EUnetHTA Joint Action 3 WP4

“Rolling Collaborative Review” of Covid-19 treatments

DEXAMETHASONE FOR THE TREATMENT OF COVID-19

Project ID: RCR08
Monitoring Report

Version 1.0, August 2020

Template version July 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
V0.1	**July 2020**	Literature searches, Literature screening, Data extraction
V0.2	**10/08/2020**	Data extraction and analysis complete
V0.3	**11/08/2020**	Check of data extraction and analysis
V1.0	**12/08/2020**	First version

Disclaimer

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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 for the treatment of COVID-19. Diemen (The Netherlands): EUnetHTA; 2020. [date of citation]. 20 pages. Report No.: RCR08. 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
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, aiming at critical appraisal of the clinical evidence based on the Submission Dossier submitted by the 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	Main outcome: • All-cause Mortality (Survival) Additional Outcomes: 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.pdf)

	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. Table 1 - Summary of findings (SoF) 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 table1 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 2 - 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	Observational studies (comparative or single-arm prospective studies and 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 3 - 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 examethasone treatment (months/years) usually causes central obesity, skin fragility, muscle atrophy, osteoporosis, growth retardation and longterm suprarenal insufficiency [4-7]. 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. The UK has approved dexamethasone for the treatment of Covid-19 on June 16, 2020 [7, 10].

3.3 Level of Evidence

One RCT was included: Randomized Evaluation of COVid-19 thERapY - the RECOVERY trial (NCT04381936, ISRCTN50189673, EudraCT 2020-001113-21). This RCR is based on the published results of the dexamethasone arm of the RECOVERY trial [11]. 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 4-2, Table 4-3 and Table 4-4. As of August 10, 2020, one terminated RCT - NCT04327401 (CoDEX), related to dexamethasone was found; no completed, withdrawn or suspended interventional studies were found in ClinicalTrials.gov and EUdraCT registers. In this terminated RCT, conducted in 299 COVID-19 patients with moderate and severe ARDS in Brazil, the Data Monitoring Committee recommended to stop the trial based on the Recovery Trial results, which was accepted by the CoDEX Steering Committee. The results of this RCT are not yet published.

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 [11].

The Summary of findings table, with moderate certainty of evidence related to effectiveness and safety of dexamethasone reported in the RECOVERY trail, prepared by Cruciani et al. [12], can be found in Table 4-1.

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)** [13].

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

Effectiveness: Preliminary results from one large RCT [11] showed that among hospitalised patients the use of dexamethasone (at a dose of 6 mg per day for up to 10 days) resulted in statistically significant lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen alone at randomization but not among those receiving no respiratory support.

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.

Safety: Adverse events and serious adverse events of dexamethasone in COVID-19 patients have not yet been reported from the RCTs.

4.2 Safety evidence from observational studies

Adverse events and serious adverse events of dexamethasone have not yet been reported from the prospective observational studies in COVID-19 patients.

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 preliminary results from one large RCT, the RECOVERY trial related to the dexamethasone arm, with moderate certainty of evidence, dexamethasone vs. standard treatment reduces the risk of mortality for all causes in COVID-19 patients. Dexamethasone vs. standard treatment reduces the risk of mortality for all causes in patients requiring invasive mechanical ventilation and COVID-19 patients requiring oxygen supplement. Dexamethasone vs. standard treatment probably increases the risk of mortality for all causes in COVID-19 patients who do not require oxygen. Dexamethasone compared to standard treatment probably has little or no effect on the increase in the number of patients discharged

to 28 days. Adverse events and serious adverse events have not yet been reported. Analyses are ongoing, also regarding cause-specific mortality, the need for renal dialysis or hemofiltration, and the duration of ventilation.

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

Table 4-1 Summary of findings table for published RCT related to effectiveness and safety of Dexamethasone

Patient or population: COVID-19 infection
Setting: Hospital
Intervention: Dexamethasone
Comparison: Standard treatment

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with Standard Treatment	Risk with Dexamethasone					
All-cause Mortality	257 per 1000	229 per 1000	RR 0.88 (0.79 to 0.96)	28 fewer per 1.000 (from 49 fewer to 5 fewer)	6425 (1 RCT)	Moderate ⊕⊕⊕◯	Downgraded of one level for high risk of detection bias
All-cause Mortality – mild/moderate patients	140 per 1000	178 for 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 detection bias
Mortality by all causes - severe patients	262 per 1000	233 for 1000	RR 0.89 (0.79 to 1.00)	29 fewer per 1.000 (from 55 fewer to 0 fewer)	3883 (1 RCT)	Moderate ⊕⊕⊕◯	Downgraded of one level for high risk of detection bias
Mortality by all causes – critically ill patients	414 per 1000	293 per 1000	RR 0.72 (0.58 to 0.86	120 fewer per 1.000 (from 174 fewer to 58 fewer)	1007 (1 RCT)	Moderate ⊕⊕⊕◯	Downgraded of one level for high risk of detection bias
Number of patients discharged within 28 days	635 per 1000	672 per 1000	RR 1.06 (1.02 to 1.10)	38 more per 1.000 (from 13 more to 64 more)	6425 (1 RCT)	Moderate ⊕⊕⊕◯	Downgraded of one level for high risk of detection bias
Number of patients discharged within 28 days - mild/moderate patients	804 per 1000	768 per 1000	RR 0.96 (0.90 to 1.01)	32 fewer per 1.000 (from 80 fewer to 8 more)	1535 (1 RCT)	Moderate ⊕⊕⊕◯	Downgraded of one level for high risk of detection bias
Number of patients discharged within 28 days - severe patients	675 per 1000	720 per 1000	RR 1.07 (1.02 to 1.12)	47 more per 1.000 (from 13 more to 81 more)	3883 (1 RCT)	Moderate ⊕⊕⊕◯	Downgraded of one level for high risk of detection bias

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Absolute effect (95% CI)	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk with Standard Treatment	Risk with Dexamethasone					
Number of patients discharged within 28 days - critically ill patients	233 per 1000	330 per 1000	RR 1.42 (1.15 to 1.74)	98 more per 1.000 (from 35 more to 172 more)	1007 (1 RCT)	Moderate ⊕⊕⊕◯	Downgraded of one level for high risk of detection bias

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

Evaluation of the quality of the tests according to the GRADE Working Group
High Quality: We are very confident that the real effect is close to that of the estimated effect
Moderate Quality: 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 Quality: Our confidence in the effect estimation is limited: the real effect may be substantially different from the estimated effect
Very Low Quality : We have very little confidence in estimating the effect: the actual effect is likely to be substantially different from the estimated one.

Explanations: Serious Risk of Bias - Lowered by one level for high for high risk of detection bias

Table 4-2 Ongoing trials of single agent Dexamethasone

Active substance	**Dexamethasone** (see other substances below)	**Dexamethasone**	**Dexamethasone**
Sponsor/Collaborator	University of Oxford / UK Research and Innovation National Institute for Health Research, United Kingdom Wellcome Bill and Melinda Gates Foundation Department for International Development, United Kingdom Health Data Research UK Medical Research Council Population Health Research Unit NIHR Clinical Trials Unit Support Funding	Dr. Negrin University Hospital / Li Ka Shing Knowledge Institute Consorcio Centro de Investigación Biomédica en Red, M.P.	Chattogram General Hospital / Health Science Center of Xi'an Jiaotong University
Trial Identifier	NCT04381936 ISRCTN 50189673 EudraCT 2020-001113-21 RECOVERY Trial	NCT04325061 EudraCT 2020-001278-31	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;	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

Active substance	**Dexamethasone** (see other substances below)	**Dexamethasone**	**Dexamethasone**
	Tocilizumab/Convalescent plasma		
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 electronic healthcare records and medical databases.	60 days	30 days
Endpoints **Primary Outcomes** **Secondary Outcomes**	Primary end point(s): All-cause mortality within 28 days of randomisation Secondary endpoints: Duration of hospitalisation, Composite endpoint of death or need for mechanical ventilation or ECMO Other prespecified clinical outcomes: cause-specific mortality;receipt of renal hemodialysis or hemofiltration; major cardiac arrhythmia (recorded in a subgroup), and receipt and duration of ventilation	Primary: 60-day mortality [Time Frame: 60 days] Secondary: Ventilator-free days [Time Frame: 28 days]	Primary: Mortality rate (In hospital); Clinical improvement [Time Frame: Following randomization 30 days] Secondary: Ventilator free days; Changes in Oxygen level [Time Frame: Following randomization 30 days]
Results/Publication	Dexamethasone arm Preliminary report [11]	Not applicable (ongoing trial)	Not applicable (ongoing trial)

*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.

Table 4-3 Ongoing trials of single agent Dexamethasone (continued)

Active substance	**Dexamethasone**	**Dexamethasone**	**Dexamethasone**
Sponsor/Collaborator	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. For the study of the effect of corticosteroids, secondary objectives include: To compare the evolution of the viral load in the respiratory tract; To compare the

Active substance	Dexamethasone	Dexamethasone	Dexamethasone
			occurrence of healthcare-associated infections; To compare the exposition to mechanical ventilation; To compare the evolution of SOFA score; To compare the exposition to renal replacement therapy; To compare the lengths of ICU and hospital-stay For the study of the effect of oxygen support modalities, secondary objectives are, to compare each of oxygen support group to the control group in terms of: overall survival; occurrence of healthcare-associated infections; length of ICU and hospital-stay
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	
Setting	Hospitals	Hospitals	Hospitals (ICU)
Location/Centres	Argentina	US	France
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	Placebo delivered intravenously on the same	Placebo

Active substance	Dexamethasone	Dexamethasone	Dexamethasone
	Usual treatment without using up to 6 mg qd of dexamethasone for 10 days.	dosing schedule as dexamethasone	
Duration of observation/ Follow-up	Up to 90 days	Up to 90 days	Up to 90 days
Endpoints **Primary Outcomes** **Secondary Outcomes**	Primary: Ventilator-free days at 28 days [Time Frame: 28 days after randomization] Secondary: Serum C-reactive Protein variation; SOFA variation; Use of prone position [Time Frame: 10 days after randomization]; 90-day mortality [Time Frame: 90 days after randomization]; 28-days mortality; Muscle weakness; Viral shedding; Frequency of nosocomial infections; Delirium [Time Frame: 28 days after randomization]	Primary: Ventilator Free Days (VFD) at Day 28 [Time Frame: 28 Days] Secondary: Clinical Status at day 14 as measured by World Health Organization (WHO) 7-point ordinal scale. [Time Frame: 14 Days]; Clinical Status at day 28 as measured by WHO 7-point ordinal scale [Time Frame: 28 Days]; In-Hospital Mortality at day 28 [Time Frame: 28 Days]; In-Hospital Mortality at day 90 [Time Frame: 90 Days]; Time to Mortality to day 28 [Time Frame: 28 Days]; ICU-free days to day 28 [Time Frame: 28 Days]; Hospital Length of Stay among survivors to day 90 [Time Frame: 90 Days]; Severity of ARDS to day 10 [Time Frame: 10 Days]; Days to resolution of fever [Time Frame: 28 Days]; Change in C-Reactive Protein (CRP) level from baseline to day 10 [Time Frame: 10 Days]; Vasopressor-free days to day 28 [Time Frame: 28 Days]; Renal replacement-free days to day 28 [Time Frame: 28 Days]; Duration of mechanical ventilation to day 28 [Time Frame: 28 Days]; Oxygenation-free days to day 28 [Time Frame: 28 Days]; Incidence of New Mechanical Ventilation to day 28 [Time Frame: 28 Days]; Change in sequential organ failure assessment (SOFA) score from baseline to day 10 [Time Frame: 10 Days]; In-hospital adverse events to day 28 [Time Frame: 28 Days]; Discontinuation of study drug infusion [Time Frame: 10 Days]	Primary: Time-to-death from all causes within the first 60 days after randomization; Time to need for mechanical ventilation (MV) Secondary: Cycle threshold for SARS-CoV-2 PCR at baseline, day 7 and day 10 in samples of the same origin; Proportion of patients with at least one episode of any healthcare-associated infection between randomization and D28; Number of days alive without mechanical ventilation at day 28; Number of days alive without renal replacement therapy at day 28
Results/Publication	Not applicable (ongoing trial)	Not applicable (ongoing trial)	Not applicable (ongoing trial)

Table 4-4 Ongoing trials of combination therapies Dexamethasone plus Hydroxychloroquine or Tocilizumab

Active substance	Dexamethasone combined with Hydroxychloroquine	Dexamethasone combined with Tocilizumab
Sponsor/Collaborator	Centre Chirurgical Marie Lannelongue	Assistance Publique - Hôpitaux de Paris/ Institut National de la Santé Et de la Recherche Médicale, France
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
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
Endpoints **Primary Outcomes** **Secondary Outcomes**	Primary: Day-28 mortality [Time Frame: 28 days after randomization] Secondary: Ventilator-free days; Intensive Care Unit mortality; Day-60 mortality; Nosocomial pneumonia; Bacteremia [Time Frame: 28 days after randomization]	Primary: Survival without needs of ventilator utilization at day 14 Secondary: WHO progression scale at day 7 and 14; Overall survival at 14, 28, 60 and 90 days; Survival without needs of mechanical ventilation at day 1; Cumulative incidence of oxygen supply independency at 14 and 28 days
Results/Publication	Not applicable (ongoing trial)	Not applicable (ongoing trial)

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