EUnetHTA Joint Action 3 WP4

Rapid Collaborative Review

DEXAMETHASONE FOR THE TREATMENT OF HOSPITALISED PATIENTS WITH COVID-19

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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 treatment and 'Rolling Collaborative Reviews' for therapeutic treatment. 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 (https://eunethta.eu/services/COVID-19/).

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

A novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), was first identified in December of 2019 in Wuhan, China as causing a respiratory illness designated as Coronavirus disease 2019, or COVID-19. On 30 January 2020, the International Health Regulations Emergency Committee of the WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern. Since then, there has been rapid spread of the virus, leading to a global pandemic of COVID-19. According to current evidence, SARS-CoV-2 is primarily transmitted between people through respiratory droplets and contact routes. Human-to-human transmission is occurring extensively. Hence, precautions to prevent human-to-human transmission are appropriate for both suspected and confirmed cases. Individuals of all ages are at risk for infection and severe disease. Although most coronavirus infections cause only mild respiratory symptoms, infection with SARS-CoV, MERS-CoV (Middle East respiratory syndrome coronavirus), and SARS-CoV-2 can be lethal [1-4].

As of October 31, 2020, across the European Union/European Economic Area (EU/EEA) and the United Kingdom (UK) there has been a considerable further increase in COVID-19 infections and the current situation represents a major threat to public health, and the impact in terms of pressure on healthcare services and mortality has become increasingly evident.

As of 16 November 2020, 10 727 551 cases and 267 394 deaths have been reported in the EU/EEA and the UK [5, 6]. Around 15% (country range: 2–78%) of reported COVID-19 cases have been hospitalised. Data from 16 countries show that in total 8% (country range: 0–60%) of hospitalised patients required ICU and/or respiratory support; these proportions vary considerably by age and sex and may be influenced by national policies and practices. 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 64.0 (country range: 0.0–244.5) per million population. The rate has been increasing for 58 days. Among 26 countries with high 14-day COVID-19 death rates (at least 10 per million), sustained increases (for at least seven days) were observed in 21 countries, https://covid19-country-overviews.ecdc.europa.eu/.

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 [1]. Clinical symptoms and COVID-19 severity of illness categories are presented in Table 1.1.

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, diarrhea, loss of taste and smell) but who

	do not have shortness of breath, dyspnea, 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: [7] and [1].
[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 occurs five to seven days into the symptomatic illness, about 8-14 days after original exposure [8]. 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 [9].

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 [10].

Standard of care 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.

Recently, remdesivir (Veklury), an antiviral medicine for systemic use, 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. On October 22, 2020 the U.S. Food and Drug Administration approved remdesivir for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms (about 88 pounds) for the treatment of COVID-19 requiring hospitalization.

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

WHO living guidance

Recently, the new WHO living guidance on corticosteroids for COVID-19 was published [7, 11]. 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 [7, 11].

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

US COVID-19 Treatment Guidelines

The US COVID-19 Treatment Guidelines Panel issued recommendations on pharmacological treatment (on the use of dexamethasone and remdesivir, either alone or in combination) for patients with COVID-19 (as of October 9, 2020) [1]:

- For patients with COVID-19 who are not hospitalised or who are hospitalised with moderate disease but do not require supplemental oxygen:
    - Recommendations: the Panel does not recommend any specific antiviral or immunomodulatory therapy for the treatment of COVID-19 in these patients. Patients are considered to have moderate disease if they have clinical or radiographic evidence of lower respiratory tract infection and a saturation of oxygen (SpO_2) ≥94% on room air at sea level. There are insufficient data for the Panel to recommend either for or against the use of remdesivir for the treatment of COVID-19. The Panel recommends against the use of dexamethasone (AI) or other corticosteroids for the treatment of COVID-19 (AIII) unless a patient has another clinical indication for corticosteroid therapy.
    - Additional considerations: the Panel recognizes there may be situations in which a clinician judges that remdesivir is an appropriate treatment for a hospitalized patient with moderate disease (e.g., a person who is at a particularly high risk for clinical deterioration). For the rationale on such recommendations see full text Guideline document [1].

- For hospitalised patients with COVID-19 who require supplemental oxygen but who do not require delivery of oxygen through a high-flow device, non-invasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation:
    - Recommendations (the options are listed in order of preference; however, all these options are considered acceptable):
        - Remdesivir 200 mg intravenously (IV) for 1 day, followed by remdesivir 100 mg IV for 4 days or until hospital discharge, whichever comes first (AI);
        - A combination of remdesivir (dose and duration as above) plus dexamethasone 6 mg IV or orally for up to 10 days or until hospital discharge (BIII);
        - If remdesivir cannot be used, dexamethasone may be used instead (BIII).
    - Additional considerations: remdesivir therapy may be extended to up to 10 days if no substantial clinical improvement is seen at Day 5. The combination of remdesivir and dexamethasone has not been studied in clinical trials; however, there are theoretical reasons for combining these drugs. The Panel recognizes there are theoretical reasons for adding dexamethasone to the drug regimen of patients who are currently receiving remdesivir but who are clinically deteriorating. If dexamethasone is not available, an alternative corticosteroid such as prednisone**,** methylprednisolone**,** or hydrocortisone can be used (BIII). For rationale on such recommendations please see full text Guideline document [1].

- For hospitalised patients with COVID-19 who require delivery of oxygen through a high-flow device or non-invasive ventilation but not invasive mechanical ventilation or extracorporeal membrane oxygenation
    - Recommendations (the options below are listed in order of preference; however, both options are considered acceptable):
        - A combination of dexamethasone plus remdesivir at the doses and durations discussed above (AIII);
        - Dexamethasone alone at the dose and duration discussed above (AI).
    - Additional considerations: the combination of dexamethasone and remdesivir has not been studied in clinical trials. Because there are theoretical reasons for combining these drugs, the Panel considers both the combination of remdesivir and dexamethasone and dexamethasone alone to be acceptable options for treating COVID-19 in this group of patients. Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in this group of patients, the Panel does not recommend using remdesivir alone. For patients who initially received remdesivir monotherapy and progressed to requiring high-flow oxygen supplementation or non-invasive ventilation, dexamethasone should be initiated and remdesivir should be continued until the treatment course is completed. If dexamethasone is not available, equivalent doses of other corticosteroids such as prednisone, methylprednisolone, or hydrocortisone may be used (BIII). For rationale on such recommendations please see the full text Guideline document [1].

- For hospitalised patients with COVID-19 who require invasive mechanical ventilation or extracorporeal membrane oxygenation
    - Recommendations (the options below are listed in order of preference; however, both options are considered acceptable):
        - Dexamethasone at the dose and duration discussed above (AI);
        - Dexamethasone plus remdesivir for patients who have recently been intubated at the doses and durations discussed above (CIII).
    - Additional considerations: the combination of dexamethasone and remdesivir has not been studied in clinical trials. There are theoretical reasons for co-administering these drugs in recently intubated patients. If dexamethasone is not available, alternative corticosteroids such as prednisone, methylprednisolone, or hydrocortisone can be used (BIII). For those who initially started remdesivir monotherapy and then progressed to mechanical ventilation or extracorporeal membrane oxygenation (ECMO), dexamethasone should be started and remdesivir should be continued to complete the treatment course. For rationale on such recommendations please see full text Guideline document [1].

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

1.3 Features of the intervention: Dexamethasone

1.1.3 Mode of Action

Dexamethasone is a long-acting glucocorticoid which is used principally as an anti-inflammatory or immunosuppressant agent. A long biological half-life of 36 to 54 hours enabling once a day dosing. During a short-term therapy, in compliance with the dosage recommendations and close monitoring of patients, the risk of side effects is low. The usual side effects of short-term dexamethasone treatment (days/weeks) include weight gain, psychological disorders, glucose intolerance and transitory adrenocortical insufficiency. Long-term dexamethasone treatment (months/years) usually causes central obesity, skin fragility, muscle atrophy, osteoporosis, growth retardation and long-term suprarenal insufficiency [12-14].

A systematic review of (mainly low-dose) corticosteroid trials in severe sepsis and septic shock an association with an increased risk of hyperglycaemia (RR 1.16, 95% CI 1.07 to 1.25) and hypernatraemia (RR 1.61, 95% CI 1.26 to 2.06) was noted. Increased risk of gastroduodenal bleeding,

superinfection or neuromuscular weakness was not identified [15]. In trials of low-to-moderate doses of corticosteroids, the main adverse effect has been hyperglycaemia [16, 17].

Daily regimen of dexamethasone 6 mg once daily is equivalent to 160 mg of hydrocortisone, 40 mg of prednisone, and 32 mg of methylprednisolone.

The proposed mechanism of glucocorticoids in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) involves the mitigation of an excessive immune response that can lead to acute respiratory distress syndrome (ARDS) and multi-organ failure. ARDS develops in approximately 20% of COVID-19 patients and is linked to multi-organ failure through cytokine release syndrome [18].

1.1.4 Regulatory Status

Dexamethasone is authorised at national level in the EU and is used in a wide range of conditions, including rheumatic problems, skin diseases, severe allergies, asthma and chronic obstructive lung disease. On 24 July 2020, EMA's human medicines committee (CHMP) started a review under Article 5(3) of Regulation 726/2004 of the results from the RECOVERY study arm.

CHMP is currently evaluating Dexamethasone Taw for a marketing authorisation for the treatment of hospitalised adult patients with COVID-19.

On September 18, 2020 EMA announced that EMA’s human medicines committee (CHMP) has completed its review of results from the RECOVERY study arm that involved the use of the corticosteroid medicine dexamethasone in the treatment of patients with COVID-19 admitted to hospital, and has concluded that dexamethasone can be considered a treatment option for COVID-19 patients on oxygen or mechanical ventilation. Based on the review of available data, and following referral procedure, EMA is endorsing the use of dexamethasone 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 [19].

The UK has approved dexamethasone for the treatment of patients with severe and critical COVID-19, on June 16, 2020 [20].

2 OBJECTIVE AND SCOPE

The aim of this EUnetHTA Rapid Collaborative Review is to summarize the best publicly available scientific evidence on the clinical effectiveness and safety of dexamethasone in the target patient populations with relevant comparators and next, to support the local productions of national/regional HTA reports based on this review. The target patient populations and relevant comparators (based on the requirements of EUnetHTA Partners) are defined in the project scope in Table 2.1. It should be noted that the scope is slightly broader than EMA recommended indication and also includes hospitalised moderate severity COVID-19 patients, thus not exclusively severe and critically ill patients who require supplemental oxygen therapy. Including a broader patient population is done because of the following reasons: COVID-19 is an emerging infectious disease and only one pharmaceutical (remdesivir) received marketing authorisation in US (for hospitalised patients with COVID-19) or conditional marketing authorisation in EU (COVID-19 patients who require supplemental oxygen therapy). Secondrestricting the evidence review only to these two COVID-19 patient subgroups could inhibit potentially useful future comparative assessments of dexamethasone with other active treatments by HTA bodies at national/regional level, thereby limiting the use of this document. And third, to avoid redundancies and duplication, this report is based on a literature search strategy performed for the EUnetHTA Rolling Collaborative Reviews and on data from already published Rolling CRs on dexamethasone and other corticosteroids (which are broader than the current EMA indication for dexamethasone).

Table 2.1: Assessment scope: relevant PICO(s) identified for the rapid review

Description	Assessment scope
PICO	
Population[a]	**Target population: hospitalised patients with COVID-19[a]** [1] • *Moderate Illness*: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO_2) ≥94% on room air at sea level; • *Severe Illness*: Individuals who have respiratory frequency >30 breaths per minute, SpO_2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO_2/FiO_2) <300 mmHg, or lung infiltrates >50%; • *Critical Illness*: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction. **Disease** SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed COVID-19. The full spectrum of COVID-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death. **ICD-Codes** [21] An emergency ICD-10 code of 'U07.1 COVID-19, virus identified' is assigned to a disease diagnosis of COVID-19 confirmed by laboratory testing. An emergency ICD-10 code of 'U07.2 COVID-19, virus not identified' is assigned to a clinical or epidemiological diagnosis of COVID-19 where laboratory confirmation is inconclusive or not available. Both U07.1 and U07.2 may be used for mortality coding as cause of death. See the International guidelines for certification and classification (coding) of COVID-19 as cause of death following the link below. In ICD-11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and the code for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1. **MeSH-terms:** COVID-19; Coronavirus Disease 2019; 2019 novel coronavirus disease; COVID19; COVID-19 pandemic; SARS-CoV-2 infection; COVID-19 virus disease; 2019 novel coronavirus infection; 2019-nCoV infection; coronavirus disease 2019; coronavirus disease-19; 2019-nCoV disease; COVID-19 virus infection.
Intervention	Dexamethasone **More information:** dexamethasone is a long-acting glucocorticoid, principally used as an anti-inflammatory or immunosuppressant agent, authorised at national level in the EU and is used in a wide range of conditions, including rheumatic problems, skin diseases, severe allergies, asthma and chronic obstructive lung disease.

	The recommended indication in COVID-19 according to the EMA is the treatment of coronavirus disease 2019 (COVID-19) in adult and adolescent patients (aged 12 years and older with body weight at least 40 kg) who require supplemental oxygen therapy. Recommended dose: adult patients 6 mg IV or PO, once a day for up to 10 days; Paediatric patients (adolescents aged 12 years and older) 6mg/dose IV or PO once a day for up to 10 days (duration of treatment should be guided by clinical response and individual patient requirements). [19, 22]
Comparison	Active pharmacological treatment (approved pharmaceuticals for COVID-19 or investigational pharmaceuticals)[b], or Standard of care/usual care. **Rationale**: at the time of the publication of this report, no agreement has been reached by the scientific community on standard treatment for COVID-19 or the relevance of the type of head-to-head comparisons.
Outcomes	**Effectiveness** (short-term at 28 days; long term until 6-months) • All-cause mortality (subgroup analysis according the disease severity: patients with moderate, severe and critical illness); • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study); • Time to 2019-nCoV RT-PCR negativity; • Time to clinical improvement; • Duration of oxygen treatment (not invasive mechanical ventilation or ECMO); • 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; • Number of patients discharged (within 28 days); • Length of hospital stay; • Pulmonary function; • Health-related Quality of life. **Safety** (short-term at 28 days; long term until 6-months) • Number of patients with one or more Adverse events (AE); • Number of patients with one or more Serious adverse events (SAE); • Number of deaths attributable to SAE; • Number of withdrawals due to AEs; • Description of most frequent AEs; • Description of most frequent SAEs. **Rationale:** priority will be given on outcomes according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 [23] and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection [24].
Study design	**Effectiveness**: randomised controlled trials (RCTs) **Safety**: RCTs; Observational studies (comparative or single-arm prospective studies and registries, with >50 patients)

[a] The scope is slightly broader than EMA recommended indication; including also hospitalised moderate COVID-19 patients, whereas the EMA indication is exclusively for severe and critical COVID-19 patients who require supplemental oxygen therapy (detailed reasons are written in text above).
[b] Approved or conditionally approved COVID-19 pharmaceutical: remdesivir with conditional marketing authorisation in EU and marketing authorisation in US. List of possible investigational pharmaceuticals: i.e., Immunomodulators (i.e., tocilizumab, sarilumab, gimsilumab, canakinumab, lenzilumab, interferon alfa or beta, anakinra); COVID-19 convalescent plasma or COVID-19 neutralising monoclonal antibodies; antivirals (i.e. favipiravir); or combination therapy with dexamethasone vs dexamethasone alone.
Abbreviations: 2019-nCoV=2019 novel coronavirus ; AE=adverse events; ECMO= Extracorporeal membrane oxygenation; ICD-Codes=Classification of Disease Codes; ICU=Intensive Care Unit; RCT=randomized controlled trial; SAE=serious adverse events; SpO_2=oxygen saturation; PaO_2/FiO_2=ratio of arterial partial pressure of oxygen to fraction of inspired oxygen.

3 METHODS

3.1 Data sources and searches

To avoid redundancies and duplication, this EUnetHTA Rapid Collaborative Review reused data from the already published EUnetHTA Rolling Collaborative Reviews on Dexamethasone [25], as well as living systematic review (SR) sources from international initiatives [26, 27] to collect information and data on COVID-19 dexamethasone treatment. The data were included according to the methodology suggested by Whitlock 2008 [28] and Robinson 2014 [29] 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 for the EUnetHTA Rolling Collaborative Review on Dexamethasone was updated in October and November 2020, to find possible new RCTs and prospective observational studies related to dexamethasone treatment in hospitalized patients with COVID-19 [30]. Details can be found in Table A2 and Table A3, Appendix 2. References were included or excluded according to the Population-Intervention-Control-Outcome (PICO)-scheme and presented according to the PRISMA Statement [31].

A separate Guideline (GL) search (G-I-N, TRIP-Database and hand search) was performed as well, in October 2020, with a further update in November 2020. Only living clinical guidelines, with regular updates, were considered in this report.

Data extraction was performed by one reviewer on pre-defined extraction tables and double-checked regarding completeness and accuracy by a second reviewer. Any differences in extraction results were discussed to achieve consensus; any disagreements were resolved by a third reviewer. Quantitative synthesis from existing living SRs/MA was used and presented in the Result section if available and appropriate for specific outcomes. If additional RCTs are found, a new meta-analysis will be done when possible. Dichotomous outcomes were analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by its 95% confidence interval (CI). Continuous outcomes were analysed by calculating the mean difference (MD) with the relative 95% CI when the study used the same instruments for assessing the outcome. The standardised mean difference (SMD) was applied when studies used different instruments. Pairwise meta-analysis was performed for primary and secondary outcomes using a random-effects model in RevMan [32, 33]. Relevant subgroup analyses were done for the most important outcome "All-cause mortality", as well as for the outcome "Number of patients discharged (within 28 days)".

3.2 Risk of bias

Each study was assessed with the Cochrane Risk of bias 2 (RoB 2) tool for randomized controlled trials [34]. 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

For rating the certainty of the evidence, the Grading of Recommendations Assessment, Development and Evaluation (GRADE)-method was applied [35]. This approach specifies four levels of quality: “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 dexamethasone in COVID-19 in October 2020: ClinicalTrials.gov (https://clinicaltrials.gov/), ISRCTN (https://www.isrctn.com/) and European Clinical Trials Registry (https://www.clinicaltrialsregister.eu/).

4 RESULTS

4.1 Information retrieval/Existing Evidence

Evidence from two RCTs evaluating dexamethasone treatment: dexamethasone 6 mg daily up to 10 days in RECOVERY trial [36] and 20 mg daily for 5 days followed by 10 mg daily for 5 days in CoDEX trial [37]. Flow diagrams depicting the selection process of RCTs and observational studies can be found in Figure A1 and Figure A2, Appendix 2. Detailed characteristics of included studies can be found in Table A4 in Appendix 3.

The RCT with the largest number of included COVID-19 patients is the **RECOVERY trial** [36]: Randomized Evaluation of COVID-19 thERapY (NCT04381936, ISRCTN50189673, EudraCT 2020-001113-21). The RECOVERY trial was designed to evaluate the effects of potential treatments in **patients hospitalized with COVID-19** at 176 National Health Service organisations in the United Kingdom and was supported by the National Institute for Health Research Clinical Research Network. The primary outcome was all-cause mortality within 28 days after randomization; further analyses were specified at 6 months. Secondary outcomes were the time until discharge from the hospital and, among patients not receiving invasive mechanical ventilation at the time of randomization, subsequent receipt of invasive mechanical ventilation (including extracorporeal membrane oxygenation) or death. Other pre-specified clinical outcomes included cause-specific mortality, receipt of renal hemodialysis or hemofiltration, major cardiac arrhythmia (recorded in a subgroup), and receipt and duration of ventilation. Results from a preliminary report of the RECOVERY trial are related to the comparison of oral or intravenous dexamethasone 6 mg given once daily for up to ten days (2104 patients) plus the usual standard of care vs usual care alone (4321 patients). At the time of randomization, 16% of patients were receiving invasive mechanical ventilation or extracorporeal membrane oxygenation; 60% were receiving oxygen only (with or without non-invasive ventilation); and 24% were receiving neither. Other patient characteristics at baseline, according to treatment assignment and level of respiratory support are presented in Table A5 in Appendix 3. Regarding to other pharmaceutical provided as off-label indication for COVID-19 as part of standard care, both groups of patients received such pharmaceutical equally (lopinavir/ritonavir <0.5%; hydroxychloroquine 1%; azithromycin 24% vs 25%; tocilizumab or sarilumab 2% vs 3%; not recorded <0.5%).

The **CoDEX trial** (NCT04327401) randomized 299 patients in 41 ICUs in Brazil with **moderate or severe ARDS and COVID-19** to open-label dexamethasone (20 mg/d for 5 days, then 10 mg/d for 5 days) vs usual care alone, with the primary outcome ventilator-free days through day 28 [37]. 28-day ventilator-free days was defined as the number of days alive and not dependent on mechanical ventilation for a minimum of 48 consecutive hours. Patients who were discharged before 28 days were considered ventilator free at 28 days, whereas patients who died before 28 days were considered to have no ventilator free days. Secondary outcomes included 28-day all-cause mortality, clinical status at day 15 (assessed using the 6-point disease severity scale by WHO, ranging from 1 [not hospitalized] to 6 [death]), ICU-free days, duration of mechanical ventilation, and organ failure assessed using sequential organ failure assessment (SOFA) scores. The SOFA scores range from 0 to 24, with a higher score indicating greater organ dysfunction. SOFA was assessed at 48 hours, 72 hours, and 7 days. Patients in the trial were followed for 28 days or until discharge, whichever came first. Patient characteristics at baseline are presented in Table A6 and Table A7 in Appendix 3. Baseline characteristics were well balanced between groups, including severity of ARDS and the use of rescue therapies at randomization. Remdesivir was not available in Brazil during the trial period. Only 1 patient received lopinavir-ritonavir treatment. Other therapeutic strategies such as tocilizumab and convalescent plasma were limited and not widely available.

4.2 Risk of bias/Quality of evidence

Overall Risk of Bias for both trials is judged as “some concerns”.

Certainty of evidence are graded as “moderate” for the outcomes: “all-cause mortality” in the mixed population (moderate to critical COVID-19), and for the subgroups of moderate and severe COVID-19 patients and for the “number of patients discharged from hospital within 28 days” in moderate, severe and critical COVID-19. Certainty of evidence is graded as “low” for the outcomes: “number of patients with SAEs” in critical COVID-19 and “mortality in critical COVID-19” and finally, as “very low” for the

outcome “number of patients discharged from hospital within 28 days” in the mixed population (moderate to critical COVID-19).

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

4.3 Results on clinical effectiveness and safety

Authors of the RECOVERY trial [36] showed that overall, 482 (22.9%) patients allocated to dexamethasone and 1110 (25.7%) patients allocated to usual care died within 28 days (age adjusted rate ratio 0.83; 95% confidence interval [CI] 0.75 to 0.93; P<0.001). The proportional and absolute mortality rate reductions varied significantly depending on level of respiratory support at randomization (test for trend p<0.001): dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation (29.3% vs 41.4%, rate ratio 0.64 [95% CI 0.51 to 0.81]), by one-fifth in patients receiving oxygen without invasive mechanical ventilation (23.3% vs 26.2%, rate ratio 0.82 [95% CI 0.72 to 0.94], but did not reduce mortality in patients not receiving respiratory support at randomization (17.8% vs 14.0%, rate ratio 1.19 [95% CI 0.91 to 1.55]) (Figure 4.1).

The effect of allocation to dexamethasone on 28-day mortality by other pre-specified baseline characteristics can be found in Figure A3 in Appendix 3.

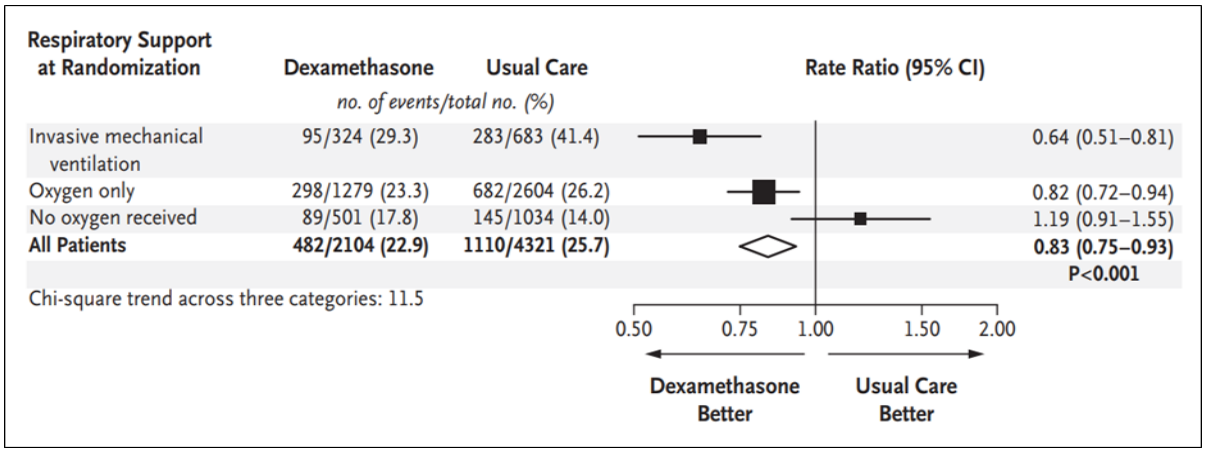

Figure 4.1: Forest plot Horby et al. 2020 - Effect of dexamethasone on 28-day Mortality, according to respiratory support at randomization

Source: [36]
Abbreviations: CI=Confidence Interval.

Allocation to dexamethasone was associated with a shorter duration of hospitalization than usual care (median 12 days vs 13 days) and a greater probability of discharge within 28 days (rate ratio 1.10 [95% CI 1.03 to 1.17]) with the greatest effect seen among those receiving invasive mechanical ventilation at baseline (11.5 by chi-square test for trend). The risk of progression to invasive mechanical ventilation was lower among those allocated to dexamethasone vs usual care (risk ratio 0.92 [95% CI 0.84 to 1.01). Analyses are ongoing regarding cause-specific mortality, the need for renal dialysis or hemofiltration, and the duration of ventilation. Adverse events were not reported in this preliminary report. Details can be found in Figure A4 and Table A8 in Appendix 3.

In the CoDEX trial (NCT04327401) a total of 299 patients (mean [SD] age, 61 [14] years; 37% women) were enrolled and all completed follow-up. The primary outcome, ventilator-free days through day 28, showed a statistically significant difference in favour of dexamethasone (6.6 vs 4.0, p=0.04). 28-day mortality was not significantly different between patients randomized to dexamethasone vs usual care (56.3% vs 61.5%, p=0.83). There was no significant difference in other pre-specified secondary outcomes of ICU-free days during the first 28 days, mechanical ventilation duration at 28 days, or the 6-point ordinal scale at 15 days. Stopping the study early, when RECOVERY results were announced, resulted in a sample size that was underpowered to adequately evaluate the effect of dexamethasone on all secondary outcomes, including mortality, but also the primary outcome [37].

Related to safety outcomes, both groups had a comparable need for insulin use for hyperglycemia: 47 patients (31.1%) in the dexamethasone group vs 42 (28.4%) in the standard care group. The number of new diagnoses of infection until day 28 was 33 (21.9%) vs 43 (29.1%). Twelve patients (7.9%) in the dexamethasone group had bacteriemia vs 14 (9.5%) in the standard care group.

Five patients (3.3%) in the dexamethasone group had serious adverse events vs 9 (6.1%) in the standard care group. In the dexamethasone group, 1 event occurred for each of the following outcomes: acute myocardial infarction, deep vein thrombosis, gastrointestinal perforation, unspecified hyperglycemia, and pneumothorax. Except for 2 myocardial infarctions in the standard care group, 1 event occurred for the following outcomes: bronchospasm, cardiogenic shock, deep vein thrombosis, diabetic ketoacidosis, unspecified hyperglycemia, ischemic hepatitis, nephropathy in transplanted kidney, pneumothorax, and pulmonary embolism.

Details can be found in Table A8 and Figure A4 in Appendix 3 and Table 4.1 below.

Table 4.1: Safety outcomes

Outcomes	RECOVERY; Horby et al. 2020 [36]	CoDEX; Tomazini et al. 2020 [37]		
		N (%) Dexamethasone	N (%) Control	Absolute difference (95% CI)
AEs				
New diagnosis of infection until day 28	Not reported	33 (21.9)	43 (29.1)	7.2 (-3.3 to 17.7)
Ventilator-associated pneumonia	Not reported	19 (12.6)	29 (19.6)	7.0 (-2.0 to 16.0)
Catheter-related bloodstream infection	Not reported	10 (6.6)	8 (5.4)	-1.2 (-7.3 to 4.8)
Catheter-associated urinary tract infections	Not reported	1 (0.7)	0 (0)	Not reported
Other	Not reported	6 (4)	7 (4.7)	0.7 (-2.5 to 4.2)
Bacteremia	Not reported	12 (7.9)	14 (9.5)	1.5 (-5.5 to 8.6)
Insulin use for hyperglycemia	Not reported	47 (31.1)	42 (28.4)	-2.7 (-13.8 to 8.3
SAEs				
	Not reported	5 (3.3)	9 (6.1)	2.8 (-2.7 to 8.2)

Source: [36, 37]
Abbreviations: AEs: Adverse events; SAEs: Serious adverse events

No published prospective observational studies were found related to dexamethasone safety.

Results of meta-analysis, with moderate, low and very low certainty of evidence, related to effectiveness and safety of dexamethasone reported in 2 RCTs, can be found below, in the Summary of Findings Table 4.2.

Table 4.2: Summary of findings (SoF) table for published RCTs related to effectiveness of Dexamethasone (2 RCTs: Horby, Tomazini)

Patient or population: Patients with moderate to critical COVID-19 (* indicates subgroup population in line with EMA recommended indication)
Setting: Hospital
Intervention: Dexamethasone on top of standard care
Comparison: Standard care

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect difference (95% CI)	Number of participants (studies)	Certainty of evidence[d] (GRADE)	Comments
	Risk with Standard care[a]	Risk with Dexamethasone					
All-cause Mortality							
Mixed population (moderate to critical COVID-19)[b]	269 per 1.000	242 per 1.000	**RR 0.90** (0.82 to 0.97)	**27 fewer per 1.000** (from 47 fewer to 8 fewer)	6724 (2 RCTs) [36, 37]	MODERATE ⊕⊕⊕◯	Downgraded one level for performance bias
Moderate COVID-19[b]	140 per 1.000	178 per 1.000	**RR 1.27** (1.00 to 1.61)	**38 more per 1.000** (from 0 fewer to 86 more)	1535 (1 RCT) [36]	MODERATE ⊕⊕⊕◯	Downgraded one level for high risk of performance bias
***Severe** COVID-19[b]	262 per 1.000	233 per 1.000	**RR 0.89** (0.79 to 1.00)	**29 fewer per 1.000** (from 55 fewer to 0 fewer)	3883 (1 RCT) [36]	MODERATE ⊕⊕⊕◯	Downgraded one level for high risk of performance bias
***Critical** COVID-19[b]	450 per 1.000	379 per 1.000	**RR 0.81** (0.62 to 1.05)	**86 fewer per 1000** (from 171 fewer to 23 more)	1306 (2 RCTs) [36, 37]	Low ⊕⊕◯◯	Downgraded two levels for high risk of performance bias (1 level), imprecision and inconsistency (1 level mainly for imprecision but also because of inconsistency)
Number of patients discharged within 28 days							
Mixed population (moderate to critical COVID-19)[b]	620 per 1.000	775 per 1.000	**RR 1.25** (0.82 to 1.91)	**155 more per 1.000** (from 112 fewer to 564 more)	6724 (2 RCTs) [36, 37]	VERY LOW ⊕◯◯◯	Downgraded by 3 levels for performance bias, inconsistency and imprecision
Moderate COVID-19[b]	804 per 1.000	772 per 1.000	**RR 0.96** (0.90 to 1.01)	**32 fewer per 1.000** (from 80 fewer to 8 more)	1535 (1 RCT) [36]	MODERATE ⊕⊕⊕◯	Downgraded one level for risk of performance (detection) bias
***Severe** COVID-19[b]	675 per 1.000	722 per 1.000	**RR 1.07** (1.02 to 1.12)	**47 more per 1.000** (from 13 more to 81 more)	3883 (1 RCT) [36]	MODERATE ⊕⊕⊕◯	Downgraded one level for risk of performance (detection) bias

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect difference (95% CI)	Number of participants (studies)	Certainty of evidence[d] (GRADE)	Comments
	Risk with Standard care[a]	Risk with Dexamethasone					
***Critical** COVID-19[c]	221 per 1.000	323 per 1.000	**RR 1.46** (1.21 to 1.76)	**102 more per 1.000** (from 46 more to 168 more)	1306 (2 RCTs) [36, 37]	MODERATE ⊕⊕⊕◯	Downgraded one level for risk of performance (detection) bias
Number of patients with serious adverse events							
***Critical** COVID-19[c]	61 per 1.000	33 per 1.000	**RR 0.54** (0.19 to 1.59)	**28 fewer per 1.000** (from 49 fewer to 36 more)	299 (1 RCT) [37]	LOW ⊕⊕◯◯	Downgraded of two levels for risk of performance (detection) bias and imprecision

Source: based on publications [36, 37] Outcome data http://deplazio.net/farmacicovid/index.html; c outcome data and GRADE assessment from Covid-nma.com [27], https://covid-nma.com/living_data/index.php; descriptions and layout modified by the authors of this report; outcome data and GRADE-assessment added by the authors for the outcome mortality in critically ill COVID-19 patients.

[a] Background risk in the control group is based on the observed risk in the studies
[b] Outcome data and GRADE assessment from the department of Epidemiology Lazio Regional Health Service (DEPLazio), Italy [26], http://deplazio.net/farmacicovid/index.html or https://eunethta.eu/wp-content/uploads/2020/08/EUnetHTA-Covid-19_RCR08_DEXAMETHASONE_August2020_FINAL.docx.pdf. Details on the risk of bias assessment with the Cochrane risk of bias 2 tool can be found in Table A9.
[c] Outcome data from the original publication; risk of bias assessments and certainty of evidence assessment adapted from https://covid-nma.com/living_data/index.php; and http://deplazio.net/farmacicovid/index.html.
[d] 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.

Abbreviations: CI= confidence interval; RR=relative risk; HR=hazard ratio.

4.4 Ongoing studies

There are several registered ongoing clinical trials evaluating dexamethasone and other glucocorticoids in COVID-19 patients in ClinicalTrials.gov and EUdraCT registers. Details related to the RCTs on dexamethasone alone, or dexamethasone in combination with another pharmacotherapy, can be found in Table A11, Table A12, Table A13 and Table A14 in Appendix 3.

5 DISCUSSION

Evidence on effectiveness and safety of dexamethasone versus standard care comes from two published RCTs. The results of a subgroup analysis of the RECOVERY trial [36] related to the most important clinical outcome "all-cause mortality" suggests that the relative effects of systemic dexamethasone treatment varied as a function of the level of respiratory support received at randomization. Dexamethasone reduced deaths by one-third in patients receiving invasive mechanical ventilation, by one-fifth in patients receiving oxygen without invasive mechanical ventilation, but did not reduce mortality in patients not receiving respiratory support at randomization. Allocation to dexamethasone was associated with a shorter duration of hospitalization than usual care and a greater probability of discharge within 28 days with the greatest effect seen among those receiving invasive mechanical ventilation at baseline. The risk of progression to invasive mechanical ventilation was lower among those allocated to dexamethasone vs usual care. Analyses are ongoing regarding cause-specific mortality, the need for renal dialysis or hemofiltration, and the duration of ventilation. Adverse events were not reported in this preliminary report.

The CoDEX trial showed that among patients with COVID-19 and moderate or severe ARDS (critically ill COVID-19 patients), use of intravenous dexamethasone plus standard care compared with standard care alone resulted in a statistically significant increase in the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days. Stopping the study early, when RECOVERY results were announced, resulted in a sample size that was underpowered to adequately evaluate the effect of dexamethasone on the primary outcome as well as on mortality and other secondary outcomes (all secondary outcomes were not statistically significant different between groups) [37].

The above findings support the use of dexamethasone only for patients with hypoxaemia, not those with moderate disease, which is in line with the EMA endorsed new indication for dexamethasone.

The data does not support use of dexamethasone or other corticosteroids in the hospitalised moderate COVID-19 patients and outpatient setting [8].

Limitations

Both trials analysed in our report have some limitations.

In the preliminary report of the **RECOVERY trial** adverse events were not reported. No information provided on administration of other usual standard of care pharmaceuticals, like anti-thrombotic or antibiotics, or other non-drug interventions, so variation in clinical practice across trial sites could not be excluded. The impact of such possible variation on balance between groups in not known. Due to open label design, some secondary outcomes like initiation of mechanical ventilation could be biased. Some baseline comorbidities were not reported, like hypertension and obesity, which could impact the generalisability of results. As only 2% of those receiving invasive mechanical ventilation were older than 80 years, this could limit generalisability also. Longer-term follow up data are not known yet [38].

The **CoDEX trial** has several limitations. It was underpowered for important secondary outcomes like mortality, but also for the primary outcome. The study was interrupted before the original sample size was obtained due to RECOVERY trial evidence of benefit, and the obtained sample size was limited to demonstrate benefits in secondary outcomes. The open-label design and investigator reported data on adverse events and infections may have led to bias in the description of these events. 35% of the patients in the control group received at least one dose of corticosteroids during the study period, potentially reducing the effect size between the study group (the use of corticosteroids in the control group would have biased the results toward the null, and the study identified a benefit of the intervention on the primary outcome). The validity of, and minimal clinically important difference in the SOFA scores were not reported by the study authors [39, 40].

Recently, prospective meta-analysis from the WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group with pooled data from 7 trials, evaluating systemic corticosteroids versus usual care in COVID-19 critically ill patients, and the new WHO living guidance on corticosteroids for COVID-19 were published [7, 41]. The resulting evidence summary suggested that systemic corticosteroids probably reduce 28-day mortality in patients with critical COVID-19 (moderate certainty evidence; seven

studies,1703 patients; relative risk [RR] 0.80, 95% CI 0.70–0.91; absolute effect estimate 87 fewer deaths per 1000 patients, 95% CI 124 fewer to 41 fewer), and also in those with severe disease (moderate certainty evidence; one study, 3883 patients; RR 0.80, 95% CI 0.70–0.92; absolute effect estimate 67 fewer deaths per 1000 patients, 95% CI 100 fewer to 27 fewer). Systemic corticosteroids may increase the risk of death when administered to patients with non-severe COVID-19 (low certainty evidence; one study, 1535 patients; RR 1.22, 95% CI 0.93–1.61; absolute effect estimate 39 more per 1000 patients, 95% CI 12 fewer to 107 more). Systemic corticosteroids probably reduce the need for invasive mechanical ventilation (moderate certainty of evidence; two studies, 5481 patients; RR 0.74, 95% CI 0.59–0.93). Harms, in the context of the mortality reduction in severe disease, are minor.

Evidence gaps

No evidence was found regarding the effectiveness and safety of dexamethasone therapy in the long term among patients with COVID-19. Long-term effects of systemic dexamethasone on mortality, functional and safety outcomes (i.e., an increased risk of infections, including bacterial, fungal, and Strongyloides infections) in COVID-19 survivors are still needed. Generalizability of study results to populations that were under-represented in the trials like patients with hypertension, obesity, children, immunocompromised patients, patients with tuberculosis, pregnant or lactating women is not known yet. Because virological measures such as viral load were not reported, the effect of dexamethasone treatment on viral replication is not known yet. This is important to guide treatment decisions, including timing. Adults requiring ventilation in RECOVERY trial were relatively young (a mean age of 59 years). In a post hoc subset analysis, dexamethasone did not benefit the two older age groups; the benefits and risks of dexamethasone for oldest adults remain unclear. No evidence was found comparing the effectiveness of systemic dexamethasone therapy to other active treatments (like remdesivir) nor in combination therapy [7, 8, 38-40, 42].

In further research, investigational therapies for severe and critical COVID-19, using well designed RCTs with adequate sample sizes and longer duration of follow-up, should be compared with systemic dexamethasone (or equivalent dose of other corticosteroids) or evaluated in combination with systemic dexamethasone (or equivalent dose of other corticosteroids) vs systemic dexamethasone (or equivalent dose of other corticosteroids) alone (Table A15, Appendix 4).

6 SUMMARY OF CLINICAL EFFECTIVENESS AND SAFETY WITH CONCLUSION

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

6.1 Effectiveness

All-cause mortality

- Mixed population (moderate to critical COVID-19)
    - According to the results of two RCTs [36, 37] with moderate certainty of evidence, dexamethasone probably reduces the risk of mortality for all causes in COVID-19 patients; RR 0.90 (95% CI 0.82 to 0.97); absolute effect estimate 27 fewer per 1000 (95% CI from 47 fewer to 8 fewer).
- Moderate COVID-19
    - In patients with moderate COVID-19, systemic dexamethasone probably increases the risk of death (moderate certainty of evidence, one RCT) [36]; RR 1.27 (95% CI 1.00 to 1.61); absolute effect estimate 38 more per 1000 (95% CI from 0 fewer to 86 more).
- Severe COVID-19
    - According to the results of one RCTs) [36] with moderate certainty of evidence, dexamethasone probably reduces the risk of all-cause mortality in severe COVID-19; RR 0.89 (95% CI 0.79 to 1.00); absolute effect estimate 29 fewer per 1000 (95% CI from 55 fewer to 0 fewer).
- Critical COVID-19
    - In critically ill COVID-19 patients, dexamethasone may reduce the risk of all-cause mortality (low certainty of evidence) (two RCTs) [36, 37]; RR 0.81 (95% CI 0.62 to 1.05); absolute effect estimate 86 fewer per 1000 (95% CI from 171 fewer to 23 more).

Number of patients discharged within 28 days

- Mixed population (moderate to critical COVID-19)
    - According to the results of two RCTs [36, 37] with very low certainty of evidence, whether or not dexamethasone impacts on the increase number of patients discharged at 28 days is uncertain; RR 1.25 (95% CI 0.82 to 1.91); absolute effect estimate 155 more per 1000 (95% CI from 112 fewer to 564 more).
- Moderate COVID-19
    - In patients with moderate COVID-19, systemic dexamethasone probably does not increase the number of patients discharged to 28 days (moderate certainty of evidence, one RCT) [36]; RR 0.96 (95% CI 0.90 to 1.01); absolute effect estimate 32 fewer per 1000 (95% CI from 80 fewer to 8 more).
- Severe COVID-19
    - In patients with severe COVID-19, dexamethasone probably increases the number of patients discharged up to 28 days (moderate certainty of evidence, one RCT) [36]; RR 1.07 (95% CI 1.02 to 1.12); absolute effect estimate 47 more per 1000 (95% CI from 13 more to 81 more).
- Critical COVID-19
    - According to the results of two RCTs [36, 37] with moderate certainty of evidence, in patients with critical COVID-19, dexamethasone probably increases the number of patients discharged to 28 days; RR 1.46 (95% CI 1.21 to 1.76); absolute effect estimate 102 more per 1000 (95% CI from 46 more to 168 more).

Progression to invasive mechanical ventilation or death

- Mixed population (moderate and severe COVID-19)

- Based on the results from one RCT [36], the risk of progression to invasive mechanical ventilation or death was probably somewhat lower among those allocated to dexamethasone vs usual care, but the difference was not statistically significant (risk ratio 0.92; 95% CI 0.84 to 1.01).

- Moderate COVID-19
  - Based on the results from one RCT [36], in moderate COVID-19, the risk of progression to invasive mechanical ventilation or death was probably higher among those allocated to dexamethasone vs usual care, but the difference was not statistically significant (risk ratio 1.19 [95% CI 0.95 to 1.49).

- Severe COVID-19
  - Based on the results from one RCT [36], in severe COVID-19 patients, the risk of progression to invasive mechanical ventilation or death was probably lower among those allocated to dexamethasone when compared to usual care (risk ratio 0.87 [95% CI 0.79 to 0.96).

28-day ventilator-free days (the number of days alive and not dependent on mechanical ventilation for a minimum of 48 consecutive hours)

- Critical COVID-19
  - In patients with critical COVID-19, dexamethasone treatment probably increases the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days (6.6 vs 4.0, p=0.04) [37].

6.2 Safety

Number of patients with serious adverse events

- Critical COVID-19
  - According to the results of 1 RCT [37] with low certainty of evidence, dexamethasone may decrease the number of critically ill COVID-19 patients with serious adverse events, but the underlying data is also compatible with an increased risk /RR 0.54 (95% CI 0.19 to 1.59); absolute effect estimate 28 fewer per 1000 (from 49 fewer to 36 more).

No published prospective observational studies were found related to dexamethasone safety.

All results described above support the new indication for dexamethasone in COVID-19 endorsed by EMA: the use of dexamethasone in COVID-19 adults and adolescents (from 12 years of age and weighing at least 40 kg) who require supplemental oxygen therapy, in dose 6 milligrams once a day for up to 10 days.

6.3 Scientific conclusion

- Systemic dexamethasone probably reduces the risk of all-cause mortality in severe COVID-19 patients (moderate certainty of evidence). In critical COVID-19, dexamethasone may reduce the risk of all-cause mortality (low certainty of evidence). For patients with moderate COVID-19 disease the risk is probably increased (moderate certainty of evidence).
- In severe COVID-19 patients, the risk of progression to invasive mechanical ventilation or death is probably lower among those allocated to dexamethasone, but not in moderate COVID-19. Also, in patients with critical COVID-19, dexamethasone treatment probably increases the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days.
- In severe and critical COVID-19, dexamethasone probably increases the number of patients discharge within 28 days (moderate certainty of evidence).

- Based on the results of one RCT with low certainty of evidence, dexamethasone may decrease the number of patients with serious adverse events.
- These results fully support the recently endorsed indication for dexamethasone in COVID-19 by EMA.
- Results of several RCTs and a meta-analysis on corticosteroids treatment in severe and critical COVID-19 suggest that the observed effectiveness in COVID-19 patients on some outcomes may be a class effect of corticosteroids.
- Results on some short and long-term effectiveness outcomes are still awaited: duration of oxygen treatment (not invasive mechanical ventilation or ECMO); 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; time to clinical improvement; length of hospital stay; 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 dexamethasone alone, or in combination with other investigational drugs, for treatment of COVID-19 patients are under way. Update of this document is envisaged after new evidence is available.

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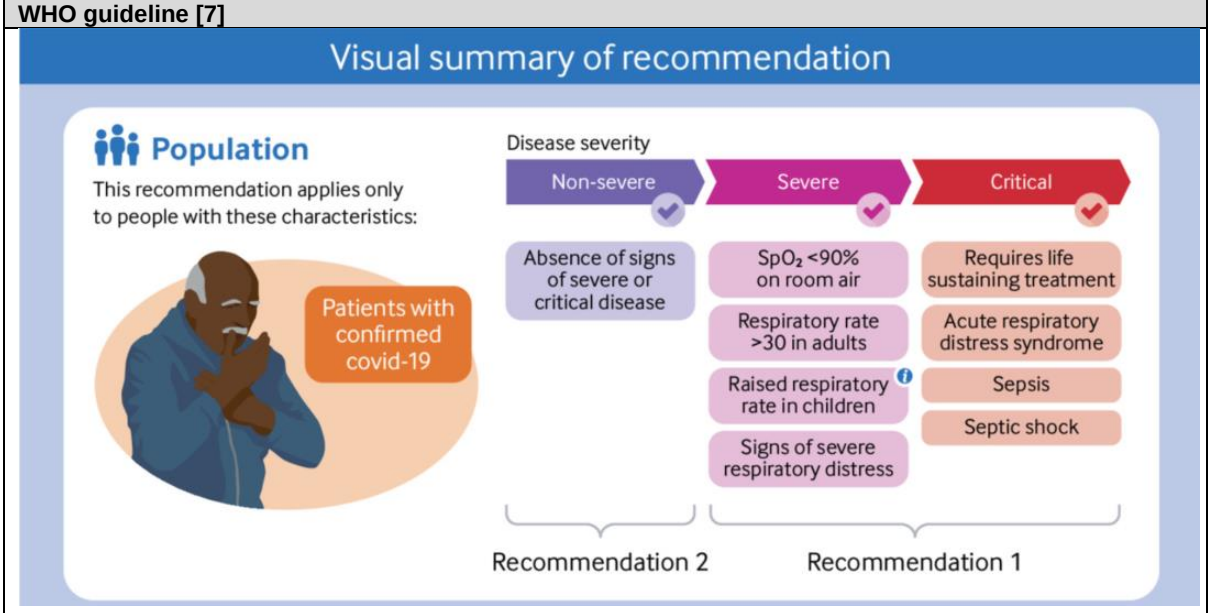
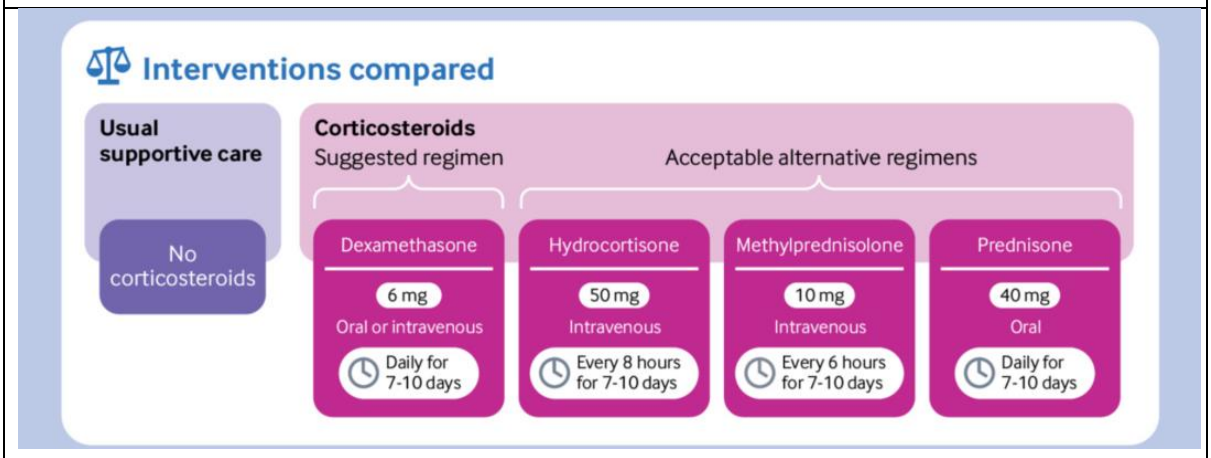
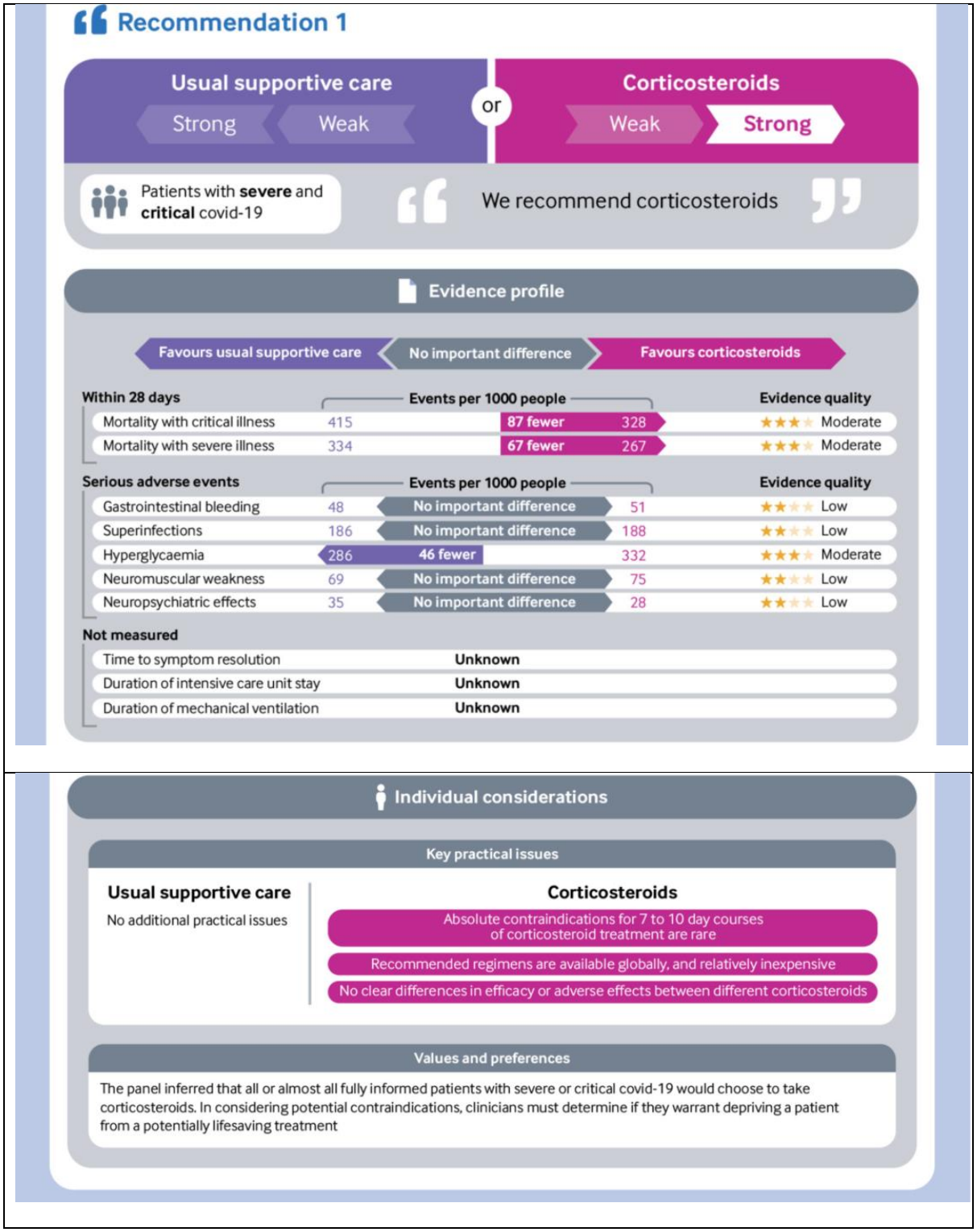
APPENDIX 1: CLINICAL GUIDELINES FOR MANAGEMENT

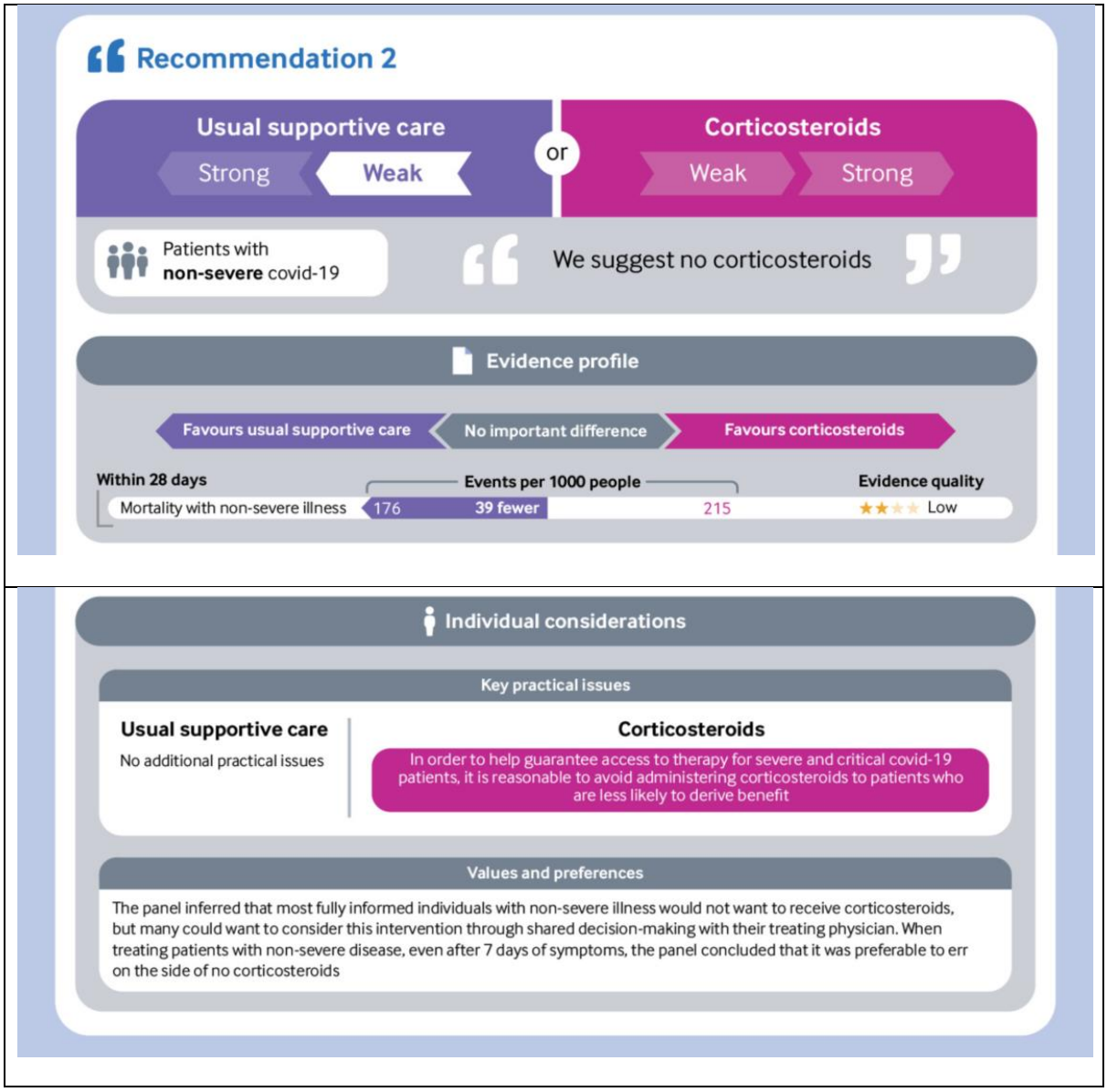
Table A1: Visual summary of recommendations on dexamethasone (corticosteroids) treatment according to COVID-19 severity: WHO guideline and US NIH Guideline

WHO guideline [7]






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 [1]

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS *(Recommendations are listed in order of preference in each category below; however, all options are considered acceptable.)*
Not Hospitalized ***or*** **Hospitalized but Does Not Require Supplemental Oxygen**	No specific antiviral or immunomodulatory therapy recommended The Panel **recommends against** the use of **dexamethasone (AI)** See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.[a]
Hospitalized and Requires Supplemental Oxygen **(but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)**	**Remdesivir** 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first **(AI)**[b,c,d] ***or*** **Remdesivir** (dose and duration as above) plus **dexamethasone**[e] 6 mg IV or PO for up to 10 days or until hospital discharge, whichever comes first **(BIII)**[f] If **remdesivir** cannot be used, **dexamethasone**[e] may be used instead **(BIII)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	**Dexamethasone**[d] plus **remdesivir** at the doses and durations discussed above **(AIII)**[f] ***or*** **Dexamethasone**[d,e] at the dose and duration discussed above **(AI)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[d,e] at the dose and duration discussed above **(AI)** ***or*** **Dexamethasone**[e] plus **remdesivir** for patients who have recently been intubated at the doses and durations discussed above **(CIII)**[f]

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

[a] The Panel recognizes that there may be situations in which a clinician judges that remdesivir is an appropriate treatment for a hospitalized patient with moderate COVID-19 (e.g., a patient who is at a particularly high risk for clinical deterioration). However, the Panel finds the data insufficient to recommend either for or against using remdesivir as routine treatment for all hospitalized patients with moderate COVID-19.
[b] Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.
[c] The Panel recognizes there is a theoretical rationale for initiating remdesivir plus dexamethasone in patients with rapidly progressing COVID-19.
[d] 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.
[e] If dexamethasone is not available, equivalent doses of other corticosteroids, such as prednisone, methylprednisolone, or hydrocortisone, may be used. See Corticosteroids for more information.
[f] The combination of dexamethasone and remdesivir has not been studied in clinical trials; see text for the rationale for using this combination.

Key: ECMO = extracorporeal membrane oxygenation; IV = intravenously; PO = orally

APPENDIX 2: LITERATURE SEARCH AND FLOW-DIAGRAMS FOR RCTS AND OBSERVATIONAL STUDIES

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 [pt]) OR (controlled clinical trial [pt])) 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])	06/11/2020
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"	06/11/2020
OVID EMBASE	ovidsp.dc2.ovid.com	1. exp Coronavirinae/ or exp Coronavirus/ 2. exp Coronavirus infection/	06/11/2020

Database	URL	Search line / Search terms	Date of search
		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"	

Table A3: Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search
OVID Medline	Imported from EPPI Centre	1 exp Coronavirus/ 2 exp Coronavirus Infections/ 3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4 (or/1-3) and ((20191* or 202*).dp. or 20190101:20301231.(ep).) 5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. 6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp. 7 (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or COVID-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or COVID-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. 8 COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os. 9 ("32240632" or "32236488" or "32268021" or "32267941" or "32169616" or "32267649" or "32267499" or "32267344" or "32248853" or "32246156" or "32243118" or "32240583" or "32237674" or "32234725" or "32173381" or "32227595" or "32185863" or "32221979" or "32213260" or "32205350" or "32202721" or "32197097" or "32196032" or "32188729" or "32176889" or "32088947" or "32277065" or "32273472" or "32273444" or "32145185" or "31917786" or "32267384" or "32265186" or "32253187" or "32265567" or "32231286" or "32105468" or "32179788" or "32152361" or "32152148" or "32140676" or "32053580" or "32029604" or "32127714" or "32047315" or "32020111" or "32267950" or "32249952" or "32172715").ui. 10 or/6-9 11 5 or 10	27/09/2020 until 25/10/2020
OVID EMBASE		1 exp Coronavirus Infections/ 2 exp coronavirinae/ 3 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-	27/09/2020 until 25/10/2020

		coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*).mp. 4 or/1-3 5 4 not (SARS or SARS-CoV or MERS or MERS-CoV or Middle East respiratory syndrome or camel* or dromedar* or equine or coronary or coronal or covidence* or covidien or influenza virus or HIV or bovine or calves or TGEV or feline or porcine or BCoV or PED or PEDV or PDCoV or FIPV or FCoV or SADS-CoV or canine or CCov or zoonotic or avian influenza or H1N1 or H5N1 or H5N6 or IBV or murine corona*).mp. 6 ((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp. 7 (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or COVID-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV on nCoV or covid or coronavirus* or corona virus or Pandemi*2)) or ((covid or covid19 or COVID-19) and pandemic*2) or (coronavirus* and pneumonia)).mp. 8 6 or 7 9 5 or 8	
Scopus		TITLE-ABS-KEY(((pneumonia OR covid* OR coronavirus* OR "corona virus*" OR ncov* OR 2019-ncov OR sars*) AND Wuhan) OR 2019-ncov OR ncov19 OR ncov-19 OR "2019-novel CoV" OR sars-cov2 OR sars-cov-2 OR sarscov2 OR sarscov-2 OR sars-coronavirus2 OR sars-coronavirus-2 OR "SARS-like coronavirus*" OR coronavirus-19 OR covid19 OR COVID-19 OR "covid 2019" OR ((novel OR new OR nouveau) W/1 (CoV OR nCoV OR covid OR coronavirus* OR "corona virus*" OR pandemi*)) OR ((covid OR covid19 OR COVID-19) AND pandemic*) OR ((coronavirus* OR "corona virus*") AND pneumonia)) AND ORIG-LOAD-DATE > 20200920[date changes from week to week] AND ORIG-LOAD-DATE < 20200928 [date changes from week to week] AND NOT INDEX(medline)	27/09/2020 until 25/10/2020

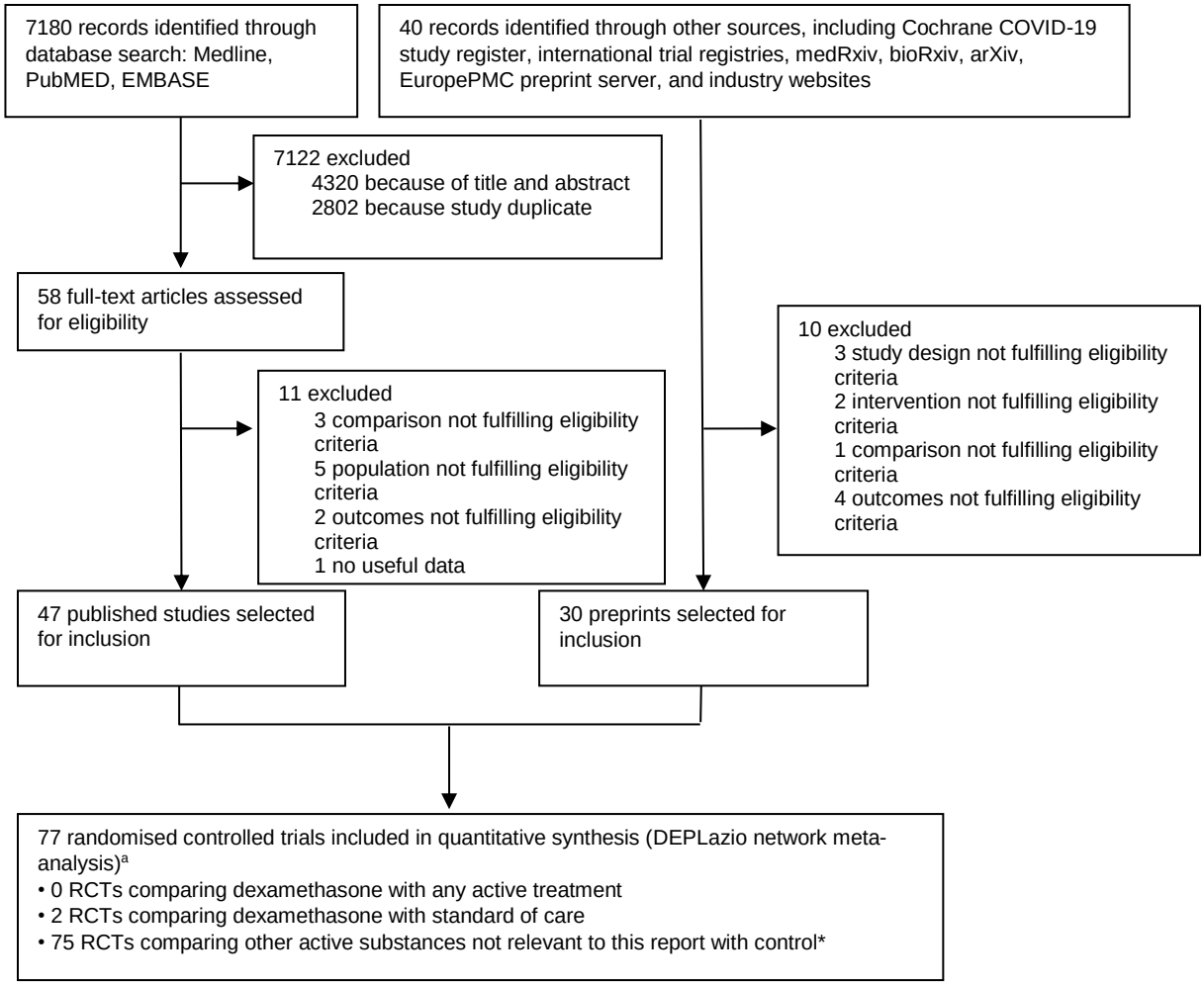


Figure A1: Flow diagram depicting the selection process of RCTs

[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.

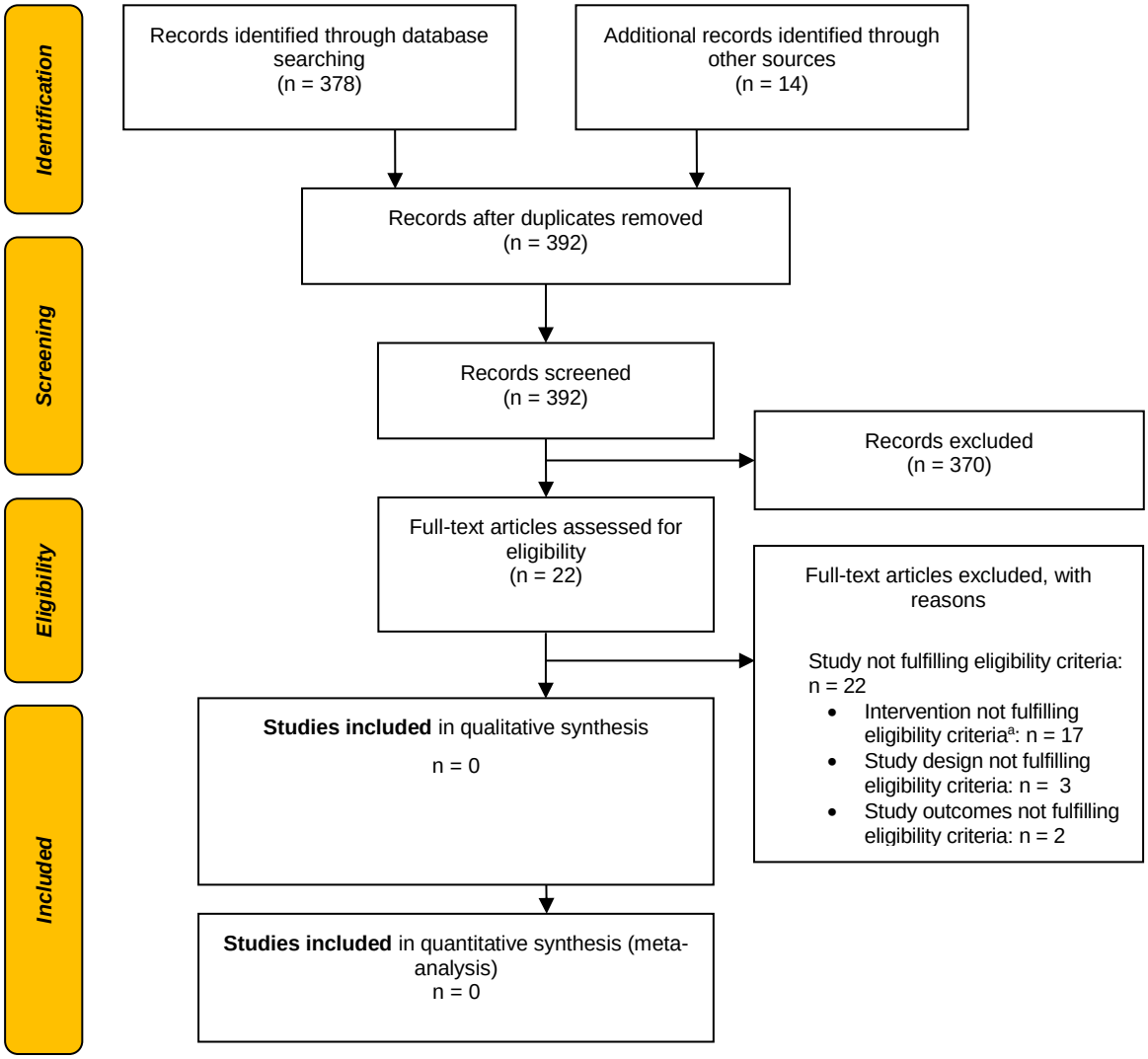


Figure A2: Flow diagram depicting the selection process of observational studies

[a] Studies evaluating active substances relevant to other EUnetHTA rolling collaborative reviews

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

In this appendix, we provide additional tables and figures related to studies characteristics, patients characteristics, effectiveness outcomes, risk of bias, certainty of evidence and ongoing studies.

STUDIES CHARACTERISTICS

Table A4: Characteristics of the studies included

Study reference/ID	Study design	Patient population	Dexamethasone (number of randomized patients)	Standard of care (number of randomized patients)	Study duration and data cut off(s)	Primary outcome; patient-relevant secondary outcomes
Direct comparison: Dexamethasone vs standard of care						
RECOVERY [36] (NCT04381936; ISRCTN number 50189673)	RCT: open label multicentre platform trial with adaptive design* No. centers: 176	N=6425 Country: UK Setting: hospitalised Mean age (SD): 66.1 (15.7) 4087 (64%) males Severity: Moderate: n=1535 Severe: n=3883 Critical: n=1007	Dexamethasone 6 mg PO/IV once daily for a duration of up to 10 days, plus standard of care as custom in the participating hospital. Group 1 (N = 2104) Relevant subpopulation: Group 1 critical COVID-19 (n = 324) Group 1 severe COVID-19 (n=3883) Group 1 moderate COVID-19 (n = 1535)	Standard of care as custom in the participating hospital Group 2 (N = 4321) Relevant subpopulation: Group 2 critical COVID-19 (n = 683)	Recruitment: from March 19 to June 8, 2020 Follow-up: 28 days Type of analysis: preliminary report with the final and planned analyses on part of the clinical outcomes, including the primary outcomes **	Primary outcome: 28-day mortality Secondary outcomes: time until discharge from the hospital composite outcome of death or receipt of invasive mechanical ventilation (including extracorporeal membrane oxygenation) or death in those who were not receiving invasive mechanical ventilation at the time of randomization. Other pre-specified clinical outcomes: Receipt of invasive mechanical ventilation cause-specific mortality, receipt of renal hemodialysis or hemofiltration, major cardiac arrhythmia (recorded in a subgroup),

Study reference/ID	Study design	Patient population	Dexamethasone (number of randomized patients)	Standard of care (number of randomized patients)	Study duration and data cut off(s)	Primary outcome; patient-relevant secondary outcomes
						receipt and duration of ventilation. Primary analyses: ITT Secondary: none, ITT only‡
CoDEX [37] (NCT04327401)	RCT: multicenter, randomized, open-label, clinical trial No. centers: 41	N=299 Country: Brazil Setting: intensive care units (ICUs) Mean age: Gender: Severity: critical n= 299, with moderate tosevere ARDS, according to the Berlin definition	Dexamethasone 20 mg IV daily for 5 days, then 10 mg IV daily for5 days plus standard of care Group 1: n = 151 Relevant subgroup: none	Standard of care, not further described Group 2: n = 148	Recruitment: from April 17 to June 23 2020 Follow-up: 28 days after randomization or until hospital discharge, whichever occurred first Type of analyses: final, stopped early following publication of the RECOVERY trial, before reaching the planned sample size of 350 patients (unplanned)	Primary outcome: Ventilator-free days during the first 28 days, defined as being alive and free from mechanical ventilation Secondary outcomes: • all-cause mortality at 28 days, • clinical status of patients at day 15§, • ICU-free days during the first 28 days, • mechanical ventilation duration at 28 days, Sequential Organ Failure Assessment (SOFA)‖. Primary analyses: ITT Sensitivity analyses: PP & AT

Source: [36, 37]
* Results from a preliminary report of the RECOVERY trial are related to the comparison of oral or intravenous dexamethasone 6 mg given once daily for up to ten days (2104 patients) plus the usual standard of care vs usual care alone (4321 patients);
**Analyses regarding cause-specific mortality, the need for renal dialysis or hemofiltration and the duration of ventilation are ongoing and not yet published.
‡ Pre-specified subgroup analyses performed for the primary outcome, by age, sex, level of respiratory support; time since onset of symptoms and predicted 28-day mortality risk;
§ using a 6-point ordinal scale: 1 not hospitalized, 2 hospitalized, not requiring supplemental oxygen, 3 hospitalized, requiring supplemental oxygen, 4 hospitalized, requiring non-invasive ventilation or nasal high-flow oxygen therapy, 5 hospitalized, requiring invasive mechanical ventilation or ECMO, and to 6, death; ‖ SOFA scores range from 0 to 24, with higher scores indicating greater organ dysfunction at 48 hours, 72 hours, and 7 days.
Abbreviations: AT=statistical analysis according to the "as-treated" principle; ITT=statistical analysis according to the intent-to-treat principle; IV=intravenous; PO=oral intake; PP= statistical analysis according to the per-protocol principle.

PATIENTS CHARACTERISTICS

Table A5: Patients characteristics at baseline, according to treatment assignment and level of respiratory support, RECOVERY trial

Characteristic	Treatment Assignment		Respiratory Support Received at Randomization		
	Dexamethasone (N=2104)	Usual Care (N=4321)	No Receipt of Oxygen (N=1535)	Oxygen Only (N=3883)	Invasive Mechanical Ventilation (N=1007)
Age†					
Mean — yr	66.9±15.4	65.8±15.8	69.4±17.5	66.7±15.3	59.1±11.4
Distribution — no. (%)					
<70 yr	1141 (54)	2504 (58)	659 (43)	2148 (55)	838 (83)
70 to 79 yr	469 (22)	859 (20)	338 (22)	837 (22)	153 (15)
≥80 yr	494 (23)	958 (22)	538 (35)	898 (23)	16 (2)
Sex — no. (%)					
Male	1338 (64)	2749 (64)	891 (58)	2462 (63)	734 (73)
Female‡	766 (36)	1572 (36)	644 (42)	1421 (37)	273 (27)
Median no. of days since symptom onset (IQR)§	8 (5–13)	9 (5–13)	6 (3–10)	9 (5–12)	13 (8–18)
Median no. of days since hospitalization (IQR)	2 (1–5)	2 (1–5)	2 (1–6)	2 (1–4)	5 (3–9)
Respiratory support received — no. (%)					
No oxygen	501 (24)	1034 (24)	1535 (100)	NA	NA
Oxygen only	1279 (61)	2604 (60)	NA	3883 (100)	NA
Invasive mechanical ventilation	324 (15)	683 (16)	NA	NA	1007 (100)
Previous coexisting disease					
Any	1174 (56)	2417 (56)	911 (59)	2175 (56)	505 (50)
Diabetes	521 (25)	1025 (24)	342 (22)	950 (24)	254 (25)
Heart disease	586 (28)	1171 (27)	519 (34)	1074 (28)	164 (16)
Chronic lung disease	415 (20)	931 (22)	351 (23)	883 (23)	112 (11)
Tuberculosis	6 (<1)	19 (<1)	8 (1)	11 (<1)	6 (1)
HIV infection	12 (1)	20 (<1)	5 (<1)	21 (1)	6 (1)
Severe liver disease¶	37 (2)	82 (2)	32 (2)	72 (2)	15 (1)
Severe kidney impairment‖	166 (8)	358 (8)	119 (8)	253 (7)	152 (15)
SARS-CoV-2 test result					
Positive	1850 (88)	3848 (89)	1333 (87)	3416 (88)	949 (94)
Negative	247 (12)	453 (10)	193 (13)	452 (12)	55 (5)
Test result not yet known	7 (<1)	20 (<1)	9 (1)	15 (<1)	3 (<1)

Source: **[36]**
† There was a significant (P=0.01) difference in the mean age between patients in the dexamethasone group and those in the usual care group, but there were no significant differences between the groups in any other baseline characteristic.
‡ Included in this category were 6 pregnant women.
§ Data regarding the number of days since symptom onset were missing for 4 patients in the dexamethasone group and 13 patients in the usual care group; these patients were excluded from estimates of the median number of days since onset.
¶ Severe liver disease was defined as requiring ongoing specialist care.
‖ Severe kidney impairment was defined as an estimated glomerular filtration rate of less than 30 ml per minute per 1.73 m2.
Abbreviations: ± values are the SD over the mean; HIV=human immunodeficiency virus; IQR=interquartile range; NA=not applicable; SARSCoV-2=severe acute respiratory syndrome coronavirus 2.

Table A6: Baseline characteristics of patients in CoDEX trial

Characteristic	No. (%)	
	Dexamethasone (n = 151)	Control (n = 148)
Age, mean (SD), y	60.1 (15.8)	62.7 (13.1)
Sex		
Women	61 (40.4)	51 (34.5)
Men	90 (59.6)	97 (65.6)
SAPS III[b]	69.4 (12.6)	71.1 (12.6)
SOFA, median (IQR)[c]	9 (7-10.5)	8 (7-11)
Time since symptom onset, median (IQR), d	9 (7-11)	10 (6-12)
Mechanical ventilation prior to randomization, median (IQR), d	1 (0-2)	1 (0-1)
COVID-19 status[d]		
Positive	144 (95.4)	142 (95.9)
Probable	7 (4.6)	5 (3.4)
Negative	0	1 (0.7)
Comorbidities and risk factors		
Hypertension	91 (60.3)	107 (72.3)
Diabetes	57 (37.8)	69 (46.6)
Obesity	46 (30.5)	35 (23.7)
Heart failure	11 (7.3)	12 (8.1)
Chronic kidney failure	7 (4.6)	9 (6.1)
Current smoker	6 (4.0)	7 (4.7)
Corticosteroids before randomization	7 (4.6)	3 (2)
Moderate or severe ARDS prior to randomization, h		
≤24	136 (90.1)	138 (93.9)
>24-≤48	15 (9.9)	9 (6.1)
Vasopressor use	99 (65.6)	101 (68.2)
Intravenous sedation	150 (99.3)	147 (100)
RASS[e]	−4.8 (0.8)	−4.6 (1.1)
Neuromuscular blockade use[f]	87 (57.6)	94 (63.5)
Prone position	33 (21.8)	33 (22)
Additional medication		
Hydroxychloroquine	36 (23.8)	28 (18.9)
Azithromycin	104 (68.9)	109 (73.6)
Other antibiotics	133 (88.1)	128 (86.5)
Oseltamivir	44 (29.1)	52 (35.1)
Respiratory variables, mean (SD)		
Tidal volume, mL/kg of predicted body weight	6.5 (1.1)	6.5 (1.4)
Minute ventilation, L/min	9.4 (2.3)	9.8 (2.7)
Inspiratory plateau pressure, cm H_2O	23.8 (4.8)	23.9 (5)
PEEP, cm H_2O	11.6 (2.9)	11.8 (2.7)
Driving pressure, cm H_2O	12.5 (3.1)	12.6 (3.6)
Pao_2, mm Hg	89 (29)	88.5 (27.1)
Pao_2:Fio_2	131.1 (46.2)	132.6 (45.7)
Laboratory variables[g]		
Serum creatinine, mg/dL, median (IQR)	1.3 (0.9-2.1)	1.3 (1-2.3)
Hemoglobin, mean (SD), g/dL	12.3 (2.3)	12.5 (2.0)
White blood cell count, median (IQR), $\times 10^9$/L	9.6 (7.7-14.0)	10.4 (7.2-14.6)
Lymphocyte count, median (IQR), $\times 10^9$/L	0.84 (0.62-1.27)	0.82 (0.58-1.21)
Platelets count, mean (SD), $\times 10^9$/L	246.2 (98.3)	247.5 (113)

Table A7: Baseline characteristics of patients in CoDEX trial continues

Characteristic	Dexamethasone (N = 151)	Control (N = 148)
Clinical Characteristics		
Temperature – ºC	36.6 (1.0)	36.6 (0.9)
Systolic blood pressure – mm Hg	119 (22)	118 (23)
Diastolic blood pressure – mm Hg	66 (12)	66 (13)
Mean arterial pressure – mm Hg	84 (13)	83 (14)
Heart rate – beats/minute	98 (19)	93 (19)
Oxygen saturation – %	94 (4)	93 (5)
Ventilation mode – no. (%)		
Pressure control ventilation	64 (42.4)	69 (46.6)
Volume control ventilation	73 (48.3)	66 (44.6)
Other	14 (9.3)	13 (8.8)
Respiratory variables at randomization		
$PaCO_2$ – mmHg	47 (14)	48 (13)
PaO_2:FiO_2 ≤100 – no. (%)	108 (71.5)	108 (73.0)
PaO_2:FiO_2 >100 and ≤200 – no. (%)	43 (28.5)	40 (27.0)
Respiratory system static compliance – mL/cm of water	32 (10)	33 (10)
Laboratory variables		
Serum pH	7.35 (0.1)	7.31 (0.1)
Serum bicarbonate – mmol/L	23.6 (5.0)	22.9 (4.6)
Bilirubin– umol/L, median (IQR)	0.44 (0.3 – 0.7)	0.49 (0.3 – 0.7)
Fibrinogen – mg/dL, median (IQR)	627 (445 – 742)	566 (467 – 711)
Triglycerides – mg/dL, median (IQR)	248 (193 – 347)	215 (146 – 343)
Ferritin – ng/mL, median (IQR)	1115 (628 – 2331)	1656 (936 – 2848)

Source: [37]
[a] Continuous variables are presented as mean (SD) unless otherwise indicated.
Abbreviations: IQR interquartile range, FiO2 fraction of inspired oxygen, PaO2 partial pressure of arterial oxygen, PaCO2 partial pressure of carbon dioxide, PaO2:FiO2 partial pressure of arterial oxygen to the fraction of inspired oxygen ratio. The number of patients with laboratory values available for each exam was: pH 299, bicarbonate 299, bilirubin 187, fibrinogen 155, triglycerides 101 and ferritin 104.

EFFECTIVENESS RESULTS – FIGURES AND TABLES

Table A8: Effectiveness outcomes

Outcomes	*Horby et al. 2020 [36] Moderate, severe and critically ill COVID-19 patients (Dexamethasone n=2104 vs Standard care n=4321)	**Tomazini et al. 2020 [37] Critically ill COVID-19 patients (Dexamethasone n=151 vs Standard care n=148)
All-cause mortality at 28 days *Overall*	482/2104 (22.9%) vs 1110/4321 (25.7%) Age adjusted rate ratio **0.83 (95% CI 0.75 to 0.93), p<0.001**	85/151 (56.3%) vs 91/148 (61.5%) Adjusted HR (95% CI) = 0.97 (0.72 to 1.31), p=0.85 Unadjusted HR (95% CI) = 0.86 (0.64 to 1.15), p=0.31
Patients *not receiving respiratory support at randomization*	89/501 (17.8%) vs 145/1034 (14.0%) Age adjusted rate ratio 1.19 (95% CI 0.91 to 1.55)	N.A
Patients *receiving oxygen without invasive mechanical ventilation*	298/1279 (23.3%) vs 682/2604 (26.2%) Age adjusted rate ratio **0.82 (95% CI 0.72 to 0.94)**	N.A
Patients *receiving invasive mechanical ventilation*	95/324 (29.3%) vs 283/683 (41.4%) Age adjusted rate ratio **0.64 (95% CI 0.51 to 0.81)**	85/151 (56.3%) vs 91/148 (61.5%) Adjusted HR (95% CI) = 0.97 (0.72 to 1.31), p=0.85 Unadjusted HR (95% CI) = 0.86 (0.64 to 1.15), p=0.31
Duration of hospitalisation	Median 12 days vs 13 days	Not measured
Discharge from hospital within 28 days	1413/2104 (67.2) vs 2745/4321 (63.5) Age adjusted rate ratio **1.10 (95% CI 1.03 to 1.17)**	42/151 (27.8%) vs 25/148 (16.9%) Adjusted OR‡ 1.89 (0.95 - 3.72), p=0.07 Unadjusted OR 1.9 (1.08 - 3.31), p=0.02
Risk of progression to invasive mechanical ventilation or death (among patients not receiving invasive mechanical ventilation at randomization)	456/1780 (25.6) vs 994/3638 (27.3) Age adjusted risk ratio, RR 0.92 (95% CI 0.84 to 1.01)	N.A
Invasive mechanical ventilation	102/1780 (5.7) vs 285/3638 (7.8) Age adjusted rate ratio 0.77 (0.62–0.95)	N.A
Death	387/1780 (21.7) vs 827/3638 (22.7) Age adjusted rate ratio 0.93 (0.84–1.03)	N.A
Days alive and ventilator free at 28-day	N.A	Mean days (95% CI) = 6.6 (5.0 to 8.2) vs 4.0 (2.9 to 5.4) Adjusted **MD (95% CI)ǂ = 2.26 (0.2 to 4.38); p=0.04** Unadjusted MD (95% CI) = 2.55 (0.46 to 4.6), p=0.02 (Favours dexamethasone)
ICU-free days at 28 days	N.A	Mean (95% CI) = 2.1 (1.0 to 4.5) vs 2.0 (0.8 to 4.2) Adjusted MD (95% CI)ǂ = 0.28 (-0.49 to 1.02) p=0.50 Unadjusted MD (95% CI) = 0.14 (-0.92 to 1.27); p=0.78
Mechanical ventilation duration (days)	Not reported in Preliminary report	Mean (95% CI) = 12.5 (11.2 to 13.8) vs 13.9 (12.7 to 15.1) Adjusted MD (95% CI)ǂ = -1.54 (-3.24 to 0.12), p=0.11

		Unadjusted MD (95% CI) = -1.46 (-3.10 to 0.57); p=0.18
Clinical status, 6-point ordinal scale at day 15ǂ	N.A	Adjusted OR (95% CI)ǂ 0.66 (0.43 to 1.03), p=0.07 Unadjusted OR (95% CI) 0.62 (0.41 to 0.94), p=0.03
Sequential Organ Failure Assessment score (SOFA) at day 7	N.A	Mean (95% CI) = 6.1 (5.5 to 6.7) vs 7.7 (6.9 to 8.1) Adjusted MD (95% CI)ǂ = -1.16 (-1.94 to -0.38), p=0.004 Unadjusted MD (95% CI) = -1.38 (-2.21 to -0.55); p=0.001

Primary outcomes in the trial are depicted in **bold**.
*Preliminary Report: analyses are ongoing regarding cause-specific mortality, the need for renal dialysis or hemofiltration, receipt and the duration of ventilation, major cardiac arrhythmia (recorded in a subgroup), and long term outcomes (e.g. 6 month survival), SAEs and AEs [36]
**Stopping the study early, when RECOVERY results were announced, resulted in a sample size that was underpowered to adequately evaluate the effect of corticosteroids on mortality and other secondary outcomes [37]
ǂ Adjusted analyses in the CoDEX trial: All models are adjusted for age and baseline at PaO2:FIO2 ratio with random intercept by site. ǂThe 6-point ordinal scale adapted from the World Health Organization R&D Blueprint expert group (1, not hospitalized; 2, hospitalized, not requiring supplemental oxygen; 3, hospitalized, requiring supplemental oxygen; 4, hospitalized, requiring non-invasive ventilation or nasal high-flow oxygen therapy; 5, hospitalized, requiring invasive mechanical ventilation or ECMO; and 6, dead). The distribution of values among the categories in the dexamethasone and control groups was 6 (35.8% vs 43.9%), 5 (31.8% vs 36.5%), 4 (4.6% vs 2.7%), 3 (16.6% vs 11.5%), 2 (0% vs 0%), and 1 (11.3% vs 5.4%).; SOFA, Sequential Organ Failure Assessment: Measured in 6 organ systems (cardiovascular, hematologic, gastrointestinal, renal, pulmonary and neurologic), with each organ scored from 0 to 4, resulting in an aggregated score that ranges from 0 to 24, with higher scores indicating greater dysfunction. An initial SOFA score up to 9 predicts a mortality risk of less than 33%. An unchanged or increasing score in the first 48 hours predicts a mortality rate of 60% when the initial score is 8 to 11. Missing values on individual SOFA components were imputed as normal [37]
Abbreviations: ICU=intensive care unit; HR= hazard ratio; IQR=interquartile range, MD=mean difference; MV=mechanical ventilation; OR,=odds ratio; PaO2:FIO2 ratio=ratio of arterial blood oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen; RR=risk ratio.

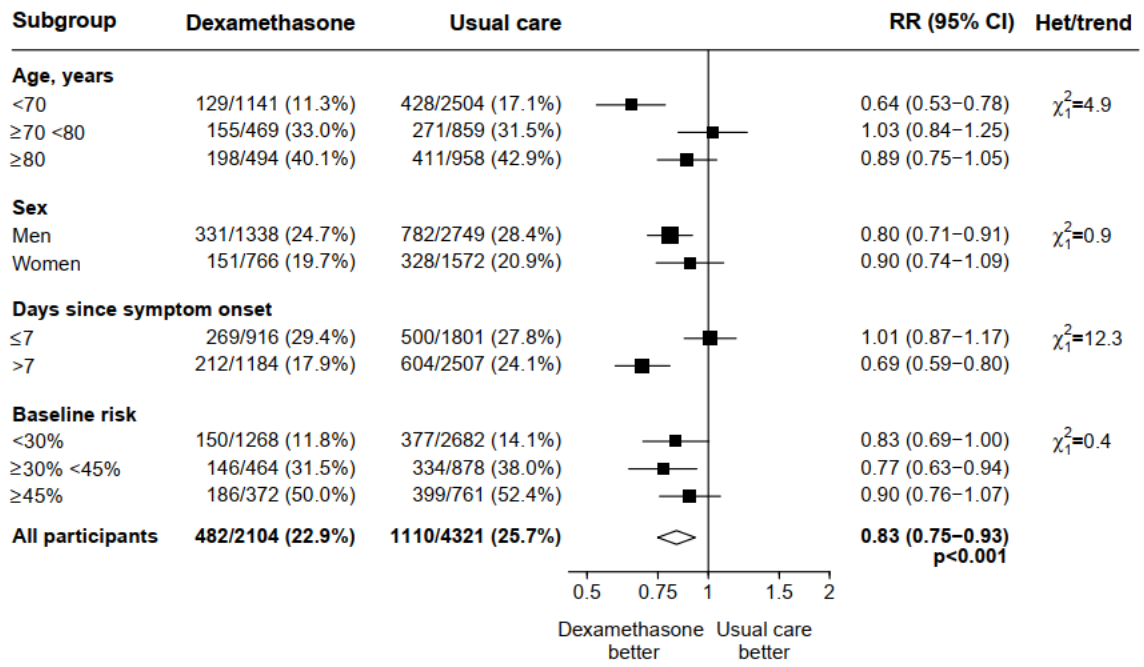


Figure A3: Forest plot Horby et al. 2020 - Effect of allocation to dexamethasone on 28-day mortality by other pre-specified baseline characteristics

Source: [36]
Abbreviation: RR=rate ratio adjusted for age

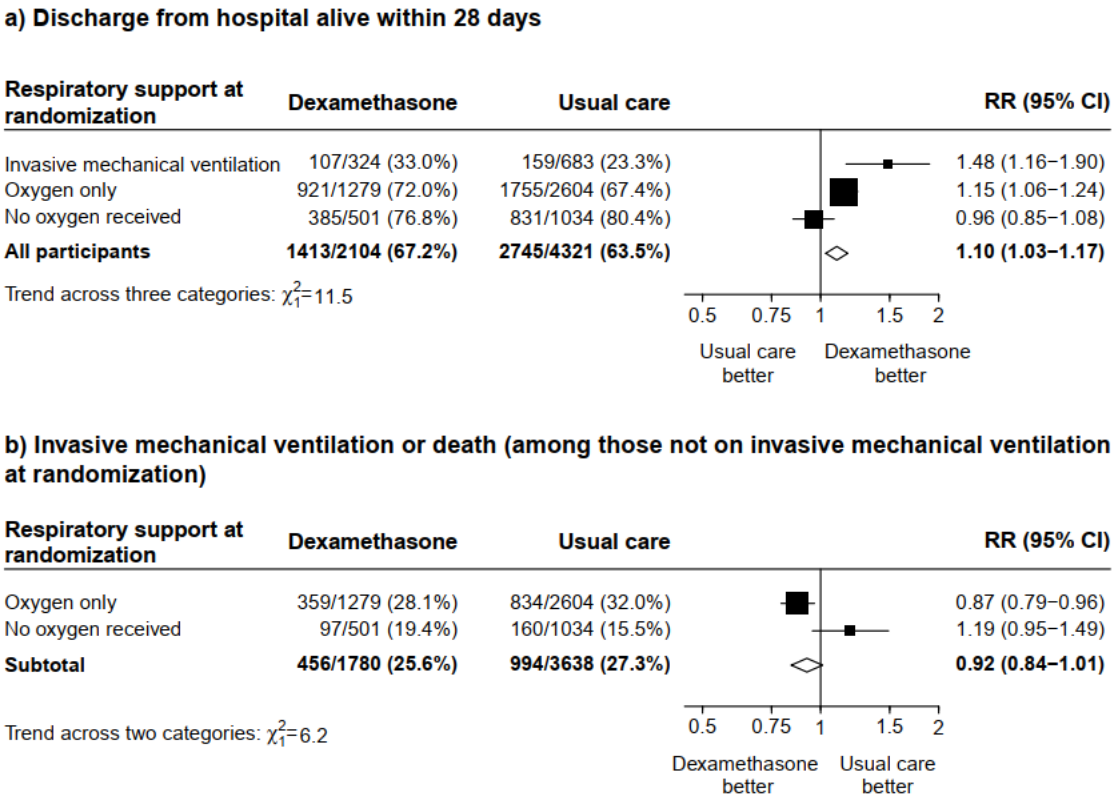


Figure A4: Forest plot Horby et al. 2020 - Effect of allocation to dexamethasone on: a) discharge from hospital alive within 28 days; and b) invasive mechanical ventilation or death, by level of respiratory support received at randomization

Source: [36]
Abbreviations: RR=age−adjusted rate ratio for panel a and age−adjusted relative risk for panel b; CI=confidence interval.

Subgroups	Dexamethasone	Control	Between group differences for ventilator free days at 28 days (95% CI)*	P-Value for interaction
	Mean (95% CI) (Number of cases)			
Age – yr				
< 60	11.7 (9.0 – 14.0) (n=68)	6.8 (4.4 – 9.7) (n=47)	4.76 (1.21 - 8.70)	0.21
≥ 60	2.5 (1.3 – 4.1) (n=83)	2.7 (1.7 – 3.8) (n=101)	-0.29 (-2.03 - 1.60)	
PaO_2:FiO_2 ratio				
≤ 100	9.0 (6.3 – 11.9) (n=43)	4.5 (2.0 – 7.7) (n=40)	4.00 (0.02 - 7.76)	0.73
> 100	5.7 (4.1 – 7.4) (n=108)	3.9 (2.6 – 5.4) (n=108)	4.63 (-0.46 - 9.28)	
SAPS III				
< 60	11.1 (6.6 – 14.2) (n=34)	6.4 (2.7 – 9.7) (n=32)	4.63 (-0.46 - 9.28)	0.75
≥ 60	5.5 (4.2 – 6.9) (n=117)	3.4 (2.1 – 5.8) (n=116)	1.94 (-0.15 - 4.03)	
Time since symptom onset – days				
≤ 7	5.4 (3.1 – 8.4) (n=54)	4.2 (2.3 – 6.6) (n=48)	1.41 (-1.75 - 4.58)	0.12
> 7	7.6 (5.7 – 9.0) (n=95)	3.9 (2.2 – 5.8) (n=99)	3.51 (1.00 - 6.03)	
Position at randomization				
Supine	6.5 (4.9 – 8.5) (n=115)	3.9 (2.7 – 5.1) (n=114)	2.52 (0.40 - 4.92)	0.89
Prone	7.3 (4.2 – 10.2) (n=33)	3.9 (1.9 – 6.8) (n=33)	3.39 (-0.98 - 7.56)	
Vasopressors at randomization				
No	10.2 (7.1 – 13.1) (n=52)	5.9 (3.2 – 7.8) (n=47)	4.32 (0.34 - 8.26)	0.81
Yes	4.8 (3.0 – 6.4) (n=99)	3.2 (2.1 – 4.5) (n=101)	1.63 (-0.44 - 3.60)	

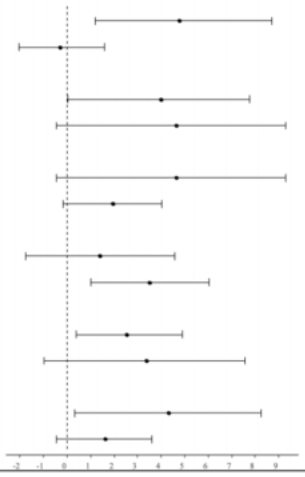


Figure A5: Subgroup analysis Tomazini et al. 2020 – Between group difference for ventilator free days at 28 days*

Source: [37]
*Generalised additive model with zero-inflated beta binomial distribution and interaction between groups and subgroups variables;
Abbreviation: CI=confidence interval.

RISK OF BIAS 2 (RoB2) Tables

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

Studies	Randomisation process	Deviations from the intended interventions	Missing outcomes	Measurement of the outcome	Selection of reported results	Overall bias
RECOVERY [36]	low	some concerns[a]	All-cause mortality: low	low	low	some concerns
RECOVERY [36]	low	some concerns[a]	Number of patients discharged: low	some concerns[b]	low	some concerns
CoDEX [37]	low	some concerns[c]	All-cause mortality: low	low	low	some concerns
CoDEX [37]	low	some concerns[c]	Number of patients discharged: low	some concerns[d]	low	some concerns
CoDEX [37]	low	some concerns[c]	Number of patients with SAE: low	some concerns[d]	low	some concerns

Source: adapted from https://covid-nma.com

[a] Unblinded trial. In the intervention arm, 1975/2079 received dexamethasone. In the control arm, 336/4278 received dexamethasone. Deviation may affect the outcomes but the direction of the bias is expected to lower the estimates of efficacy towards the 1. No information on administration of co-interventions of interest: glucocorticoids and anticoagulants. Antivirals and biologics were reported. Data were analysed using intention-to-treat analysis

[b] Unblinded trial. Outcomes are observer-measured and mortality does do not involve clinical decision-making or involve assessor judgment. Risk assessed to be "low" for the outcome: Mortality. Risk assessed to be "some concerns" for hospital discharge since this outcome involves clinical decision-making.

[c] Unblinded trial. In the dexamethasone arm, 25 protocol deviations occurred in the intervention arm (16.55%); 1 patient received a corticosteroid other than dexamethasone. In the control arm, 52 patients received corticosteroids, of which 14 were protocol deviations (9.45%). No information on co-interventions of interest, antivirals, anticoagulants and biologics, were reported. Deviations might have arisen because of the experimental context and are likely to have affected the outcome. Difference in between-group deviations <10% Appropriate analysis method was used (intention-to-treat)

[d] Appropriate method of outcome measurement and methods did not differ between groups. Unblinded trial. Mortality is an observer-reported outcome not involving judgement. Risk assessed to be low for outcome: mortality. The outcome number of patients discharged reflects decisions made by the intervention provider. Furthermore, adverse events and serious adverse events reported contain both clinically- and laboratory-detected events. Assessment of these outcomes could possibly be influenced by knowledge of the intervention assignment but we did not consider this likely to have happened in the context of a pandemic. Risk assessed with some concerns for the outcomes: Adverse events. Serious adverse events.

CERTAINTY OF EVIDENCE

Table A10: GRADE evidence

Patient or population: Patients with moderate to critical COVID-19
Setting: Hospital
Intervention: Dexamethasone on top of standard care
Comparison: Standard care

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	SoC	Relative (95% CI)*	Absolute (95% CI)	
All-cause mortality – Mixed population (moderate to critical COVID-19)											
2[1,2]	randomised trials	serious [a]	not serious	not serious	not serious	none	567/2255 (25.1%)	1201/4469 (26.9%)	**RR 0.90** (0.82 to 0.97)	**27 fewer per 1.000** (from 47 fewer to 8 fewer)	⊕⊕⊕◯ MODERATE
All-cause mortality - Moderate COVID-19											
1[2]	randomised trials	serious [b]	not serious	not serious	not serious	none	89/501 (17.8%)	145/1034 (14.0%)	**RR 1.27** (1.00 to 1.61)	**38 more per 1.000** (from 0 fewer to 86 more)	⊕⊕⊕◯ MODERATE
All-cause mortality - Severe COVID-19 **– in line with EMA recommended indication**											
1[2]	randomised trials	serious [b]	not serious	not serious	not serious	none	289/1279	682/2604	**RR 0.89** (0.79 to 1.00)	**29 fewer per 1.000** (from 55 fewer to 0 fewer)	⊕⊕⊕◯ MODERATE
All-cause mortality - Critical COVID-19 **– in line with EMA recommended indication**											
2[1,2]	randomised trials	serious [a]	not serious	not serious [f]	serious [g]	none	180/475 (37.9%)	374/831 (45.0%)	**RR 0.81** (0.62 to 1.05)	**86 fewer per 1.000** (from 171 fewer to 23 more)	⊕⊕◯◯ LOW

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	SoC	Relative (95% CI)*	Absolute (95% CI)	
Number of patients discharged within 28 days - Mixed population (moderate to critical COVID-19)											
2[1,2]	randomised trials	serious [c]	serious [d]	not serious [f]	serious [g]	none	1455/2255 (64.5%)	2770/4469 (62.0%)	**RR 1.25** (0.82 to 1.91)	**155 more per 1.000** (from 112 fewer to 564 more)	⊕◯◯◯ VERY LOW
Number of patients discharged within 28 days - Moderate COVID-19											
1[2]	randomised trials	serious [b]	not serious	not serious [f]	not serious	none	385/501 (76.8%)	831/1034 (80.4%)	**RR 0.96** (0.90 to 1.01)	**32 fewer per 1.000** (from 80 fewer to 8 more)	⊕⊕◯◯ MODERATE
Number of patients discharged within 28 days - Severe COVID-19 **– in line with EMA recommended indication**											
1[2]	randomised trials	serious [b]	not serious	not serious [f]	not serious	none	921/1279 (72.0%)	1755/2604 (67.54%)	**RR 1.07** (1.02 to 1.12)	**47 more per 1.000** (from 13 more to 81 more)	⊕⊕◯◯ MODERATE
Number of patients discharged within 28 days – Critical COVID-19 **– in line with EMA recommended indication**											
2[1,2]	randomised trials	serious [c]	not serious	not serious [f]	not serious	none	149/475 (31.4%)	184/831 (22.1%)	**RR 1.46** (1.21 to 1.76)	**102 more per 1.000** (from 46 more to 168 more)	⊕⊕⊕◯ MODERATE
Number of patients with serious adverse events - Critical COVID-19 **– in line with EMA recommended indication**											

Certainty assessment							№ of patients		Effect		Certainty
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone	SoC	Relative (95% CI)*	Absolute (95% CI)	
1[1]	randomised trials	serious [e]	not serious	not serious [f]	serious[g]	none	5/151 (3.3%)	9/148 (6.1%)	**RR 0.54** (0.19 to 1.59)	**28 fewer per 1.000** (from 49 fewer to 36 more)	⨁⨁◯◯ LOW

Sources

[1]Tomazini BM, Maia IS, Cavalcanti AB, et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial [published online ahead of print, 2020 Sep 2]. JAMA. 2020;10.1001/jama.2020.17021. doi:10.1001/jama.2020.17021 [37]

[2]RECOVERY Collaborative Group, Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with COVID-19 - Preliminary Report [published online ahead of print, 2020 Jul 17]. N Engl J Med. 2020;NEJMoa2021436. doi:10.1056/NEJMoa2021436 [36]

Explanations

* relative risks are calculated from the unadjusted data as reported by the trial authors

[a] Downgraded of one level for high risk of performance bias in both studies

[b]. Downgraded of one level for high risk of performance bias in one study

[c] Downgraded of one level for high risk of performance and detection bias in both studies

[d] Downgraded of one level for heterogeneity. Tau^2=0.074; I^2=75%

[e] Downgraded of one level for high risk of performance and detection bias in one study

[f] We did not downgrade for indirectness. Our PICO was set up inclusively, including patients with moderate, severe and critical COVID-19. We therefor provide the evidence for a mixed population, but also by type of severity. Directness of the evidence is given for each of the COVID-19 severity types. Indirectness with regard to the dosing schedules were not considered serious.

[g] Downgraded of one level due to wide confidence interval consistent with the possibility for benefit and the possibility for no effect

Abbreviations: SoC=standard of care; RR=relative risk as calculated from the unadjusted data as reported by the trial authors.

ONGOING TRIALS

Table A11: Ongoing trials of single agent dexamethasone

Active substance	Dexamethasone (see other substances below)	Dexamethasone	Dexamethasone
Sponsor	University of Oxford	Dr. Negrin University Hospital	Chattogram General Hospital
Trial Identifier	NCT04381936 ISRCTN 50189673 EudraCT 2020-001113-21 (RECOVERY Trial)	NCT04325061 EudraCT 2020-001278-31 (DEXA-COVID19 Trial)	NCT04499313
Phase & Intention	Phase 2/3, to provide reliable estimates of the effect of study treatments on death within 28 days of randomisation (with subsidiary analyses of cause of death)	Phase 4, to examine the effects of dexamethasone on hospital mortality and on ventilator-free days in patients with moderate-to-severe ARDS due to confirmed COVID-19 infection admitted into a network of Spanish intensive care units (ICUs)	Phase 3, to evaluate the efficacy of Dexamethasone and Methylprednisolone as a treatment for severe Acute Respiratory Distress Syndrome (ARDS) caused by coronavirus disease 19 (COVID-19)
Study design	RCT, open-label, standard of care comparator, factorial assignment	RCT, open-label, standard of intensive care comparator parallel assignment	RCT, open-label, parallel assignment
Status of trial	Ongoing (preliminary report on Dexamethasone arm)	Recruiting	Recruiting
Duration/End of Study	March 19, 2020 - December 2021	April 3, 2020 - October 30, 2020	August 2, 2020 – November 30, 2020
Study details			
Number of Patients	15000	200	60
Disease severity	Hospitalised COVID-19 patients	Moderate-to-severe ARDS caused by confirmed COVID-19 infection (mechanically ventilated adult patients)	Moderate to severe COVID-19 requires hospitalization
Setting	Hospitals	Hospitals (ICUs)	Hospitals
Location/Centres	UK	Spain	Bangladesh
Intervention drug name and dosage*	Standard of care plus Corticosteroids low dose (Dexamethasone 6 mg for 10 days; in pregnancy Prednisolone 40 mg or Hydrocortisone 80 mg twice daily); Hydroxychloroquine; Lopinavir/ritonavir/Azithromycin; Tocilizumab/Convalescent plasma	Dexamethasone 20 mg once daily from day 1 to day 5, followed by 10 mg once daily from day 6 to day 10 plus Standard intensivecare	Dexamethasone (20 mg/iv/daily/from Day 1 of randomization, followed by a tapering dose according to the patient's condition
Comparator (drug name and dosage)	Standard of care alone	Standard intensive care alone	Methylprednisolone Sodium Succinate at a dose of 0.5mg/kg (Injectable solution)
Duration of observation/ Follow-up	Until death, discharge from hospital or 28 days post-randomisation (whichever is sooner). Longer term follow-up through linkage to	60 days	30 days

Active substance	Dexamethasone (see other substances below)	Dexamethasone	Dexamethasone
	electronic healthcare records and medical databases.		
Primary Outcomes	Primary end point(s): All-cause mortality within 28 days of randomisation	Primary: 60-day mortality [Time Frame: 60 days]	Primary: Mortality rate (In hospital); Clinical improvement [Time Frame: Following randomization 30 days]
Results/Publication	Dexamethasone arm Preliminary report [36]	Not applicable (ongoing trial)	Not applicable (ongoing trial)

Source: [25]

Table A12: Ongoing trials of single agent dexamethasone (continued)

Active substance	Dexamethasone	Dexamethasone	Dexamethasone
Sponsor	Centro de Educación Medica e Investigaciones Clínicas Norberto Quirno	University of Colorado, Denver	Hôpitaux de Paris
Trial Identifier	NCT04395105	NCT04360876	NCT04344730 EudraCT 2020-00145743
Phase & Intention	Phase 3, to evaluate High Versus Low Dose Dexamethasone for the Treatment of COVID-19 Related ARDS	Phase 2, to determine the safety and estimate efficacy of targeted corticosteroids in mechanically ventilated patients with the hyper-inflammatory sub phenotype of ARDS due to coronavirus disease 2019 (COVID-19) by implementing a Phase 2A clinical trial	To assess the impact of dexamethasone on overall mortality at day-60 after randomization in patients admitted in ICU for severe COVID-19 infection.
Study design	RCT, open-label, parallel assignment	RCT, pragmatic, double-blind, parallel assignment	RCT, pragmatic, quadruple-blind, factorial assignment
Status of trial	Recruiting	Not yet recruiting	Recruiting
Duration/End of Study	May 21, 2020 - December 31, 2020	September 1, 2020 – December 31, 2020	April 2020 – December 2020
Study details			
Number of Patients	284	90	550
Disease severity	ADRS due to COVID-19	ARDS due to COVID-19 pneumonia	Severe COVID-19
Setting	Hospitals	Hospitals	Hospitals (ICU)
Location/Centres	Argentina	US	France

Active substance	Dexamethasone	Dexamethasone	Dexamethasone
Intervention drug name and dosage	Dexamethasone administered once daily: 16 mg from day 1 to 5 and 8 mg from day 6 to 10	Dexamethasone intravenous 20mg daily for 5 days followed by 10mg daily for 5 days	Box of 10 dexamethasone 20 mg / 5 ml, solution for injection in ampoule of 5mL (each allocated box contains complete treatment from D1 to D10 for one patient) (Procedure: conventional oxygen; CPAP; HFNO; mechanical ventilation)
Comparator (drug name and dosage)	Usual care with low dose dexamethasone Usual treatment without using up to 6 mg qd of dexamethasone for 10 days	Placebo delivered intravenously on the same dosing schedule as dexamethasone	Placebo
Duration of observation/ Follow-up	Up to 90 days	Up to 90 days	Up to 90 days
Primary Outcomes	Primary: Ventilator-free days at 28 days [Time Frame: 28 days after randomization]	Primary: Ventilator Free Days (VFD) at Day 28 [Time Frame: 28 Days]	Primary: Time-to-death from all causes within the first 60 days after randomization; Time to need for mechanical ventilation (MV)
Results/Publication	Not applicable (ongoing trial)	Not applicable (ongoing trial)	Not applicable (ongoing trial)

Source: [25]

Table A13: Ongoing trials of single agent dexamethasone (continued)

Active substance	Dexamethasone	Dexamethasone
Sponsor	Scandinavian Critical Care Trials Group	Edda Sciutto Conde
Trial Identifier	NCT04509973, EudraCT Number 2020-003363-25	NCT04513184
Phase & Intention	Phase 3, to assess the effects of higher (12 mg) vs lower doses (6 mg) of intravenous dexamethasone on the number of days alive without life-support in adult patients with COVID-19 and severe hypoxia	Phase 2, to evaluate the safety, efficacy and tolerability of intranasal dexamethasone in patients hospitalized with SARS-CoV-2 with moderate-severe COVID-19, with or without the requirement of mechanic ventilation, including syndrome of acute respiratory distress or pneumonia (as diagnosed by CAT) with alveolar / interstitial lung involvement
Study design	RCT, quadruple masking, parallel assignment	RCT, double masking, parallel assignment
Status of trial	Recruiting	Recruiting
Duration/End of Study	August 27, 2020 – February 17, 2022	August 2020 – December 31, 2020
Study details		
Number of Patients	1000	60

Active substance	Dexamethasone	Dexamethasone
Disease severity	COVID-19adult patients receiving at least 10 L/min of oxygen independent of delivery system OR mechanical ventilation	Moderate-severe COVID-19, with or without the requirement of mechanic ventilation, including syndrome of acute respiratory distress or pneumonia (as diagnosed by CAT) with alveolar / interstitial lung involvement
Setting	Hospitals	Hospitals
Location/Centres	Denmark, India, Sweden, Switzerland	Mexico
Intervention drug name and dosage	Dexamethasone administered once daily in addition to standard care: 12 mg up to 10 days	Nasal Dexamethasone (0.12 mg/kg/daily for 3 days from day 1, followed by 0.06 mg/kg/daily from day 4 to 10 after randomization) IV Dexamethasone (6 mg from Day 1 to 10 after randomization)
Comparator (drug name and dosage)	Dexamethasone administered once daily in addition to standard care: 6 mg up to 10 days	Standard care
Duration of observation/ Follow-up	Up to 180 days	Up to 28 days
Primary Outcomes	Primary: Days alive without life support at day 28 [Time Frame: Day 28 after randomisation]	Time of clinical improvement [Time Frame: 10 days after randomization]
Results/Publication	Not applicable (ongoing trial)	Not applicable (ongoing trial)

Source: [25]

Table A14: Ongoing trials of combination therapies dexamethasone plus hydroxychloroquine or tocilizumab

Active substance	Dexamethasone combined with Hydroxychloroquine	Dexamethasone combined with Tocilizumab
Sponsor	Centre Chirurgical Marie Lannelongue	Assistance Publique - Hôpitaux de Paris
Trial Identifier	NCT04347980 (DHYSCO) EudraCT 2020-001333-13	NCT04476979 EudraCT 2020-001246-18 (TOCIDEX)
Phase & Intention	Phase 3, to evaluate dexamethasone combined with hydroxychloroquine compared to hydroxychloroquine alone for treatment of Severe Acute Respiratory Distress Syndrome induced by Coronavirus Disease 19 (COVID-19)	Phase 2, to determine the therapeutic effect and tolerance of tocilizumab combined with dexamethasone in patients with moderate, severe pneumonia or critical pneumonia associated with Coronavirus disease 2019 (COVID-19)
Study design	RCT, single-blind, parallel assignment	RCT, open label, parallel assignment
Status of trial	Recruiting	Not yet recruiting
Duration/End of Study	April 2020 - August 2020	July 16, 2020 – December 31, 2021
Study details		
Number of Patients	122	120
Disease severity	Severe ARDS COVID-19 patients	Moderate, severe pneumonia or critical pneumonia associated with Coronavirus disease 2019 (COVID-19)
Setting	Hospital (ICUs)	Hospital
Location/Centres	France	France

Active substance	Dexamethasone combined with Hydroxychloroquine	Dexamethasone combined with Tocilizumab
Intervention drug name and dosage	Dexamethasone 20 mg intravenously for 15 min once a day for 5 days (D1 to D5) then at a rate of 10 mg per day from D6 to D10, combined with hydroxychloroquine	Dexamethasone + Tocilizumab Dexamethasone: 10 mg once daily for the first five days (day 1 to day 5) then 5 mg per day for up to 5 days, 2.5mg per day for up to 4 days (or until oxygen supply independency if sooner) + Tocilizumab 8mg/kg D1 and if no response (no decrease of oxygen requirement) a second fixed dose of 400mg will be administered at D3
Comparator (drug name and dosage)	Hydroxychloroquine alone 200 mg x 3 / day enterally from J1 of the HCQ for 10 days	Dexamethasone: 10 mg once daily for the first five days (day 1 to day 5) then 5 mg per day for up to 5 days, 2.5mg per day for up to 4 days (or until oxygen supply independency if sooner)
Duration of observation/ Follow-up	Up to 60 days	Up to 90 days
Primary Outcomes	Primary: Day-28 mortality [Time Frame: 28 days after randomization]	Primary: Survival without needs of ventilator utilization at day 14
Results/Publication	Not applicable (ongoing trial)	Not applicable (ongoing trial)

Source: [25]

APPENDIX 4: EVIDENCE GAPS

Table A15: Evidence gaps

Additional evidence generation needs (to be published)	
Population	For subgroups of patients with hypertension, obesity, children, immunocompromised patients, older patients, patients with tuberculosis, pregnant or lactating women
Intervention	Direct comparison with remdesivir or other investigational drugs; combination therapy
Comparator	Remdesivir or combination therapy or other investigational COVID-19 pharmaceuticals
Outcome(s)	Short term and long term outcomes: All-cause mortality; AEs and SAEs; HRQoL; Lung function; Time to 2019-nCoV RT-PCR negativity; Duration of oxygen treatment (not invasive mechanical ventilation or ECMO); 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; Number of patients discharged (within 28 days); Length of hospital stay; Pulmonary function; Health-related Quality of life.
Time stamp	Short-term (28 days) and long-term (up to 6 months)
Study design	RCT with high certainty of evidence provided

APPENDIX 5: PROJECT ORGANISATION

Participants

Table A16: 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. Author will review and comment the sections drafted by the co-author. All important milestones will be discussed in advance with the co-author.
Co-Author	Swiss Network for HTA (SNHTA)	Switzerland	Co-author will support drafting the report. Co-author will review and comment on all parts of the report.
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 A17: Milestones and deliverables

Task	Start	End
Call for Collaboration	01-10-2020	08-10-2020
Scoping PICO and development of first draft RCR	09-10-2020	04-11-2020
PICO survey – request relevant PICO from Member States	16-10-2020	28-10-2020
Adapt draft RCR based on PICO survey	29-10-2020	04-11-2020
Review of first draft RCR	05-11-2020	09-11-2020
Development of second draft RCR & answers to DR comments	10-11-2020	17-11-2020
TC with the whole assessment team	10-11-2020	
Finalize RCR	18-11-2020	