EUnetHTA Joint Action 3 WP4

"Rolling Collaborative Review" of Covid-19 treatments

DEXAMETHASONE AND OTHER CORTICOSTEROIDS FOR THE TREATMENT OF COVID-19

Project ID: RCR08
Monitoring Report

Version 2.0, September 2020

Template version August 2020

This Rolling Collaborative Review Living Document is part of the project / joint action '724130 / EUnetHTA JA3' which has received funding from the European Union's Health Programme (2014-2020)

DOCUMENT HISTORY AND CONTRIBUTORS

Version	Date	Description of changes
V 1.0	**14/08/2020**	First version
V 1.1	**September 2020**	Literature searches, Literature screening, Data extraction
V 1.2	**09/09/2020**	Data extraction and analysis complete
V 1.3	**11/09/2020**	Check of data extraction and analysis
V 2.0	**15/09/2020**	Second version

Major changes from previous version

Chapter, page no.	Major changes from version [1.0]
Title page	Title was changed (Dexamethasone and other corticosteroids)
Section 3.2	New data related to regulatory issue on Dexamethasone Taw
Section 3.3	New WHO Guideline recommendations related to Corticosteroids in COVID-19 patients added
Section 3.3	New RCTs published on dexamethasone and other corticosteroids (5 RCTs added)
Table 4-1	New Summary of Findings table prepared (related to 6 RCTs)
Table 4-5	New ongoing RCTs related to dexamethasone added

Disclaimer

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

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Conflict of interest

All authors and co-authors involved in the production of this living document 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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How to cite this assessment

Please cite this assessment as follows:

EUnetHTA Rolling Collaborative Review (RCR08) Authoring Team. Dexamethasone and other corticosteroids for the treatment of COVID-19. Diemen (The Netherlands): EUnetHTA; 2020. [date of citation]. 23 pages. Report No.: RCR08. Version 2.0, September 2020. Available from: https //www.eunethta.eu.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ARR	Absolute Risk Reduction
ATC	Anatomical Therapeutic Chemical [Classification System]
ATMP	Advanced therapy medicinal product
CI	Confidence Interval
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
HRQOL	Health-related Quality of Life
ICD	International Classification of Diseases
ITT	Intention-to-treat
MD	Mean Difference
MeSH	Medical Subject Headings
NA	Not applicable
NR	Not reported
OR	Odds Ratio
PP	Per Protocol
RCT	Randomized Controlled Trial
RCR	Rolling Collaborative Review
REA	Relative Effectiveness Assessment
RR	Relative Risk
SAE	Serious Adverse Event
SD	Standard Deviation
SMD	Standardized Mean Difference
SmPC	Summary of product characteristics
SOP	Standard Operating Procedure
WP4	Work Package 4

1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

- to inform health policy at the national/regional and at the European level at an early stage in the life-cycle of therapies which interventions are currently undergoing clinical trials,
- to monitor (ongoing studies and their results) permanently - in the format of a Living Document - potential therapies against covid-19,
- to present comparative data on effectiveness and safety of potential therapies and
- to support preparations for an evidence-based purchasing of regional/ national health politicians, if necessary.

To avoid redundancies and duplication, the EUnetHTA Rolling Collaborative Review will reuse sources from international initiatives to collect information and data on Covid-19 treatments.

The scope of the Rolling Collaborative Review is of descriptive nature. These **EUnetHTA Rolling Collaborative Reviews are not meant to substitute a joint Relative Effectiveness Assessment (REA)** adhering to the agreed procedures and aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the (prospective) Marketing Authorization Holder (MAH).

2 METHODS

This Rolling Collaborative Review is prepared according to the project plan ("Rolling Collaborative Review (RCR) on Covid-19 treatments: Project description and planning", published on the EUnetHTA website) and will be updated monthly. Monthly updates are published on the EUnetHTA Covid-19 Website (https://eunethta.eu/services/covid-19/) and on the EUnetHTA Rolling Collaborative Review Sharepoint page each 15th of the month.

2.1 Scope

Table 2-1 Scope of the RCR

Description	Project Scope
Population	**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** (https://www.who.int/classifications/icd/covid19/en) • 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 **Target population** (https://www.covid19treatmentguidelines.nih.gov/overview/management-of-covid-19/)

	• Asymptomatic or pre-symptomatic Infection: Individuals who test positive for SARS-CoV-2 by virologic testing using a molecular diagnostic (e.g., polymerase chain reaction) or antigen test, but have no symptoms. • 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) without shortness of breath, dyspnoea, or abnormal chest imaging. • Moderate Illness: Individuals who have evidence of lower respiratory disease by clinical assessment or imaging and a saturation of oxygen (SpO2) ≥94% on room air at sea level. • Severe Illness: Individuals who have respiratory frequency >30 breaths per minute, SpO2 <94% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mmHg, or lung infiltrates >50%. • Critical Illness: Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction.
Intervention	Dexamethasone is a long-acting glucocorticoid, principally used as an anti-inflammatory or immunosuppressant agent.
Comparison	Any active treatment, placebo, or standard of care. **Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.
Outcomes	<u>Main outcome:</u> • All-cause Mortality (Survival) <u>Additional Outcomes:</u> Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc) 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.
Study design	Efficacy: randomised controlled trials (RCT) Safety: observational studies (comparative or single-arm prospective studies and registries)

2.2 Sources of information

According to the project plan, this Rolling Collaborative Review is based on three main sources of information, as described below:

1. Summary of findings(SoF) table for published RCTs related to effectiveness and safety:

This table is based on the living systematic review and Network Meta-Analysis (NMA) created by the partnering institute of DEPLazio: find the PROSPERO protocol here. DEPLazio provides updates for the SoF table on a monthly basis to the EUnetHTA partners authoring the respective Rolling CR documents who are integrating this information accordingly.

The literature search is conducted in the following databases:

- Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

Population	People affected by COVID-19, as defined by the authors of the studies. No limits in terms of gender or ethnicity. SARS-CoV-2 is a novel coronavirus causing a respiratory illness termed Covid-19. It started spreading in December 2019, and was declared a pandemic by the World Health Organisation on 11th March 2020. The full spectrum of Covid-19 ranges from mild, self-limiting respiratory tract illness to severe progressive pneumonia, multi-organ failure, and death.
Intervention	Interventions for the treatment of people affected by COVID-19, including pharmacological interventions (e.g. antibiotics, antibodies, antimalarial, antiviral, antiretroviral, immune-suppressors/modulators, kinase inhibitors) and their combinations.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	All-cause mortality Additional outcomes: Length of hospital stay, 2019-nCoV RT-PCR negativity, PaO2/FiO2, Duration of mechanical ventilation, radiological imaging, Adverse events, Severe adverse events.
Study design	Randomised controlled trials (RCT); no restriction on language of publication

To identify preprints of preliminary reports of work that have not been peer-reviewed, the following sources are searched:

- medRxiv Health Sciences
- bioRxiv Biology

In addition to the sources and strategies described above, registers of ongoing studies are screened. Key conferences and conference proceedings are considered.

Data extraction, Risk of bias assessment, data synthesis:

Two reviewers from DEPLazio are screening search results, assessing full texts of studies and extract study characteristics and outcome data according to pre-defined criteria.

Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [1].

Dichotomous outcomes are 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 are 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) is applied when studies used different instruments. Pairwise meta-analyses is performed for primary and secondary outcomes using a random-effects model in RevMan for every treatment comparison [2]. Network meta-analysis (NMA) is performed for the primary outcome. For rating the certainty of the evidence, the GRADE approach is being used [3].

- Sources: http://deplazio.net/farmacicovid/index.html for SoF (or https://covid-nma.com/)

2. Table(s) on published (peer reviewed) observational studies for safety results:

The literature search is conducted on a monthly basis using the following sources:

- https://www.fhi.no/en/qk/systematic-reviews-hta/map/
- https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=topics.General%20Info

Population	See project Scope
Intervention	Dexamethasone is a long-acting glucocorticoid, principally used as an anti-inflammatory or immunosuppressant agent.
Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	Prospective non-randomised controlled trials, prospective case series, registries Exclusion criteria: retrospective case series, case studies

One researcher carries out title and abstract screening and assesses the full texts of all potentially eligible studies. One researcher extracts the data and assesses the risk of bias using Robins-I (https://training.cochrane.org/handbook/current/chapter-25).

Results are presented in tabular form for all included studies.

3. Table(s) on ongoing trials:

The following clinical trial registries are searched on a monthly basis:

- ClinicalTrials.gov: https://clinicaltrials.gov/
- ISRCTN: https://www.isrctn.com/
- European Clinical Trials Registry: https://www.clinicaltrialsregister.eu/

Inclusion criteria: Randomised controlled trials, Controlled trials

One researcher is searching and extracting the data for the eligible studies.

Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

Dexamethasone (Dexamethasone Mylan), manufactured by Mylan, is a long-acting glucocorticoid which is used principally as an anti-inflammatory or immunosuppressant agent. 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 [4-7]. 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 [8, 9].

3.2 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 and will provide an opinion on the results of this study and on the potential use of dexamethasone to treat adults with COVID-19. CHMP is currently evaluating Dexamethasone Taw for a marketing authorisation for the treatment of hospitalised adult patients with COVID-19. The applicant, Taw Pharma, is developing Dexamethasone Taw as a hybrid medicine; like its “reference medicine”, Fortecortin Inject, Dexamethasone Taw is injectable. The evaluation of Dexamethasone Taw began on 31 August 2020. It has no impact on the use of other dexamethasone medicines [10]. As part of its evaluation, the CHMP will consider the outcome of its ongoing review of the use of dexamethasone to treat COVID-19, mentioned above.

The UK has approved dexamethasone for the treatment of Covid-19 on June 16, 2020 [7, 11]

3.3 Level of Evidence

Six RCTs were published and included in our meta-analysis: two related to dexamethasone treatment – the largest, **RECOVERY trial** (**NCT04381936**) [12], and **CoDEX trial** (**NCT04327401**) **[13]**; two related to hydrocortisone treatment - **CAPE-COVID trial** (**NCT02517489**) **[14]** and **REMAPCAP trial** (**NCT02735707**) [15], and two RCTs related to methylprednisolone - **MetCOVID trial** (**NCT04343729**) [16] and **GLUCOCOVID trial** (**EudraCT 2020-001934-37)** [17]**.** Corticosteroid regimens included: **dexamethasone** 6 mg daily up to 10 days in RECOVERY trial and 20 mg daily for 5 days followed by 10 mg daily for 5 days in CoDEX trial [12][13], **hydrocortisone** 200 mg daily for 4 to 7 days followed by 100 mg daily for 2 to 4 days and then 50 mg daily for 2 to 3 days in CAPE-COVID trial [14] and **hydrocortisone** 200 mg daily for 7 days in REMAPCAP trial [15]; **methylprednisolone** 0.5 mg/kg twice daily, for 5 days in MetCOVID trial [16] and 40 mg every 12 hours for 3 days and then 20 mg every 12 hours for 3 days in GLUCOCOVID trial [17]. According to the classification as low or high corticosteroids dose, three RCTs are classified as low dose (RECOVERY, CAPE-COVID, REMAPCAP) [12][14][15], and the rest as high dose [13, 16, 17]**.** REMAPCAP was an international study (recruiting in 14 European countries, Australia, Canada, New Zealand, Saudi Arabia and the United Kingdom) [15]; the rest were conducted in individual countries [12-14, 16, 17].

The RCT with the largest number of included COVID-19 patients is the **RECOVERY trial** [12]: 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. The randomization of patients to receive dexamethasone, hydroxychloroquine, or lopinavir–ritonavir has now been stopped, the trial continues randomization to groups receiving azithromycin, tocilizumab, or convalescent plasma. 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). Authors 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 [RR] 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%, RR 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%, RR 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%, RR 1.19 [95% CI 0.91 to 1.55]. 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 [12].

The **CoDEX trial** randomized 299 patients in 41 ICUs in Brazil with moderate or severe ARDS and COVID-19 to open-label high-dose 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, which were greater in patients randomized to dexamethasone (6.6 vs 4.0, p=0.04). 28-day mortality was not significantly different between patients randomized to corticosteroids vs usual care (56.3% vs 61.5%, p=0.83); 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 [13, 18].

The **CAPE COVID trial,** a blinded, placebo-controlled trial randomized 149 patients in 9 ICUs in France with severe respiratory disease from COVID-19 to low-dose hydrocortisone (200 mg/d infusion, tapered per protocol) vs placebo. The primary outcome of 21-day treatment failure, defined as death or ongoing respiratory support with mechanical ventilation or high-flow oxygen, occurred in 42.1% of patients randomized to hydrocortisone vs 50.7% of those randomized to placebo (p=0.29) [14, 18] .

The **REMAP-CAP trial**, an existing multicenter, multinational adaptive platform trial for pneumonia, randomized 403 patients with severe COVID-19 (in the intensive care unit and receiving respiratory or cardiovascular organ support) to 1 of 3 open-label groups: fixed low-dose hydrocortisone, shock-dependent hydrocortisone, or no hydrocortisone. The primary study outcome was days patients remained alive and free of organ support to day 21. The Bayesian model found that fixed-dose hydrocortisone (93% probability), as well as shock-dependent hydrocortisone (80% probability), were both likely superior to no hydrocortisone, but data were insufficient to confirm a single optimal regimen. In addition, the probabilities did not meet the prespecified probabilities to define success [15, 18].

The **MetCOVID trial** was a parallel, double-blind, placebo-controlled, randomized, phase IIb clinical trial, performed with hospitalized patients aged ≥ 18 years with clinical, epidemiological and/or radiological suspected COVID-19 at a tertiary care facility in Brazil. Patients were randomly allocated (1:1 ratio) to receive either intravenous methylprednisolone (0.5 mg/kg) or placebo (saline solution), twice daily, for 5 days. The primary outcome was 28-day mortality. 416 patients were randomized, and 393 analysed as mITT, methylprednisolone in 194 and placebo in 199 individuals. SARS-CoV-2 infection was confirmed by RT-PCR in 81.3%. Mortality at day 28 was not different between groups. A subgroup analysis showed that patients over 60 years in the methylprednisolone group had a lower mortality rate at day 28. Patients in the methylprednisolone arm tended to need more insulin therapy, and no difference was seen in virus clearance in respiratory secretion until day 7 [16].

The **GLUCOCOVID trial**, a multicentric, partially randomized, preference, open-label trial, including adults with COVID-19 pneumonia, impaired gas exchange and biochemical evidence of hyper-inflammation, aimed to determine whether a 6-day course of intravenous methylprednisolone improves outcome in patients with SARS CoV-2 infection at risk of developing Acute Respiratory Distress Syndrome (ARDS). Patients were assigned to standard of care (SOC), or SOC plus intravenous methylprednisolone (40mg/12h 3 days, then 20mg/12h 3 days). The primary endpoint was a composite of death, admission to the intensive care unit (ICU) or requirement of non-invasive ventilation (NIV). 85 patients (34, randomized to MP; 22, assigned to MP by clinician's preference; 29, control group) were analysed. Patients' age (mean 68±12 yr) was related to outcome. The use of methylprednisolone was associated with a reduced risk of the composite endpoint in the intention-to-treat, age-stratified analysis (combined risk ratio -RR- 0.55 [95% CI 0.33-0.91]; p=0.024). In the per-protocol analysis, RR was 0.11 (0.01-0.83) in patients aged 72 yr or less, 0.61 (0.32-1.17) in those over 72 yr, and 0.37 (0.19-0.74, p=0.0037) in the whole group after age-adjustment by stratification. The decrease in C-reactive protein levels was more pronounced in the methylprednisolone group (p=0.0003). Hyperglycaemia was more frequent in the methylprednisolone group [17].

Data on moderate, low and very low certainty of evidence, related to effectiveness and safety of dexamethasone and other corticosteroids reported in these 6 RCTs, prepared by Cruciani et al. [19], can be found in the Summary of Findings Table 4-1

Two prospective observational studies were found, Salton et al. 2020 [20] and Bani-Sadr et al. 2020 [21] but only one reported safety data [20]. Details could be found in Table 4-2.

Salton et al. 2020 [20] conducted a non-randomised, longitudinal study on 173 patients with confirmed COVID-19 (severe) pneumonia admitted to fourteen centers in Italy (NCT04323592) to explore the association between exposure to prolonged, low-dose, methylprednisolone (MP) treatment and need for ICU referral, intubation or death within 28 days (composite primary endpoint). 83 patients received methylprednisolone (80 mg iv for at least eight days, followed by 16 orally or 20 mg iv, twice daily) and 90 patients received control treatment. Unexposed patients (controls) were selected from concurrent consecutive COVID-19 patients with the same inclusion and exclusion criteria. Patients in both study groups received standard of care, comprising noninvasive respiratory support, antibiotics, antivirals, vasopressors, and renal replacement therapy as deemed suitable by the healthcare team. The overal adverse events rate was similar for the two groups (p=0.87).

Bani-Sadr et al. 2020 [21] published results from a before–after study which was performed to evaluate the effect of addition of corticosteroids to our institution's COVID-19 treatment protocol on hospital mortality. A total of 257 patients with a COVID-19 diagnosis were included in this study between 3 March 2020 and 14 April 2020. As corticosteroids were widely used after 27 March 2020, two periods were considered for the purposes of this study: the 'before' period from 3–20 March 2020 (n=85); and the 'after' period from 26 March–14 April 2020 (n=172). Safety data are not reported.

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 4-3, Table 4-4, Table 4-5 and Table 4-6.

Based on results of the RECOVERY trial, the US COVID-19 Treatment Guidelines Panel **recommends using dexamethasone** (at a dose of 6 mg per day for up to 10 days) in patients with COVID-19 who are mechanically ventilated **(AI)** and in patients with COVID-19 who require supplemental oxygen but who are not mechanically ventilated **(BI)**. The Panel **recommends against** using dexamethasone in patients with COVID-19 who do not require supplemental oxygen **(AI)**. If dexamethasone is not available, the Panel **recommends using** alternative glucocorticoids such as **prednisone**, **methylprednisolone**, or **hydrocortisone (AIII)** [22].

Recently, a 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 [23], and the new WHO living guidance on corticosteroids for COVID-19 were published [24, 25]. 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. 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 [24, 25].**

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

Effectiveness

Outcome: All-cause mortality

According to the results of six RCTs [12-17] with moderate certainty of evidence, corticosteroids probably reduce the risk of mortality for all causes in COVID-19 patients /RR 0.90 (95% CI 0.83 to 0.97); absolute effect estimate 27 fewer per 1000 (95% CI from 47 fewer to 8 fewer)/. The same is true for severe COVID-19 patients (three RCTs [15, 17][12]) /RR 0.89 (95% CI 0.80 to 1.00); absolute effect estimate 29 fewer per 1000 (95% CI from 53 fewer to 0 fewer)/ and critically ill COVID-19 patients (two RCTs [14][12]) /RR 0.69 (95% CI 0.58 to 0.83); absolute effect estimate 124 fewer per 1000 (95% CI from 168 fewer to 68 fewer)/.

In patients with mild/moderate COVID-19 disease, systemic corticosteroids probably increase the risk of death (moderate certainty of evidence, one RCT [12] /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).

Outcome: Number of patients discharged within 28 days

According to the results of two RCTs [13][12] with very low certainty of evidence, whether or not corticosteroids impact on the increase number of patients discharged to 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).

Safety

Outcome: Number of patients with serious adverse events

According to the results of 3 RCTs [13-15] with low certainty of evidence, corticosteroids may not increase the number of patients with serious adverse events /RR 1.47 (95% CI 0.31 to 7.04); absolute effect estimate 15 more per 1000 (95% CI from 21 fewer to 188 more).

4.2 Safety evidence from observational studies

Adverse events of corticosteroids have been reported in one prospective observational study in COVID-19 patients, with high risk of bias; no statistically significant difference was found in overall AEs between the groups [20]. The occurrence of hyperglycaemia in non-diabetic patients, or severe glycaemic decompensation in diabetic patients, and agitation was significantly higher in the corticosteroid group compared to control (8 vs. 0, p=0.002 and 9 vs. 2, p=0.03 respectively).

4.3 Ongoing studies

There are several registered ongoing RCTs, evaluating dexamethasone alone or in combination with another pharmacotherapy, as well as on other glucocorticoids in Covid-19 patients, in ClinicalTrials.gov and EUdraCT registers.

4.4 Scientific conclusion about status of evidence generation

Based on the results with moderate certainty of evidence, systemic corticosteroids probably reduce the risk of all-cause mortality in COVID-19 patients (six RCTs). The same is true for sever and critically ill COVID-19 patients (three RCTs and two RCTs respectively), but not for patients with mild/moderate COVID-19 disease (one RCT).

Whether or not systemic corticosteroids impact the increase number of patients discharged to 28 days is uncertain (two RCTs). Based on the results of three RCTs with low certainty of evidence, corticosteroids may not increase the number of patients with serious adverse events.

Further RCTs examining dexamethasone and other systemic glucocorticoids for the treatment of COVID-19 patients are under way.

Table 4-1 Summary of findings (SoF) table for published RCT related to effectiveness and safety of dexamethasone and other corticosteroids

Patient or population: COVID-19 infection
Setting: Inpatient
Intervention: Corticosteroids
Comparison: No corticosteroids

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect difference (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with no corticosteroids	Risk with corticosteroids					
All-cause Mortality	274 per 1000	247 per 1000	**RR 0.90** (0.83 to 0.97)	**27 fewer per 1.000** (from 47 fewer to 8 fewer)	7590 (6 RCTs)	MODERATE ⊕⊕⊕◯	Downgraded of one level for performance bias; high risk in 4 studies and unclear in one study; selection bias: high risk in 1 study and unclear in another study
Mortality in patients with mild/moderate severity	140 per 1000	178 per 1000	**RR 1.27** (1.00 to 1.61)	**38 more per 1.000** (from 0 fewer to 86 more)	1535 (1 RCT)	MODERATE ⊕⊕⊕◯	Downgraded of one level for high risk of performance bias
Mortality - severe patients	263 per 1000	234 per 1000	**RR 0.89** (0.80 to 1.00)	**29 fewer per 1.000** (from 53 fewer to 0 fewer)	4184 (3 RCTs)	MODERATE ⊕⊕⊕◯	Downgraded of one level for high risk of performance bias in all 3 studies
Mortality – critical patients	401 per 1000	277 per 1000	**RR 0.69** (0.58 to 0.83)	**124 fewer per 1.000** (from 168 fewer to 68 fewer)	1156 (2 RCTs)	MODERATE ⊕⊕⊕◯	Downgraded of one level for high risk of performance bias in 1 study
Number of patients discharged within 28 days	620 per 1000	645 per 1000	**RR 1.25** (0.82 to 1.91)	**155 more per 1.000** (from 112 fewer to 564 more)	6724 (2 RCTs)	VERY LOW ⊕◯◯◯	Downgraded of one level for high risk of performance bias in both studies and of two levels for heterogeneity. I^2=75%
Number of patients with serious adverse events	31 per 1000	33 per 1000	**RR 1.47** (0.31 to 7.04)	**15 more per 1.000** (from 21 fewer to 188 more)	686 (3 RCsT)	LOW ⊕⊕◯◯	Downgraded of one level for high risk of performance bias in 2 studies and of one level for heterogeneity. I^2=49%

CI: Confidence interval; **RR:** Risk ratio
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.
*Source**: [19]***

Table 4-2 Summary of safety from observational studies (AE and SAE) of corticosteroids

Author, year	Salton et al. 2020 [20]	Bani-Sadr et al. 2020 [21]
Country	Italy	France
Sponsor	University of Trieste	None
Intervention/Product (drug name)	Methylprednisolone	Corticosteroids
Dosage	80 mg up to 8 days iv, then oral administration at 16 mg or 20 mg iv twice daily	Not reported
Comparator	No corticosteroids	No corticosteroids
Study design	Non-randomised, multicenter, longitudinal study (NCT04323592)	Before (control group) – after study (corticosteroid group)
Setting	Inhospital	Inhospital
Number of pts	173 (83 in methylprednisolone vs 90 in control group)	257 (85 in control group, 172 in methylprednisolone group)
Inclusion criteria	SARS-CoV-2 positive (on swab or bronchial wash); age >18 years and <80 years; PaO2:FiO2 <250 mmHg; bilateral infiltrates; CRP >100 mg/L; and/or diagnosis of acute respiratory distress syndrome (ARDS) according to the Berlin definition as an alternative to criteria 4) and 5)	Positive result by reverse transcriptase (RT)-PCR testing of a nasopharyngeal sample or the presence of characteristic findings on chest computed tomography (CT) scan
Age of patients (yrs)	64.4 (10.7) in methylprednisolone vs 67.1 (8.2) in control group	11 (12.9 vs 119 (69.2) in corticosteroid group
Disease severity	Severe COVID-19 pneumonia	Not reported
Follow-up (months)	28 days	Mean duration of follow-up 16.0 ± 7.0 days
Loss to follow-up, n (%)	None	Not reported
RoB	High	High
Overall AEs, n (%)	Methylprednisolone group 29 (34.9%) vs 30 (33.3%) in control group; p=0.87 Occurrence of hyperglycaemia in non-diabetic patients, or severe glycaemic decompensation in diabetic patients, and agitation was significantly higher in the in methylprednisolone group compared to control (8 vs. 0, p=0.002 and 9 vs. 2, p=0.03 respectively).	Unavailable safety data
Serious AE (SAE), n (%)	Not reported as such (see above)	Unavailable safety data
Most frequent AEs n (%)	Not reported as such (see above)	Unavailable safety data
Most frequent SAEs, n (%)	Not reported as such (see above)	Unavailable safety data
AEs of special interest, n (%)	Not reported as such (see above)	Unavailable safety data
Death as SAE, n (%)	None reported	Unavailable safety data
Withdrawals due AEs, n (%)	None reported	Unavailable safety data

*by arms

Abbreviations: RoB=Risk of Bias (Robins-I: https://training.cochrane.org/handbook/current/chapter-25)

Table 4-3 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	60 days	30 days

Active substance	**Dexamethasone** (see other substances below)	**Dexamethasone**	**Dexamethasone**
	term follow-up through linkage to 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 [12]	Not applicable (ongoing trial)	Not applicable (ongoing trial)

Table 4-4 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)

Table 4-5 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)

Table 4-6 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)

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