (based on moderate certainty evidence) for systemic (i.e. intravenous or oral) corticosteroid therapy (e.g. 6 mg of dexamethasone orally or intravenously daily or 50 mg of hydrocortisone intravenously every 8 hours) for 7 to 10 days in patients with severe and critical COVID-19, and a conditional recommendation (based on low certainty evidence) not to use corticosteroid therapy in patients with non-severe COVID-19 [4, 6, 15].

Recently, the new WHO living guidance on remdesivir for COVID-19 was published [8, 15]. The WHO panel made a conditional recommendation against the use of remdesivir in hospitalized patients with COVID-19, regardless of disease severity, with new information and recommendations on remdesivir after publication of results from the WHO SOLIDARITY trial [3]. The recommendation on remdesivir was informed by results from a systematic review and network meta-analysis (NMA) that pooled data from four randomized trials with 7333 participants hospitalized for COVID-19. The resulting evidence summary suggested that remdesivir has possibly no effect on mortality (odds ratio 0.90, 95% confidence interval [CI] 0.70 - 1.12; absolute effect estimate 10 fewer deaths per 1000 patients, 95% CI from 29 fewer - 11 more deaths per 1000 patients; low certainty evidence); and possibly no effect on the other important outcomes identified by the panel, with similar low to very low certainty of evidence. The panel judged the overall credibility of subgroup analyses assessing differences in mortality by severity of illness to be insufficient to make subgroup recommendations.

Visual summary of recommendations can be found in Table A1 in Appendix 1.

US COVID-19 Treatment Guidelines

The US COVID-19 Treatment Guidelines Panel issued new recommendations on pharmacological treatment for patients with COVID-19 (as of December 3, 2020) [5]:

In summary, in the earliest stages of infection, before the host has mounted an effective immune response, anti-SARS-CoV-2 antibody-based therapies may have their greatest likelihood of having an effect. In this regard, although there are insufficient data from clinical trials to recommend either for or against the use of any specific therapy in this setting, preliminary data suggests that outpatients may benefit from receiving anti-SARS-CoV-2 monoclonal antibodies early in the course of infection. The anti-SARS-CoV-2 monoclonal antibodies bamlanivimab and casirivimab plus imdevimab are available through Emergency Use Authorizations for outpatients who are at high risk for disease progression.

Remdesivir, an antiviral agent, is currently the only drug that is approved by the Food and Drug Administration for the treatment of COVID-19. It is recommended for use in hospitalized patients who require supplemental oxygen. However, it is not routinely recommended for patients who require mechanical ventilation due to the lack of data showing benefit at this advanced stage of the disease.

Dexamethasone, a corticosteroid, has been found to improve survival in hospitalized patients who require supplemental oxygen, with the greatest effect observed in patients who require mechanical ventilation. Therefore, the use of dexamethasone is strongly recommended in this setting.

Visual summary of recommendations on pharmacological management of patients with COVID-19 based on disease severity can be found in Table A1 in Appendix 1.

1.3 Features of the intervention: Remdesivir

1.3.1 Regulatory Status

Remdesivir (Veklury) is an antiviral medicine for systemic use which received a conditional marketing authorisation[3] in EU in July, 2020 [13]. Remdesivir is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and adolescents (aged 12 years and older with body weight at least 40 kg) with pneumonia requiring supplemental oxygen. The drug is for administration by intravenous infusion after further dilution. The recommended dosage of remdesivir in patients 12 years of age and older and weighing at least 40 kg is: Day 1 – single loading dose of remdesivir 200 mg given by intravenous infusion, Day 2 onwards – 100 mg given once daily by intravenous infusion. The total duration of treatment should be at least 5 days and not more than 10 days. Concomitant use of remdesivir with chloroquine phosphate or hydroxychloroquine sulphate is not recommended due to antagonism observed in vitro.

The most common adverse reaction in healthy volunteers is increased transaminases (14%). The most common adverse reaction in patients with COVID-19 is nausea (4%) [12, 13].

Remdesivir is subject to additional monitoring for safety. Due to a conditional marketing authorisation, the Marketing Authorisation Holder (MAH) should complete some measures to confirm the efficacy and safety within different timeframe [12].

On October 02, 2020 EMA announced that EMA's safety committee (PRAC) has started a review of a safety signal to assess reports of acute kidney injury in some patients with COVID-19 taking remdesivir [16].

On October 22, 2020 the U.S. Food and Drug Administration approved remdesivir for use in adult and paediatric patients 12 years of age and older and weighing at least 40 kilograms (about 88 pounds) for the treatment of COVID-19 requiring hospitalization [13].

The FDA has also issued an emergency use authorization (EUA) for the Janus kinase inhibitor baricitinib to be used in combination with remdesivir in patients with COVID-19 who require oxygen or ventilatory support [17]**.**

[3] https://ec.europa.eu/commission/presscorner/detail/en/mex_20_1266

2 OBJECTIVE AND SCOPE

The aim of the original report was to provide a PICO, summarize the available evidence from published RCTs identified and any existing meta-analyses, discuss the limitations, and to identify evidence gaps and make recommendations for research [1].

The aim of this first update of EUnetHTA Rapid Collaborative Review is to incorporate the most recent available scientific evidence on the clinical effectiveness and safety of remdesivir in the target patient populations with relevant comparators. The target patient populations and relevant comparators (based on the requirements of EUnetHTA Partners) have previously been defined in the project scope in Table 2.1 [1].

Table 2.1. Assessment scope: relevant PICO(s) identified for the planned assessment

Description	Assessment scope		
PICO			
Population	Adults (aged > 18 years) and adolescents (aged 12 years and older with body weight at least 40 kg) hospitalized with confirmed COVID-19 pneumonia		
Intervention	Remdesivir plus standard of care/supportive treatment[a] (may include other drugs that potentially also change the course of the disease, such as dexamethasone)		
Comparison	Standard of care/supportive treatment* (may include other drugs that potentially also change the course of the disease, such as dexamethasone)		
Outcomes	**Clinical effectiveness**	**Rate**	**Relative importance**
	All-cause mortality	9	critical
	Time to recovery (using an Ordinal Scale for Clinical Improvement, e.g. WHO)	6	important
	Clinical improvement; using difference of stage on Ordinal Scale for Clinical Improvement, e.g. WHO)	6	important
	Additional need for non-invasive ventilation or high-flow oxygen	8	critical
	Duration of non-invasive ventilation or high-flow oxygen, in patients requiring it	7	critical
	Additional need for invasive mechanical ventilation or ECMO	8	critical
	Duration of invasive mechanical ventilation or ECMO, in patients requiring it	7	critical
	Length of stay (hospital and critical care unit)	5	important
	Safety		
	Adverse events	6	important
	Serious adverse events	8	critical
	Adverse events leading to treatment discontinuation	7	critical
	Treatment-related mortality	9	critical

[a] Standard of care may include, but is not limited to, supplemental oxygen or ventilatory support, dexamethasone, pharmacological thromboprophylaxis, empiric/targeted antimicrobial therapy, hemodynamic support, renal replacement therapy, investigational agents, other supportive measures.

3 METHODS

3.1 Data sources and searches

To avoid redundancies and duplication, this 1st update of the original EUnetHTA Rapid Collaborative Review reused data relevant to our PICO from two already published living systematic reviews/meta-analysis (SRs/MA) sources from international initiatives [18-21] and the new WHO living guideline [4, 6]. The data were included according to the methodology suggested by Whitlock 2008 [22] and Robinson 2014 [23] on how to integrate existing SRs into new SRs. As described by Robinson et al., four different approaches could be followed: 1) use the existing SR(s)' list of included studies as a quality check for our literature search and screening strategy (Scan References), 2) use the existing SR(s) to completely or partially provide the body of included studies for one or more research questions of our assessment ("Use Existing Search"), 3) use the data abstraction, risk of bias assessments, and/or analyses from existing SRs for one or more research questions of our assessment ("Use Data Abstraction/Syntheses") and 4) use the existing SR(s), including conclusions, to fully or partially answer one or more research questions of our REA ("Use Complete Review"). Approach number 3 was followed for this report.

Literature search used from the EUnetHTA Rolling Collaborative Reviews, updated in December 2020, to find possible new RCTs related to remdesivir treatment in hospitalized patients with COVID-19 [11, 18]. Details can be found in Table A2, Appendix 2. References were included or excluded according to the Population-Intervention-Control-Outcome (PICO)-scheme and presented according to the PRISMA Statement [24].

A separate Guideline (GL) search (G-I-N, TRIP-Database and hand search) was performed as well, in December 2020. Only living clinical guidelines, with regular and the most recent updates, were considered in this report.

As stated above, quantitative synthesis (using pairwise meta-analyses) from existing living SRs/MA was presented in the Result section if available for specific outcomes [4, 18-21] . According to published protocols of living SRs/MA and the new WHO guidelines, pairwise meta-analysis was performed for primary and secondary outcomes using a random-effects model to incorporate the anticipated clinical and methodological heterogeneity across studies [4, 6, 19, 20]. Relevant subgroup analyses, according to severity of illness categories defined in two clinical guidelines mentioned above, were not provided because disease severity in included RCTs was not consistent with WHO and US Guidelines definitions of disease severity for COVID-19 [4-6].

3.2 Risk of bias

Risk of bias assessment related to 4 RCTs on remdesivir was reused from one living SR/MA source [20]. Each study was presented with the Cochrane Risk of bias 2 (RoB 2) tool for randomized controlled trials [25]. The Cochrane RoB 2 tool is structured into 5 domains: 1) risk of bias arising from the randomization process, 2) risk of bias due to deviations from intended interventions, 3) risk of bias due to missing outcome data, 4) risk of bias in measurement of the outcome, 5) risk of bias in selection of the reported result. Within each domain, a series of 'signalling questions' elicit information relevant to risk of bias assessment. The response options to the signalling questions are: "Yes", "Probably yes", "Probably no", "No" and "No information". A risk of bias judgement arising from each domain is generated by an algorithm, based on answers to the signalling questions. Judgement can be "Low", "Some concerns" or "High" risk of bias. Overall risk of bias will be considered as "low risk of bias" if all domains are at low risk, "some concerns" if at least one domain is some concern and no domain is of high risk of bias, and "high risk of bias" if there is at least one domain at high risk, or several domains with some concerns.

3.3 Certainty of evidence

Certainty of evidence related to these 4 RCTs included in MAs was reused from three different sources:

- two already published living systematic reviews/meta-analysis (SRs/MA) sources from international initiatives [19-21];
- and the new WHO living guideline related to remdesivir [4, 6].

Table 3.1 shows from which sources the certainty of evidence related to the specific outcomes is presented.

Table 3.1. The sources used to present the certainty of evidence related to outcomes

Living SR/MA source (Boutron, 2020) [20]	Living SR/MA source (de Crescenzo, 2020) [19, 21]	WHO living guideline [4, 6]
All-cause mortality	Number of patients discharged within 28 days	Mechanical ventilation
Clinical improvement		Time to clinical improvement
WHO progression score (level 6 or above) D 14-28		Duration of hospitalisation
WHO progression score (level 7 or above) D 14-28		Duration of ventilation
Viral negative conversion		
Adverse events		Serious adverse events leading to discontinuation
Serious adverse events		

For rating the certainty of the evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE) is being presented [19-21, 26]. The GRADE approach specifies four levels of certainty: “High”, further research is very unlikely to change our confidence in the estimate of effect; “Moderate”, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimates; “Low”, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; “Very low”, we are very uncertain about the estimate.

3.4 Ongoing studies

The following clinical trial registries were searched for ongoing RCTs on remdesivir in COVID-19 in December 2020: ClinicalTrials.gov[4], ISRCTN[5] and European Clinical Trials Registry[6].

[4] https://clinicaltrials.gov/

[5] https://www.isrctn.com/

[6] https://www.clinicaltrialsregister.eu/

4 RESULTS

4.1 Information retrieval/Existing Evidence

In addition to two already published RCTs (Wang, Spinner) comparing remdesivir with standard of care/placebo [27, 28] which are described in the original report [1], evidence from two RCTs publications evaluating remdesivir treatment was added in this update:

- Final report related to ACTT-1 trial [2];
- A new preliminary report related to SOLIDARITY trial [3].

All four RCTs on 7333 patients hospitalized with various severities of COVID-19 are described in brief in Table 4.1.

Flow diagram depicting the selection process of RCTs can be found in Figure A1, Appendix 2.

Table 4.1. Main characteristics of 4 RCTs related to remdesivir

Study/ID/Reference	Country	N of patients	Mean age (years)	Severity (as per WHO criteria)	% IMV (at baseline)	Treatments (dose and duration)	Outcomes
Wang [28] NCT04257656	China	237	65	Severe a (100%)	16.1%	Remdesivir IV (100 mg/day for 10 days)	Effectiveness and safety
Spinner (SIMPLE MODERATE) [27] NCT04292730	United States, Europe, Asia	596	56-58	Non-severe (100%)	0%	Remdesivir IV (200 mg at day 1, then 100 mg for 4 days or 9 days)	Effectiveness and safety
Beigel (ACTT-1) [2] NCT04280705	United States, Europe, Asia	1063	58.9	Non-severe (11.3%) Severe b (88.7%)	44.1%	Remdesivir IV (100 mg/day for 10 days)	Effectiveness and safety
WHO Solidarity Trial Consortium (SOLIDARITY trial) [3] ISRCTN83971151, NCT04315948	Worldwide	5451	< 50 35% 50-70 47% > 70 18%	Non-severe (24%) Severe c (67%) Critical (9%)	8.9%	Remdesivir IV (200 mg at day 1, then 100 mg day 2-10)	Effectiveness

Source: adapted from [4] and [6]
Abbreviations: IMV=invasive mechanical ventilation; IV=intravenous; N=number; NR=not reported; Sx – =symptom.
Severity criteria based on WHO definitions unless otherwise stated: [a] defined severe as SpO2 < 94% on room air; [b] defined severe as SpO2 < 94% on room air OR respiratory rate > 24 breaths /min; [c] defined severe as requiring oxygen support

The **final report with results from ACTT-1 RCT (NCT04280705)** was published by Beigel et al [2] in November 2020. In brief, it was a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. Patients (with mild, moderate, or severe Covid-19) were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only. Randomization was stratified by study site and disease severity at enrolment. Patients were considered to have **severe disease** if they required mechanical ventilation, if they required supplemental oxygen, if the oxygen saturation as measured by pulse oximetry (Spo2) was 94% or lower while they were breathing ambient air, or if they had tachypnea (respiratory rate ≥24 breaths per minute).

The primary outcome was the time to recovery, defined as the first day, during the 28 days after enrolment, on which a patient met the criteria for category 1, 2, or 3 on the eight-category ordinal scale. The categories are as follows: 1, not hospitalized and no limitations of activities; 2, not hospitalized, with limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control or other nonmedical reasons); 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (related to Covid-19 or to other medical conditions); 5, hospitalized, requiring any supplemental oxygen; 6, hospitalized, requiring non-invasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 8, death.

The key secondary outcome was clinical status at day 15, as assessed on the ordinal scale. Other secondary outcomes included the time to improvement of one category and of two categories from the baseline ordinal score; clinical status as assessed on the ordinal scale at days 3, 5, 8, 11, 15, 22, and 29; mean change in status on the ordinal scale from day 1 to days 3, 5, 8, 11, 15, 22, and 29; time to discharge or National Early Warning Score of 2 or less (maintained for 24 hours), whichever occurred first; change in the National Early Warning Score from day 1 to days 3, 5, 8, 11, 15, 22, and 29; number of days with supplemental oxygen, with non-invasive ventilation or high-flow oxygen, and with invasive ventilation or ECMO up to day 29 (if these were being used at baseline); the incidence and duration of new oxygen use, of non-invasive ventilation or high-flow oxygen, and of invasive ventilation or ECMO; number of days of hospitalization up to day 29; and mortality at 14 and 28 days after enrolment. Secondary safety outcome measures included grade 3 and 4 adverse events and serious adverse events that occurred during the trial, discontinuation or temporary suspension of infusions, and changes in assessed laboratory values over time.

Pre-specified subgroups were defined according to sex, baseline disease severity (according to stratification criteria and on the basis of the ordinal scale), age (18 to 39 years, 40 to 64 years, or ≥65 years), race, ethnic group, duration of symptoms before randomization (measured as ≤10 days or >10 days, in quartiles, and as the median), site location, and presence of coexisting conditions. To assess the effect of disease severity on treatment benefit (recovery and mortality), post hoc analyses evaluated interactions of efficacy with baseline ordinal score (as a continuous variable).

Patient characteristics at baseline are presented in Table A3 in Appendix 3.

In March 2020, the WHO began a large, simple, international, open-label, randomized trial involving hospital inpatients to evaluate the effects of these four drugs on in-hospital mortality - the **Solidarity Trial** [3]. The trial was adaptive; unpromising drugs could be dropped and others added. Participants were randomly assigned in equal proportions to receive no trial drug or one of the trial drug regimens that was locally available (up to five options; all patients were to receive the local standard of care). In this open-label trial, no placebos were used. The control for a drug were patients assigned to the standard of care at a time and place in which that drug was locally available (except that when interferon was being given only with lopinavir, its controls were patients given only lopinavir). Assignment to the standard of care at a hospital in which more than one trial drug was available would put that patient into the control group for each of those drugs. Hence, there was partial overlap among the four control groups. Each comparison between a trial drug and its control, however, was evenly randomized (in a 1:1 ratio) and unbiased, because both groups were affected equally by differences between countries or hospitals and by time trends in patient characteristics or the standard of care.

The regimen for remdesivir (intravenous) was 200 mg on day 0 and 100 mg on days 1 through 9.

The protocol-specified primary objective was to assess effects on in-hospital mortality (i.e., death during the original hospitalization; follow-up ceased at discharge), regardless of whether death occurred before or after day 28. The only protocol-specified secondary outcomes were the initiation of mechanical ventilation and hospitalization duration. Add-on studies that were led from Canada, France, India, and Norway recorded other outcomes (not reported here). Meta-analyses of the major trial results are based on the inverse-variance–weighted average of $b=\log_e$ rate ratio from each stratum of each trial, with the use of odds ratios when hazard ratios or rate ratios for death were unavailable.

At 405 hospitals in 30 countries, 11,330 adults underwent randomization; 2750 were assigned to receive remdesivir, 954 to hydroxychloroquine, 1411 to lopinavir (without interferon), 2063 to interferon

(including 651 to interferon plus lopinavir), and 4088 to no trial drug. Adherence was 94 to 96% midway through treatment, with 2 to 6% crossover.

Patient characteristics at baseline are presented in Table A5 in Appendix 3.

4.2 Risk of bias/Quality of evidence

Overall **Risk of Bias** for two trials is judged as “some concerns”, and for the other two as “low” [20].

Certainty of evidence are graded as “high” for the outcomes: the incidence of WHO progression score level 7 or above D14-28 and adverse events; as “moderate” for the outcomes: all-cause mortality and for the incidence of WHO progression score (level 6 or above) D14-D28, number of patients with SAEs, [20] the number of patients discharged from hospital within 28 days [19, 21]. Certainty of evidence is graded as “low” for the outcomes: mechanical ventilation; time to clinical improvement; duration of hospitalization; serious adverse events leading to discontinuation [4, 6] and finally, as “very low” for the outcome viral clearance [20]

Details can be found in Table A9 and Table A10 in Appendix 3.

4.3 Results on clinical effectiveness and safety

Details related to two RCTs, Wang et al. 2020 and Spinner et al. 2020 [27, 28] could be found in the original EUnetHTA Report [1].

4.3.1 Summary of Wang and Spinner RCTs

In brief, Wang Y et al. 2020 [1, 13, 28] published results of the first randomised, double-blind, placebo-controlled, multicentre trial, conducted in China (**NCT04257656**), on intravenous remdesivir in adults admitted to hospital with **severe** COVID-19. The study was terminated before attaining the pre-specified sample size (237 of the intended 453 patients were enrolled) because the outbreak of COVID-19 was brought under control in China. Remdesivir treatment was not associated with a statistically significant difference in time to clinical improvement (hazard ratio 1·23 [95% CI 0·87–1·75]); duration of invasive mechanical ventilation; viral load; adverse events.

Spinner et al. 2020 [1, 13, 27] published results from a randomised, open-label, phase 3 trial (**NCT04292730**) performed on 596 hospitalised patients with **moderate** COVID-19 pneumonia (pulmonary infiltrates and room-air oxygen saturation >94%). Patients were randomized in a 1:1:1 ratio to receive a 10-day course of remdesivir (n = 197), a 5-day course of remdesivir (n = 199), or standard care (n = 200). On day 11, patients in the 5-day remdesivir group had statistically significantly higher odds of a better clinical status distribution vs standard care (odds ratio, 1.65; 95% CI, 1.09-2.48; p=0.02), but the difference was of uncertain clinical importance. The clinical status distribution on day 11 between the 10-day remdesivir and standard care groups was not significantly different (p=0.18 by Wilcoxon rank sum test). The odds of improvement in clinical status did not differ significantly between the 10-day remdesivir group and the standard-of-care group (odds ratio, 1.31; 95% CI, 0.88 to 1.95).

There were no significant differences between the 5-day or 10-day remdesivir groups and standard care for any of the exploratory end points—time to 2-point or greater improvement in clinical status, time to 1-point or greater improvement in clinical status, time to recovery, time to modified recovery, and time to discontinuation of oxygen support, duration of oxygen therapy or hospitalization and all-cause mortality at day 28.

The difference in AEs proportions between the 5-day remdesivir group and standard care was not statistically significant (4.8%; 95% CI, –5.2% to 14.7%; p=0.36), but the difference between the 10-day remdesivir group and standard care was significant (12.0%; 95% CI, 1.6%-21.8%; p=0.02). Nausea (10% vs 3%), hypokalemia (6% vs 2%), and headache (5% vs 3%) were more frequent among remdesivir-treated patients compared with standard care. Serious adverse events were less common in the remdesivir groups, but the difference was not statistically significant.

4.3.2 ACTT-1 trial

Beigel et al. 2020 [2] reported final results from ACTT-1 trial, double-blind, randomized, placebo-controlled trial of intravenous remdesivir in 1062 adults hospitalized with Covid-19 (541 assigned to remdesivir and 521 to placebo) (**NCT04280705**).

159 (15.0%) were categorized as having **mild-to-moderate** disease, and 903 (85.0%) were in the **severe** disease stratum. A total of 517 patients in the remdesivir group and 508 in the placebo group completed the trial through day 29, recovered, or died. The median number of days between symptom onset and randomization was 9 (interquartile range, 6 to 12) (Table A3). A total of 957 patients (90.1%) had severe disease at enrolment; 285 patients (26.8%) met category 7 criteria on the ordinal scale, 193 (18.2%) category 6, 435 (41.0%) category 5, and 138 (13.0%) category 4. Eleven patients (1.0%) had missing ordinal scale data at enrolment; all these patients discontinued the study before treatment. During the study, 373 patients (35.6% of the 1048 patients in the as-treated population) received hydroxychloroquine and 241 (23.0%) received a glucocorticoid (Table A4).

Remdesivir group had a median recovery time of 10 days (95% confidence interval [CI], 9 to 11) vs 15 days (95% CI, 13 to 18) among placebo group (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; P<0.001, by a log-rank test). The rate ratio for recovery was largest among patients with a baseline ordinal score of 5 (statistically significant different in favour of remdesivir, rate ratio for recovery, 1.45; 95% CI, 1.18 to 1.79). The Kaplan–Meier estimates of mortality were 6.7% with remdesivir vs 11.9% in placebo group by day 15 (hazard ratio, 0.55; 95% CI, 0.36 to 0.83); 11.4% with remdesivir vs 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). The between group differences in mortality varied considerably according to baseline severity, with the statistically significant difference seen among patients with a baseline ordinal score of 5 (hazard ratio, 0.30; 95% CI, 0.14 to 0.64) (Table A6 and Table A7):

Patients who underwent randomization during the first 10 days after the onset of symptoms had a rate ratio for recovery of 1.37 (95% CI, 1.14 to 1.64), whereas patients who underwent randomization more than 10 days after the onset of symptoms had a rate ratio for recovery of 1.20 (95% CI, 0.94 to 1.52), Figure A2.

Additional Secondary Outcomes

Patients in the remdesivir group had a shorter time to clinical improvement of one or of two categories on the ordinal scale from baseline than patients in the placebo group (one-category improvement: median, 7 vs. 9 days; rate ratio for recovery, 1.23; 95% CI, 1.08 to 1.41; two-category improvement: median, 11 vs. 14 days; rate ratio, 1.29; 95% CI, 1.12 to 1.48) (Table A8).

Patients in the remdesivir group had a shorter time to discharge or to a National Early Warning Score of 2 or lower than those in the placebo group (median, 8 days vs. 12 days; hazard ratio, 1.27; 95% CI, 1.10 to 1.46). The initial length of hospital stay was shorter in the remdesivir group than in the placebo group (median, 12 days vs. 17 days); 5% of patients in the remdesivir group were readmitted to the hospital, as compared with 3% in the placebo group. Among the 913 patients receiving oxygen at enrolment, those in the remdesivir group continued to receive oxygen for fewer days than patients in the placebo group (median, 13 days vs. 21 days), and the incidence of new oxygen use among patients who were not receiving oxygen at enrolment was lower in the remdesivir group than in the placebo group (incidence, 36% [95% CI, 26 to 47] vs. 44% [95% CI, 33 to 57]). For the 193 patients receiving non-invasive ventilation or high-flow oxygen at enrolment, the median duration of use of these interventions was 6 days in both the remdesivir and placebo groups. Among the 573 patients who were not receiving non-invasive ventilation, high-flow oxygen, invasive ventilation, or ECMO at baseline, the incidence of new non-invasive ventilation or high-flow oxygen use was lower in the remdesivir group than in the placebo group (17% [95% CI, 13 to 22] vs. 24% [95% CI, 19 to 30]). Among the 285 patients who were receiving mechanical ventilation or ECMO at enrolment, patients in the remdesivir group received these interventions for fewer subsequent days than those in the placebo group (median, 17 days vs. 20 days), and the incidence of new mechanical ventilation or ECMO use among the 766 patients who were not receiving these interventions at enrolment was lower in the remdesivir group than in the placebo group (13% [95% CI, 10 to 17] vs. 23% [95% CI, 19 to 27]) (Table A8).

Safety Outcomes

In the as-treated population, serious adverse events occurred in 131 of 532 patients (24.6%) in the remdesivir group and in 163 of 516 patients (31.6%) in the placebo group (Table 4.2). There were 47 serious respiratory failure adverse events in the remdesivir group (8.8% of patients), including acute respiratory failure and the need for endotracheal intubation, and 80 in the placebo group (15.5% of patients). No deaths were considered by the investigators to be related to treatment assignment. Grade 3 or 4 adverse events occurred on or before day 29 in 273 patients (51.3%) in the remdesivir group and in 295 (57.2%) in the placebo group; 41 events were judged by the investigators to be related to remdesivir and 47 events to placebo. The most common non-serious adverse events occurring in at least 5% of all patients included decreased glomerular filtration rate, decreased haemoglobin level, decreased lymphocyte count, respiratory failure, anaemia, pyrexia, hyperglycaemia, increased blood creatinine level, and increased blood glucose level. The incidence of these adverse events was generally similar in the remdesivir and placebo groups.

Table 4.2. AE Grade 3 or 4 and SAEs

	Remdesivir **(N=532)**			Placebo **(N=516)**			
Safety outcomes	n	%	95% CI	n	%	95% CI	p-value
Grade 3 or 4 AE	273	51	47.0 to 55.6	295	57	52.8 to 61.5	0.058
SAE	130	24	20.9 to 28.3	163	32	27.7 to 35.7	0.010

Source: [2]
Abbreviations: N=Number of participants in the Treated Population. n=Number of participants in a given treatment group who experienced the specified safety event outcome.
95% CI calculated using C-P/Blaker method.
P-value calculated using Two-Sided Barnard's Exact Test.

4.3.3 WHO SOLIDARITY trial

In the WHO SOLIDARITY trial (**ISRCTN83971151, NCT04315948**), with 2750 patients allocated to remdesivir, majority was in the subgroup with supplemental oxygen at entry - 66.6%, 24.1% without oxygen at entry, and 9.3% already receiving mechanical ventilation [3, 4, 16]. Patient characteristics were well balanced between remdesivir and control group. Interim results showed that death rate ratio was not statisticaly significant different between remdesivir and standard care; 0.95 (0.81-1.11, p=0.50; 301/2743 active vs 303/2708 control). The same was true for the outcomes: initiation of mechanical ventilation among patients not already receiving ventilation and hospitalisation duration. Ventilation was initiated after randomization in 295 patients receiving remdesivir and in 284 receiving its control. In-hospital mortality rate ratios, stratified by age and respiratory support at entry, remdesivir vs its control, by entry characteristics and by steroid use at any time could be found in Figure 4.1. No statistically significant difference was found in any subgroups between remdesivir and control group.

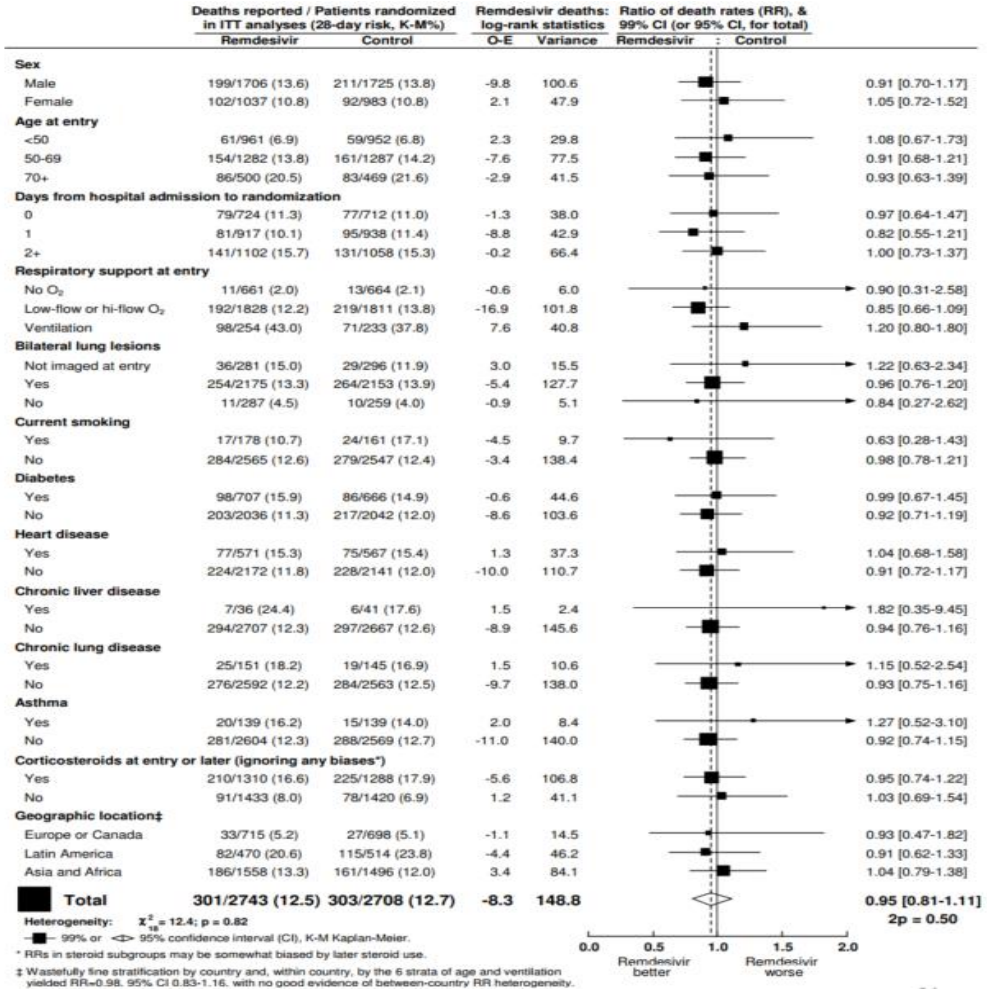

Figure 4.1. SOLIDARITY trial: In-hospital mortality rate ratios, stratified by age and respiratory support at entry, remdesivir vs its control, by entry characteristics and by steroid use at any time*

Source: [3]

Meta-analysis on 4 RCTs provided in this publication [3] shows the mortality results from each out of 4 trials, stratified according to initial respiratory support Figure A3. A rate ratio for death in all 4 RCTs, all severity groups, (remdesivir vs. control) was not statistically significant different; 0.91 (95% CI, 0.79 to 1.05).

Safety outcomes

Adverse events were not published in this preliminary report.

4.3.4 Living Systematic Reviews with Meta-analyses results

According to the current two Living Systematic Reviews with Meta-Analyses (MAs) with high, moderate, low and very low certainty of evidence related to 4 RCTs (Wang, Beigel, Spinner and SOLIDARITY-Remdesivir) [19-21][7], and the WHO meta-analysis [4, 6] on remdesivir compared with standard care/placebo, only three outcomes are statistically significant different in favour of remdesivir: Incidence of WHO progression score (level 6 or above) D14-D28 compared to standard treatment: RR 0.68 (0.55 to 0.85) (moderate certainty of evidence); Incidence of WHO progression score level 7 or above at days

[7] https://covid-nma.com/living_data/index.php

D14-D28 (2 RCTs): RR 0.70, 95% CI 0.59 to 0.82) (high certainty of evidence); and Serious adverse events (3 RCTs): RR 0.74, 95% CI 0.62 to 0.88 (moderate certainty of evidence). Details on other outcomes can be found in the Summary of Findings Table 4.3 and in Table A10 in Appendix 3.

A subgroup analysis of the WHO meta-analysis [4, 6] indicated that remdesivir treatment possibly increased mortality in the critically ill and possibly reduced mortality in the non-severely and severely ill. The panel judged the overall credibility of this subgroup effect (evaluated using the ICEMAN tool) to be insufficient to make subgroup recommendations. The overall low certainty evidence on the benefits and harms of remdesivir, driven by risk of bias and imprecision limitations in the included studies, also contributed to the judgment. For this analysis, critical illness was defined as those requiring invasive or non-invasive ventilation; severe illness as those requiring oxygen therapy (but not meeting critical illness criteria); and non-severe as all others. Patients requiring high-flow nasal cannula represented a small proportion and were characterized as either severe (SOLIDARITY) or critical (ACTT-1, Wang). The analysis focused on within-study subgroup comparisons across the different severities, and therefore the SIMPLE-MODERATE trial could not be included in the subgroup analysis as it only enrolled patients with non-severe COVID-19. Important factors influencing this decision included a lack of *a priori* hypothesized direction of subgroup effect by trial investigators, little or no previously existing supportive evidence for the subgroup finding, and relatively arbitrary cut points used to examine the subgroups of interest. The overall low certainty evidence for the benefits and harms of remdesivir, driven by risk of bias and imprecision limitations, also contributed to the judgment.

Table 4.3. Summary of findings (SoF) table for published RCTs related to effectiveness of Remdesivir (4 RCTs: Wang, Spinner, Beigel, WHO SOLIDARITY trial consortium)

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

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect difference (95% CI)	Number of participants (studies)	Certainty of evidence[e] (GRADE)	Comments
	Risk with Standard care[a]	Risk with Remdesivir					
All-cause Mortality[b]	112 per 1.000	**101 per 1.000** (82 to 125)	**RR 0.90** (0.73 to 1.11)	**11 fewer per 1.000** (from 30 fewer to 12 more)	7345 (4 RCTs) Spinner, 2020 [27]; SOLIDARITY [3], 2020; Beigel, 2020 [2]; Wang, 2020 [28]	⊕⊕⊕◯ MODERATE	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
Clinical improvement D14-D28[b]	759 per 1.000	**805 per 1.000** (751 to 858)	**RR 1.06** (0.99 to 1.13)	**46 more per 1.000** (from 8 fewer to 99 more)	832 (2 RCTs) Spinner, 2020 [27]; Wang, 2020 [28]	⊕⊕⊕◯ MODERATE	Imprecision downgraded by 1 level: due to low number of events and/or participants
WHO progression score (level 6 or above) D14-D28[b]	193 per 1.000	**131 per 1.000** (106 to 164)	**RR 0.68** (0.55 to 0.85)	**62 fewer per 1.000** (from 87 fewer to 29 fewer)	1894 (3 RCTs) Beigel, 2020 [2]; Spinner, 2020 [27]; Wang, 2020 [28]	⊕⊕⊕◯ MODERATE	Risk of bias downgraded by 1 level: some concerns due to deviation from intended intervention and outcome measurement
WHO progression score level 7 or above D14-28[b]	178 per 1.000	**124 per 1.000** (100 to 156)	**RR 0.70** (0.56 to 0.88)	**53 fewer per 1.000** (from 78 fewer to 21 fewer)	1894 (3 RCTs) Beigel, 2020 [2]; Spinner, 2020 [27]; Wang, 2020 [28]	⊕⊕⊕⊕ HIGH	
Viral negative conversion D7[b]	492 per 1.000	**502 per 1.000** (374 to 679)	**RR 1.02** (0.76 to 1.38)	**10 more per 1.000** (from 118 fewer to 187 more)	196 (1 RCT) Wang, 2020 [28]	⊕◯◯◯ VERY LOW	Risk of bias downgraded by 1 level: some concerns with missing data Indirectness downgraded by 1 level: despite a multicenter design this is a single study from a single country, therefore results in this population might not be generalizable to other settings Imprecision downgraded by 1 level: due to wide confidence

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect difference (95% CI)	Number of participants (studies)	Certainty of evidence[e] (GRADE)	Comments
	Risk with Standard care[a]	Risk with Remdesivir					
							interval consistent with the possibility for benefit and the possibility for harm and low number of events
Adverse events[b]	583 per 1.000	**542 per 1.000** (496 to 589)	**RR 0.93** (0.85 to 1.01)	**41 fewer per 1.000** (from 87 fewer to 6 more)	1894 (2 RCTs) Wang, 2020 [28]; Beigel, 2020 [2];	⊕⊕⊕⊕ HIGH	Presume that the adverse event rates, and the corresponding relative risks, are similar across diverse settings; therefore not downgraded for indirectness
Serious adverse events[b]	40 per 1.000	**24 per 1.000** (15 to 38)	**RR 0.60** (0.38 to 0.96)	**16 fewer per 1.000** (from 25 fewer to 2 fewer)	1894 (3 RCTs) Beigel, 2020 [2]; Spinner, 2020 [27]; Wang, 2020 [28]	⊕⊕⊕◯ MODERATE	Presume that the adverse event rates, and the corresponding relative risks, are similar across diverse settings; therefore not downgraded for indirectness Imprecision downgraded by 1 level: few events and a wide confidence interval consistent with the possibility of a benefit and the possibility of no effect.
Serious adverse events leading to discontinuation [c]	15 per 1.000	15 per 1000	**OR 1.00** (0.37 - 3.83)	**0 fewer per 1.000** (from 9 fewer to 40 more)	1894 (3 RCTs) Beigel, 2020 [2]; Spinner, 2020 [27]; Wang, 2020 [28]	⊕⊕◯◯ **Low**	Very serious imprecision
Mechanical ventilation [c]	105 per 1000	95 per 1000	**OR**: **0.89** (0.76 - 1.03)	**10 fewer per 1000** (from 23 fewer to 3 more)	6549 (4 RCTs) Spinner, 2020 [27]; SOLIDARITY [3], 2020; Beigel, 2020 [2]; Wang, 2020 [28]	⊕⊕◯◯ Low	Due to serious risk of bias and serious imprecision

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect difference (95% CI)	Number of participants (studies)	Certainty of evidence[e] (GRADE)	Comments
	Risk with Standard care[a]	Risk with Remdesivir					
Duration of ventilation [c]	14.7 Days mean	13.4 Days mean	Measured by: Scale: lower better	Difference: **MD 1.3 lower** (from 4.1 lower to 1.5 higher)	440 (2 RCTs) Wang, 2020 [28]; Beigel, 2020 [2];	⨁⨁◯◯ Low	Due to very serious imprecision
Time to clinical improvement [c]	11.0 Days mean	9.0 Days mean	Measured by: Scale: lower better	Difference: **MD 2.0 lower** (from 4.2 lower to 0.9 higher)	1882 (3 RCTs) Beigel, 2020 [2]; Spinner, 2020 [27]; Wang, 2020 [28]	⨁⨁◯◯ Low	Due to serious imprecision and serious indirectness
Duration of hospitalization [c]	12.8 Days mean	12.3 Days mean	Measured by: Scale: lower better	Difference: **MD 0.5 lower** (from 3.3 lower to 2.3 higher)	1882 (3 RCTs) Beigel, 2020 [2]; Spinner, 2020 [27]; Wang, 2020 [28]	⨁⨁◯◯ Low	Due to serious imprecision and serious indirectness
Number of patients discharged within 28 days [d]	478 per 1.000	**540 per 1,000** (488 to 593)	**RR 1.13** (1.02 to 1.24)	**62 more per 1.000** (from 10 more to 115 more)	1894 (3 RCTs) Beigel, 2020 [2]; Spinner, 2020 [27]; Wang, 2020 [28]	⨁⨁⨁◯ MODERATE	Downgraded of one level for high risk of performance bias in two studies and unclear risk of selection, attrition and reporting bias in one study

Source: based on publications [2-4, 6, 27, 28]
For an overview of which sources were used to present the certainty of evidence on the specific outcomes, please also see Table 3.1

[a] Background risk in the control group is based on the observed risk in the studies;
[b] outcome data and GRADE assessment from Covid-nma.com ref 19, https://covid-nma.com/living_data/index.php (The evidence profile and summary of findings table were updated on November 17th, 2020);
[C] Outcome data and GRADE assessment from WHO guideline **[4, 6]**
[d] Outcome data and GRADE assessment from the department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy [19, 21], http://deplazio.net/farmacicovid/index.html;
[e] GRADE Working Group grades of evidence: High certainty=we are very confident that the real effect is close to that of the estimated effect; Moderate certainty=we are moderately confident in the effect estimation: the real effect may be close to the estimated effect, but there is a possibility that it is substantially different; Low certainty=our confidence in the effect estimation is limited: the real effect may be substantially different from the estimated effect; Very Low certainty=we have very little confidence in estimating the effect: the actual effect is likely to be substantially different from the estimated one. Risk of bias assessments from https://covid-nma.com/living_data/index.php
Abbreviations: CI= confidence interval; RR=relative risk; OR=odds ratio.

4.4 Ongoing studies

There are several registered ongoing clinical trials evaluating remdesivir alone or in combination with another pharmacotherapy in COVID-19 patients in ClinicalTrials.gov and EUdraCT registers (e.g., with the Janus kinase inhibitor baricitinib in ACTT-2 trial - NCT04401579, interferon beta-1a in ACTT-3 trial – NCT04492475, with cenicriviroc or icatibant or razuprotafib or apremilast in I-SPY_COVID trial – NCT04488081, with infliximab or abatacept in ACTIV-1 IM trial – NCT04593940, with risankizumab in BET-A trial – NCT04583956).

5 DISCUSSION

Evidence on effectiveness and safety of remdesivir versus placebo plus standard care comes from four published RCTs [2, 3, 27, 28].The biggest is the SOLIDARITY trial, in which the number of participants is almost ten times that of ACTT-1 trial [3].

In a meta-analysis of these four trials that included over 7000 patients with COVID-19 of all severities, according to the results of four RCTs with moderate certainty of evidence, remdesivir has no effect on mortality in COVID-19 patients compared to standard treatment [20]. According to the results of three RCTs, remdesivir decreases the incidence of WHO progression score level 6 or above (moderate certainty of evidence), as well as the WHO progression score level 7 or above D14-D28 (high certainty of evidence), compared to standard treatment. According to the results of one RCT with very low certainty of evidence, remdesivir has no effect on viral clearance, compared to standard treatment [20]. According to the results of three RCTs with moderate certainty of evidence, remdesivir increases the number of discharged patients within 28 days compared to standard treatment [19, 21]. According to low certainty of evidence, remdesivir has no effect on outcomes mechanical ventilation (4 RCTs); time to clinical improvement (3 RCTs); duration of hospitalisation (3 RCTs); duration of mechanical ventilation (2 RCTs) and serious adverse events leading to discontinuation (3 RCTs), compared to standard treatment [4, 6]. According to the results of two RCTs with high certainty of evidence, remdesivir does not increase adverse events compared to standard treatment and according to the results of three RCTs with moderate certainty of evidence, remdesivir decreases the number of patients with SAEs compared to standard treatment [20].

A WHO subgroup analysis indicated that remdesivir treatment possibly increased mortality in the critically ill COVID-19 patients and possibly reduced mortality in the non-severely and severely ill but the WHO panel judged the overall credibility of this subgroup effect (evaluated using the ICEMAN tool) to be insufficient to make subgroup recommendations. The overall low certainty evidence on the benefits and harms of remdesivir, driven by risk of bias and imprecision limitations in the included studies, also contributed to the judgment [4, 6]. The WHO panel highlighted that despite the conditional recommendation against remdesivir, they support further enrolment into RCTs evaluating remdesivir, especially to provide higher certainty of evidence for specific subgroups of patients.

After the original report was published [1], on October 22, 2020 the U.S. Food and Drug Administration approved remdesivir for use in adult and paediatric patients 12 years of age and older and weighing at least 40 kilograms (about 88 pounds) for the treatment of COVID-19 requiring hospitalization. Recently, the FDA has also issued an emergency use authorization (EUA) for the Janus kinase inhibitor baricitinib to be used in combination with remdesivir in patients with COVID-19 who require oxygen or ventilatory support [17].

According to the currently published scientific evidence, the effect of remdesivir on acute kidney injury compared to standard treatment should be interpreted with caution due to low certainty of evidence (two RCTs, Odds ratio: 0.85 (95% CI 0.51 - 1.41); 8 fewer per 1000 (95% CI 27 fewer - 21 more)), compared to standard treatment [4, 29]. On October 02, 2020 EMA announced that EMA’s safety committee (PRAC) has started a review of a safety signal to assess reports of acute kidney injury in some patients with COVID-19 taking remdesivir [16].

Recently, the WHO panel made a conditional recommendation against the use of remdesivir in hospitalized patients with COVID-19, regardless of disease severity [4, 6], with new information and recommendations on remdesivir after publication of results from the WHO SOLIDARITY trial [3].

When moving from evidence to the conditional recommendation against the use of remdesivir in hospitalized patients with COVID-19, the panel emphasized the evidence suggesting no important effect on mortality, need for mechanical ventilation, time to clinical improvement, and other patient important outcomes. Considering the low or very low certainty evidence for all outcomes, the panel concluded that the evidence did not prove that remdesivir has no benefit; rather, there is no evidence based on currently available data that it does improve patient-important outcomes. The panel placed low value on small and uncertain benefits in the presence of the remaining possibility of important harms. In addition, the panel considered contextual factors such as resources, feasibility, acceptability and equity for countries and health care systems [4, 6].

The US COVID-19 Treatment Guidelines Panel issued new recommendations on pharmacological treatment for patients with COVID-19 (as of December 3, 2020) [5]: Remdesivir is recommended for use in hospitalized patients who require supplemental oxygen. However, it is not routinely recommended for patients who require mechanical ventilation due to the lack of data showing benefit at this advanced stage of the disease.

Limitations

In ACTT-1 trial the primary endpoint was initially defined as the difference in clinical status using an ordinal scale, but was subsequently changed to the time to recovery. However, as the treatment effect on the ordinal scale (the initial primary endpoint) was statistically significant, the change in the definition of the primary endpoint appears not to be a threat to the internal validity of the study [2, 30]. Some study personnel were unblinded to treatment allocation (i.e., the pharmacist who prepared the study drug and the nurse who administered the treatment). But outcomes were assessed by blinded study personnel. Due to shortage of placebo at some sites, normal saline was used as a replacement, but efforts were made to maintain the blinding by administration of study drugs in opaque bags and tubing. Baseline information on comorbidities was missing or incomplete for 14 (1.3%) patients. The use of co-interventions was permitted according the local protocol. More patients in the placebo group received antibiotics (85.9% vs 78.9%), vasopressors (37.8% vs 27.6%), and corticosteroids (24.4% vs 21.6%). More patients in the placebo group required mechanical invasive ventilation (42.6% vs 32.5%), suggesting that patients in the placebo group might suffer from more severe disease than patients in the remdesivir group [2, 30].

SOLIDARITY trial also has some limitations. Full study report is not yet published. In the preliminary report with interim results adverse events were not reported. The Solidarity trial has one possible source of heterogeneity not normally encountered in explanatory trials — variation within and between countries in the standard of care and in the burden of disease in patients who arrive at hospitals. This could be a limitation for internal validity to demonstrate efficacy (the goal of explanatory trials), but also could represent the strength of the study, conducted in real word environments, to demonstrate comparative effectiveness [31, 32]. Due to open label design, some secondary outcomes like initiation of mechanical ventilation could be biased. Hospitalisation duration could have been influenced by the study's open-label design as management strategies impacting these outcomes are at the discretion of the investigator, who was aware of treatment assignment. This outcome may also be influenced by resource availability. Some baseline comorbidities were not reported, like hypertension and obesity, which could impact the generalisability of results. The same is true for the timing of symptoms duration before treatment initiations. Detailed data on disease severity was not collected. Longer-term follow up data are not known yet [3, 33-35].

These four RCT had patients included with varying severity of COVID-19 and disease severity was not consistent with WHO definitions of disease severity for COVID-19, specifically in two RCTs in which severe stratum included also patients with critical COVID-19 (44.1% of patients in Beigel (ACTT-1) trial received invasive mechanical ventilation at baseline and 16.1% in Wang RCT; 8.9% of patients in SOLIDARITY) trial).

Evidence gaps

Uncertainties for remdesivir are related to effects on critical outcomes of interest, particularly those that impact resource allocation (the need for mechanical ventilation, duration of mechanical ventilation, and duration of hospitalisation); specific subgroups, such as different severities of illness, different time (days) since onset of illness, children and older adults, pregnant women, duration of therapy; long term outcomes (such as 1-year endpoint) examining mortality or long term quality of life; long term safety and rare but important side effects; patient-reported outcomes such as symptom burden; outcomes when used in combination with other agents such as, but not limited to, corticosteroids; Impact on viral shedding, viral clearance, patient infectivity [3, 30, 33-35]

None of the included RCTs enrolled children, and although older people were included in the trials, their outcomes were not reported separately. The applicability of this recommendation to children is currently uncertain. Further enrolment of patients is needed into RCTs evaluating remdesivir, especially to provide higher certainty of evidence for specific subgroups of patients. There remains uncertainty related to the

optimal dosing of remdesivir in paediatric patients, pregnant patients, and patients with renal or hepatic impairment [3, 30, 33-35] (Table A11, Appendix 4).

Treatment with an antiviral drug alone is not likely to be sufficient for all patients. There are several registered ongoing clinical trials evaluating remdesivir alone or in combination with another pharmacotherapy in COVID-19 patients in ClinicalTrials.gov and EUdraCT registers. The availability of full clinical study reports for completed trials to allow open and robust scrutiny of the trials is needed.

6 SUMMARY OF CLINICAL EFFECTIVENESS AND SAFETY WITH CONCLUSION

Please find below a summary of the effectiveness and safety evidence from the four included RCTs.

6.1 Clinical effectiveness

6.1.1 All-cause mortality

- Mixed population (moderate to critical COVID-19)

According to the results of four RCTs [2, 3, 27, 28] with moderate certainty of evidence, remdesivir has no effect on all-cause mortality in COVID-19 patients; RR 0.90 (0.73 to 1.11); absolute effect estimate 11 fewer per 1.000 (from 30 fewer to 12 more).

6.1.2 Clinical improvement D14-D28

- Mixed population (moderate to severe COVID-19)

According to the results of two RCTs [27, 28], remdesivir has no effect on clinical improvement D14-D28 (moderate certainty of evidence): RR 1.06 (0.99 to 1.13); 46 more per 1.000 (from 8 fewer to 99 more).

6.1.3 Incidence of WHO progression score

- Mixed population (moderate to critical COVID-19)

According to the results of three RCTs [2, 27, 28], with moderate certainty of evidence, remdesivir decreases the incidence of WHO progression score (level 6 or above) D14-D28 compared to standard treatment: RR 0.68 (0.55 to 0.85); 62 fewer per 1.000 (from 87 fewer to 29 fewer)

According to the results of three RCTs [2, 27, 28], with high certainty of evidence, remdesivir decreases the incidence of WHO progression score level 7 or above D14-28 compared to standard treatment. RR 0.70 (0.56 to 0.88); 53 fewer per 1.000 (from 78 fewer to 21 fewer).

6.1.4 Viral clearance

- Severe COVID-19

According to the results of one RCT [28], with very low certainty of evidence, remdesivir has no effect on viral clearance compared to standard treatment: RR 1.02 (0.76 to 1.38); 10 more per 1.000 (from 118 fewer to 187 more).

6.1.5 Number of patients discharged within 28 days

- Mixed population (moderate to critical COVID-19)

According to the results of three RCTs [2, 27, 28], remdesivir increases the number of discharged patients compared to standard treatment (moderate certainty of evidence); RR 1.13 (1.02 to 1.24); absolute effect estimate 62 more per 1.000 (from 10 more to 115 more).

6.1.6 Mechanical ventilation; Time to clinical improvement; Duration of ventilation; Duration of hospitalization

According to low certainty of evidence, remdesivir has no effect on outcomes Mechanical ventilation (4 RCTs [2, 3, 27, 28], Odds ratio: 0.89 (95% CI 0.76 - 1.03); 10 fewer per 1000 (95% CI 23 fewer - 3 more); Time to clinical improvement (3 RCTs [2, 27, 28], 11.0 Days mean vs 9.0 Days mean; MD 2.0 lower (95% CI 4.2 lower - 0.9 higher); Duration of ventilation (2 RCTs, [2, 28]), 14.7 Days mean vs 13.4 Days mean; MD 1.3 lower (95% CI 4.1 lower – 1.5 higher), and Duration of hospitalization (3 RCTs [2, 27, 28], 12.8 Days mean vs 12.3 Days mean; MD 0.5 lower (95% CI 3.3 lower - 2.3 higher), compared to standard treatment.

6.2 Safety

6.2.1 Number of patients with adverse events and serious adverse events

Number of patients with adverse events

- Mixed population (moderate to critical COVID-19)

According to the results of two RCTs[2, 28], remdesivir has no effect on increase of adverse events compared to standard treatment (high certainty of evidence).

Number of patients with serious adverse events

- Mixed population (moderate to critical COVID-19)

According to the results of three RCTs [2, 27, 28], remdesivir decreases the number of patients with SAEs compared to standard treatment (moderate certainty of evidence).

Serious adverse events leading to discontinuation

Remdesivir has no effect on Serious adverse events leading to discontinuation (three RCTs [2, 27, 28], Odds ratio: 1.00 (95% CI 0.37 - 3.83); 0 fewer per 1000 (95% CI 9 fewer - 40 more), compared to standard treatment (low certainty of evidence).

6.3 Scientific conclusion

Based on the living synthesis of currently available scientific evidence from 4 RCTs:

- According to the results of four RCTs with moderate certainty of evidence, remdesivir has no effect on mortality in COVID-19 patients compared to standard treatment;
- According to the results of three RCTs, remdesivir decreases the incidence of WHO progression score level 6 or above (moderate certainty of evidence), as well as the WHO progression score level 7 or above D14-D28 (high certainty of evidence), compared to standard treatment;
- According to the results of one RCT with very low certainty of evidence, remdesivir has no effect on viral clearance, compared to standard treatment;
- According to the results of three RCTs with moderate certainty of evidence, remdesivir increases the number of discharged patients within 28 days compared to standard treatment;
- According to low certainty of evidence, remdesivir has no effect on outcomes mechanical ventilation (4 RCTs); time to clinical improvement (3 RCTs); duration of ventilation (2RCTs); duration of hospitalisation (3 RCTs) and serious adverse events leading to discontinuation (3 RCTs), compared to standard treatment;
- According to the results of two RCTs with high certainty of evidence, remdesivir does not increase adverse events compared to standard treatment;
- According to the results of three RCTs with moderate certainty of evidence, remdesivir decreases the number of patients with SAEs compared to standard treatment.

Evidence gaps:

- Results on some short or long-term effectiveness outcomes are still awaited: frequency of ICU admission; time to ICU admission; length of ICU stay; frequency of multiple organ dysfunction syndrome/acute respiratory distress syndrome/shock/organ failure; duration of invasive mechanical ventilation or ECMO; pulmonary function; health-related quality of life, as well for other short term and long-term safety outcomes on appropriate patient sample size;
- Further RCTs examining remdesivir alone, or in combination with other investigational drugs, for treatment of COVID-19 patients are under way. The availability of full clinical study reports for completed trials to allow open and robust scrutiny of the trials is needed;
- Update of this document is envisaged after new evidence is available.

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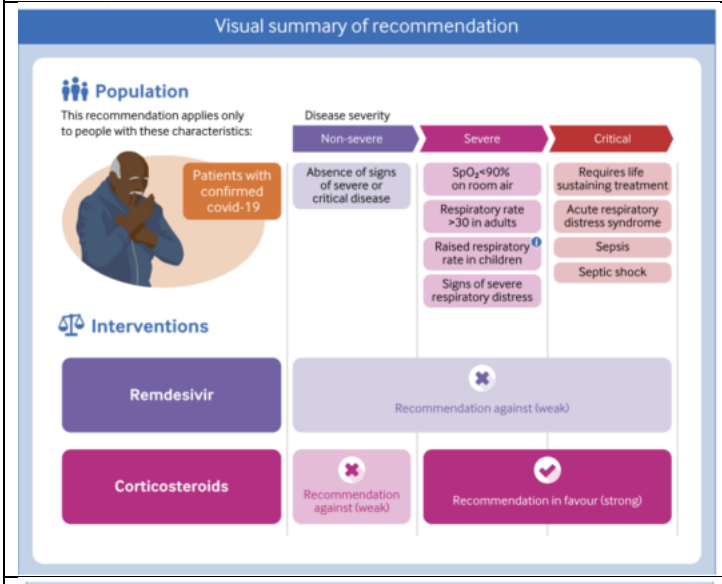
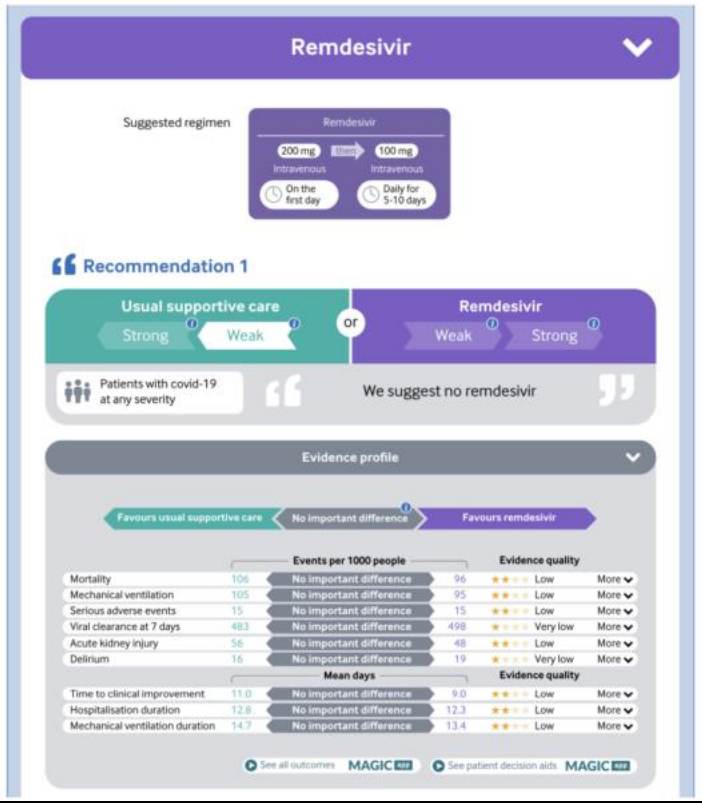
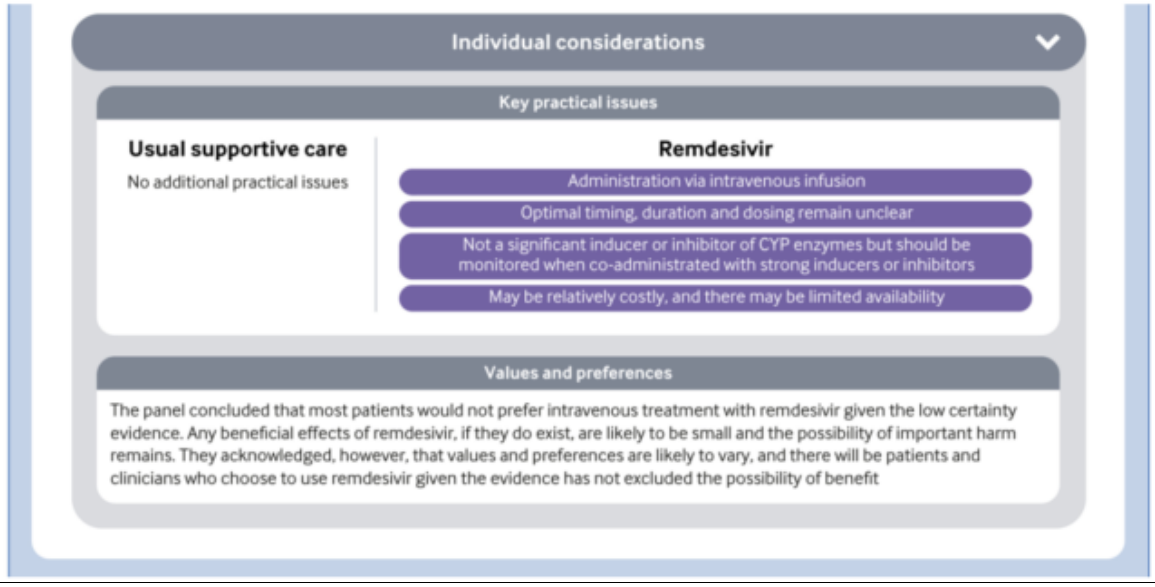
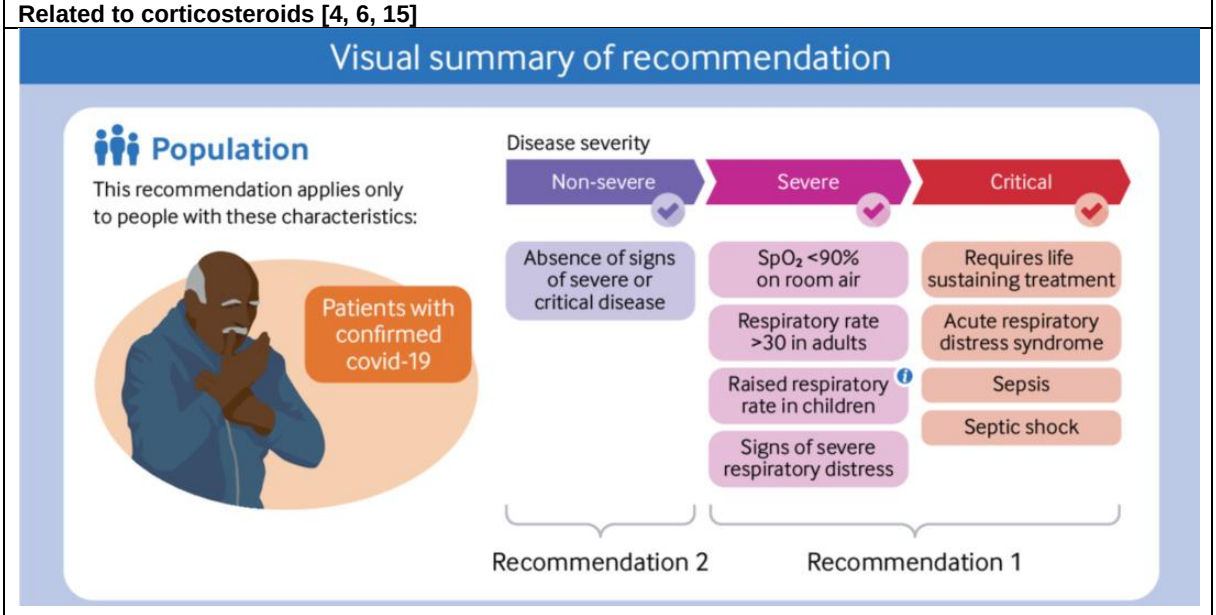
APPENDIX 1: CLINICAL GUIDELINES FOR MANAGEMENT

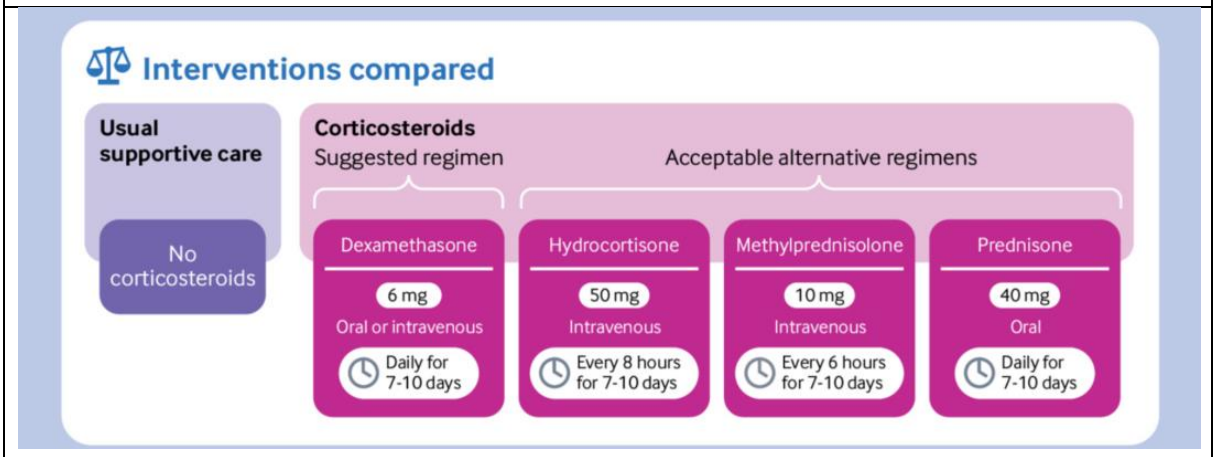
Table A1. Visual summary of recommendations on remdesivir and dexamethasone (corticosteroids) treatment according to COVID-19 severity: WHO guideline and US NIH Guideline

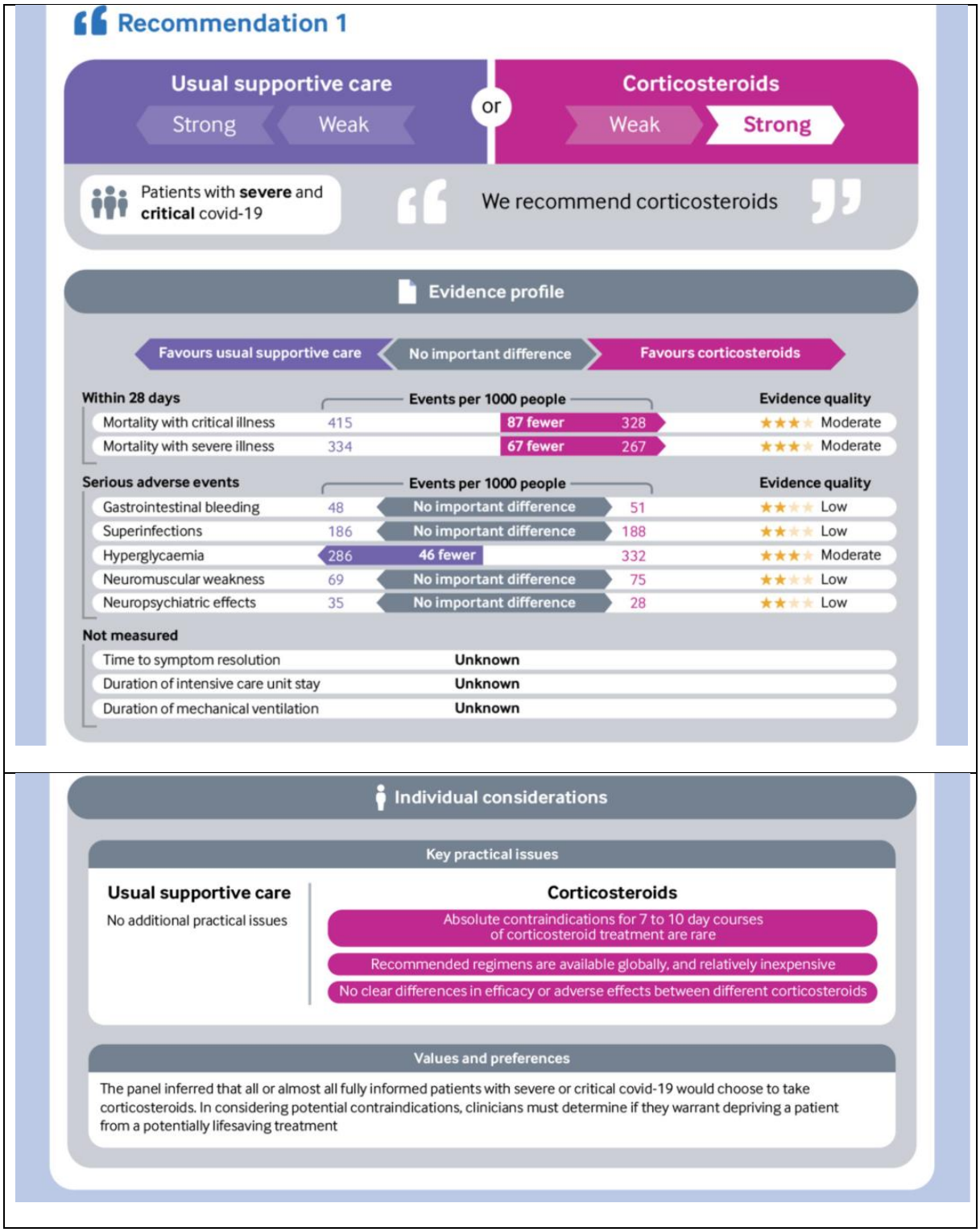
WHO guideline [4, 6]	
Related to remdesivir	
	
	

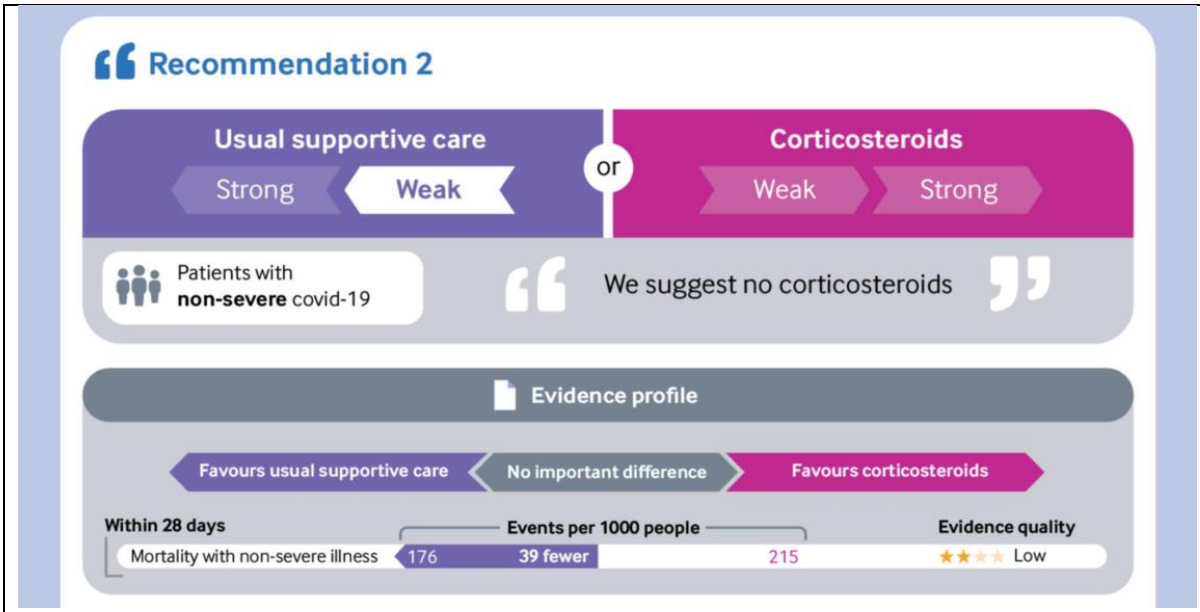


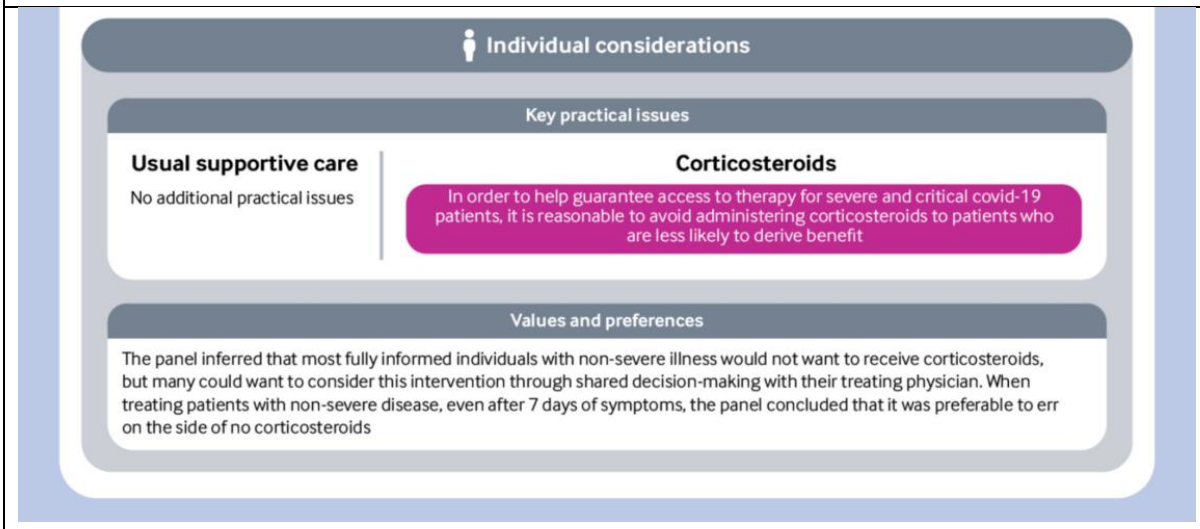
Related to corticosteroids [4, 6, 15]



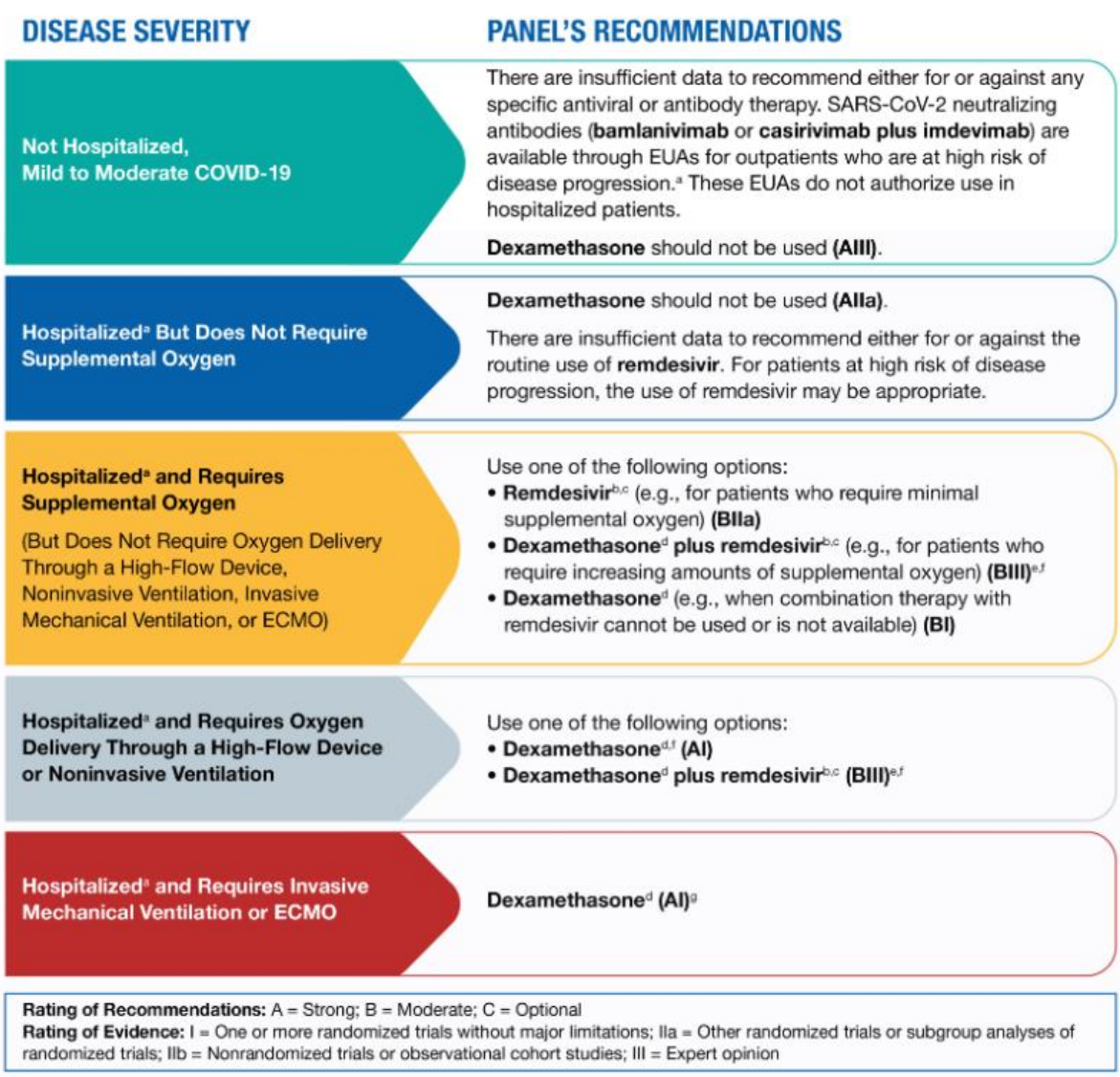



Recommendation 1
Usual supportive care
Strong
Weak
or
Corticosteroids
Weak
Strong
Patients with severe and critical covid-19
We recommend corticosteroids
Evidence profile
Favours usual supportive care
No important difference
Favours corticosteroids
Within 28 days
Events per 1000 people
Evidence quality
Mortality with critical illness 415 87 fewer 328 Moderate
Mortality with severe illness 334 67 fewer 267 Moderate
Serious adverse events
Events per 1000 people
Evidence quality
Gastrointestinal bleeding 48 No important difference 51 Low
Superinfections 186 No important difference 188 Low
Hyperglycaemia 286 46 fewer 332 Moderate
Neuromuscular weakness 69 No important difference 75 Low
Neuropsychiatric effects 35 No important difference 28 Low
Not measured
Time to symptom resolution Unknown
Duration of intensive care unit stay Unknown
Duration of mechanical ventilation Unknown
Individual considerations
Key practical issues
Usual supportive care
No additional practical issues
Corticosteroids
Absolute contraindications for 7 to 10 day courses of corticosteroid treatment are rare
Recommended regimens are available globally, and relatively inexpensive
No clear differences in efficacy or adverse effects between different corticosteroids
Values and preferences
The panel inferred that all or almost all fully informed patients with severe or critical covid-19 would choose to take corticosteroids. In considering potential contraindications, clinicians must determine if they warrant depriving a patient from a potentially lifesaving treatment


Recommendation 2
Usual supportive care
Strong
Weak
or
Corticosteroids
Weak
Strong
Patients with non-severe covid-19
We suggest no corticosteroids
Evidence profile
Favours usual supportive care
No important difference
Favours corticosteroids
Within 28 days
Events per 1000 people
Evidence quality
Mortality with non-severe illness
176
39 fewer
215
Low


Individual considerations
Key practical issues
Usual supportive care
No additional practical issues
Corticosteroids
In order to help guarantee access to therapy for severe and critical covid-19 patients, it is reasonable to avoid administering corticosteroids to patients who are less likely to derive benefit
Values and preferences
The panel inferred that most fully informed individuals with non-severe illness would not want to receive corticosteroids, but many could want to consider this intervention through shared decision-making with their treating physician. When treating patients with non-severe disease, even after 7 days of symptoms, the panel concluded that it was preferable to err on the side of no corticosteroids

US NIH guideline [5]



DISEASE SEVERITY	PANEL'S RECOMMENDATIONS
Not Hospitalized, Mild to Moderate COVID-19	There are insufficient data to recommend either for or against any specific antiviral or antibody therapy. SARS-CoV-2 neutralizing antibodies (**bamlanivimab** or **casirivimab plus imdevimab**) are available through EUAs for outpatients who are at high risk of disease progression.[a] These EUAs do not authorize use in hospitalized patients. **Dexamethasone** should not be used **(AIII)**.
Hospitalized[a] But Does Not Require Supplemental Oxygen	**Dexamethasone** should not be used **(AIIa)**. There are insufficient data to recommend either for or against the routine use of **remdesivir**. For patients at high risk of disease progression, the use of remdesivir may be appropriate.
Hospitalized[a] and Requires Supplemental Oxygen (But Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)	Use one of the following options: • **Remdesivir**[b,c] (e.g., for patients who require minimal supplemental oxygen) **(BIIa)** • **Dexamethasone**[d] **plus remdesivir**[b,c] (e.g., for patients who require increasing amounts of supplemental oxygen) **(BIII)**[e,f] • **Dexamethasone**[d] (e.g., when combination therapy with remdesivir cannot be used or is not available) **(BI)**
Hospitalized[a] and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	Use one of the following options: • **Dexamethasone**[d,f] **(AI)** • **Dexamethasone**[d] **plus remdesivir**[b,c] **(BIII)**[e,f]
Hospitalized[a] and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[d] **(AI)**[g]

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials without major limitations; IIa = Other randomized trials or subgroup analyses of randomized trials; IIb = Nonrandomized trials or observational cohort studies; III = Expert opinion

[a] See the Panel's statements on the FDA EUAs for bamlanivimab and casirivimab plus imdevimab. These EUAs do not authorize use in hospitalized patients.
[b] The remdesivir dose is 200 mg IV for one dose, followed by 100 mg IV once daily for 4 days or until hospital discharge (unless the patient is in a health care setting that can provide acute care that is similar to inpatient hospital care). Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.
[c] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.
[d] The dexamethasone dose is 6 mg IV or PO once daily for 10 days or until hospital discharge. If dexamethasone is not available, equivalent doses of other corticosteroids, such as prednisone, methylprednisolone, or hydrocortisone, may be used. See the Corticosteroids section for more information.
[e] The combination of dexamethasone and remdesivir has not been studied in clinical trials.
[f] In the rare circumstances where corticosteroids cannot be used, baricitinib plus remdesivir can be used **(BIIa)**. The FDA has issued an EUA for baricitinib use in combination with remdesivir. The dose for baricitinib is 4 mg PO once daily for 14 days or until hospital discharge.
[g] The combination of dexamethasone and remdesivir may be considered for patients who have recently been intubated **(CIII)**. Remdesivir alone **is not recommended**.

Key: ECMO = extracorporeal membrane oxygenation; EUA = Emergency Use Authorization; FDA = Food and Drug Administration; IV = intravenous; the Panel = the COVID-19 Treatment Guidelines Panel; PO = orally; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2

APPENDIX 2: LITERATURE SEARCH AND FLOW-DIAGRAMS FOR RCTS

Table A2. Search strategy to identify randomised controlled studies

Database	URL	Search line / Search terms	Date of search
Pubmed	pubmed.ncbi.nlm.nih.gov	1. (((((("Coronavirus"[Mesh]) OR (coronavirus*[Title/Abstract] OR coronovirus*[Title/Abstract] OR coronavirinae*[Title/Abstract] OR Coronavirus*[Title/Abstract] OR Coronovirus*[Title/Abstract] OR Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR Huanan[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR 2019nCoV[Title/Abstract] OR nCoV2019[Title/Abstract] OR "nCoV-2019"[Title/Abstract] OR "COVID-19"[Title/Abstract] OR COVID19[Title/Abstract] OR "CORVID-19"[Title/Abstract] OR CORVID19[Title/Abstract] OR "WN-CoV"[Title/Abstract] OR WNCoV[Title/Abstract] OR "HCoV-19"[Title/Abstract] OR HCoV19[Title/Abstract] OR CoV[Title/Abstract] OR "2019 novel*"[Title/Abstract] OR Ncov[Title/Abstract] OR "n-cov"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR SARSCov19[Title/Abstract] OR "SARS-Cov19"[Title/Abstract] OR "SARSCov-19"[Title/Abstract] OR "SARS-Cov-19"[Title/Abstract] OR Ncovor[Title/Abstract] OR Ncorona*[Title/Abstract] OR Ncorono*[Title/Abstract] OR NcovWuhan*[Title/Abstract] OR NcovHubei*[Title/Abstract] OR NcovChina*[Title/Abstract] OR NcovChinese*[Title/Abstract])) OR ((((respiratory*[Title/Abstract] AND (symptom*[Title/Abstract] OR disease*[Title/Abstract] OR illness*[Title/Abstract] OR condition*))[Title/Abstract] OR "seafood market*"[Title/Abstract] OR "food market*")[Title/Abstract] AND (Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR China*[Title/Abstract] OR Chinese*[Title/Abstract] OR Huanan*))[Title/Abstract])) OR ("severe acute respiratory syndrome*")) OR ((corona*[Title/Abstract] OR corono*)[Title/Abstract] AND (virus*[Title/Abstract] OR viral*[Title/Abstract] OR virinae*)[Title/Abstract])) AND (((((((randomized controlled trial) OR (controlled clinical trial)) OR (randomized [tiab])) OR (placebo [tiab])) OR (clinical trials as topic [mesh: noexp])) OR (randomly [tiab])) OR (trial [ti]))) NOT (animals [mh] NOT humans [mh]) AND (2019/10/01:2020[dp])	10/12/2020

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	1. exp coronavirus/ 2. ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ti,ab,kw. 3. (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw. 4. (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. 5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw. 6. "severe acute respiratory syndrome*".ti,ab,kw. 7. or/1-6 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. random*.ab. 11. placebo.ab. 12. clinical trials as topic.sh. 13. random allocation.sh. 14. trial.ti. 15. or/8-14 16. exp animals/ not humans.sh. 17. 15 not 16 18. 7 and 17 19. limit 18 to yr="2019 -Current"	10/12/2020
OVID EMBASE	ovidsp.dc2.ovid.com	1. exp Coronavirinae/ or exp Coronavirus/ 2. exp Coronavirus infection/ 3. ((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) adj4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and (wuhan or china or chinese)) or "Corona virinae19" or "Corona virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2").ti,ab,kw. 4. or/1-3 5. Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/ 6. (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind$3 or mask$3)) or (random$ adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab. 7. 5 or 6 8. 4 and 7 9. limit 8 to yr="2019 -Current"	10/12/2020

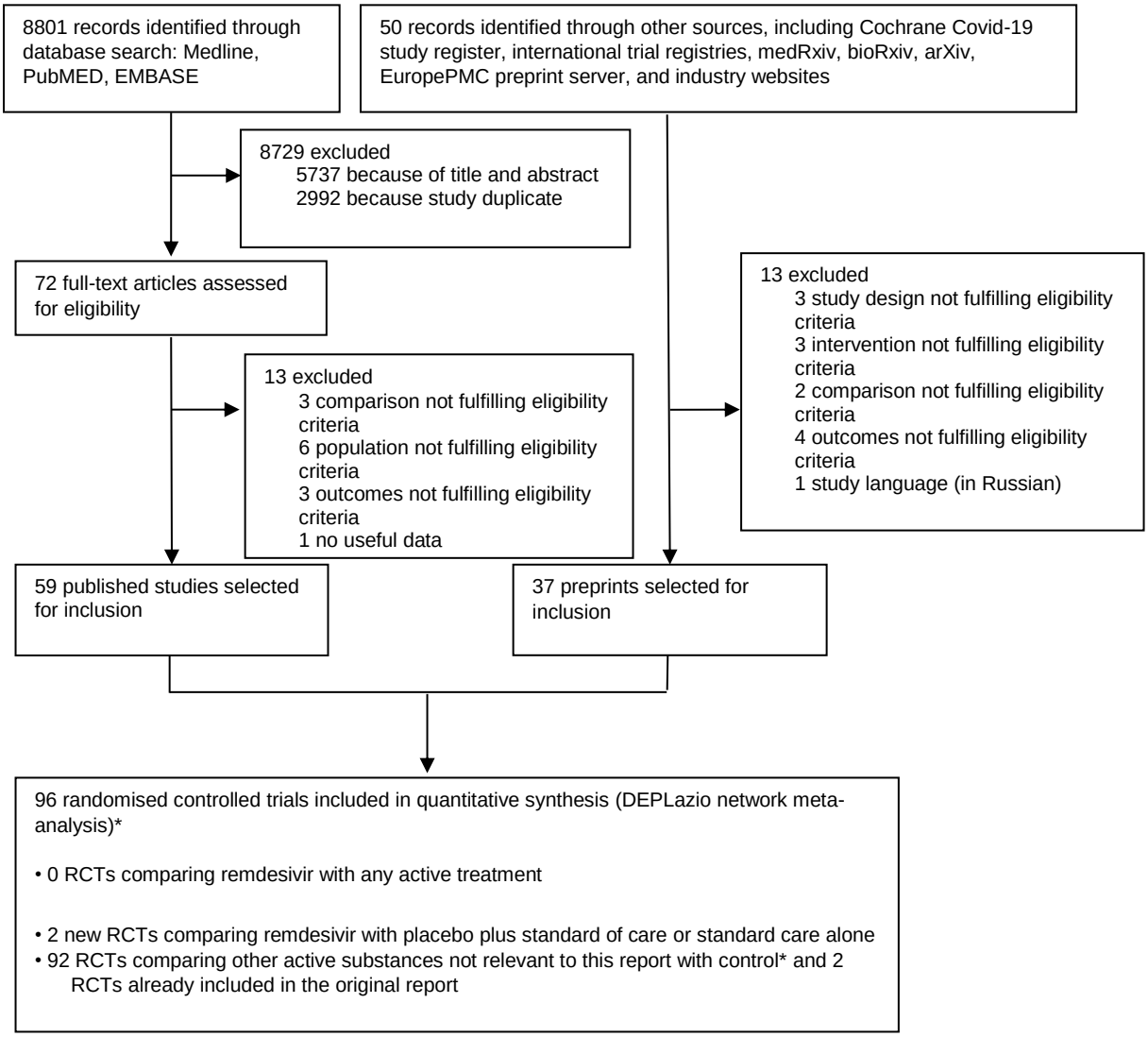


Figure A1. Flow diagram depicting the selection process of RCTs

[a] The selection process was part of an external project, see https://www.deplazio.net/farmacicovid and Prospero ID CRD42020176914.
Abbreviations: RCT=randomised controlled trial.

APPENDIX 3: TABLES AND FIGURES RELATED TO PATIENTS CHARACTERISTICS, EFFECTIVENESS OUTCOMES, RISK OF BIAS AND CERTAINTY OF EVIDENCE

In this appendix, additional tables and figures related to patients characteristics, effectiveness outcomes, risk of bias and certainty of evidence are provided.

Patients characteristics

Table A3. Patients characteristics at baseline*, ACTT-1 trial

Characteristic	All (N=1062)	Remdesivir (N=541)	Placebo (N=521)
Age — yr	58.9±15.0	58.6±14.6	59.2±15.4
Male sex — no. (%)	684 (64.4)	352 (65.1)	332 (63.7)
Race or ethnic group — no. (%)†			
American Indian or Alaska Native	7 (0.7)	4 (0.7)	3 (0.6)
Asian	135 (12.7)	79 (14.6)	56 (10.7)
Black or African American	226 (21.3)	109 (20.1)	117 (22.5)
White	566 (53.3)	279 (51.6)	287 (55.1)
Hispanic or Latino — no. (%)	250 (23.5)	134 (24.8)	116 (22.3)
Median time (IQR) from symptom onset to randomization — days‡	9 (6–12)	9 (6–12)	9 (7–13)
No. of coexisting conditions — no. /total no. (%)‡			
None	194/1048 (18.5)	97/531 (18.3)	97/517 (18.8)
One	275/1048 (26.2)	138/531 (26.0)	137/517 (26.5)
Two or more	579/1048 (55.2)	296/531 (55.7)	283/517 (54.7)
Coexisting conditions — no./total no. (%)			
Type 2 diabetes	322/1051 (30.6)	164/532 (30.8)	158/519 (30.4)
Hypertension	533/1051 (50.7)	269/532 (50.6)	264/519 (50.9)
Obesity	476/1049 (45.4)	242/531 (45.6)	234/518 (45.2)
Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	138 (13.0)	75 (13.9)	63 (12.1)
5. Hospitalized, requiring supplemental oxygen	435 (41.0)	232 (42.9)	203 (39.0)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	193 (18.2)	95 (17.6)	98 (18.8)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	285 (26.8)	131 (24.2)	154 (29.6)
Baseline score missing	11 (1.0)	8 (1.5)	3 (0.6)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. IQR denotes interquartile range, and ECMO extracorporeal membrane oxygenation.
† Race and ethnic group were reported by the patients.
‡ Data on symptom onset were missing for 3 patients; data on coexisting conditions were missing for 11 patients and were incomplete for 3 patients.
Source: [2]

Table A4. Patients' Status and Treatments Received - As-Treated Population, ACTT-1 trial

	All (N=1048)	Remdesivir (N=532)	Placebo (N=516)
Highest level of respiratory support – no. (%)			
Extracorporeal membrane oxygenation	26 (2.5)	11 (2.1)	15 (2.9)
Invasive mechanical ventilation	393 (37.5)	173 (32.5)	220 (42.6)
Non-invasive mechanical ventilation	204 (19.5)	106 (19.9)	98 (19.0)
Other oxygen delivery device	342 (32.6)	194 (36.5)	148 (28.7)
None	83 (7.9)	48 (9.0)	35 (6.8)
Treatments during study – no. (%)			
Antibiotics	863 (82.3)	420 (78.9)	443 (85.9)
Vasopressors	342 (32.6)	147 (27.6)	195 (37.8)
Corticosteroids	241 (23.0)	115 (21.6)	126 (24.4)
Other anti-inflammatory medications	79 (7.5)	42 (7.9)	37 (7.2)
Monoclonal antibodies targeting cytokines	50 (4.8)	23 (4.3)	26 (5.0)
Other biologic therapies	34 (3.2)	21 (3.9)	13 (2.5)
Hydroxychloroquine	373 (35.6)	184 (34.6)	189 (36.6)
Other putative SARS-CoV-2 medications	22 (2.1)	8 (1.5)	14 (2.7)
Other antiviral medications	18 (1.7)	10 (1.9)	8 (1.6)

Source: [2]

Table A5. Baseline characteristics of patients in SOLIDARITY trial, remdesivir arm

Variable	Remdesivir vs. Its Control	
	Active (N=2743)	Control (N=2708)
Entry characteristics		
Age		
<50 yr	961	952
50–69 yr	1282	1287
≥70 yr	500	469
Respiratory support		
No supplemental oxygen at entry	661	664
Supplemental oxygen at entry	1828	1811
Already receiving ventilation	254	233
Lesions in both lungs		
No	287	259
Yes	2175	2153
Not imaged at entry	281	296
Previous days in the hospital		
0	724	712
1	917	938
≥2	1102	1058
Geographic region		
Europe and Canada¶	715	698
Latin America‖	470	514
Asia and Africa**	1558	1496
Other characteristics		
Male sex	1706	1725
Current smoker	178	161
Coexisting conditions		
Diabetes	707	666
Heart disease	571	567
Chronic lung disease	151	145
Asthma	139	139
Chronic liver disease	36	41
Adherence to assigned treatment		
Percent taking trial drug midway through scheduled duration††‡‡	96	2
Percent ever reported as discharged who were still in the hospital at various times††		
On day 7	69	59
On day 14	22	19
On day 21	9	8

¶ Countries in Europe were Albania, Austria, Belgium, Finland, France, Ireland, Italy, Lithuania, Luxembourg, North Macedonia, Norway, Spain, and Switzerland.
‖ Countries included Argentina, Brazil, Colombia, Honduras, and Peru.
** Countries included Egypt, India, Indonesia, Iran, Kuwait, Lebanon, Malaysia, Pakistan, the Philippines, Saudi Arabia, and South Africa.
†† Percentage of patients (rather than number of patients) is shown for this variable.
‡‡ Adherence was calculated only among patients who died or were discharged alive and was defined as the percentage of patients who were taking the trial drug midway through its scheduled duration (or midway through the time from entry to death or discharge, if this was shorter)
Source: [3]

Effectiveness results – figures and tables

Table A6. Effectiveness outcomes - Overall and According to Score on the Ordinal Scale in the Intention-to-Treat Population*, ACTT-1 trial

	Overall		Ordinal Score at Baseline							
			4		5		6		7	
	Remdesivir (N=541)	Placebo (N=521)	Remdesivir (N=75)	Placebo (N=63)	Remdesivir (N=232)	Placebo (N=203)	Remdesivir (N=95)	Placebo (N=98)	Remdesivir (N=131)	Placebo (N=154)
Recovery										
No. of recoveries	399	352	73	58	206	156	57	61	63	77
Median time to recovery (95% CI) — days	10 (9–11)	15 (13–18)	5 (4–6)	6 (4–7)	7 (6–8)	9 (7–10)	15 (10– 27)	20 (14– 26)	29 (24–NE)	28 (24–NE)
Rate ratio (95% CI)†	1.29 (1.12–1.49 [P<0.001]		1.29 (0.91–1.83)		1.45 (1.18–1.79)		1.09 (0.76–1.57)		0.98 (0.70–1.36)	
Mortality through day 14‡										
Hazard ratio for data through day 15 (95% CI)	0.55 (0.36–0.83)		0.42 (0.04–4.67)		0.28 (0.12–0.66)		0.82 (0.40–1.69)		0.76 (0.39–1.50)	
No. of deaths by day 15	35	61	1	2	7	21	13	17	14	21
Kaplan–Meier estimate of mortality by day 15 — % (95% CI)	6.7 (4.8–9.2)	11.9 (9.4–15.0)	1.3 (0.2–9.1)	3.2 (0.8–12.1)	3.1 (1.5–6.4)	10.5 (7.0–15.7)	14.2 (8.5–23.2)	17.3 (11.2–26.4)	10.9 (6.6–17.6)	13.8 (9.2–20.4)
Mortality over entire study period‡										
Hazard ratio (95% CI)	0.73 (0.52–1.03)		0.82 (0.17–4.07)		0.30 (0.14–0.64)		1.02 (0.54–1.91)		1.13 (0.67–1.89)	
No. of deaths by day 29	59	77	3	3	9	25	19	20	28	29
Kaplan–Meier estimate of mortality by day 29 — % (95% CI)	11.4 (9.0–14.5)	15.2 (12.3–18.6)	4.1 (1.3– 12.1)	4.8 (1.6–14.3)	4.0 (2.1–7.5)	12.7 (8.8–18.3)	21.2 (14.0–31.2)	20.4 (13.7–29.8)	21.9 (15.7–30.1)	19.3 (13.8–26.5)
Ordinal score at day 15 (±2 days) — no. (%)§										
1	157 (29.0)	115 (22.1)	38 (50.7)	28 (44.4)	90 (38.8)	62 (30.5)	18 (18.9)	14 (14.3)	11 (8.4)	11 (7.1)
2	117 (21.6)	102 (19.6)	20 (26.7)	15 (23.8)	70 (30.2)	58 (28.6)	22 (23.2)	19 (19.4)	5 (3.8)	10 (6.5)
3	14 (2.6)	8 (1.5)	8 (10.7)	4 (6.3)	6 (2.6)	4 (2.0)	0	0	0	0
4	38 (7.0)	33 (6.3)	3 (4.0)	7 (11.1)	17 (7.3)	13 (6.4)	12 (12.6)	4 (4.1)	6 (4.6)	9 (5.8)
5	58 (10.7)	60 (11.5)	3 (4.0)	5 (7.9)	25 (10.8)	18 (8.9)	2 (2.1)	14 (14.3)	28 (21.4)	23 (14.9)
6	28 (5.2)	24 (4.6)	1 (1.3)	0	5 (2.2)	7 (3.4)	12 (12.6)	11 (11.2)	10 (7.6)	6 (3.9)
7	95 (17.6)	121 (23.2)	1 (1.3)	3 (4.8)	13 (5.6)	21 (10.3)	16 (16.8)	20 (20.4)	57 (43.5)	74 (48.1)
8	34 (6.3)	58 (11.1)	1 (1.3)	1 (1.6)	6 (2.6)	20 (9.9)	13 (13.7)	16 (16.3)	14 (10.7)	21 (13.6)
Odds ratio (95% CI)	1.5 (1.2–1.9)		1.5 (0.8–2.7)		1.6 (1.2–2.3)		1.4 (0.9–2.3)		1.2 (0.8–1.9)	

P values and confidence intervals have not been adjusted for multiple comparisons. NE denotes not possible to estimate.
† Recovery rate ratios and hazard ratios were calculated from the stratified Cox model; the P value for this ratio was calculated with the stratified log-rank test (overall model stratified by
actual disease severity). Recovery rate ratios greater than 1 indicate a benefit with remdesivir; hazard ratios less than 1 indicate a benefit with remdesivir.
‡ Mortality over the first 14 days includes data from all patients who were still alive through 14 days postenrollment, with data censored on day 15, as if 14 days was the maximum followup time. Mortality over the entire study period uses the totality of the study data and censors data from patients who completed follow-up alive at 28 days postenrollment.
§ The ordinal score at day 15 is the patient's worst score on the ordinal scale during the previous day. Four patients died 15 days after randomization and are recorded as having died for the ordinal score at the day 15 outcome but not for the mortality day 15 outcome. Scores on the ordinal scale are as follows: 1, not hospitalized, no limitations of activities; 2, not hospitalized, limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection-control reasons); 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19–related or other medical conditions);
5, hospitalized, requiring any supplemental oxygen; 6, hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 8, death.
Odds ratios and P values were calculated with the use of a proportional odds model (overall model adjusted for actual disease severity).
Odds ratio values greater than 1 indicate a benefit with remdesivir
Source: [2]

Table A7. Outcomes Overall and by Baseline Disease Severity – ITT Population, ACTT-1 trial

Baseline Disease Severity Stratum	Overall*		Mild-Moderate Disease Stratum		Severe Disease Stratum	
	Remdesivir (n=541)	Placebo (n=521)	Remdesivir (n=55)	Placebo (n=50)	Remdesivir (n=486)	Placebo (n=471)
Recovery						
No. of recoveries	399	352	54	46	345	306
Median time to recovery (95% CI) - days	10 (9, 11)	15 (13, 18)	5 (4, 6)	5 (4, 7)	11 (10, 14)	18 (15, 20)
Restricted Mean Recovery Time (95% CI) - days	14.1 (13.2, 15.1)	16.9 (15.9, 17.8)	6.5 (5.2, 7.8)	7.9 (5.9, 9.8)	15.0 (14.1, 16.0)	17.8 (16.8, 18.8)
Rate ratio (95% CI)†	1.29 (1.12, 1.49); p<0.001		1.22 (0.82, 1.81)		1.31 (1.12, 1.52)	
Mortality over first 14 days‡						
Hazard ratio (95% CI) for data through Day 15	0.55 (0.36, 0.83)		0.45 (0.04, 5.00)		0.55 (0.36, 0.84)	
Number of deaths by Day 15	35	61	1	2	34	59
Kaplan-Meier estimate of mortality by Day 15 – % (95% CI)	6.7 (4.8, 9.2)	11.9 (9.4, 15.0)	1.8 (0.3, 12.2)	4.1 (1.0, 15.3)	7.3 (5.2, 10.0)	12.7 (10.0, 16.1)
Mortality over entire study period‡						
Hazard ratio (95% CI) over entire study period	0.73 (0.52, 1.03); p=0.07		0.60 (0.10, 3.56)		0.74 (0.52, 1.04)	
Number of deaths by Day 29	59	77	2	3	57	74
Kaplan-Meier estimate of mortality by Day 29 – % (95% CI)	11.4 (9.0, 14.5)	15.2 (12.3, 18.6)	3.8 (1.0, 14.3)	6.2 (2.0, 18.0)	12.3 (9.6, 15.7)	16.1 (13.0, 19.8)
Restricted Mean Survival Time (95% CI) - days	26.2 (25.7, 26.7)	25.3 (24.7, 25.9)	27.4 (26.5, 28.4)	27.2 (26.2, 28.1)	26.1 (25.6, 26.6)	25.1 (24.5, 25.8)
Ordinal Scale at day 15 (±2 days) – no. (%)**						
1	157 (29.0)	115 (22.1)	28 (50.9)	22 (44.0)	129 (26.5)	93 (19.7)
2	117 (21.6)	102 (19.6)	14 (25.5)	13 (26.0)	103 (21.2)	89 (18.9)
3	14 (2.6)	8 (1.5)	7 (12.7)	3 (6.0)	7 (1.4)	5 (1.1)
4	38 (7.0)	33 (6.3)	3 (5.5)	5 (10.0)	35 (7.2)	28 (5.9)
5	58 (10.7)	60 (11.5)	1 (1.8)	4 (8.0)	57 (11.7)	56 (11.9)
6	28 (5.2)	24 (4.6)	1 (1.8)	0 (0)	27 (5.6)	24 (5.1)
7	95 (17.6)	121 (23.2)	0 (0)	2 (4.0)	95 (19.5)	119 (25.3)
8	34 (6.3)	58 (11.1)	1 (1.8)	1 (2.0)	33 (6.8)	57 (12.1)
Odds ratio (95% CI)	1.5 (1.2, 1.9); p<0.001		1.5 (0.7, 3.0)		1.6 (1.2, 1.9)	

* P values and confidence intervals have not been adjusted for multiple comparisons. NE denotes not possible to estimate.
† Recovery rate ratios and hazard ratios were calculated from the stratified Cox model; P values for these ratios were calculated with the stratified log-rank test (overall model stratified by actual disease severity). Recovery rate ratios greater than 1 indicate a benefit for remdesivir; hazard ratios less than 1 indicate a benefit for remdesivir.
‡ Mortality over the first 14 days treats all patients who were still alive through 14 days post enrolment as censored on Day 15, as if 14 days was the maximum follow-up time. Mortality over the entire study period uses the totality of the study data and censors patients who completed follow-up alive at 28 days post enrolment.
** The ordinal score at day 15 is the patient's worst score on the ordinal scale during the previous day. Four patients died 15 days after randomization and are recorded as deceased for the ordinal score at day 15 outcome but not for the mortality by day 15 outcome. Scores on the ordinal scale are as follows: 1, not hospitalized, no limitations of activities; 2, not hospitalized, limitation of activities, home oxygen requirement, or both; 3, hospitalized, not requiring supplemental oxygen and no longer requiring ongoing medical care (used if hospitalization was extended for infection control reasons); 4, hospitalized, not requiring supplemental oxygen but requiring ongoing medical care (Covid-19–related or other medical conditions); 5, hospitalized, requiring any supplemental oxygen; 6, hospitalized, requiring non-invasive ventilation or use of high-flow oxygen devices; 7, hospitalized, receiving invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO); and 8, death.
Odds ratios and P values were calculated with the use of a proportional odds model (overall model adjusted for actual disease severity).
Odds ratio values greater than 1 indicate a benefit for remdesivir.
Source: [2]

Table A8. Results on additional secondary outcomes, ACTT-1 trial

	Remdesivir (N=541)	Placebo (N=521)	Rate Ratio (95% CI)
Median time to clinical improvement (95% CI) — days			
Improvement of one category on ordinal scale	7.0 (6.0 to 8.0)	9.0 (8.0 to 11.0)	1.23 (1.08 to 1.41)
Improvement of two categories on ordinal scale	11.0 (10.0 to 13.0)	14.0 (13.0 to 15.0)	1.29 (1.12 to 1.48)
Discharge or National Early Warning Score ≤2 for 24 hr*	8.0 (7.0 to 9.0)	12.0 (10.0 to 15.0)	1.27 (1.10 to 1.46)
			Difference (95% CI)
Hospitalization			
Median duration of initial hospitalization (IQR) — days†	12 (6 to 28)	17 (8 to 28)	−5.0 (−7.7 to −2.3)
Median duration of initial hospitalization among those who did not die (IQR) — days	10 (5 to 21)	14 (7 to 27)	−4.0 (−6.0 to −2.0)
Patients rehospitalized — % (95% CI)	5 (3 to 7)	3 (2 to 5)	2 percentage points (0 to 4)
Oxygen			
Median days receiving oxygen if receiving oxygen at baseline (IQR)	13 (5 to 28)	21 (8 to 28)	−8.0 (−11.8 to −4.2)
New use of oxygen			
No. of patients/total no.	27/75	28/63	
Percent of patients (95% CI)	36 (26 to 47)	44 (33 to 57)	−8 (−24 to 8)
Median days receiving oxygen (IQR)	4 (2 to 12)	5.5 (1 to 15)	−1.0 (−7.6 to 5.6)
Noninvasive ventilation or high-flow oxygen			
Median days of noninvasive ventilation or high-flow oxygen use during study if receiving these interventions at baseline (IQR)	6 (3 to 18)	6 (3 to 16)	0 (−2.6 to 2.6)
New use of new noninvasive ventilation or high-flow oxygen use during the study			
No. of patients/total no.	52/307	64/266	
Percent of patients (95% CI)	17 (13 to 22)	24 (19 to 30)	−7 (−14 to −1)
Median days of use during the study (IQR)	3 (1 to 10.5)	4 (2 to 23.5)	−1.0 (−4.0 to 2.0)
Mechanical ventilation or ECMO			
Median days of mechanical ventilation or ECMO during study if receiving these interventions at baseline (IQR)	17 (9 to 28)	20 (8 to 28)	−3.0 (−9.3 to 3.3)
New use of mechanical ventilation or ECMO during study			
No. of patients/total no.	52/402	82/364	
Percent of patients (95% CI)	13 (10 to 17)	23 (19 to 27)	−10 (−15 to −4)
Median days of use during the study (IQR)	21.5 (9 to 28)	23 (12 to 28)	1.0 (−6.0 to 8.0)

* The National Early Warning Score includes six physiological measures; total scores range from 0 to 20, with higher scores indicating greater clinical risk.
† The duration of initial hospitalization for patients who died was imputed as 28 days
Source: [2]

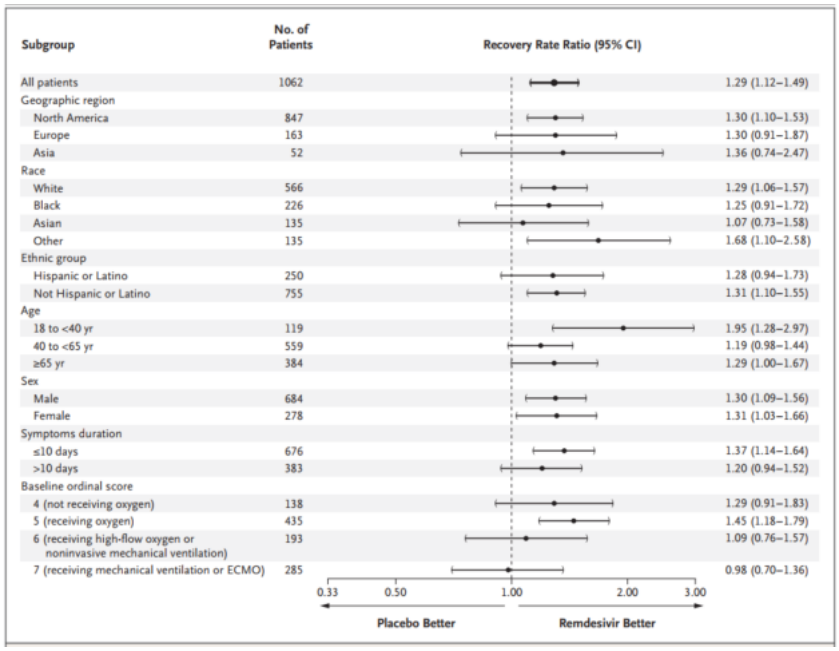


Figure A2. Time to Recovery According to Subgroup, ACTT-1 trial

Source: [2]

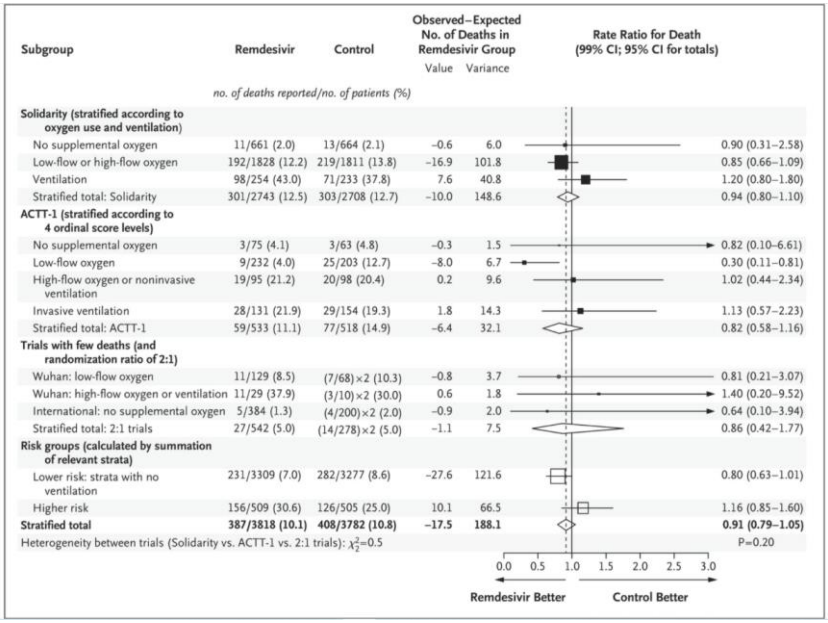


Figure A3. Meta-Analysis of Mortality in 4 Trials of Random Assignment of Remdesivir or Its Control to Hospitalized Patients with Covid-19

Percentages show Kaplan–Meier 28-day mortality. Values for observed minus expected number of deaths (O−E) are log-rank O−E for the Solidarity trial, O−E from 2-by-2 tables for the Wuhan7 and international8 trials, and w.loge hazard ratio for each stratum in the Adaptive Covid-19 Treatment Trial (ACTT-1)6 (with the weight w being the inverse of the variance of the loge hazard ratio, which was calculated from the confidence interval of the hazard ratio). Rate ratios were calculated by taking the loge rate ratio to be (O−E)/V with a Normal distribution and variance 1/V. Subtotals or totals of (O−E) and of V yield inverse-variance–weighted averages of the loge rate ratios. For balance, controls in the 2:1 trials were counted twice in the control totals and subtotals. Diamonds show 95% confidence intervals for treatment effects. Squares and horizontal lines show treatment effects in particular subgroups and their 99% confidence intervals, with an arrow if the upper 99% confidence limit is outside the range shown. The area of each square is proportional to the variance of O−E in the subgroup it describes.
Source: [3]

RISK OF BIAS 2 (RoB2) Tables

Table A9. Risk of bias assessed with the Cochrane risk of bias 2 tool

Studies	Randomi-sation process	Deviations from the intended interventions	Missing outcomes	Measurement of the outcome	Selection of reported results	Overall bias
Wang [28]	low	some concerns[a]	some concerns[b]	low	low	some concerns
Biegel ACTT-1 [2]	low	low	low	low	low	low
Spinner [27]	low	low	low	some concerns[c]	low	some concerns
SOLIDARITY [3]	low	low	low	low	low	low

Source: adapted from https://covid-nma.com [20]
[a] Efficacy outcome data were analyzed by using modified intention-to-treat analysis (1 participant withdrew consent post-randomization in the control arm). Safety outcome data (adverse events) were analyzed by using "naïve" per protocol analysis for participants who received no doses of the treatment in the intervention arm (3 participants who did not receive remdesivir were excluded from analysis).
[b] 237 randomized/237 analyzed for all outcomes except negative viral conversion incidence. For this outcome, respiratory specimens were not collected at one study site (n=27 participants with missing data in remdesivir group and n=13 in control group), in which the safety of medical care workers during aerosol generating procedures could not be guaranteed. Risk assessed to be low for the outcomes: Time to death. Mortality. Clinical improvement incidence. Time to clinical improvement. WHO clinical progression scale Score 6 and above. WHO clinical progression scale Score 7 and above. Adverse events. Serious adverse events. Risk assessed to be "some concerns" for the outcomes: Negative viral conversion incidence.
[c] Open label trial.Mortality is an observer-reported outcome not involving judgement. For the outcome WHO score 7 or above (intubation or death) and Serious adverse events (when it includes events not involving judgement e.g., laboratory measures), The assessment cannot possibly be influenced by knowledge of the intervention assignment. Risk assessed to be low for outcomes: Mortality. Time to death. WHO score 7 and above. Serious adverse events. For the outcomes Clinical improvement, Time to clinical improvement, WHO score 6 and above, although the assessment could possibly be influenced by knowledge of the intervention assignment, did not consider this likely to have happened in the context of a pandemic. The same applies to the outcome Adverse events when the outcome includes patient or observer reported events. Risk assessed to be some concerns for outcomes: Clinical improvement. Time to clinical improvement. WHO score 6 and above. Adverse events.

CERTAINTY OF EVIDENCE

Table A10. GRADE evidence

Remdesivir compared to Standard Care/Placebo for Mild/Moderate/Severe/Critical COVID-19

Author(s): N. Henschke, C. Bollig, C. Schmucker, J.J. Meerpohl
Question: Remdesivir compared to Standard Care/Placebo for Mild/Moderate/Severe/Critical COVID-19 [a]
Setting: Wordwide
Bibliography: https://covid-nma.com, except for outcome - Number of patients discharged from the hospital, http://deplazio.net/farmacicovid/files/tabelle-grade/Remdesivir-vs-Standard-treatment-for-COVID-19.pdf

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	Standard Care/Placebo	Relative (95% CI)	Absolute (95% CI)		
Viral negative conversion D3												
1 [b]	randomised trials	serious [c]	not serious	serious [d]	very serious [e]	none	37/131 (28.2%)	19/65 (29.2%)		**9 fewer per 1.000**		
WHO progression score (level 6 or above) D14-D28												
3 [k]	randomised trials	serious [l]	not serious	not serious	not serious	none	125/1095 (11.4%)	154/799 (19.3%)	**RR 0.68** (0.55 to 0.85)	**62 fewer per 1.000** (from 87 fewer to 29 fewer)	⊕⊕⊕◯ MODERATE	
WHO progression score (level 7 or above) D7												
2 [i]	randomised trials	not serious	not serious	not serious	serious [h]	none	163/699 (23.3%)	215/599 (35.9%)	**RR 0.70** (0.59 to 0.82)	**108 fewer per 1.000** (from 147 fewer to 65 fewer)	⊕⊕⊕◯ MODERATE	
WHO progression score level 7 or above D14-28												
3 [k]	randomised trials	not serious	not serious	not serious	not serious	none	118/1095 (10.8%)	142/799 (17.8%)	**RR 0.70** (0.56 to 0.88)	**53 fewer per 1.000** (from 78 fewer to 21 fewer)	⊕⊕⊕⊕ HIGH	
All-cause mortality D7												
2 [i]	randomised trials	not serious	serious [m]	not serious	very serious [e]	none	27/699 (3.9%)	38/599 (6.3%)	**RR 0.68** (0.28 to 1.64)	**20 fewer per 1.000** (from 46 fewer to 41 more)	⊕◯◯◯ VERY LOW	
All-cause mortality D14-D28												
4 [n]	randomised trials	not serious	not serious	not serious	serious [f]	none	387/3838 (10.1%)	394/3507 (11.2%)	**RR 0.90** (0.73 to 1.11)	**11 fewer per 1.000** (from 30 fewer to 12 more)	⊕⊕⊕◯ MODERATE	
Adverse events												
2 [i]	randomised trials	not serious	not serious	not serious [o]	not serious	none	618/1095 (56.4%)	466/799 (58.3%)	**RR 0.93** (0.85 to 1.01)	**41 fewer per 1.000** (from 87 fewer to 6 more)	⊕⊕⊕⊕ HIGH	
Serious adverse events												
3 [k]	randomised trials	not serious	not serious	not serious [o]	serious [p]	none	33/1095 (3.0%)	32/799 (4.0%)	**RR 0.60** (0.38 to 0.96)	**16 fewer per 1.000** (from 25 fewer to 2 fewer)	⊕⊕⊕◯ MODERATE	

CI: Confidence interval; **RR**: Risk ratio

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	Trattamento standard	Relative (95% CI)	Absolute (95% CI)	
Number of patients discharged from the hospital											
3 [1,2,3]	randomised trials	serious [a]	not serious	not serious	not serious	none	625/1095 (57.1%)	382/799 (47.8%)	**RR 1.13** (1.02 to 1.24)	**62 more per 1.000** (from 10 more to 115 more)	⊕⊕⊕◯ MODERATE

Abbreviations: CI=Confidence interval; **R=**Risk ratio
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 interval consistent with the possibility of a benefit and the possibility of no effect.
Outcome Number of patients discharged from the hospital: [1,2,3] Beigel JH, 2020; Spinner CD, 2020; Wang Y, 2020;
[a]. Downgraded of one level for high risk of performance bias in two studies and unclear risk of selection, attrition and reporting bias in one study

APPENDIX 4: EVIDENCE GAPS

Table A11. Evidence gaps

Additional evidence generation needs (to be published) **Research question: What is the relative clinical effectiveness and safety of remdesivir alone or in combination therapy, compared with other interventions, in patients hospitalised with COVID-19 pneumonia?**	
Population	For subgroups of patients with obesity, children, immunocompromised patients, older patients, pregnant or lactating women
Intervention	Direct comparison with corticosteroids or other investigational drugs; combination therapy
Comparator	Remdesivir in combination therapy or other investigational COVID-19 pharmaceuticals
Outcome(s)	Short term outcomes: Frequency of ICU admission; Length of ICU stay; Time to ICU admission; Frequency of multiple organ dysfunction syndrome/acute respiratory distress syndrome/shock/organ failure; Invasive mechanical ventilation or ECMO (among those not on invasive mechanical ventilation on randomisation); Duration of invasive mechanical ventilation or ECMO; Health-related Quality of life. Long term outcomes All-cause mortality; AEs and SAEs; HRQoL; Lung function
Time stamp	Short-term (28 days) and long-term (up to 6 months)
Study design	RCTs with high certainty of evidence provided; The availability of full clinical study reports for completed trials to allow open and robust scrutiny of the trials is needed

APPENDIX 5: PROJECT ORGANISATION

Participants

Table A12. Project participants

Role in the project	Agency	Country	Distribution of work
Assessment Team			
Author	Austrian Institute for Health Technology Assessment (AIHTA)	Austria	Author will draft the report
Dedicated Reviewer	National Authority of Medicines and Health Products (INFARMED)	Portugal	Review of first draft
Dedicated Reviewer	National Centre for Pharmacoeconomics (NCPE)	Ireland	Review of first draft
Dedicated Reviewer	Regione Emilia-Romagna (RER)	Italy	Review of first draft
Dedicated Reviewer	HTA Department SEC Ministry of Health Ukraine	Ukraine	Review of first draft
Contributors			
Project Manager	Zorginstituut Nederland (ZIN)	Netherlands	Coordination between involved parties throughout the assessment period

Milestones and deliverables

Table A13. Milestones and deliverables

Task	Start	End
First Draft of Update 1	01/12/2020	06/12/2020
Review of first draft of Update 1 of RCR	07/12/2020	09/12/2020
Development of second draft RCR & answers to DR comments	10/12/2020	14/12/2020
TC with the entire assessment team	10/12/2020	
Finalize Update 1 of RCR	16/12/2020	