EUnetHTA Joint Action 3 WP4

"Rolling Collaborative Review" of COVID-19 treatments

HIGH-DOSE VITAMIN D FOR THE TREATMENT OF COVID-19

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Monitoring Report

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Version	Date	Description of changes
V 1.0	**15/02/2021**	First version
V 2.0	**15/03/2021**	Second version
V 3.0	**17/05/2021**	Third version

Major changes from previous version

Chapter, page no.	Major changes from version 2.0
Page 22-24, Table 4-8 to Table 4-10	Six ongoing studies have been 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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LIST OF ABBREVIATIONS

ARDS	Acute respiratory distress syndrome
AE	Adverse Event
CI	Confidence Interval
DOI	Declaration of interest
EUnetHTA	European Network of Health Technology Assessment
GÖG	Gesundheit Österreich GmbH
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HR	Hazard Ratio
ICD	International Classification of Diseases
MD	Mean Difference
MeSH	Medical Subject Headings
NA	Not applicable
NR	Not reported
OR	Odds Ratio
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
WP4	Work Package 4
VDR	Vitamin D-receptors

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/covid-19-treatment/) 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	• Substances: Vitamin D2 (ergocalciferol), vitamin D3 (cholecalciferol) and their metabolites ercalcidiol, calcifediol, calcitriol and ercalcitriol* • Dosing: "high-dose" interventions greater than 4,000 IU per day**
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, • Rates and 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)

* Combined interventions of vitamin D and other substances are included if the interventions in two trial arms differ only by the presence or absence of vitamin D. ** There is no consensus definition of "high-dose" vitamin D. The adequate intake for adults recommended by EFSA is 600 IU/day, assuming minimal cutaneous production. [1] Various medical societies recommend different daily intake doses, including 2,000 IU or more. Generally, the upper intake level for Vitamin D can be assumed at 4,000 IU per day and continuing supplementation exceeding this level is recommended against by many experts. [2] We therefore provisionally applied this threshold to define "high-dose" vitamin D treatment. In the current version of the report, no published RCTs were excluded because of the dosing of vitamin D. One observational study was excluded that investigated a cohort of patients that had been using vitamin D supplementation at an average dosage of 1,800 IU/day.

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:

Deviating from the other RCRs, this table is not based on the living systematic review and Network Meta-Analysis (NMA) created by the partnering institute of DEPLazio (find the PROSPERO protocol here).

The literature search is conducted in the following databases:

- MEDLINE, accessed via OVID
- PubMed

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

- medRxiv Health Sciences
- bioRxiv Biology
- arXiv

In addition to the sources and strategies described above, registers of ongoing studies are screened. Appendix Table 6-1 describes in detail the sources searched, the search terms used and the dates at which the searches are executed.

Literature selection, data extraction, risk of bias assessment, data synthesis, certainty of evidence:

At least two reviewers are independently screening search results and assessing full texts of studies according to the pre-defined criteria (see Table 2-1), with disagreements solved by discussion with a third member of the review team. One reviewer extracts study characteristics and outcome data. Studies investigating a combination of vitamin D and other dietary supplements or medicines versus a comparator that does not include this combination therapy are excluded. Data extraction is checked by a second reviewer. The process of study selection is depicted as a flow diagram in Appendix Figure 6-1. Two authors independently assess the risk of bias of the included studies using the Cochrane RoB tool v2.0 [3,4]. 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. Two reviewers independently use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach [5], to evaluate the certainty of evidence.

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

The literature search is conducted on a monthly basis. For version 1.0 of this report, the search was conducted in a two-step-process, in January and February 2021.
The sources and search methods are described in more detail in Table 6-2.

Population	See project Scope
Intervention	• Substances: Vitamin D2 (ergocalciferol), vitamin D3 (cholecalciferol) and their metabolites ercalcidiol, calcifediol, calcitriol and ercalcitriol* • Dosing: “high-dose” interventions greater than 4,000 IU per day**

Comparison	Any active treatment, placebo, or standard of care.
Outcomes	See project Scope
Study design	Inclusion criteria: Prospective non-randomised controlled trials, prospective case series (i.e. comparative or single-arm prospective studies), registries Exclusion criteria: retrospective studies, case studies/ case reports, observational studies that do not report safety data

* Combined interventions of vitamin D and other substances are included if the interventions in two trial arms differ only by the presence or absence of vitamin D. ** There is no consensus definition of "high-dose" vitamin D. The adequate intake for adults recommended by EFSA is 600 IU/day, assuming minimal cutaneous production. [1] Various medical societies recommend different daily intake doses, including 2,000 IU or more. Generally, the upper intake level for Vitamin D can be assumed at 4,000 IU per day and continuing supplementation exceeding this level is recommended against by many experts. [2] We therefore provisionally applied this threshold to define "high-dose" vitamin D treatment. In the current version of the report, no published RCTs were excluded because of the dosing of vitamin D. One observational study was excluded that investigated a cohort of patients that had been using vitamin D supplementation at an average dosage of 1,800 IU/day.

Two researchers from NIPHNO carry out title and abstract screening and assess the full texts of all potentially eligible studies. The study selection process is depicted in a flow diagram (Appendix Figure 6-2). One researcher of GÖG 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 of GÖG is searching and extracting the data for the eligible studies. At least two reviewers are independently screening search results, with disagreements solved by discussion with a third member of the review team. At the drafting stage of each update, the author team verifies whether the status of previously identified studies has changed. This is done by verifying the date of the last update posted in the trial registers. In addition, trial register IDs of all previously identified studies are entered in both PubMed and Google (google.com) to verify if previously identified studies have been published since the last update. In Google, the first 10 hits are screened for this purpose.

Search methods are described in more detail in Appendix Table 6-3. Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

Vitamin D is a generic term used for a group of seco-sterols, mostly referring to vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol) and their metabolites. Both vitamins can be taken up by diet, whereas vitamin D3 is also produced endogenously from 7-dihydrocholesterol in sun-exposed skin. After absorption, vitamin D2 and D3 undergo hepatic and renal hydroxylation into 25-OH-D2 (ercalcidiol) and 25-OH-D3 (calcifediol) and hereafter into the biologically active forms 1,25-OH2- D2 (ercalcitriol) and 1,25-OH2-D3 (calcitriol). The effects of vitamin D are mediated through binding on vitamin D-receptors (VDR). [6,7]

In addition to the well-studied role of vitamin D in bone metabolism, it also modulates several immunomodulatory pathways both in the innate and adaptive immune system (VDR are, for example, expressed on macrophages, dendritic cells, T-cells, and B-cells). Vitamin D generally maintains a balance between effector responses and inflammatory processes. [6]

In acute infections, vitamin D plays a role in enhancing the innate immune system to defend against pathogens by immune cell activation and proliferation (macrophages, neutrophils, dendritic cells) resulting in controlled release of proinflammatory cytokines and antimicrobial peptides like cathelicidin. The role of vitamin D in initial immune response is physiologically beneficial and may also be relevant in COVID-19 infections.

However, excessive immune reactions, like acute respiratory distress syndrome (ARDS) in COVID-19, can result in cytokine storm, strong inflammation and herewith tissue damaging. It is postulated that vitamin D limits these destructive pathways by modulating adaptive and innate immune response towards anti-inflammatory, anti-proliferative processes. [8,9] In addition, vitamin D might interfere with viral entry into the host cells by downregulating ACE2 expression. [10,11]

3.2 Regulatory Status

The mutual recognition information (MRI) index[1] hosted by the Heads of Medicines Agencies (HMA) network of the EU lists over 70 approved vitamin D-containing mono-preparations that may be marketed in the member states under different domestic market names. The majority of those contain cholecalciferol, while only some preparations contain calcitriol, calcifediol or ergocalciferol. Vitamin D-containing preparations are available as capsules, tablets, oral drops/solution, and effervescent granules in various strengths ranging from 10 to 100,000 IU per unit. In addition, there are several combination preparations of cholecalciferol with calcium carbonate, calcium phosphate or bisphosphonates (used for the treatment of bone turnover disorders).

In addition to medicinal products, vitamin D may be marketed in the EU as food supplement.[2] These products can be marketed in several forms, such as capsules, powders or liquids and may contain either cholecalciferol or ergocalciferol. However, article 6 of the directive mandates that 'The labelling, presentation and advertising must not attribute to food supplements the property of preventing, treating or curing a human disease, or refer to such properties.'

[1] https://mri.cts-mrp.eu/Human/. Last accessed 11.05.2021.

[2] Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A02002L0046-20170726#B-6. Last accessed: 11.05.2021.

3.3 Level of Evidence

The evidence for vitamin D for treatment of COVID-19 is still in early stage. There is currently no standardized or recommended level of what constitutes a (beneficial) “high dose”. Three RCTs [12-14] of varying size and quality have been published to date. We moreover identified 23 ongoing RCTs with estimated primary completion dates ranging from June 2020 to February 2023 (5 in 2020, 7 in 2021, 3 in 2022, 1 in 2023, 7 entries have no information on study completion date).

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

Two RCTs investigate vitamin D3 administered in the form of cholecalciferol [13,14] and one investigates vitamin D3 administered in the form of calcifediol [12]. One of the cholecalciferol trials [13] included only patients with mild or asymptomatic COVID-19 and vitamin D deficiency (25 (OH)D level<20 ng/ml) and compared vitamin D3 with placebo. In the other two RCTs, patients hospitalized with (severe) COVID-19 were included and vitamin D3 was administered in addition to standard care. One of these trials compared vitamin D3 to placebo plus standard care [14], the other compared to standard care only [12]. While Murai et al. [14], who in sum included 240 patients, conducted a post hoc analysis with regard to a subgroup of 116 patients with vitamin D deficiency (25 (OH)D level<20 ng/ml), no information on the proportion of patients with vitamin D deficiency was available in Castillo et al. [12]. Because of the differences between studies regarding intervention (form and dosing, see also below) and population, results could not be pooled.

Rastogi et al. [13] used a dosage of 60,000 IU cholecalciferol daily during the first week and thereafter weekly for those with 25(OH)D >50 ng/ml (and continuing daily for the others). They report 10 of 16 patients in the cholecalciferol group reaching SARS-CoV-2 negativity (primary outcome) before week 3 compared to 5 of 24 patients in the placebo group. SARS-CoV-2 negativity was determined by PCR but no cut-off Ct-value was reported. They do not report baseline characteristics on important risk factors such as obesity. Also, sample size calculation was done with regard to the secondary outcome (serum level of inflammatory marker).

Castillo et al. [12] used a dosage of 0.532 mg calcifediol on day 1, 0.266 mg on day 3 and 7, then weekly until discharge or admission to intensive care unit. They conducted an open label pilot trial with 76 patients. The study publication refers to a planned bigger trial with over 1,000 patients, registered in ClinicalTrials.gov (NCT04366908) with an estimated study completion date in August 2020. However, no publication could be found. They report only 1 of 50 calcifediol patients requiring admission to intensive care unit compared to 13 of 26 patients in the control group. Two patients died in the control group, none in the calcifediol group. These results remained statistically significant when adjusted for the two risk factors with significant baseline differences, hypertension and diabetes mellitus type 2. However, data on obesity were not collected (nor on vitamin D deficiency, see above).

Murai et al. [14] used a single dose of 200,000 IU cholecalciferol. They report on four relevant outcomes, mortality, length of hospital stay, admission to intensive care unit and mechanical ventilation. They find no significant effects in either direction, neither in the overall group, nor in the subgroup with vitamin D deficiency.

Regarding safety, Rastogi et al. [13] reported that ‘No episodes of hypercalcaemia were observed in either group’ but did not provide any further information on adverse events. Murai et al. [14] reported one patient who vomited directly after vitamin D administration. Castillo et al. [12] do not mention any adverse event.

4.2 Safety evidence from observational studies

No observational study on safety fulfilling inclusion criteria was identified.

4.3 Ongoing studies

215 hits were retrieved from database search, 194 of which remained after deduplication. Of these, 23 hits were included.

4.4 Scientific conclusion about status of evidence generation

Currently, the evidence for vitamin D for COVID-19 is still in early stage, but a considerable number of studies is ongoing. The three published RCTs are heterogeneous with regard to the form and dosage of vitamin D, baseline disease severity and risk factors (with relevant risk factors not always being reported/available). Overall, results are inconsistent.

Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of Vitamin D (calcifediol) compared to no Vitamin D for treating COVID 19

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with no Vitamin D	Risk with Vitamin D (calcifediol)				
All-cause Mortality Population: consecutive patients hospitalized with COVID-19 infection % vitamin D deficient: no data	77 per 1,000	0 per 1,000	not estimable	76 (1 RCT[12])	⊕◯◯◯ VERY LOW	No deaths in the Vitamin D group
ICU admission Population: consecutive patients hospitalized with COVID-19 infection % vitamin D deficient: no data	500 per 1,000	480 fewer per 1,000 (from 497 fewer to 356 fewer)	RR 0.040 (0.006 to 0.289)	76 (1 RCT [12])	⊕⊕◯◯ LOW	Own calculation of RR based on reported frequencies

Abbreviations: CI = Confidence interval; HR = Hazard Ratio; ICU = intensive care; RR = Risk ratio

Table 4-2 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of Vitamin D (cholecalciferol) compared to placebo for treating COVID19

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with placebo	Risk with Vitamin D (cholecalciferol)				
All-cause Mortality Population: hospitalised patients with moderate to severe COVID-19 % vitamin D deficient[a]: 47.90 (VitD) / 59.15 (pbo)	50 per 1,000	24 more per 1,000 (from 23 fewer to 152 more)	RR 1.487 (0.547 to 4.048)	240 (1 RCT [14])	⊕⊕◯◯ LOW	Own calculation of RR based on reported frequencies
Length of hospital stay Population: hospitalised patients with moderate to severe COVID-19 % vitamin D deficient[b]: 47.90 (VitD) / 59.15 (pbo)	-	-	HR 1.07 (0.82 to 1.39)	240 (1 RCT [14])	⊕⊕⊕◯ MODERATE	

[a] 25-hydroxyvitamin D < 20 ng/mL
[b] 25-hydroxyvitamin D < 20 ng/mL

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with placebo	Risk with Vitamin D (cholecalciferol)				
Viral burden (SARS-CoV-2 negativity) Population: mild or asymptomatic COVID-19 % vitamin D deficient[c]: 100 (both groups)	208 per 1,000	417 more per 1,000 (from 54 more to 1,000 more)	RR 3.000 (1.260 to 7.142)	40 (1 RCT [13])	⊕◯◯◯ VERY LOW	Own calculation of RR based on reported frequencies
ICU admission Population: hospitalised patients with severe COVID-19 % vitamin D deficient[d]: 47.90 (VitD) / 59.15 (pbo)	208 per 1,000	51 fewer per 1,000 (from 117 fewer to 61 more)	RR 0.754 (0.439 to 1.293)	240 (1 RCT [14])	⊕⊕⊕◯ MODERATE	Own calculation of RR based on reported frequencies
Mechanical ventilation Population: hospitalised patients with moderate to severe COVID-19 % vitamin D deficient[e]: 47.90 (VitD) / 59.15 (pbo)	142 per 1,000	67 fewer per 1,000 (from 107 fewer to 18 more)	RR 0.525 (0.244 to 1.130)	240 (1 RCT [14])	⊕⊕◯◯ LOW	Own calculation of RR based on reported frequencies

Abbreviations: CI = Confidence interval; HR = Hazard Ratio; ICU = intensive care; pbo = Placebo; RR = Risk ratio; VitD = Vitamin D

Table 4-3 Study characteristics of included RCTs

Author, year, reference number/Study name/Study ID	Rastogi 2020 [13], NCT04459247 (SHADE)	Murai 2020 [14-17], NCT04449718	Castillo 2020 [12], NCT04366908[f]
Study design	RCT	RCT	Pilot RCT, open label
Centres (single centre or multicentre), country, setting	Single centre, India, tertiary care hospital	Multicentre, Brazil, one quarternary hospital and one field hospital in Sao Paulo	Single centre, Spain, university hospital
Patient population (number of included patients/ Mean age and sex/ Disease severity[g])	n=40[h], Intervention group:	n=240 age (mean, SD): 56.2 (14.4) gender (% male): 56.1%	n=76 age (mean, SD): 53+/-10 gender (% male): 59.2%

[c] 25-hydroxyvitamin D < 20 ng/mL

[d] 25-hydroxyvitamin D < 20 ng/mL

[e] 25-hydroxyvitamin D < 20 ng/mL

[f] refers to a planned RCT with estimated study completion date in August 2020, for which no publication could be identified – Castillo 2020 report the results of a preceding pilot trial

[g] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

[h] Age and sex not reported for whole cohort

	age (median, IQR): 50.0 (36-51); gender (% male): 37.5% Comparator group: age (median, IQR): 47.5 (39.3-49.2); gender (% male): 58.3% Severity: mild or asymptomatic COVID-19	Severity: hospitalised patients with moderate to severe COVID-19	Severity: consecutive patients hospitalized with COVID-19 infection
Inclusion criteria	Individuals with SARS-CoV-2 infection who were mildly symptomatic or asymptomatic with or without comorbidities (hypertension, diabetes mellitus, chronic obstructive airway disease, chronic liver disease, chronic kidney disease) Patients with vitamin D deficiency defined as 25 (OH)D level<20 ng/ml[i]	• adults aged 18 years or older • diagnosis of COVID-19 by either polymerase chain reaction (PCR) for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from nasopharyngeal swabs or computed tomography scan findings (bilateral multifocal ground-glass opacities ≥ 50%) compatible with the disease • diagnosis of flu syndrome with hospitalization criteria on hospital admission, presenting respiratory rate ≥ 24 breaths per minute, saturation < 93% on room air or risk factors for complications, such as heart disease, diabetes mellitus, systemic arterial hypertension, neoplasms, immunosuppression, pulmonary tuberculosis, and obesity, followed by COVID-19 confirmation before randomization	• consecutive patients hospitalized with COVID-19 infection (acute respiratory infection, confirmed by a radiographic pattern of viral pneumonia and by a positive SARS-CoV-2 PCR with CURB-65 severity scale recommending hospital admission in case of total score > 1)
Exclusion criteria	Rastogi 2020: Patients unable to take oral supplementation like those requiring invasive ventilation or with significant comorbidities like uncontrolled	• patient unable to read and sign the written informed consent • patient already admitted under invasive mechanical ventilation	• Patients younger than 18 years and pregnant women

[i] not consistent with study registry mentioning only „SARS-CoV-2 RNA positive Asymptomatic individuals“

	hyperglycaemia or hypertension were excluded.[j]	• previous vitamin D3 supplementation (> 1,000 IU/day) • renal failure requiring dialysis or creatinine ≥ 2.0 mg/dL • hypercalcemia defined by total calcium > 10.5 mg/dL • pregnant or lactating women • patients with expected hospital discharge in less than 24 hours	
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Cholecalciferol (day 1-7: 60,000 IU per day (5 ml oral solution in nano droplet form), day 8-14: weekly 60,000 IU cholecalciferol to those with 25(OH)D >50 ng/ml or else continued daily 60,000 IU cholecalciferol) n=16, no subgroups reported	Cholecalciferol (single dose of 200,000 IU of dissolved in a 10 mL of peanut oil solution on day of randomization plus standard care[k]) n=120 (randomised), n = 119 (mITT[l]), n=117 (per protocol), no subgroups reported	Calcifediol (0.532 mg on day 1, 0.266 mg on day 3 and 7, then weekly until discharge or ICU admission plus standard care as per hospital protocol (see below) n=50, no subgroups reported
Comparator(s) (standard care or generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	Placebo (5 ml distilled water) for 7 days n=24, no subgroups reported	Placebo (10 mL of peanut oil solution plus standard care[m]) n=120 (randomised), n = 118 (mITT[n]), n= 118 (per protocol), no subgroups reported	Standard care as per hospital protocol (hydroxychloroquine 400 mg every 12 h on the first day, and 200 mg every 12 h for the following 5 days combined with azithromycin 500 mg orally for 5 days; for patients with pneumonia and NEWS ≥ 5 additionally ceftriaxone 2 g intravenously every 24 h for 5 days) n=26, no subgroups reported
Primary Outcome(s)	• Proportions of participants who turn SARS-CoV-2 negative (confirmed	• Hospital length of stay, defined as the total number of days that patients	• Rate of ICU admission

[j] slight inconsistencies with criteria in study registry: “Uncontrolled Diabetes Uncontrolled Hypertension Chronic Liver Disease Chronic obstructive Pulmonary disease Requiring Invasive Ventilation”

[k] no further definition

[l] Patients that withdrew consent before receiving the intervention were excluded from analysis.

[m] no further definition

[n] Patients that withdrew consent before receiving the intervention were excluded from analysis.

	twice at 24-hour interval) before week 3 in the two groups	remained hospitalized from the date of randomization until the date of hospital discharge[o]	• mortality
Patient-relevant secondary outcome(s)	NR	• mortality • number of patients admitted to ICU • number of patients who needed mechanical ventilation and duration of mechanical ventilation	NR
Follow-up (days, months)	21 days (oropharyngeal swabs and SARS-CoV-2 RNA detection by PCR on days 5, 7, 10, 14, 18, 21)	Outcomes were assessed at baseline and on hospital discharge or death records.	Until ICU admission, hospital discharge or death
Sponsor/ lead institution	Department Of Internal Medicine, Nehru Hospital, PGIMER, Chandigarh 160012, India The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.	Clinical Hospital of the School of Medicine of the University of Sao Paulo, Ibirapuera Field Hospital supported by Sao Paulo Research Foundation (grants 20/05752-4; 19/24782-4; 20/11102-2; 16/00006-7; 17/13552-2; 15/26937-4; 19/18039-7) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (305556/2017-7).	Maimónides Biomedical Research Institute of Córdoba public funding (COVID-011-2020 Programa de Investigacion clínica en COVID-19 de Andalucía, Consejería de Salud y Familia, Fundacion Progreso y Salud, Fundacion para la Investigacion Biomedica de Cordoba)

Abbreviations: CURB = Confusion, Urea, Respiratory rate, Blood pressure; ICU = Intensive Care Unit; IU = international unit; mITT = modified intention to treat; mg = milligram; ml = per millilitre; NEWS = National Early Warning Score; ng = nanogram; NR = not reported; RCT = randomised clinical trial

[o] The criteria used for patient discharge were: 1) no need for supplemental oxygen in the last 48 hours; 2) no fever in the last 72 hours; and 3) oxygen saturation > 93% in room air without respiratory distress.

Table 4-4 Ongoing trials of single agent: Vitamin D

Trial Identifier/registry ID(s)/contact	IRCT20200324046850N1 [18]	NCT04344041 [19]	NCT04621058 [20]	NCT04536298 [21]
Estimated study completion date	No information	May 2021	November 2021	Juni 2021
Study design, study phase	RCT, phase 3	RCT, phase 3	RCT, phase 3	RCT, phase 3
Recruitment status	Recruitment complete	Recruitment completed	Recruiting	Recruiting
Number of Patients, Disease severity[p]	100 patients diagnosed with COVID-19	260 high-risk COVID-19 Patients	108 patients with COVID-19 and pneumonia	2,700 Patients newly diagnosed with COVID-19 (inclusion within 72 hours of testing)
Setting (hospital, ambulatory...)	Hospital	Hospital, ambulatory, nursing home	Hospital	Ambulatory
Intervention (generic drug name and dosage)	Standard country protocol drugs with vitamin D3 ampoules of 50,000 units once a week and N-acetylcysteine placebo tablets every 12 hours[q]	High dose of vitamin D3 Drug: cholecalciferol 200,000 IU	If vitamin D deficiency < 30 ng/ml: treatment with 2 capsules of 0.266 mg If vitamin D deficiency < 40 ng/ml: treatment with 1 capsule of 0.266 mg	Vitamin D capsules including 3,200 IU of vitamin D3. Three capsules per day (9,600 IU/day) will be taken on days 1 and 2, and one capsule per day (3,200 IU/day) will be taken on days 3 through 28
Comparator (standard care or generic drug name and dosage)	Standard country protocol drugs with placebo vitamin D3 once a week and placebo tablets N-acetylcysteine every 12 hours[r]	Standard dose of vitamin D3, drug: cholecalciferol 50,000 IU	Placebo	Placebo
Primary Outcome(s)	Time to clinical improvement	Mortality	Mortality	Hospitalization or death in index cases
Sponsor/ lead institution, country (also country of recruitment if different)	Abadan University of Medical Sciences, Iran	CHU Angers, France	Bioaraba Health Research Institute Fundación Eduardo Anitua, Spain	Brigham and Women's Hospital, USA

Abbreviations: RCT = randomised clinical trial; IU = international unit; ICU = Intensive Care Unit; ng/ml = nanograms per millilitre; mg = milligram

[p] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

[q] only relevant study arm displayed

[r] only relevant study arm displayed

Table 4-5 Ongoing trials of single agent: Vitamin D, continued

Trial Identifier/registry ID(s)/contact	NCT04552951 [22]	NCT04641195 [23]	EudraCT: 2020-001960-28 [24]	NCT04363840 [25]
Estimated study completion date	December 2020	March 2022	No information	December 2020
Study design, study phase	RCT, phase 4	RCT, phase 3	RCT, phase 3	RCT, phase 2
Recruitment status	Recruiting	Recruiting	No information	Not yet recruiting
Number of Patients, Disease severity[s]	80 patients diagnosed with COVID-19	700 patients diagnosed with COVID-19	108 patients diagnosed with COVID-19	1,080 patients newly diagnosed with COVID-19 (within 24 hours after diagnoses)
Setting (hospital, ambulatory...)	Not clear	Start as inpatient, continuation as outpatients	Hospital	Ambulatory
Intervention (generic drug name and dosage)	Cholecalciferol Single dose of 100,000 IU	Vitamin D3 (cholecalciferol) 180,000 international units (IU) of vitamin D3 at enrolment, followed by 2,000 IU once per day from enrolment to 8 weeks[t]	Hidroferol 0.266 mg capsules	Aspirin 81 mg to be taken orally once daily for 14 days. In combination with Dietary Supplement: Vitamin D 50,000 IU to be taken orally once weekly for 2 weeks
Comparator (standard care or generic drug name and dosage)	No intervention / no vitamin D	Placebo	Placebo	Aspirin 81 mg to be taken orally once daily for 14 days.
Primary Outcome(s)	• Mortality • ICU admission • Time of hospitalization [u]	Time to recovery	Mortality ICU admission	Hospitalization
Sponsor/ lead institution, country (also country of recruitment if different)	Fundación para la Investigación Biosanitaria del Principado de Asturias, Spain	Harvard School of Public Health, US Recruitment: India	Investigation Institute Bioaraba, Spain	Louisiana State University Health Sciences Center in New Orleans, USA

Abbreviations: RCT = randomised clinical trial; IU = international unit; ICU = Intensive Care Unit

[s] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

[t] only relevant study arm displayed, additional study arms for treatment with Zinc and treatment with zinc in combination with Vitamin D

[u] only relevant primary outcome measures displayed

Table 4-6 Ongoing trials of single agent: Vitamin D, continued

Trial Identifier/registry ID(s)/contact	NCT03188796 [26]	NCT04525820 [27]	CTRI/2020/06/026189 [28]
Estimated study completion date	February 2023	June 2021	February 2022
Study design, study phase	RCT, phase 3	RCT, Phase: no information	RCT, phase 2
Recruitment status	Recruiting	Recruiting	Not yet recruiting
Number of Patients, Disease severity[v]	2400 critical ill patients including patients infected with COVID-19	80 hospitalized patients diagnosed with COVID-19	210 patients with mild to moderate COVID- 19
Setting (hospital, ambulatory...)	Hospital, ambulatory	Hospital	COVID care facility
Intervention (generic drug name and dosage)	Cholecalciferol oral/enteral loading dose of 37.5 ml MCT including 540,000 IU vitamin D3 followed by 10 drops daily (4,000 IU) for 90 days	Single high dose vitamin D one dose orally of 140,000 IU (7 ml) followed by vitamin D 800 IU per day (treatment as usual)	Standard COVID-19 treatment, and Vitamin D 400,000 IU single dose plus Magnesium Glycinate 250 mg BD for 14 days
Comparator (standard care or generic drug name and dosage)	Placebo	Single dose of a placebo solution followed by vitamin D 800 IU per day (treatment as usual)	Standard COVID-19 treatment, and Vitamin D 60,000 IU single dose plus Magnesium Glycinate 250mg BD for 14 days
Primary Outcome(s)	Mortality	Length of hospitalization	• Negative RT- PCR test for COVID 19 infection • Improvement in Signs and symptoms of COVID 19 infection, use of ventilator, length of stay in ICU • Reduction in CRP levels • Reduction in rate of COVID -19 complication. • Speed of recovery and duration to becoming asymptomatic • Length of hospital stay
Sponsor/ lead institution, country (also country of recruitment if different)	Medical University of Graz, Austria, Belgium	Prof. Dr. Jörg Leuppi, Cantonal Hospital Baselland Liestal, Switzerland	Suraksha Pharma Private Limite, India

Abbreviations: RCT = randomised clinical trial; IU = international unit; mcg = microgram

[v] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Table 4-7 Ongoing trials of single agent: Vitamin D, continued

Trial Identifier/registry ID(s)/contact	NCT04334005 [29]	NCT04489628 [30]	NCT04385940 [31]	NCT04636086 [32]
Estimated study completion date	June 2020	August 2021	December 2020	February 2022
Study design, study phase	RCT, Phase: no information	RCT, Phase 1	RCT, Phase 3	RCT, Phase 4
Recruitment status	Not yet recruiting	Not yet recruiting	Not yet recruiting	Recruiting
Number of Patients, Disease severity[w]	200 non-severe symptomatic patients diagnosed with COVID-19	110 patients diagnosed with COVID-19 and present asymptomatic or with mild symptoms	64 patients diagnosed with COVID-19	100 patients diagnosed with COVID-19
Setting (hospital, ambulatory...)	Ambulatory	Ambulatory	Ambulatory	Hospital
Intervention (generic drug name and dosage)	25,000 IU of vitamin D supplement in addition to usual care	8 capsules of cholecalciferol 50,000 IU	High dose vitamin D: 50,000 IU, Oral Vitamin D3	25,000 IU/ml of cholecalciferol: one ampoule on Day 1, Day 2, Day 3, Day 4, Day 8, Day 15, Day 22, Day 29 and Day 36
Comparator (standard care or generic drug name and dosage)	Usual care	8 capsules of placebo	Low dose vitamin D: Vitamin D3 1,000 IU	Placebo
Primary Outcome(s)	Composite of cumulative death (i.e. mortality) for all causes and for specific causes	Patients requiring admission to the hospital or experiencing death	Symptoms recovery	Vitamin D serum concentration[x]
Sponsor/ lead institution, country (also country of recruitment if different)	Universidad de Granada, Spain	University Hospitals Cleveland Medical Center, US	University of Alberta, USA	University of Liege, Belgium

Abbreviations: RCT = randomised clinical trial; IU = international unit; mcg = microgram

[w] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

[x] Mortality is mentioned as secondary outcome measure.

Table 4-8 Ongoing trials of single agent: Vitamin D, continued

Trial Identifier/registry ID(s)/contact	NCT04411446 [33]	NCT04733625 [34]	EudraCT: 2020-002119-23 [35]
Estimated study completion date	Oktober 2021	December 2020[y]	No information
Study design, study phase	RCT, Phase 4	RCT, phase: not applicable	RCT
Recruitment status	Recruiting	Completed	No information
Number of Patients, Disease severity[z]	1264 patients diagnosed with COVID-19	56 elderly, type II diabetes, vitamin D deficient patients diagnosed with COVID-19	80 oncological patients in active oncological treatment diagnosed with Covid-19, non-hospitalized
Setting (hospital, ambulatory...)	Hospital	University hospital	Ambulatory
Intervention (generic drug name and dosage)	5 capsules of 100,000 IU Vitamin D orally given all at once	Cholecalciferol single injection of Vitamin D 200,000 IU	Cholecalciferol, oral drops, 10,000 IU
Comparator (standard care or generic drug name and dosage)	Placebo	Placebo	Placebo
Primary Outcome(s)	Respiratory organ failure assessment score (SOFA) Need of a high dose of oxygen or mechanical ventilation.	Death (in hospital) or need for intubation	Rate of hospitalization due to COVID-19 related pneumonia
Sponsor/ lead institution, country (also country of recruitment if different)	Vitamin D Study Group; Ag Nac Promoción de la Investigación, el Desarrollo Tecnológico y la Innovación, Argentinia	Cairo university hospitals, Egypt, Sponsors and Collaborators: Kasr El Aini Hospital	Istituto europeo di oncologia, Italy

Abbreviations: RCT = randomised clinical trial; IU = international unit; ml = millilitre

[y] given as “actual study completion date”

[z] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

Table 4-9 Ongoing trials of single agent: Vitamin D, continued

Trial Identifier/registry ID(s)/contact	CTRI/2020/12/030083 [36]	NCT04828538 [37]
Estimated study completion date	No information	July 2021
Study design, study phase	RCT	RCT
Recruitment status	No information	Recruiting
Number of Patients, Disease severity[aa]	No information on number, patients diagnosed with COVID-19	1,800 patients diagnosed with COVID-19
Setting (hospital, ambulatory...)	No information	Hospital
Intervention (generic drug name and dosage)	Vitamin D3 (cholecalciferol, syrup): 1. Uncomplicated illness: 360,000-600,000[bb] IU 6-10 days once a day 2. Mild Pneumonia: 360,000-600,000[cc] IU 6-10 days once a day 3. Severe Pneumonia: 360,000 - 600,000[dd] IU 3-5days twice a day	Factorial 1: 4000 IU Vitamin D (vs. placebo) Factorial 2: 1000mg Omega DHA/EPA (vs. placebo) Factorial 3: Combination 1000 mg Vitamin C, Vitamin B complex** and Zinc Acetate, 100 mg/day (vs. placebo)
Comparator (standard care or generic drug name and dosage)	Standard treatment according to physician's decision, based on the current recommendations	Placebo
Primary Outcome(s)	• Difference in two study groups with respect to the duration and severity of signs and symptoms • Time taken for double negative RT-PCR between the two study groups • Duration of hospital stay	• mortality • ICU admission • intubation • mechanical ventilation
Sponsor/ lead institution, country (also country of recruitment if different)	No information	Hospital de la Soledad, Mexiko

Abbreviations: RCT = randomised clinical trial; IU = international unit; mg = milligram; ml = millilitre

[aa] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

[bb] Given as “3,60,000-6,00,000”

[cc] See above

[dd] See above

Table 4-10 Ongoing trials of single agent: Vitamin D, continued

Trial Identifier/registry ID(s)/contact	EudraCT: 2020-001903-17 [38]	IRCT20200411047024N1 [39]	IRCT20140305016852N4 [40]
Estimated study completion date	No information	No information	No information
Study design, study phase	RCT, Phase 3b	RCT, no information	RCT, no information
Recruitment status	No information	Recruitment complete	Recruitment complete
Number of Patients, Disease severity[ee]	120 patients in a moderate to severe degree (4-7 in WHO severity scale) needing oxygen therapy	100 COVID-19 patients with vitamin D deficiency	Patients with COVID-19
Setting (hospital, ambulatory...)	hospital	hospital	hospital
Intervention (generic drug name and dosage)	Vitamin D3 (Cholecalciferol) single dose, 200,000 UI / 1 ml, solution for injection, plus Tocilizumab (solution for injection/infusion)	intramuscularly Injections of 300 mg of vitamin D at the beginning of the first week, as well as another dose at the beginning of the second week	Group one: 50,000 units of vitamin D daily for one week and routine treatment under the supervision of an infectious disease specialist Group two: 500 mg vitamin C daily for one week and routine treatment under the supervision of an infectious disease specialist
Comparator (standard care or generic drug name and dosage)	Tocilizumab (solution for injection/infusion)	No intervention	Routine treatment under the supervision of a specialist
Primary Outcome(s)	number of patients with fatal outcome	Clinical course, paraclinical findings, in-hospital outcome (not clearly reported in the registry)	Complete recovery of clinical COVID-19 symptoms, normalization of chest symptoms in CT scan
Sponsor/ lead institution, country (also country of recruitment if different)	Hospital Universitario de Móstoles, Spain, Support by Madrilenian Health Service	Shahroud University of Medical Sciences, Iran	Sabzevar University of Medical Sciences, Iran

Abbreviations: RCT = randomised clinical trial; IU = international unit; mg = milligram; ml = millilitre

[ee] Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19

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6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

GÖG is responsible for setting up the search strategy to identify randomised controlled trials (RCTs). GÖG performed a search in Medline and PubMed (Appendix Table 6-1) and searched medRxiv.org (https://www.medrxiv.org/), bioRxiv.org (https://www.bioRxiv.org/), and arXiv.org (https://www.arXiv.org/) for preprints of preliminary reports of randomised trials. The Cochrane COVID-19 Study Register (https://covid-19.cochrane.org/), ClinicalTrials.gov (www.clinicaltrials.gov) ISRCTN registry (https://www.isrctn.com/) and EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/ctr-search/search?query=covid-19+AND+vitamin+D) were searched in addition. We applied no restriction on language of publication.

Table 6-1 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 "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 "SARS-Cov-19"[Title/Abstract] OR Ncovor[Title/Abstract] OR Ncorona*[Title/Abstract] OR (((((respiratory*[Title/Abstract] AND (symptom*[Title/Abstract] OR disease*[Title/Abstract] OR illness*[Title/Abstract] OR condition*))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 ((vitamin D[Title/Abstract] OR vitamin D3[Title/Abstract] OR vitamin D2[Title/Abstract] OR ergocalciferol[Title/Abstract] OR ercalcitriol[Title/Abstract] OR calcitriol[Title/Abstract] OR high-dose Vitamin D[Title/Abstract]) OR Calcifediol or (vitamin D[MeSH Major Topic]))	5/3/2021 until 5/5/2021

Database	URL	Search line / Search terms	Date of search
Ovid MEDLINE(R) ALL)	ovidsp.dc2.ovid.com	1 exp coronavirus/ 2 ((corona* or corono*) adj1 (virus* or viral* or virinae*)).ab,kw,ti. 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 "SARSCov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ab,kw,ti. 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*)).ab,kw,ti. 5 ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ab,kw,ti. 6 "severe acute respiratory syndrome* ".ab,kw,ti. 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.da,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" 20 exp Vitamin D/ 21 (vitamin D or Vitamin D3 or Vitamin D2 or Calcifediol or ergocalciferol or ercalcitriol or calcitriol).ab,kw,ti. 22 high-dose Vitamin C.ab,kw,ti. 23 20 or 21 or 22 24 18 and 23	7/4/2021 until 5/5/2021

6.2 Search strategy to identify observational studies

As of October 2020, NIPHNO is responsible for setting up the search strategy to identify observational studies.

From September to December 2020, we received records that EPPI Centre has screened after searching weekly in Medline and Embase (until beginning of November 2020), from November onwards Microsoft Academics Graph (MAG). We supplemented these studies with a weekly search in Scopus (Elsevier). Detailed descriptions of the EPPI and NIPHNO searches are given at their websites [41,42]. The retrieved hits were imported to a reference management tool, Endnote (Clarivate Analytics), for deduplication. We then searched the EndNote database using the generic names and synonyms for the included COVID-19 drugs.

From January onwards, an information specialist at NIPHNO has conducted searches in Medline (Ovid), Embase (Ovid) using the search strategy described in table 6.2. To screen the references, two reviewers use a binary machine learning (ML) classifier. References that scored above the identified threshold of 30% certainty to be relevant were retained for screening; while those scoring below this threshold score were set aside.

Prior to using the binary ML classifier score to discard low scoring records, we screened 1028 references manually to train the classifier. The classifier is continuously being updated a long with new references being screened. References that have been set aside, can potentially be picked up in a later stage by a new classifier version. For drugs that have less than 5 publications included in the training batch, we combine the classifier with manual text word searches.

As a supplement we used Microsoft Academics Graph (MAG) to identify further relevant research. We used articles previously included in the EUnetHTA rolling collaborative review until last search and ran the Bring up-to-date function in EPPI Reviewer. Bring up-to-date uses the neural networks of MAG to identify publications similar to input articles, added to the MAG database.

Table 6-2 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search	Hits retrieved
Embase 1974 to 2021		Lines 1 and 2 are copies of Ovid's Expert searches for covid-19 in MEDLINE and Embase	From 26/2/2021 until 05/4/2021	1759
Ovid MEDLINE(R) ALL 1946 to 2021		1 ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) 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) adj2 (CoV or 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. or COVID-19.rx,px,ox,sh. or severe acute respiratory syndrome coronavirus 2.os.) use medall [COVID-19 in MEDLINE] 2 ((((pneumonia or covid* or coronavirus* or corona virus* or ncov* or 2019-ncov or sars*).mp. or exp pneumonia/) and Wuhan.mp.) or (coronavirus disease 2019 or 2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or severe acute respiratory syndrome coronavirus 2 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 or 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. or	From 06/04/2021 until 03/05/2021	1032

		(coronavirus disease 2019 or severe acute respiratory syndrome coronavirus 2).sh,dj.) use oemezd [COVID-19 in Embase] 3 (COVID-19 serotherapy/ or Immunization, Passive/ or tocilizumab/ or camostat/ or nafamostat/ or AP301 peptide/ or Interleukin 1 Receptor Antagonist Protein/ or alunacedase alfa/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferons/ or gimsilumab/ or canakinumab/ or baricitinib/ or molnupiravir/ or Aspirin/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or Ivermectin/) use medall [MeSH-terms for drugs in MEDLINE] 4 (Hyperimmune globulin/dt or tocilizumab/ or camostat/ or camostat mesilate/ or nafamstat/ or solnatide/ or anakinra/ or darunavir/ or favipiravir/ or sarilumab/ or exp Interferon/ or gimsilumab/ or canakinumab/ or baricitinib/ or acetylsalicylic acid/ or mavrilimumab/ or exp Vitamin D/dt or Vitamin D Deficiency/dt or ivermectin/) use oemezd [Emtree-terms for drugs in Embase] 5 ((convalescent adj (plasma or sera or serum)) or serotherap* or ((atoxin or hyperimmunoglobulin or hyperimmune globulin or hyperimmune gammaglobulin) adj therap*) or passive immuni?ation or (tocilizumab or atlizumab or (MRA adj monoclonal antibod*) or MSB-11456 or MSB11456 or R-1569 or R1569 or RO-4788533 or RO4788533 or Actemra or Roactemra) or (camostat* or FOY-305 or FOY305 or FOY S 980) or (nafamostat or nafamstat or FUT-175 or FUT175) or (solnatide or AP301 or AP-301 or (TIP adj peptide)) or (anakinra or ((interleukin 1 or IL1 or IL-1) adj2 (antagonist or block* or inhibitor*)) or IL-1Ra or Kineret) or (alunacedase or APN01 or APN-01 or rhACE2 or recombinant human angiotensin converting enzyme 2 or GSK-2586881 or GSK2586881) or (darunavir or prezista or TMC-114 or TMC114 or UIC-94017 or UIC94017) or (favipi?avir or T-705 or T705 or Avigan or Olumiant) or (sarilumab or REGN-88 or REGN88 or SAR-153191 or SAR153191 or Kevzara) or (interferon* or (IFN adj1 (alpha* or beta* or gamma*)) or novaferon or CL-884 or CL884) or (gimsilumab or KIN-1901 or KIN1901 or morab-022 or morab022) or (canakinumab or ACZ-885 or ACZ885 or immunoglobulin G1 or Ilaris) or (baricitinib or LY-3009104 or LY3009104 or INCB-028050 or INCB028050 or INCB-28050 or INCB28050 or Olumiant) or (molnupiravir or MK-4482 or MK4482 or EIDD-2801 or EIDD2801) or (aspirin or acetylsalicylic acid) or (mavrilimumab or immunoglobulin G4 or CAM-3001 or CAM3001) or ((vitamin? D? or D?-vitamin?) adj4 (high-dose* or highdose* or supplement*)) or (ivermect* or MK-933 or MK933)).mp,bt,ot,du,dy,tn,nm. [other terms (title, abstract, author keywords and more) in MEDLINE and Embase] 6 (20210406 OR 20210407 OR 20210408 OR 20210409 OR 2021041* OR 2021042* OR 2021043* OR 202105*).dt. use medall [time limits in MEDLINE] 7 (20210406 OR 20210407 OR 20210408 OR 20210409 OR 2021041* OR 2021042* OR 2021043* OR 202105*).dc. use oemezd [time limits in Embase] 8 (1 and (3 or 5) and 6) use medall 9 (2 and (4 or 5) and 7) use oemezd		

6.3 Search strategy to identify ongoing studies

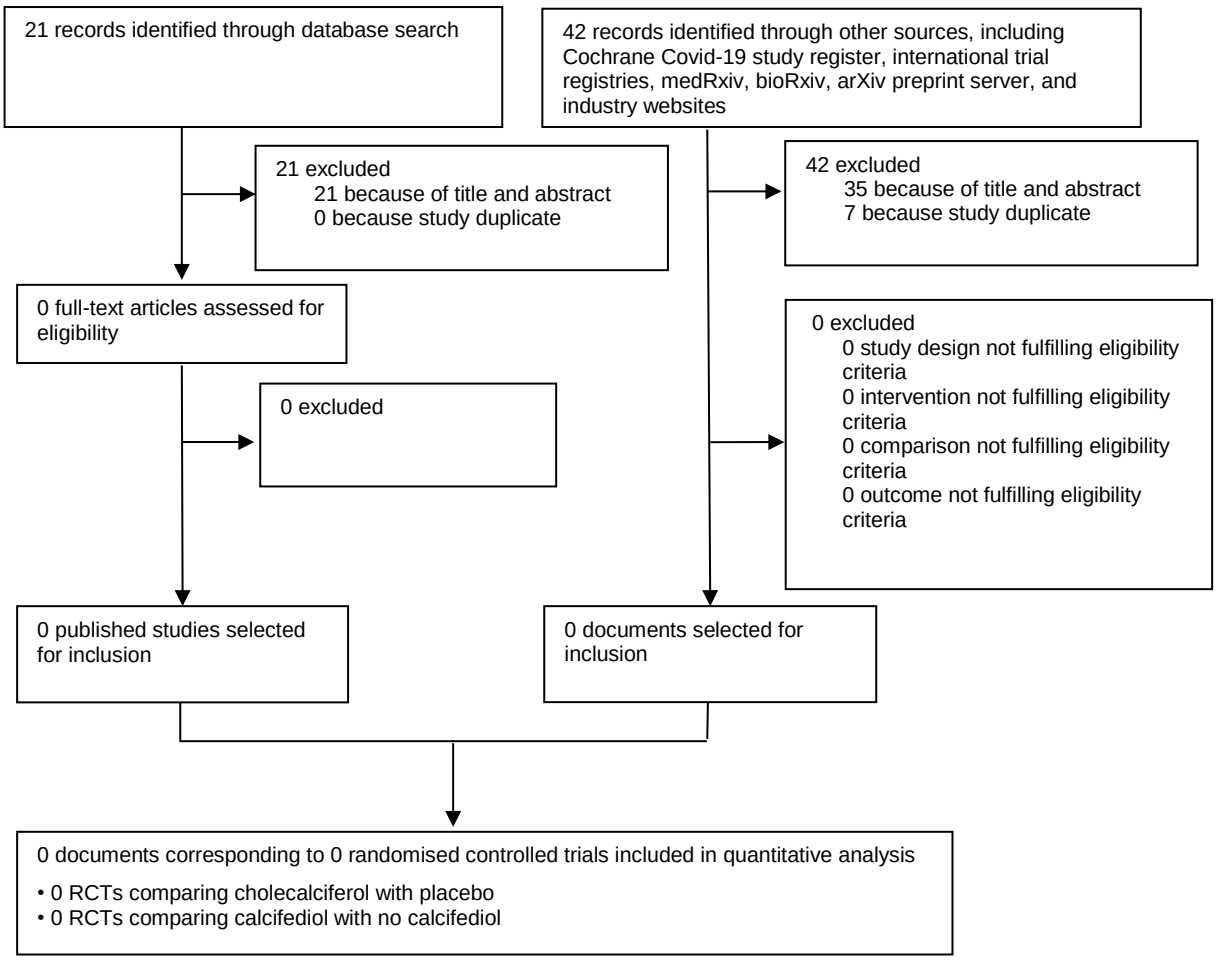
GÖG is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and Vitamin D are described in Table 6-3.

Table 6-3 Search strategy to identify ongoing studies

Database	URL	Search line / search terms	Date of search	Hits retrieved
ClinicalTrials.gov	https://clinicaltrials.gov/	"Basic search mode*" Terms used at Condition or disease: • covid-19 or corona Terms used at "other terms": • vitamin D or Vitamin D2 OR Vitamin D3 OR Calcifediol or ergocalciferol or ercalcitriol or calcitriol	07/04/2021 05/05/2021	6 new** 4 new**
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: • covid-19 and Vitamin D	07/04/2021 05/05/2021	0 0
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: • covid-19 and Vitamin D	07/04/2021 05/05/2021	0 0

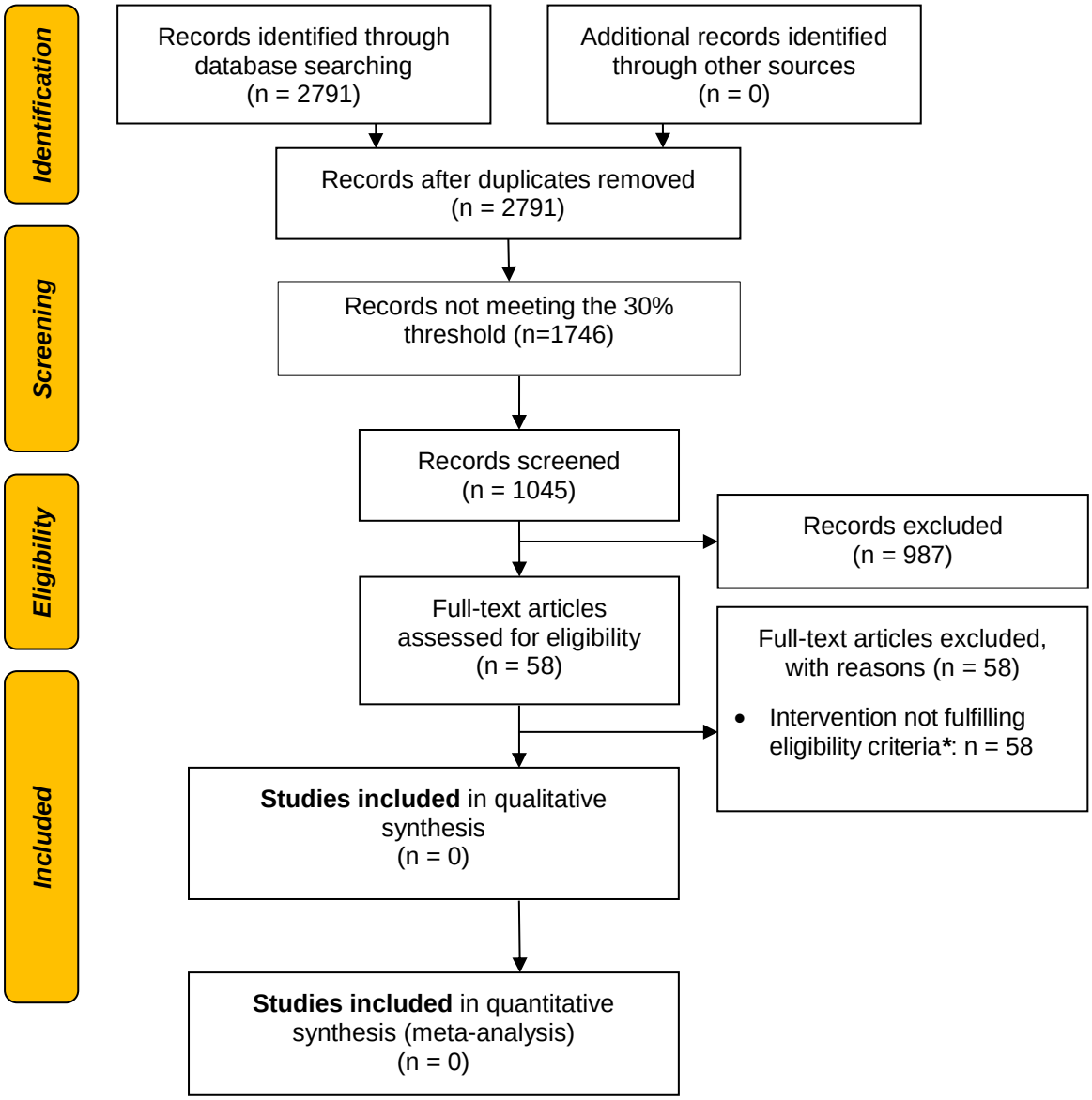
***** In "Basic Search mode", one term was added to the field "condition or disease" and one term in the field "other terms".
** plus 9+16 hits from the Cochrane Covid-19 study register (Appendix Figure 6-1)

6.4 Flow diagrams



Appendix Figure 6-1. Flow diagram depicting the selection process of RCTs

RCT = randomised controlled trial



Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies (search of April and May 2021 combined)

***** studies evaluating active substances relevant to other EUnetHTA rolling collaborative reviews