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EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT

Gesundheit Österreich GmbH

"Rolling Collaborative Review" of Covid-19 treatments

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

Project ID: RCR20

Monitoring Report

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V 1.0	**15/02/2021**	First version
V 2.0	**15/03/2021**	Second version
V 3.0	**17/05/2021**	Third version
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Major changes from previous version

Chapter, page no.	Major changes from version 3.0
Chapter 4, p. 11	3 RCTs have been added (one from the list of ongoing trials).
Chapter 4, p. 27	2 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. As of May 2021, RCR20 is updated on a bi-monthly basis.

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 (vitamin D2 and D3): "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, • 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)

* 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 two main mandatory sources and one optional source of information, as described below:

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

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 was conducted on a monthly basis for versions 1.0 to 3.0, with the last search done on 3 May 2021. No relevant observational studies were identified until this date. The authoring team decided not to update the search for observational studies on a regular basis.

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 authoring 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 6-2. 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 6-2.

Table 6-2 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	5/5/2021 until 12/7/2021	8 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: • covid-19 and Vitamin D	5/5/2021 until 12/7/2021	0 0
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: • covid-19 and Vitamin D	5/5/2021 until 12/7/2021	0 0

***** In "Basic Search mode", one term was added to the field "condition or disease" and one term in the field "other terms".

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”. Six RCTs [12-17] of varying size and quality have been published to date. We moreover identified 24 ongoing RCTs with estimated primary completion dates ranging from June 2020 to February 2023 (6 in 2020, 7 in 2021, 3 in 2022, 1 in 2023, 6 entries have no information on study completion date).

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

One RCT each is available for the following comparisons: 1) cholecalciferol vs. placebo (Rastogi 2020) [13]; 2) cholecalciferol vs. no treatment (Sánchez-Zuno 2021) [17]; 3) cholecalciferol plus standard treatment vs. placebo plus standard treatment (Murai 2020) [18]; 4) cholecalciferol plus standard treatment vs. standard treatment (Lakkireddy 2021) [16]; 5) calcifediol plus standard treatment vs. standard treatment (Castillo 2020) [12]; 6) comparison of two different dosages of cholecalciferol (Sabico 2021) [15]. All cholecalciferol studies used different dosing regimens. The studies investigated the effects of the interventions on COVID-19 patients with asymptomatic infection or mild disease [13], mild disease [17], mild to moderate disease [15, 16], moderate to severe disease [18] or patients hospitalised for COVID 19 without reported disease severity [12]. Also, the proportion of patients with vitamin D deficiency varies between studies (when reported). Because of these 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).

Sánchez-Zuno et al. used 10,000 IU of cholecalciferol per day for 14 days in outpatients and compared with no treatment. They report SARS-CoV-2 negativity by RT-PCR on day 7 and day 14 and find no significant differences.

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.

Lakkireddy et al. used 60,000 IU of cholecalciferol per day for 8 days in patients with BMI of 18-25 and for 10 days in patients with BMI >25 in conjunction with standard treatment and compared to standard treatment alone. They report no significant differences in length of hospital stay, ICU admission rate or mortality.

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).

Sabico et al. compared 5,000 IU of cholecalciferol with 1,000 IU of cholecalciferol per day for 14 days in inpatients and outpatients. They report no significant difference in the rate of ICU admission. One patient died in the 5,000 IU group, no one in the 1,000 IU group. They also report no significant difference in "days to discharge" but it is unclear if this refers only to the hospitalised patients or a composite endpoint of discharge from hospital of inpatients and deisolation of outpatients.

Lakkireddy et al. reported no significant difference in the median duration of symptoms (5 days vs. 5 days; Z=0.9, p=0.4). Sabico et al. report the average duration to resolution of 11 specific symptoms and find significant shorter durations in the 5,000 IU group for cough (6.2+/-0.8 days vs. 9.1+/-0.8 days; p=0.007) and ageusia (11.4+/-1.0 days vs. 16.9+/-1.7 days; p=0.035) but not for the other symptoms. Sánchez-Zuno et al. report the rate of patients with any, more than 1, more than 2 or more than 3 symptoms at baseline, at day 7 and at day 14. They find a significantly smaller rate of patients with more than 3 symptoms in the cholecalciferol group (0 of 22 patients vs. 4 of 20 patients, both at day 7 and day 14; p=0.04) but no difference in the other comparisons.

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. Lakkireddy et al. and Sabico et al. reported that no patients had any adverse reactions. Castillo et al. [12] and Sánchez-Zuno et al. did not report on adverse events.

4.2 Safety evidence from observational studies

No observational study on safety fulfilling inclusion criteria was identified during the search period 1 September 2020 to 3 May 2021.

4.3 Ongoing studies

245 hits were retrieved from database search, 224 of which remained after deduplication. Of these, 24 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 six 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, and certainty of evidence is mostly low.

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	20 per 1,000 (3 to 145)	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 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: hospitalised patients with moderate to severe COVID-19 % vitamin D deficient[3]: 100 (both groups)	77 per 1,000	31 per 1,000 (6 to 153)	RR 0.400 (0.081 to 1.990)	130 (1 RCT [16])	⨁◯◯◯ VERY LOW	Own calculation of RR based on reported frequencies
ICU admission Population: hospitalised patients with moderate to severe COVID-19 % vitamin D deficient[4]: 100 (both groups)	77 per 1,000	62 per 1,000 (17 to 219)	RR 0.800 (0.225 to 2.486)	130 (1 RCT [16])	⨁◯◯◯ VERY LOW	Own calculation of RR based on reported frequencies

[3] 25-hydroxyvitamin D < 30 ng/mL

[4] 25-hydroxyvitamin D < 30 ng/mL

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)				
Viral burden (SARS-CoV-2 negativity) at day 7 Population: outpatients with mild COVID-19 % vitamin D deficient: not reported[5]	400 per 1,000	454 per 1,000 (224 to 620)	RR 1.136 (0.561 to 2.301)	42 (1 RCT[17])	⊕◯◯◯ VERY LOW	Own calculation of RR based on reported frequencies
Viral burden (SARS-CoV-2 negativity) at day 14 Population: outpatients with mild COVID-19 % vitamin D deficient: not reported[6]	1,000 per 1,000	955 per 1,000 (871 to 1,000)	RR 0.955 (0.871 to 1.046)	42 (1 RCT[17])	⊕⊕◯◯ LOW	Own calculation of RR based on reported frequencies

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

Table 4-3 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of Vitamin D (cholecalciferol) compared to placebo for treating COVID 19

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[7]: 47.90 (VitD) / 59.15 (pbo)	50 per 1,000	74 per 1.000 (27 to 202)	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[8]: 47.90 (VitD) / 59.15 (pbo)	-	-	HR 1.07 (0.82 to 1.39)	240 (1 RCT [14])	⊕⊕⊕◯ MODERATE	
Viral burden (SARS-CoV-2 negativity) at day 14	208 per 1,000	625 per 1.000 (263 to 1.000)	RR 3.000 (1.260 to 7.142)	40 (1 RCT [13])	⊕◯◯◯ VERY LOW	Own calculation of RR based on

[5] Baseline level in n = 42 (median (range)): 22.4 (12.1-45.9)

[6] Baseline level in n = 42 (median (range)): 22.4 (12.1-45.9)

[7] 25-hydroxyvitamin D < 20 ng/mL

[8] 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)				
Population: hospitalised patients with mild or asymptomatic COVID-19 % vitamin D deficient[9]: 100 (both groups)						reported frequencies
ICU admission Population: hospitalised patients with severe COVID-19 % vitamin D deficient[10]: 47.90 (VitD) / 59.15 (pbo)	208 per 1,000	157 per 1.000 (91 to 269)	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[11]: 47.90 (VitD) / 59.15 (pbo)	142 per 1,000	74 per 1.000 (35 to 160)	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

[9] 25-hydroxyvitamin D < 20 ng/mL
[10] 25-hydroxyvitamin D < 20 ng/mL
[11] 25-hydroxyvitamin D < 20 ng/mL

Table 4-4 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of Vitamin D (cholecalciferol) 5000 IU compared to Vitamin D (cholecalciferol) 1000 IU for treating COVID 19

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence	Comments
	Risk with Vitamin D (cholecalciferol) 1,000 IU	Risk with Vitamin D (cholecalciferol) 5,000 IU				
All-cause Mortality Population: inpatients and outpatients with mild to moderate disease % vitamin D deficient[12]: 55	0 per 1.000	0[13] per 1.000	not estimable	69 (1 RCT [15])	⨁◯◯◯ VERY LOW	No deaths in the 1,000 IU group, one death in the 5,000 IU group.
ICU admission Population: inpatients and outpatients with mild to moderate disease % vitamin D deficient[14]: 55	91 per 1,000	56 per 1,000 (10 to 312)	RR 0.611 (0.109 to 3.432)	69 (1 RCT [15])	⨁◯◯◯ VERY LOW	Own calculation of RR based on reported frequencies

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

[12] 25-hydroxyvitamin D < 20 ng/mL

[13] One person died.

[14] 25-hydroxyvitamin D < 20 ng/mL

Table 4-5 Study characteristics of included RCTs

Author, year, reference number/Study name/Study ID	Rastogi 2020 [13], NCT04459247 (SHADE)	Murai 2020 [14, 19-21], NCT04449718	Castillo 2020 [12], NCT04366908[15]	Lakkireddy 2021 [16], CTRI/2020/12/030083	Sánchez-Zuno 2021 [17]	Sabico 2021 [15], SCTR H-01-R-012
Study design	RCT	RCT	Pilot RCT, open label	RCT, open label	RCT, open label	RCT, open label[16]
Centres (single centre or multicentre), country, setting	Single centre, India, tertiary care hospital (inpatient)	Multicentre, Brazil, one quarternary hospital and one field hospital in Sao Paulo (inpatient)	Single centre, Spain, university hospital (inpatient)	Single centre, India, public teaching hospital (inpatient)	Single centre, Mexico, university hospital (outpatient)	Multicentre, Saudi Arabia, tertiary care hospitals (inpatient and outpatient)
Patient population (number of included patients/ Mean age and sex/ Disease severity[17])	n=40[18] Intervention group: 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	n=240 age (mean, SD): 56.2 (14.4) gender (% male): 56.1% Severity: hospitalised patients with moderate to severe COVID-19	n=76 age (mean, SD): 53+/-10 gender (% male): 59.2% Severity: consecutive patients hospitalized with COVID-19 infection	n=130 (allocated), n=87 (analysed) age (mean, SD): 45+/-13 (n=87) gender (% male): 75% Severity: mild to moderate COVID-19	n=42 age (median, range): 43 (20-74) gender (% male): 47.7% Severity: mild disease	n=73 (allocated) n=69 (analysed) age (mean, SD): 49.8+/-14.3 (n=69) gender (% male): 49.3% Severity: mild to moderate disease
Inclusion criteria	Individuals with SARS-CoV-2 infection who were mildly symptomatic or asymptomatic	• adults aged 18 years or older • diagnosis of COVID-19 by either polymerase chain	• consecutive patients hospitalized with COVID-19 infection (acute	• Patients with confirmed COVID-19 above the age of 18 years with	• individuals with mild disease, • over 18 years of age,	• Aged 20-75 years • RT-PCR confirmed

[15] 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

[16] Blinded data collector

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

[18] age and sex not reported for whole cohort

Author, year, reference number/Study name/Study ID	Rastogi 2020 [13], NCT04459247 (SHADE)	Murai 2020 [14, 19-21], NCT04449718	Castillo 2020 [12], NCT04366908[15]	Lakkireddy 2021 [16], CTRI/2020/12/030083	Sánchez-Zuno 2021 [17]	Sabico 2021 [15], SCTR H-01-R-012
	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[19]	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	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)	hypovitaminosis D (vit.D level below 30 ng/ml) and mild to moderate illness (SpO2 > 90%) as per the revised guidelines for COVID-19 issued by the Directorate General of Health Services, Government of India on 31-03-2020[20]	• who were not taking any vitamin D supplementation at the recruiting time	SARS-CoV-2 (positive test no more than 3 days prior to inclusion) • Mild to moderate symptoms of COVID-19

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

[20] inclusion criteria not consistent with study registry

Author, year, reference number/Study name/Study ID	Rastogi 2020 [13], NCT04459247 (SHADE)	Murai 2020 [14, 19-21], NCT04449718	Castillo 2020 [12], NCT04366908[15]	Lakkireddy 2021 [16], CTRI/2020/12/030083	Sánchez-Zuno 2021 [17]	Sabico 2021 [15], SCTR H-01-R-012
Exclusion criteria	Rastogi 2020: Patients unable to take oral supplementation like those requiring invasive ventilation or with significant comorbidities like uncontrolled hyperglycaemia or hypertension were excluded.[21]	• patient unable to read and sign the written informed consent • patient already admitted under invasive mechanical ventilation • 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	• Patients younger than 18 years and pregnant women	• Patients with severe illness[22] • Patients who have taken high dose vitamin D (60,000 IUs) in the last 3 months • Patients with active malignancy, chronic renal disease and HIV, pregnant and breastfeeding mothers were excluded	• NR	• Severe disease • Children • Pregnant women • Baseline 25(OH)D level above 75 nmol/L
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in	Cholecalciferol (day 1-7: 60,000 IU per day (5 ml oral solution in nano droplet form), day 8-14: weekly	Cholecalciferol (single dose of 200,000 IU of dissolved in a 10 mL of peanut oil solution on day of randomization plus standard care[23])	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	Cholecalciferol (60,000 IU per day for 8 days for subjects with BMI of 18–25 and 10 days for subjects with BMI	Cholecalciferol (10,000 IU per day in soft capsule form for 14 days; in the morning with the company of a meal)	Cholecalciferol (5,000 IU in tablet form per day for 14 days) n=38 (allocated)

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

[22] exclusion criteria not consistent with study registry

[23] no further definition

Author, year, reference number/Study name/Study ID	Rastogi 2020 [13], NCT04459247 (SHADE)	Murai 2020 [14, 19-21], NCT04449718	Castillo 2020 [12], NCT04366908[15]	Lakkireddy 2021 [16], CTRI/2020/12/030083	Sánchez-Zuno 2021 [17]	Sabico 2021 [15], SCTR H-01-R-012
subgroups - Mild, Moderate, Severe, Critical COVID-19)	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	n=120 (randomised), n = 119 (mITT[24]), n=117 (per protocol), no subgroups reported	hospital protocol (see below) n=50, no subgroups reported	> 25[25]) plus standard treatment[26] n=65 (allocated) n=4 (analysed) no subgroups reported	n=22, no subgroups reported	n=36 (analysed) 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[27]) n=120 (randomised), n = 118 (mITT[28]), 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	Standard treatment[29] n=65 (allocated) n=43 (analysed) no subgroups reported	None n=20 no subgroups reported	Cholecalciferol (1,000 IU in tablet form per day for 14 days) n=35 (allocated) n=33 (analysed) no subgroups reported

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

[25] dosing not consistent with study registry

[26] No further information in study publication; in study registry "according to physician's decision, based on the current recommendations".

[27] no further definition

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

[29] No further information in study publication; in study registry "according to physician's decision, based on the current recommendations".

Author, year, reference number/Study name/Study ID	Rastogi 2020 [13], NCT04459247 (SHADE)	Murai 2020 [14, 19-21], NCT04449718	Castillo 2020 [12], NCT04366908[15]	Lakkireddy 2021 [16], CTRI/2020/12/030083	Sánchez-Zuno 2021 [17]	Sabico 2021 [15], SCTR H-01-R-012
			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 twice at 24-hour interval) before week 3 in the two groups	• Hospital length of stay, defined as the total number of days that patients remained hospitalized from the date of randomization until the date of hospital discharge[30]	• Rate of ICU admission • mortality	Relevant primary outcomes according to study registry: • 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 Relevant reported outcomes: • Duration of symptoms • Duration of hospital stay	• SARS-CoV-2 PCR positivity • Presence of symptoms[31]	• number of days to resolve symptoms

[30] 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.

[31] Fever, headache, loss of smell, dry cough, sore throat, ageusia, runny nose, nausea or vomiting, tiredness, diarrhoea, myalgia, arthralgia, shortness of breath

Author, year, reference number/Study name/Study ID	Rastogi 2020 [13], NCT04459247 (SHADE)	Murai 2020 [14, 19-21], NCT04449718	Castillo 2020 [12], NCT04366908[15]	Lakkireddy 2021 [16], CTRI/2020/12/030083	Sánchez-Zuno 2021 [17]	Sabico 2021 [15], SCTR H-01-R-012
				• Adverse reactions		
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	Relevant secondary outcomes according to study registry: • ICU admission • Recovery • Composite of cumulative death, i.e., all causes and specific causes mortality Relevant reported outcomes: • ICU admission • Number of deaths	NR	• days to discharge • ICU admission • mortality • adverse events
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	After treatment completion (9 or 11 days depending on BMI, see above)[32]	14 days	7 days or on discharge day and 30 days after discharge and/or the last vitamin dose
Sponsor/ lead institution	Department Of Internal Medicine, Nehru Hospital, PGIMER, Chandigarh 160012, India	Clinical Hospital of the School of Medicine of the University of Sao Paulo, Ibirapuera Field Hospital supported by Sao Paulo Research Foundation (grants	Maimónides Biomedical Research Institute of Córdoba public funding (COVID-011-2020 Programa de	Sponsor: Pulse Pharmaceuticals Lead: Department of Orthopaedics/ Biochemistry/ Internal Medicine, Nizam's	National Council of Science and Technology (CONACYT Ciencia Básica grant number A1-S-	Deanship of Scientific Research, Chair for Biomarkers of Chronic Diseases at King Saud

[32] Not consistent with study registry

Author, year, reference number/Study name/Study ID	Rastogi 2020 [13], NCT04459247 (SHADE)	Murai 2020 [14, 19-21], NCT04449718	Castillo 2020 [12], NCT04366908[15]	Lakkireddy 2021 [16], CTRI/2020/12/030083	Sánchez-Zuno 2021 [17]	Sabico 2021 [15], SCTR H-01-R-012
	The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.	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).	Investigacion clínica en COVID-19 de Andalucía, Consejería de Salud y Familia, Fundacion Progreso y Salud, Fundacion para la Investigacion Biomedica de Cordoba)	Institute of Medical Sciences, Punjagutta, Hyderabad, Telangana, Indi	8774) and the Universidad de Guadalajara through Fortalecimiento de la Investigación y el Posgrado 2020	University, Riyadh, KSA. Vitamin D supplements used in the intervention were provided by Synergy Pharma (Dubai, UAE). According to registry entry, Synergy Pharma was a sponsor

Abbreviations: BMI = body mass index, 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; SpO2 = saturation of peripheral oxygen

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

Trial Identifier/registry ID(s)/contact	IRCT20200324046850N1 [22]	NCT04344041 [23]	NCT04621058 [24]	NCT04536298 [25]
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[33]	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[34]	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[35]	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

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

[34] only relevant study arm displayed

[35] only relevant study arm displayed

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

Trial Identifier/registry ID(s)/contact	NCT04552951 [26]	NCT04641195 [27]	EudraCT: 2020-001960-28 [28]	NCT04363840 [29]
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[36]	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[37]	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[38]	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

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

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

[38] only relevant primary outcome measures displayed

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

Trial Identifier/registry ID(s)/contact	NCT03188796 [30]	NCT04525820 [31]	CTRI/2020/06/026189 [32]
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[39]	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

[39] 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	NCT04334005 [33]	NCT04489628 [34]	NCT04385940 [35]	NCT04636086 [36]
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[40]	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[41]
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

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

[41] Mortality is mentioned as secondary outcome measure.

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

Trial Identifier/registry ID(s)/contact	NCT04411446 [37]	NCT04733625 [38]	EudraCT: 2020-002119-23 [39]
Estimated study completion date	Oktober 2021	December 2020[42]	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[43]	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

[42] given as "actual study completion date"

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

Table 4-11 Ongoing trials of single agent: Vitamin D, continued

Trial Identifier/registry ID(s)/contact	NCT04828538 [40]	EudraCT: 2020-001903-17 [41]	IRCT20200411047024N1 [42]
Estimated study completion date	July 2021	No information	No information
Study design, study phase	RCT	RCT, Phase 3b	RCT, no information
Recruitment status	Recruiting	No information	Recruitment complete
Number of Patients, Disease severity[44]	1,800 patients diagnosed with COVID-19	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
Setting (hospital, ambulatory...)	Hospital	hospital	hospital
Intervention (generic drug name and dosage)	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)	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
Comparator (standard care or generic drug name and dosage)	Placebo	Tocilizumab (solution for injection/infusion)	No intervention
Primary Outcome(s)	• mortality • ICU admission • intubation • mechanical ventilation	number of patients with fatal outcome •	• Clinical course, paraclinical findings, in-hospital outcome (not clearly reported in the registry)
Sponsor/ lead institution, country (also country of recruitment if different)	Hospital de la Soledad, Mexico	Hospital Universitario de Móstoles, Spain, Support by Madrilenian Health Service	Shahroud University of Medical Sciences, Iran

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

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

Table 4-12 Ongoing trials of single agent: Vitamin D, continued

Trial Identifier/registry ID(s)/contact	IRCT20140305016852N4 [43]	NCT04883203 [44]	NCT04952857 [45]
Estimated study completion date	No information	October 31, 2020	March 31, 2022
Study design, study phase	RCT, no information	RCT, Phase 3	RCT, Phase 4
Recruitment status	Recruitment complete	Recruitment complete	Not yet recruiting
Number of Patients, Disease severity[45]	30 Patients with COVID-19	130 patients with asymptomatic to mild COVID-19	90 patients with moderate to severe COVID-19
Setting (hospital, ambulatory...)	hospital	No information	No information
Intervention (generic drug name and dosage)	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	A single vial of Cholecalciferol (1 ml) (200,000 IU / 1 ml), Oral form	Cholecalciferol 600,000 IU
Comparator (standard care or generic drug name and dosage)	Routine treatment under the supervision of a specialist	Placebo (a single vial of physiological saline oral form)	Placebo equal volume/weight
Primary Outcome(s)	Complete recovery of clinical COVID-19 symptoms, normalization of chest symptoms in CT scan	Delay between the first positive RT-PCR and the second negative RT-PCR	Sequential Organ Failure Assessment (SOFA) score
Sponsor/ lead institution, country (also country of recruitment if different)	Sabzevar University of Medical Sciences, Iran	University of Monastir, Tunisia	Postgraduate Institute of Medical Education and Research, India

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

[45] 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 (covid-19.cochrane.org), ClinicalTrials.gov (www.clinicaltrials.gov) ISRCTN registry (www.isrctn.com) and EU Clinical Trials Register (www.clinicaltrialsregister.eu) 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]))	5/5/2021 until 12/7/2021

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	5/5/2021 until 12/7/2021

6.2 Search strategy to identify ongoing studies

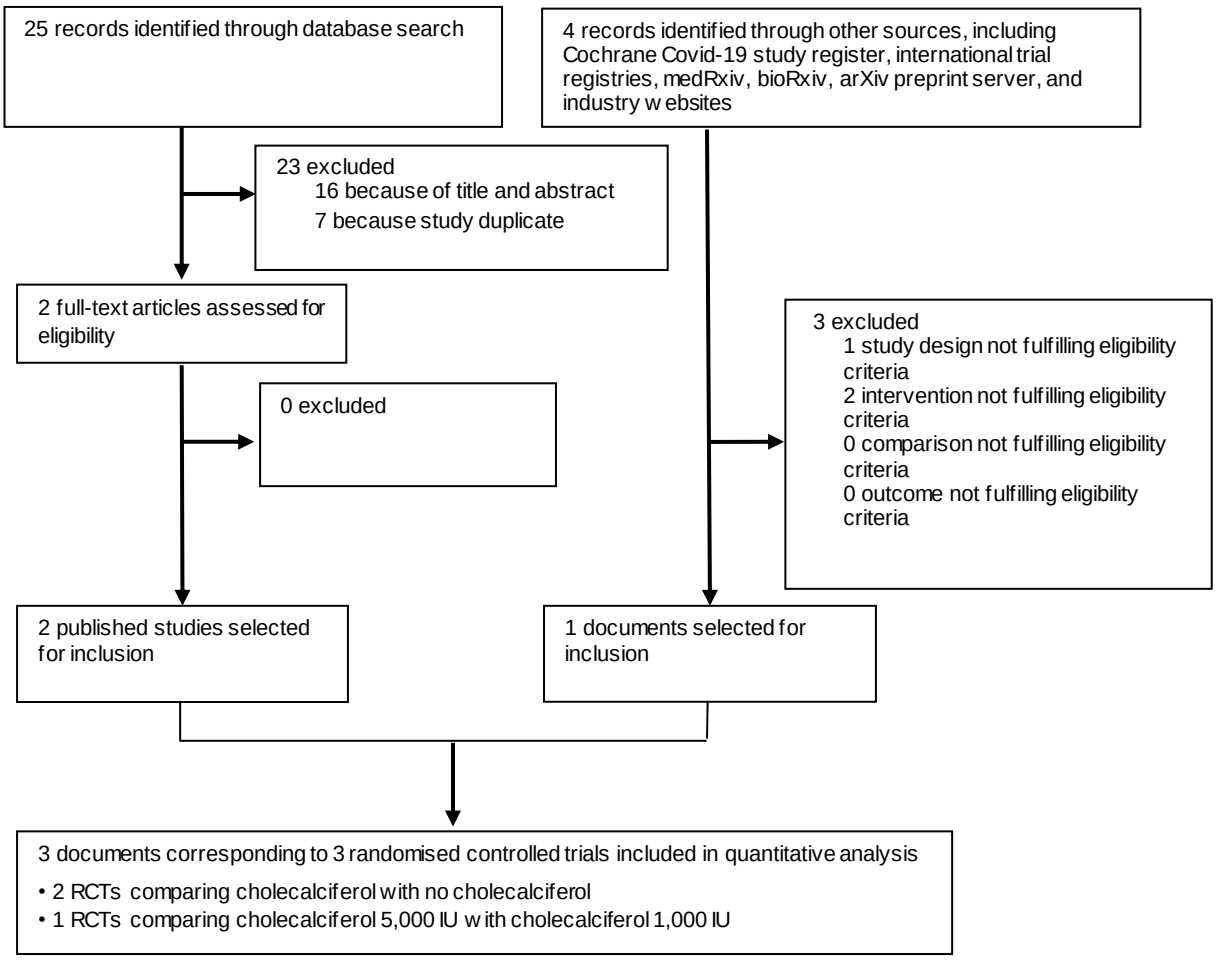
GÖG is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and Vitamin D are described in Table 6-2.

Table 6-2 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	5/5/2021 until 12/7/2021	8 new
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: • covid-19 and Vitamin D	5/5/2021 until 12/7/2021	0 0
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode Search terms: • covid-19 and Vitamin D	5/5/2021 until 12/7/2021	0 0

***** In "Basic Search mode", one term was added to the field "condition or disease" and one term in the field "other terms".

6.3 Flow diagrams



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

Abbreviations: RCT = randomised controlled trial