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"Rolling Collaborative Review" of Covid-19 treatments

IVERMECTIN FOR THE TREATMENT OF COVID-19

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4.3, p. 13	New ongoing trials added

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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

AE	Adverse Event
AOTMiT	Agency for Health Technology Assessment and Tariff System
ASA	Acetylsalicylic acid
AZM	Azithromycin
BID	Bis in die
CI	Confidence Interval
DOI	Declaration of interest
DOX	Doxycycline
EUnetHTA	European Network of Health Technology Assessment
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HCQ	Hydroxychloroquine
HR	Hazard Ratio
ICD	International Classification of Diseases
IQR	Interquartile range
IVM	Ivermectin
MD	Mean Difference
MeSH	Medical Subject Headings
MNT	Montelukast
NA	Not applicable
NR	Not reported
PLB	Placebo
PO	Per os
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
SoC	Standard of Care
SoF	Summary of findings
TNR4	Ivermectin + Azithromycin + Montelukast + Acetylsalicylic acid
WP4	Work Package 4

1 OBJECTIVE

The aim of this EUnetHTA Rolling Collaborative Review is

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

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

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

2 METHODS

This Rolling Collaborative Review is prepared according to the project plan ("Rolling Collaborative Review (RCR) on Covid-19 treatments: Project description and planning", published on the EUnetHTA website) and will be updated monthly. Monthly updates are published on the EUnetHTA Covid-19 Website (https://eunethta.eu/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	Ivermectin
Comparison	Any active treatment, placebo, or standard of care. **Rationale**: Since there is no gold standard treatment any comparator is acceptable as well as the above listed interventions.
Outcomes	Main outcome: • All-cause Mortality (Survival) Additional Outcomes: Efficacy: • Length of hospital stay, • Viral burden (2019-nCoV RT-PCR negativity), • Clinical progression (WHO Clinical Progression Scale measured daily over the course of the study), • Rates of hospitalization and of patients entering ICU, • Duration of mechanical ventilation, • Quality of life. Safety: • Adverse events (AE), • Severe adverse events (SAE), • Withdrawals due to AEs, • Most frequent AEs, • Most frequent SAEs. **Rationale:** We will give priority according to the Core Outcome Set for Clinical Trials on Coronavirus Disease 2019 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102592/pdf/main.pdfc) and A minimal common outcome measure set for COVID-19 clinical research from the WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection.
Study design	Efficacy: randomised controlled trials (RCT) Safety: observational studies (comparative or single-arm prospective studies and registries)

2.2 Sources of information

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

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

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

The literature search is conducted in the following databases:

- PubMed
- MEDLINE, accessed via OVID
- Embase, accessed via OVID

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

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

- medRxiv Health Sciences
- bioRxiv Biology

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

Data extraction, Risk of bias assessment, data synthesis:

Two reviewers from DEPLazio are screening search results, assessing full texts of studies and extract study characteristics and outcome data according to pre-defined criteria. The process of study selection is depicted as a flow diagram in Appendix Figure 6-1.
Risk of bias is assessed using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions [1].

Dichotomous outcomes are analysed by calculating the relative risk (RR) for each trial with the uncertainty in each result being expressed by its 95% confidence interval (CI).Continuous outcomes are analysed by calculating the mean difference (MD) with the relative 95% CI when the study used the same instruments for assessing the outcome.

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

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

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

The literature search is conducted on a monthly basis.

The sources and search methods are described in more detail in Appendix Table 6-2.

Population	See project Scope
Intervention	Ivermectin
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

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 AOTMiT 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 AOTMiT is searching and extracting the data for the eligible studies. 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 Table 6-3.

Data are presented in tabular form.

3 ABOUT THE TREATMENT

3.1 Mode of Action

Ivermectin is a broad-spectrum antiparasitic medicine which in recent years has been intensively studied with respect to its potential antiviral action in vitro [4-7]. Ivermectin is a macrocyclic lactone and avermectin derivative. It is composed of two homological components 22,23–dihydroavermectin B1a and 22,23–dihydroavermectin B1b [8].

The mechanism of action of ivermectin is based on its capability to increase cell membrane permeability to chloride ions which leads to neural or muscle cell hyperpolarization, neuromuscular motor paralysis and death. [9] The increase of cell membrane permeability results from ivermectin's interaction with glutamate-gated and gamma-aminobutyric acid (GABA)-gated chloride channels leading to increased conductance of chloride ions. Ivermectin is safe for mammals as they do not have glutamate-gated chloride channels, and ivermectin does not readily cross the blood/brain barrier (SPC) [10].

Moreover, ivermectin has an anti-inflammatory potential resulting from its ability to inhibit lipopolysaccharide-induced pro-inflammatory cytokine production. It has been observed on animal models of dermatitis [11].

The proposed anti-SARS-CoV-2 action of ivermectin comes from its *in vitro* ability to prevent viral proteins from entering the nucleus. It is mediated by the binding of ivermectin to the host nuclear transport importin α/β1 heterodimer (IMPα/β1), which leads to its destabilization and prevention of IMPα/β1 binding to the viral proteins. This allows for more efficient antiviral response [10, 12].

3.2 Regulatory Status

Ivermectin is not approved by the European Medicines Agency (EMA) or the American Food and Drug Administration (FDA) for COVID-19 patients. It is approved by the Food and Drug Administration (FDA) for the treatment of [13] [14]:

- onchocerciasis,
- strongyloidiasis;

and for topical use in the treatment of:

- inflammatory lesions of rosacea,
- head lice infestation.

Ivermectin is not approved by the European Medicines Agency (EMA) for the use in humans, however, it was granted a product-specific waiver for the treatment of rosacea (topical use) [15].

Ivermectin is not FDA or EMA-approved for the treatment of any viral infections, nor it is authorised in Covid-19 patients [13, 16].

3.3 Level of Evidence

Eight RCTs and two observational prospective studies have documented the effectiveness and safety of ivermectin (Table 4-6, Table 4-7). Moreover, 38 ongoing studies are reported in international clinical trial registries. Except for one study, all of the studies were conducted in non-European countries. Among these, three were designed as multicenter and five were double-blinded. Study population size ranged from 24 to 180 patients. The population included in the studies was heterogeneous in terms of disease severity. Mild patients were included in two studies, mild to moderate patients in four studies, mild to severe patients in one study, and mild to critical patients in one study. Furthermore, there was a wide variation in standards of care across trials. Ivermectin dosing and duration of treatment was also heterogeneous. Few studies that were included were not yet published or peer reviewed.

A detailed description of methodology of included RCTs is presented in Table 4-6.

4 SUMMARY

4.1 Effectiveness and Safety evidence from RCTs

There are five different comparisons for ivermectin. The data currently available are presented in Table 4-1, Table 4-2, Table 4-3, Table 4-4 and Table 4-5.

Ivermectin versus standard care / placebo

Five RCTs [17-21] contributed to the estimates presented in the Summary of Findings Table 4-1. Certainty of the evidence was very low to moderate for particular outcomes listed in the table. Currently available evidence shows that ivermectin compared with standard treatment could reduce the risk of all-cause mortality, but the certainty of evidence is low. Data on progression of COVID-19 disease, number of patients discharged, SARS-CoV-2 clearance, frequency of any adverse events and severe adverse events is not conclusive, as there is no statistically significant difference between study arms. Ivermectin compared with standard treatment could reduce the time to SARS-CoV-2 clearance, but the quality of evidence is very low. Ivermectin has no effect on the duration of hospitalization compared to standard treatment.

Ivermectin + doxycycline vs standard care / placebo

The certainty of the evidence from two studies [21, 22] contributing to this comparison was very low and low for particular outcomes listed in Table 4-2. No significant difference was observed in all-cause mortality in total population or in the subpopulation of severe patients. No deaths were reported in mild/moderate patients. Ivermectin has no effect on progression of the disease in the whole population or in the subpopulation of severely ill patients. No cases of disease progression were observed in mild/moderate patients. Ivermectin in combination with doxycycline could reduce the time to SARS-CoV-2 clearance compared to standard of care, but the certainty of evidence is very low. Ivermectin in combination with doxycycline, compared with standard care/placebo, may increase the duration of hospitalisation, but the evidence is very uncertain. No serious adverse events have been reported within the study population.

Ivermectin + doxycycline versus ivermectin

The certainty of the evidence from one study [21] contributing to this comparison was very low for particular outcomes listed in Table 4-3. Ivermectin in combination with doxycycline, compared to ivermectin, may slightly increase the time to SARS-CoV-2 clearance as well as the length of hospital stay, but the quality of evidence is very low. No serious adverse events have been reported within the study population.

Ivermectin + doxycycline versus hydroxychloroquine + azithromycin

The certainty of the evidence from one study [23] contributing to this comparison was moderate for particular outcomes listed in Table 4-4. Ivermectin in combination with doxycycline compared to hydroxychloroquine with azithromycin has no influence on SARS-CoV-2 clearance or frequency of any adverse events.

Ivermectin vs lopinavir/ritonavir

The certainty of the evidence from one study [24] contributing to this comparison was very low for particular outcomes listed in Table 4-5. No deaths were reported within the study population. Ivermectin significantly reduced time to SARS-CoV-2 clearance in the whole ivermectin group as well as in the ivermectin 6 mg group and the ivermectin 12 mg group compared to lopinavir/ritonavir.

4.2 Safety evidence from observational studies

Two prospective cohort studies [25, 26] were included. A summary of methodology and safety outcomes is presented in Table 4-7. In one study related to the combination therapy of ivermectin with doxycycline, with a critical risk of bias, there was no significant difference in the safety profile between groups –

diarrhoea, vomiting and pruritus occurred with a similar frequency. In the other study, with severe risk of bias, that was designed to assess the effectiveness of a multidrug-therapy consisting of ivermectin, azithromycin, montelukast and acetylsalicylic acid ("TNR4" therapy), presented safety results were inconclusive.

4.3 Ongoing studies

According to the databases of clinicaltrials.gov, ISRCTN and EudraCT, there are currently 33, 1 and 5 ongoing studies for ivermectin with indications related to COVID-19 (1 study both in clinicaltrials.gov and EudraCT), respectively. Making up to 38 ongoing studies on ivermectin with indications related to COVID-19.

4.4 Scientific conclusion about status of evidence generation

The current evidence is not sufficient to support the use of ivermectin for COVID-19 and requires validation in larger RCTs evaluating fixed dosing schedules. At the moment, conclusions on the efficacy of ivermectin are of high uncertainty.

Table 4-1 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of ivermectin versus standard of care / placebo

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with [comparison]	Risk with [intervention]			
All-cause mortality [17, 18][a]	127 per 1000	20 per 1000 (4 to 103)	RR 0.16 (0.03 to 0.81)	205 (2 RCTs)	low
Number of patients with any adverse event [19] [20]	400 per 1000	460 per 1000 (252 to 840)	RR 1.15 (0.63 to 2.10)	65 (2 RCT)	very low
Number of patients with severe adverse events [19-21]	0 per 1000	0 per 1000 (0 to 0)	RR 1.55 (0.07 to 35.89)	113 (3 RCT)	very low
Time to SARS-CoV 2 clearance [21]	-	SMD 0.68 lower (1.27 lower to 0.1 lower)	-	48 (1 RCT)	very low
Length of stay in hospital [21]	-	SMD 0.02 lower (0.59 lower to 0.54 higher)	-	48 (1 RCT)	very low
SARS-CoV-2 clearance [18]	310 per 1000	227 per 1000 (124 to 422)	RR 0.73 (0.40 to 1.36)	115 (1 RCT)	moderate
Progression of COVID-19 disease [18]	103 per 1000	88 per 1000 (28 to 271)	RR 0.85 (0.27 to 2.62)	115 (1 RCT)	moderate
Number of patients discharged [18]	724 per 1000	775 per 1000 (623 to 956)	RR 1.07 (0.86 to 1.32)	115 (1 RCT)	moderate

Source: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M
Abbreviations: CI=Confidence interval; RR=Risk ratio, SMD=Standardized mean difference.
a. One study (1) considers 4 arms with different doses of Ivermectin. Data refer to the arm with the highest dose (400, 200, 200 mcg / kg7day).

Table 4-2 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of ivermectin + doxycycline versus standard of care / placebo

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with [comparison]	Risk with [intervention]			
All-cause Mortality [22]	86 per 1000	28 per 1000 (6 to 137)	RR 0.33 (0.07 to 1.60)	140 (1 RCT)	low
All-cause Mortality mild / moderate ill patients [22]	No deaths observed			96 (1 RCT)	very low
All-cause Mortality severe ill patients [22]	273 per 1000	41 per 1000 (3 to 655)	RR 0.15 (0.01 to 2.40)	33 (1 RCT)	very low
Progression of COVID-19 disease [22]	100 per 1000	43 per 1000 (12 to 159)	RR 0.43 (0.12 to 1.59)	140 (1 RCT)	low
Progression of COVID-19 disease mild / moderate ill patients [22]	No events reported			96 (1 RCT)	very low
Progression of COVID-19 disease severe ill patients [22]	318 per 1000	92 per 1000 (13 to 649)	RR 0.29 (0.04 to 2.04)	33 (1 RCT)	very low
Time to SARS-CoV 2 clearance [21]	-	SMD 0.31 lower (0.88 lower to 0.26 higher)	-	48 (1 RCT)	very low
Length of stay in hospital [21]	-	SMD 0.11 higher (0.46 lower to 0.68 higher)	-	48 (1 RCT)	very low
Number of patients with serious adverse events [21]	No serious adverse event reported			48 (1 RCT)	very low

Source: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M
Abbreviations: CI=Confidence interval; RR=Risk ratio, SMD=Standardized mean difference.

Table 4-3 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of ivermectin + doxycycline versus ivermectin

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with [comparison]	Risk with [intervention]			
Time to SARS-CoV-2 clearance [21]	-	SMD 0.39 higher (0.18 lower to 0.96 higher)	-	48 (1 RCT)	very low
Length of stay in hospital [21]	-	SMD 0.11 higher (0.46 lower to 0.67 higher)	-	48 (1 RCT)	very low
Number of patients with serious adverse events [21]	No serious adverse event reported			48 (1 RCT)	very low

Source: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M
Abbreviations: CI=Confidence interval; RR=Risk ratio, SMD=Standardized mean difference.

Table 4-4 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of ivermectin + doxycycline versus HCQ + AZM

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with [comparison]	Risk with [intervention]			
SARS-CoV-2 clearance [23]	871 per 1000	949 per 1000 (854 to 1000)	RR 1.09 (0.98 to 1.22)	125 (1 RCT)	moderate
Number of patients with any adverse event [23]	419 per 1000	302 per 1000 (188 to 486)	RR 0.72 (0.45 to 1.16)	125 (1 RCT)	moderate

Source: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M
Abbreviations: CI=Confidence interval; RR=Risk ratio.

Table 4-5 Summary of findings (SoF) table for published RCTs related to effectiveness and safety of ivermectin versus lopinavir/ritonavir

Outcome	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of evidence
	Risk with [comparison]	Risk with [intervention]			
All-cause mortality [24]	No deaths reported			62 (1 RCT)	very low
Time to SARS-CoV-2 clearance [24]	-	SMD 0.77 lower (1.32 lower to 0.22 lower)	-	62 (1 RCT)	very low
All-cause mortality (Ivermectin 6mg) [24]	No deaths reported			41 (1 RCT)	very low
Time to SARS-CoV-2 clearance (Ivermectin 6mg) [24]	-	SMD 0.55 lower (1.18 lower to 0.07 higher)	-	41 (1 RCT)	very low
All-cause mortality (Ivermectin 12mg) [24]	No deaths reported			41 (1 RCT)	very low
Time to SARS-CoV-2 clearance (Ivermectin 12mg) [24]	-	SMD 0.78 lower (1.42 lower to 0.14 lower)	-	41 (1 RCT)	very low

Source: Cruciani F, De Crescenzo F, Vecchi S, Saulle R, Mitrova Z, Amato L, Davoli M
Abbreviations: CI=Confidence interval; RR=Risk ratio, SMD=Standardized mean difference.

Table 4-6 Study characteristics of included RCTs

Author, year, reference number/Study name/Study ID	Niae et al. 2020 [17] IRCT20200408046987N1	Ravikirti et al. 2021 [18] CTRI/2020/08/027225	Krolewiecki et al. 2020 [19] NCT004381884	Chaccour et al. 2021 [20] NCT04390022	Ahmed et al. 2020 [21] NCT04407130	Hashim et al. 2020 [22] NCT04591600	Chowdhury et al. 2020 [23] NCT04434144	Babalola et al. 2020 [24]
Study design, study phase	randomized, double-blind, placebo-controlled, phase 2	randomized, double-blind, placebo-controlled	a pilot, randomized, controlled, open-label, outcome-assessor blinded	randomized, double-blind, phase 2	randomized, double-blind, placebo-controlled, phase 2	randomized, open-label, outcome-assessor blinded, phase 1, 2	randomized, open-label	randomized, double blind, controlled trial, of a parallel group, dose-response design
Centres (single centre or multicentre), country, setting	multicenter Iran	single-centre India	multicenter Argentina	single-centre Spain	Bangladesh	multicenter Iraq	single-centre Bangladesh	Nigeria
Patient population (number of included patients/ Mean age and sex/ Disease severity*)	180 patients mean age: 56 (45-67) female: 50% mild to severe	115 patients mean age: 52.5 (SD: 14.7) female: 27.7% mild to moderate	45 patients mean age: 40,89 (SD: 12.48) male: 56% mild to moderate (3 to 5 from the WHO 8-Category ordinal scale)	24 patients ivermectin: median age 26 (IQR: 19-36), male: 58% placebo: median age 26 (IQR: 21-44), male: 42% mild	72 patients mean age: 42 female: 54% mild	140 patients ivermectin + doxycycline + SoC: mean age 50.1 (SD: 9.3), male: 53% SoC: mean age 47.2 (SD: 7.8), male: 51% mild to critical	116 patients mean age: 33.94 years (±14.12) male: 72% mild to moderate	63 patients mean age: 44.1 (SD14.7) male: 68% asymptomatic or mild/moderate symptoms
Inclusion criteria	age >18 years; signed the informed consent; clinical symptoms of suggestive of COVID-19 pneumonia: cough (with or without sputum), fever, pleuritic chest pain or dyspnea; mild to severe COVID-19 disease confirmed by chest computed tomography scan findings compatible with COVID-19 or positive rRT-PCR	all patients above the age of 18 admitted with a diagnosis of COVID -19 (on the basis of a positive RT-PCR or Rapid Antigen Test report) at AIIMS, Patna, India with mild or moderate disease as defined by the ministry of health and family welfare guidelines and not meeting any of the exclusion criteria	age 18 to 69 years; COVID-19 confirmed with RT-PCR; hospitalized with disease stages 3 to 5 from the WHO 8-Category ordinal scale of clinical status and no requiring intensive care unit admission; symptoms onset ≤ 5 days at	18-59 years; Consecutive outpatients attending the Emergency Room of the Clínica Universidad de Navarra with symptoms compatible with COVID-19, no more than 72 h of fever or cough and a positive PCR for SARS-CoV-2; Negative	age 18–65 years; admitted to hospital within the last 7 days; presence of a fever (>37.5ºC), cough, and/or sore throat; diagnosed positive for SARS-CoV-2 by rRT-PCR	COVID-19 patients diagnosed by clinical, radiological and laboratory PCR testing, at different stages of the disease (mild-moderate, severe, and critical according to WHO	SARS-CoV-2 infection by RT PCR at Chakoria Upazilla Health Complex, Cox's Bazar; Bangladesh from May 2nd to June 5th, 2020; with and without symptoms	COVID 19 PCR proven positive patients, who gave informed, written consent to participate in the study, and were either asymptomatic or had mild/moderate symptoms

Author, year, reference number/Study name/Study ID	Niae et al. 2020 [17] IRCT20200408046987N1	Ravikirti et al. 2021 [18] CTRI/2020/08/027225	Krolewiecki et al. 2020 [19] NCT004381884	Chaccour et al. 2021 [20] NCT04390022	Ahmed et al. 2020 [21] NCT04407130	Hashim et al. 2020 [22] NCT04591600	Chowdhury et al. 2020 [23] NCT04434144	Babalola et al. 2020 [24]
			recruitment, absence of use of drugs with potential activity against SARS-CoV-2	pregnancy test for women of child bearing age*; Consent to participate in the study; The patient should, in the investigator's opinion, be able to comply with all the requirements of the clinical trial (including home follow up during isolation)		guidelines), who were symptomatic for no more than three days for mild-moderate cases, no more than two days after being severe cases, and no more than one day after being critical cases, outpatients or inpatients		
Exclusion criteria	presence of severe immunosuppression (e.g., use of immune-suppressants and HIV positive), pregnant women, chronic kidney disease, malignancy, and indications that the patients were unable and/or unlikely to comprehend and/or follow the protocol	known allergy to or adverse drug reaction with ivermectin; unwillingness or inability to provide consent to participate in the study; prior use of ivermectin during the course of this illness; pregnancy and lactation	the use of immunomodulators within 30 days of recruitment, pregnancy, breast feeding, poorly controlled comorbidities and known allergies to IVM	ivermectin allergy; hypersensitivity to any component of Stromectol®; COVID-19 Pneumonia (diagnosed by the attending physician; identified in a chest X-ray); fever or cough present for > 48 hours; positive IgG against SARS-CoV-2 by rapid test; indicated co-morbidities (or any other disease that might interfere with the study in the eyes of the investigator): e.g. immunosuppression, COPD,diabetes; recent travel history to countries that are endemic for Loa loa;	allergic to ivermectin or doxycycline, or if there was the potential for a drug–drug interaction with ivermectin or doxycycline; had chronic illnesses (e.g., ischemic heart disease, heart failure, documented cardiomyopathy, chronic kidney disease, chronic liver disease); had received ivermectin and/or doxycycline in the last 7 days; were pregnant or lactating; or	no data	unstable comorbid conditions like bronchial asthma, COPD, ischemic heart disease, uncontrolled diabetes mellitus, advanced renal and hepatic disease, carcinoma, hospitalized, and immuno-compromised patients	COVID 19 negative patients, patients who had COVID pneumonia or requiring ventilator therapy, renal failure, thromboemboli c complications, or unconscious by reduced Glasgow Coma Scale

Author, year, reference number/Study name/Study ID	Niae et al. 2020 [17] IRCT20200408046987N1	Ravikirti et al. 2021 [18] CTRI/2020/08/027225	Krolewiecki et al. 2020 [19] NCT004381884	Chaccour et al. 2021 [20] NCT04390022	Ahmed et al. 2020 [21] NCT04407130	Hashim et al. 2020 [22] NCT04591600	Chowdhury et al. 2020 [23] NCT04434144	Babalola et al. 2020 [24]
				current use of CYP 3A4 or P-gp inhibitor drugs such as quinidine, amiodarone, diltiazem, spironolactone, verapamil, clarithromycin, erythromycin, itraconazole, ketoconazole, cyclosporine, tacrolimus, indinavir, ritonavir or cobicistat; use of critical CYP3A4 substrate drugs such as warfarin.	had participated in any other clinical trial within the last month			
Intervention (generic drug name and dosage, time frame; number of randomized/ enrolled patients in subgroups - Mild, Moderate, Severe, Critical COVID-19)	1. ivermectin: single dose (200 mcg/kg, 1 pill per day), 30 patients: 26.7% mild, 70% moderate, 3.3% severe; 2. ivermectin: three low interval doses of ivermectin (200, 200, 200 mcg/kg , 3 pills in 1, 3 and 5 interval days), 30 patients: 6.7% mild, 66.7% moderate, 20% severe; 3. ivermectin: single dose (400 mcg/Kg, 2 pills per day), 30 patients: 13.3% mild, 70% moderate, 16.7% severe; 4. ivermectin: three high interval doses of ivermectin (400, 200, 200 mcg/kg, 4 pills in 1, 3 and 5 interval days), 30 patients: 6.7% mild,	ivermectin (12 mg on day 1 and day 2 of admission) 57 patients: 76.4% mild, 23.6% moderate	ivermectin 0.6 mg/kg/day for 5 days + SoC 34 patients	ivermectin (Stromectol®, single dose of 400 mcg/kg) 12 patients	**ivermectin:** oral IVM alone (12 mg once daily for 5 days); 24 patients **ivermectin + doxycycline**: (12 mg IVM single dose and 200 mg doxycycline on day 1, followed by 100 mg every 12 h for the next 4 days); 24 patients	ivermectin + doxycycline + SoC: IVM 200 mcg/kg PO per day for 2 days, in some patients third dose 200 mcg/kg PO per day was given 7 days after the first dose; doxycycline 100 mg capsule PO every 12h per day, for 5-10 days, based on the clinical improvement of patients; 70 patients: 48% mild-moderate,	ivermectin (200µgm/kg single dose) + doxycycline (100 mg BID for 10 days); additionally symptomatic treatment for fever, headache, cough, myalgia, etc.; 60 patients	**ivermectin 6mg** (given every 84 hours) twice a week, 21 patients; **ivermectin 12mg** (given every 84 hours) for 2 weeks, 21 patients

Author, year, reference number/Study name/Study ID	Niae et al. 2020 [17] IRCT20200408046987N1	Ravikirti et al. 2021 [18] CTRI/2020/08/027225	Krolewiecki et al. 2020 [19] NCT004381884	Chaccour et al. 2021 [20] NCT04390022	Ahmed et al. 2020 [21] NCT04407130	Hashim et al. 2020 [22] NCT04591600	Chowdhury et al. 2020 [23] NCT04434144	Babalola et al. 2020 [24]
	76.7% moderate, 16.7% severe					11% severe; 11% critical		
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)	1. common regimen: hydroxychloroquine 200mg/kg twice per day), 30 patients: 13.3% mild, 76.7% moderate, 10% severe; 2. placebo plus common regimen, 30 patients: 16.7% mild, 76.7% moderate, 6.7% severe	placebo 58 patients: 80.7% mild, 19.3% moderate	SoC, 15 patients	placebo 12 patients	placebo, 24 patients	SoC 70 patients: 48% mild-moderate, 22% severe; 0% critical	hydroxychloroquine (400 mg 1st day, then 200 mg BID for 9 days) + azithromycin (500 mg daily for 5 days); additionally symptomatic treatment for fever, headache, cough, myalgia, etc.; 56 patients	lopinavir / ritonavir daily for 2 weeks, 20 patients
Primary Outcome(s)	clinical recovery	negative RT-PCR on day 6	reduction in SARS-CoV-2 viral load between baseline and day-5	positive SARS-CoV-2 PCR	time required for virological clearance (a negative rRT-PCR result on nasopharyngeal swab); remission of fever (≥37.5°C) and cough within 7 days.	mortality rate	negative PCR, resolution of symptoms	time to SARS-CoV-2 negativity
Patient-relevant secondary outcome(s)	duration of hospitalization, duration of low O_2 saturation, tachypnea off, fever off, mortality	symptom free on day 6, discharged by day 10, admission to ICU, discharde, in-hospital mortality	clinical evolution at day-7, relationship between IVM plasma concentrations and the primary outcome, and frequency and severity of adverse events	progression of symptoms (fever, cough), adverse events, all-cause mortality	failure to maintain an SpO2 >93% despite oxygenation and days on oxygen support, duration of hospitalization, all-cause mortality,	time to recovery, progression of the disease	adverse effects	adverse effects, symptomatic improvement, mortality

Author, year, reference number/Study name/Study ID	Niae et al. 2020 [17] IRCT20200408046987N1	Ravikirti et al. 2021 [18] CTRI/2020/08/027225	Krolewiecki et al. 2020 [19] NCT004381884	Chaccour et al. 2021 [20] NCT04390022	Ahmed et al. 2020 [21] NCT04407130	Hashim et al. 2020 [22] NCT04591600	Chowdhury et al. 2020 [23] NCT04434144	Babalola et al. 2020 [24]
					serious adverse drug events			
Follow-up (days, months)	45 days	10 days	21-30 days	28 days	14 days	patients were monitored till recovery or death	patients were followed until PCR negativity or symptom resolution	day seven was used as a midway point in the trial
Sponsor/ lead institution	Qazvin University of Medical Sciences and Science and Technology Park	All India Institute of Medical Sciences. Sun Pharma Pvt. Ltd. (placebo provision)	supported by grant IP-COVID-19-625 from Agencia Nacional de Promoción de la Investigación, el Desarrollo Tecnológico y la Innovación, Argentina and Laboratorio ELEA/Phoenix, Argentina	Idipharma SL, ISGlobal, the University of Navarra, the Spanish Ministry of Science and Innovation through the “Centro de Excelencia Severo Ochoa 2019–2023”; Program (CEX2018–000,806-S), and support from the Generalitat de Catalunya through the CERCA Program	Beximco Pharmaceutical Limited, Bangladesh	Alkarkh Health Directorate-Baghdad	Upazila Health & Family Planning Officer's (UHFPO) Office, Chakoria, Cox's Bazar	no data

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: IVM=Ivermnectin; IQR=Interquartile range; SoC=Standard of Care.

Table 4-7 Summary of safety from observational studies (AE and SAE) of ivermectin

Author, year	Spoorti et al. 2020 [25]	Lima-Morales et al. 2021 [26]
Country	India	Mexico
Sponsor/ lead institution	Nil	Ministry of Health of Tlaxcala State
Intervention/Product (drug name)	ivermectin + doxycycline	ivermectin + azithromycin + montelukast + acetylsalicylic acid (TNR4 therapy)
Dosage	IVM 200 mcg/kg (single dose), DOX 100 mg BID for 7 days	IVM 12 mg single dose, AZM 500 mg for 4 days, MNT 60 mg on the first day and then 10 mg between days 2 to 21, ASA 100 mg for 30 days
Comparator	placebo (vitamin B6)	another treatment or self-medication for cold and flu^ (participants who did not accept the TNR4 therapy because they were asymptomatic)
Study design	observational, prospective	observational, prospective
Setting	tertiary care centre	ambulatory
Number of pts	overall: 100; treatment group: 50; control group: 50	overall: 768; treatment group: 481; control group: 287
Inclusion criteria	All patients diagnosed with Covid-19 by RT-PCR, with mild to moderate symptoms; Respiratory Rate < 24/min and SpO2 >93% on room air; Absence of Oxygen support on admission; Duration of symptoms prior to admission ≤ 7 days.	Confirmed cases of COVID-19^^ with mild or moderate symptoms of COVID-19
Exclusion criteria	Patients with a history of allergy to Ivermectin or Doxycycline; Pregnant or lactating women; Patients with a history of chronic liver disease (SGPT > 3 times of normal value); chronic kidney disease (eGFR <60 ml/min/1.73 m^2) or chronic heart disease.	Patients under 18 years or older than 80 years; who initiated the treatment on the same day or one day before they were hospitalized or died; or who refused participate.
Age of patients (yrs)	treatment group: 50.95±13.64; control group: 48.72±13.42	treatment group: 41.3±13.5; control group: 46.2±14.8
Disease severity	mild to moderate	mild to moderate
Follow-up	n.a.	14 days
Loss to follow-up, n (%)	n.a.	n.a.
RoB	critical	severe
Safety – Outcomes*		
Overall AEs, n (%)	n.a.	Inconclusive data
Serious AE (SAE), n (%)	n.a.	n.a.

Author, year	Spoorti et al. 2020 [25]	Lima-Morales et al. 2021 [26]
Most frequent AEs n (%)	Diarrhea – IVM+DOX: n=4 PLB: n=2 Vomitting – IVM+DOX: n=3 PLB: n=2 Pruritus – IVM+DOX: n=1 PLB: n=0	TNR4 therapy: Gastrointestinal (abdominal pain, nausea, vomiting, diarrhea, constipation, diarrhea and constipation) – 5.9% Headache and dizziness – 3.1% Asthenia, fatigue, and confusion – 1.4% Urticarial and itchy feeling – 0.9%
Most frequent SAEs, n (%)	n.a.	n.a.
AEs of special interest, n (%)	n.a.	n.a.
Death as SAE, n (%)	n.a.	n.a.
Withdrawals due AEs, n (%)	n.a.	n.a.

*** by arms, if available, (Robins-I): https://training.cochrane.org/handbook/current/chapter-25**

^ 19% did not take any medications, 61.4% used NSAIDs, 14.4% combined antibiotics with NSAIDs or corticosteroids, and 5.2% took antiviral drugs along with NSAIDs or corticosteroids.

^^ Patients with suspected COVID-19 (evaluated by medical personnel) – acute respiratory illness and sudden onset of at least one of the following symptoms: cough, sore throat, shortness of breath or fever [≥ 38°C (measured) or history of fever (subjective)]. Other criteria: having at least one of the following during the 14 days prior to onset of symptoms: (1) close contact with a confirmed or probable case of SARS-CoV-2 infection; (2) travel to areas with local transmission of SARS-CoV-2; (3) worked in, or attended, a health care facility where patients with SARS-CoV-2 infections were being treated; or (4) was admitted with severe pneumonia of unknown aetiology.

Abbreviations: ASA=acetylsalicylic acid, AZM=azithromycin, IVM=Ivermectin; DOX=doxycycline; MNT=montelukast, PLB=placebo, TNR4=ivermectin + azithromycin + montelukast + acetylsalicylic acid.

Table 4-8 Ongoing trials of single agent ivermectin

Trial Identifier/registry ID(s)/contact	NCT04510233	NCT04530474	NCT04681053 CCOVID-1	NCT04429711	NCT04703205 CORVETTE-01
Study design, study phase	Phase 2 Randomized, parallel, open-label. Ivermectin Inhalation Forms in the Management of COVID-19 Egyptian Patients.	Phase 3 Randomized, parallel. Outpatient Use of Ivermectin in COVID-19.	Phase 3 Non-randomized, parallel-group, open-label. Efficacy and Safety of Inhaled Ivermectin in the Treatment of SARS-COV-2 (COVID-19).	Randomized, parallel-group, double-blinded. Ivermectin vs. Placebo for the Treatment of Patients With Mild to Moderate COVID-19 to Prevent Progression to Severe Infection and to Decrease Viral Shedding	Phase 2 Randomized, parallel-group, double-blinded. Study in COvid-19 Patients With iveRmectin; An inVEstigator iniTiaTEd Trial.
Recruitment status	Not yet recruiting	Not yet recruiting	Not yet recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	60, mild to moderate	200, n.a.	80, mild to moderate	100, n.a.	240, mild to moderate
Setting (hospital, ambulatory,..)	n.a.	hospital	n.a.	n.a.	n.a.
Intervention (generic drug name and dosage)	(1) Ivermectin (nasal spray): 1 ml in each nostril two times daily. (2) Ivermectin: 6 mg orally three times daily.	Ivermectin: single dose 0,15–2 mg/kg/dose to a maximum of 12 mg	Ivermectin Powder: 6 mg for 3 days (1) oral and inhaled (2) oral (3) inhaled	Ivermectin: 12–15mg/day for 3 days, orally.	Ivermectin: day 1: 200 µg/kg, single oral dose (fasting state)
Comparator (standard care or generic drug name and dosage)	SoC: oxygen via masks or ventilators	Placebo	SoC	Placebo	Placebo
Primary Outcome(s)	Negative PCR result of SARS-Cov2 RNA	Clinical Improvement as measured by a standardized scale.	Rate of virological cure by Rt-PCR. All PCR for COVID-19 must be negative	Viral clearance at day 6.	Period until the COVID-19 PCR test (SARS-CoV-2 nucleic acid detection) becomes negative.
Sponsor/ lead institution, country (also country of recruitment if different)	Tanta University, Egypt	Temple University, United States	Mansoura University, Egypt	Sheba Medical Center, Israel	Kitasato University, Japan

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: SoC=Standard of Care.

Table 4-9 Ongoing trials of single agent ivermectin, continued

Trial Identifier/registry ID(s)/contact	NCT04425707	NCT04729140 COVIVER-OUT PLUS	NCT04438850 / 2020-002283-32 COVER	NCT04529525 IVERCORCOVID19	NCT04373824
Study design, study phase	Randomized, parallel-group, open label. The Use of Ivermectin In the Treatment of COVID 19 Patients.	Phase 4 Randomized, parallel-group, double-blinded, prospective, Placebo-controlled. Outpatient Clinical Trial in High Risk Population Confirmed COVID-19 Patients Using Ivermectin and Doxycycline to Prevent COVID-19 Illness-related Hospitalization	Phase 2 Multicentre, randomized, double-blinded. Proof of Concept, Dose Finding Clinical Trial on Ivermectin for the Early Treatment of COVID-19.	Phase 2/Phase 3 Randomized, double-blinded, parallel-group, placebo-controlled. Ivermectin to Prevent Hospitalizations in COVID-19	Non-randomized, crossover-groups, open label
Recruitment status	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	100, mild to moderate	150, n.a.	122, n.a.	500, n.a.	50, n.a.
Setting (hospital, ambulatory,..)	Hospital	Ambulatory	Hospital, ambulatory	n.a.	hospital
Intervention (generic drug name and dosage)	(1) Ivermectin (2) Ivermectin + SoC: hydroxychloroquine	(1) Ivermectin (days 1–2: 200 mcg/kg) + Doxycycline (100 mg twice a day for seven days). (2) Ivermectin (days 1–2: 200 mcg/kg) + placebo (twice a day for seven days)	(1) Ivermectin: 600 µg/kg daily for 5 consecutive days, orally (2) Ivermectin: 1200 µg/kg daily at empty stomach with water for 5 consecutive days, orally	Ivermectin: day 1–2: > 48 kg and < 80 kg: 12 mg; > 80 kg and < 110 kg: 18 mg; > 110 kg: 24 mg	Ivermectin, days 1–2: 200 to 400 mcg/kg + SoC
Comparator (standard care or generic drug name and dosage)	SoC: hydroxychloroquine	Placebo	Placebo	Placebo	SoC
Primary Outcome(s)	The role of Ivermectin in the cure of COVID 19 patients	Decreased admission rate to the hospital secondary to respiratory illness related to COVID-19	Number of serious adverse drug reactions, Quantitative viral load as measured by quantitative, digital droplet PCR	Percentage of hospitalizations of medical cause in patients with COVID-19 in each arm	Test for virus at 1, 3 & 5 days from beginning of trial drug started for the patient in the hospital
Sponsor/ lead institution, country (also country of recruitment if different)	Ministry of Health and Population, Egypt	Max Health, Subsero Health United States, Florida	IRCCS Sacro Cuore Don Calabria di Negrar, Italy	Instituto de Cardiología de Corrientes, Argentina	Max Healthcare Insititute Limited, India

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: SoC=Standard of Care.

Table 4-10 Ongoing trials of single agent ivermectin, continued

Trial Identifier/registry ID(s)/contact	NCT04716569	NCT04403555	NCT04703608 PaTS-COVID	NCT04445311	NCT04431466 IFORS
Study design, study phase	Phase 2/Phase 3 Randomized, parallel-group, open-label. Evaluation of Ivermectin Mucoadhesive Nanosuspension as Nasal Spray in Management of Early Covid-19.	Phase 2/Phase 3 Randomized, parallel-group, open-label. The Efficacy of Ivermectin in COVID-19 Treatment.	Single blind non-identical placebo-controlled study of prevention and treatment for COVID -19 associated severe pneumonia	Phase 2/Phase 3 Randomized, parallel-group, open-label. Use of Ivermectin as a Therapeutic Option for Patients With COVID-19.	Phase 2 Multicentre, randomised, parallel-group clinical trial to compare the efficacy and safety of different doses of ivermectin in patients diagnosed with the new coronavirus infection
Recruitment status	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	150, n.a.	160, n.a.	1200, mild, moderate	100, n.a.	64, n.a.
Setting (hospital, ambulatory,..)	n.a.	n.a.	household	n.a.	n.a.
Intervention (generic drug name and dosage)	Ivermectin: intranasal spray	Ivermectin: 12 mg/day for 3 days.	(1) IC: Ivermectin 0.3-0.4 mg/kg daily for 3 days; HH: Ivermectin 0.3-0.4mg/kg daily for 3 days / Placebo; (2) Aspirin 150 mg daily for 28 days or until hospital discharge (whichever is sooner)	Ivermectin (3 days) +SoC	(1) Ivermectin 100 mcg/kg PO single dose; (2) Ivermectin, day 1: 100 mcg/kg PO, after 72 h: 100 mcg/kg PO; (3) Ivermectin 200 mcg/kg PO single dose; (4) Ivermectin, day 1: 200 mcg/kg PO, after 72 h: 200 mcg/kg PO
Comparator (standard care or generic drug name and dosage)	Regular protocol drugs	SoC	placebo	SoC	SoC
Primary Outcome(s)	Progress of Symptoms (Fever, Cough, Sore Throat, Myalgia, Diarrhoea, Shortness of Breath) with radiological assessment and blood tests.	The number of patients with improvement or mortality	(1) Percentage of patients with mild disease/moderate pneumonia progressing to severe pneumonia; Percentage of HH members that get infected with SARS-CoV-2; (2) Percentage of COVID-19 associated severe pneumonia patients worsening their condition	Time to be symptoms free	Time to undetectable SARS-CoV-2 viral load in the nasopharyngeal swab.
Sponsor/ lead institution, country (also country of recruitment if different)	South Valley University, Egypt	Tanta University, Egypt	London School of Hygiene and Tropical Medicine, Great Britain Gambia	Zagazig University, Egypt	Universidade Federal de Sao Carlos, Brazil

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: SoC=Standard of Care.

Table 4-11 Ongoing trials of single agent ivermectin, continued

Trial Identifier/registry ID(s)/contact	NCT04635943 SAINT-PERU	NCT04374019	NCT04727424	NCT04472585 SIZI-COVID-PK	NCT04602507
Study design, study phase	Phase 2 A triple-blind, randomized controlled trial with two parallel groups to compare the efficacy of ivermectin versus placebo to obtain negative PCR results in patients with early phase COVID-19.	Phase 2 Randomised, open label, multi-arm trial for rapid efficacy and toxicity assessment of multiple therapies immediately after COVID19 positive testing in high-risk individuals.	Phase 3 Multicenter, prospective, adaptive, double-blinded, randomized, placebo-controlled, parallel-group study to evaluate the effect of fluvoxamine, ivermectin and metformin in reducing hospitalization of patients with mild COVID-19 and a high risk of complications	Phase 1/Phase 2 Randomized, controlled, multi-armed, open-label, interventional, parallel-group study of efficacy of subcutaneous Ivermectin with or without Zinc in COVID-19 patients	Phase 2 Randomized, double-blinded, parallel assignment, placebo-controlled study
Recruitment status	Recruiting	Recruiting	Recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	68, n.a.	240, n.a.	2724, mild	60, mild to moderate	100, severe
Setting (hospital, ambulatory,..)	n.a.	n.a.	ambulatory	n.a.	hospital
Intervention (generic drug name and dosage)	Ivermectin, 300 mcg/kg, orally, once daily for three days	Ivermectin; orally, on days 1–2: weight < 75 kg: 12 mg total daily dose, weight > 75 kg: 15 mg total daily dose	Ivermectin: 6 mg, orally: 3 tabs if weight 40–60 kg, single dose; 4 tabs if weight > 60 kg, single dose	Ivermectin, sub-cutaneous injection, 200 ug/kg every 48 hours + SoC + placebo (empty capsule)	Ivermectin; orally, 400 µg/kg (2 drops per kg), single dose.
Comparator (standard care or generic drug name and dosage)	Placebo	Camostat Mesilate; days 1–14: 600 mg total daily dose, orally (arm D) Artemesia annua, tea or coffee, days 1–14: 1350 mg total daily dose (arm E) Artesunate, days 1-14: n.a. (arm F)	(1) Fluvoxamine Maleate 100 mg orally, twice a day for 9 days; (2) Metformin HCL 750 mg twice a day for 9 days; (3) placebo	(1) Ivermectin, sub-cutaneous injection, 200 ug/kg every 48 hours + Zinc Sulphate 20mg 8 hourly + SoC; (2) placebo (injectable and empty capsule) + SoC	Placebo
Primary Outcome(s)	Proportion of patients with a positive SARS-CoV-2 PCR.	Proportion of patients experiencing clinical deterioration.	Evaluation of emergency visits and observation unit stay > 12 hours, Hospitalization due to COVID-19 progression	Time needed to turn positive COVID-19 PCR to negative, Time taken for alleviation of symptoms, Severity of symptoms	Admission to the intensive care unit.
Sponsor/ lead institution, country (also country of recruitment if different)	Universidad Peruana Cayetano Heredia, Peru	University of Kentucky Markey Cancer Center, United States	Cardresearch, Brazil	Sheikh Zayed Federal Postgraduate Medical Institute, Pakistan	CES University, Colombia

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: SoC=Standard of Care.

Table 4-12 Ongoing trials of single agent ivermectin, continued

Trial Identifier/registry ID(s)/contact	2020-001994-66 ECIT-PRO19	2020-001971-33 CORIVER	2020-001474-29 SAINT	2021-000166-15 IVM-2021-01	ISRCTN90437126
Study design, study phase	Phase III A Randomised, Double-Blind, Placebo-Controlled clinical trial of ivermectin for treatment and prophylaxis of COVID-19	Phase III A Randomised, Double-Blind, Parallel-Group, Placebo-Controlled Pragmatic study: Ivermectin as antiviral treatment for patients infected by SARS-COV2 (COVID-19)	Phase II Randomised, Double-Blind, Placebo-Controlled study to evaluate the potential of ivermectin to reduce COVID-19 transmission	A randomized, double-blind, placebo-controlled study to assess the safety and efficacy of ivermectin in asymptomatic and mild severity COVID-19 patients	Phase III Randomized, Double-Blinded, Placebo-Controlled trial. Study on the effects of using ivermectin to prevent COVID-19 in an adult population in Brazil.
Recruitment status	Ongoing, n.a.	Ongoing, n.a.	Ongoing, n.a.	Ongoing, n.a.	Ongoing, n.a.
Number of Patients, Disease severity*	266, mild	45, n.a.	24, n.a.	70, asymptomatic and mild	800, asymptomatic
Setting (hospital, ambulatory,..)	n.a.	n.a.	n.a.	n.a.	n.a.
Intervention (generic drug name and dosage)	Ivermectin, orally, 3 mg	Ivermectin, orally, 200 to 400 µg/kg	Ivermectin, orally, 3 mg	Ivermectin, orally	Ivermectin, oral, 400 µg/kg
Comparator (standard care or generic drug name and dosage)	placebo	(1) hydroxychloroquine, oral, 400 mg; (2) azithromycin, oral, 400 mg; (3) placebo	placebo	placebo	Placebo
Primary Outcome(s)	Virological clearance at 3, 6, 9 and 12 days after starting treatment with Ivermectin, Incidence of secondary cases diagnosed by molecular biology and serology on the 7th, 14th, 21st day after starting prophylaxis with Ivermectin and with placebo	Comparison of clinical cure, microbiology, need for hospital admission due to clinical or analytical, blood gas and/or radiological deterioration	Proportion of patients with a positive SARS-CoV-2 PCR from a nasopharyngeal swab	Percentage of SARS-CoV-2 virus copy number at Day 7 compared to baseline (i.e. 100 * (the number of virus copies at Day 7 / number of virus copies at Screening))	Covid-19 case diagnosis (conversion from being asymptomatic pre-treatment to symptomatic post-treatment for COVID-19) by using a questionnaire for screening clinical symptoms of COVID-19, at baseline, and during the follow up at 7, 14, 30 and 90 days.
Sponsor/ lead institution, country (also country of recruitment if different)	Fundació Assistencial Mútua Terrassa / Fundació Docència i Recerca Mútua Terrassa Spain	Hospital Universitario Virgen de las Nieves Spain	Clínica Universidad de Navarra/Universidad de Navarra Spain	Cortex Pharma Services Hungary	Research organisation: Clinical Research Institute Scinet, Brazil

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: SoC=Standard of Care.

Table 4-13 Ongoing trials of combination therapies ivermectin

Trial Identifier/registry ID(s)/contact	NCT04712279 IVACOV	NCT04360356	NCT04351347	NCT04435587 IDRA-COVID	NCT04392427
Study design, study phase	Phase 2/Phase 3 Randomized, parallel-group. High-Dose Ivermectin for Mild-to-Moderate COVID-19	Phase 2/Phase 3 Randomized, parallel-group, double-blinded. Clinical Trial Evaluating Safety and Efficacy of Ivermectin and Nitazoxanide Combination as Adjuvant Therapy in COVID-19 Newly Diagnosed Egyptian Patients	Phase 2/Phase 3 Open label, randomized study evaluating the efficacy of ivermectin and nitazoxanide in Covid-19 treatment	Open label, randomised controlled study of oral ivermectin versus combined of hydroxychloroquine plus darunavir/ ritonavir treatment among asymptomatic carriers of SARS-CoV2.	Phase III, Randomised, Sequential Assignment
Recruitment status	Not yet recruiting	Not yet recruiting	Recruiting	Recruiting	Not yet recruiting
Number of Patients, Disease severity*	294, mild to moderate	100, n.a.	300, n.a.	80, mild	100, n.a.
Setting (hospital, ambulatory,..)	n.a.	n.a.	n.a.	n.a.	n.a.
Intervention (generic drug name and dosage)	(1) Ivermectin (0,6 mg/kg/day q.d.) + HCQ (200 mg/day q.d) (2) Ivermectin (1,0 mg/kg/day q.d.) + HCQ (200 mg/day q.d.)	Ivermectin (200 mcg/kg once orally on empty stomach) +Nitazoxanide (500 mg twice daily orally with meal for 6 days)	(1) Invermectin, n.a., (2) Nitazoxanide with Ivermectin, n.a.	Ivermectin, 600 mcg/kg/day, once daily for 3 days + Zinc sulfate 100mg/tab, 2 tabs every 12 hours for 3 days	Nitazoxanide + Ribavirin + Ivermectin
Comparator (standard care or generic drug name and dosage)	Placebo + HCQ (200 mg/day q.d.)	SoC: Oxygen via Ventilators	SoC	HCQ: day 1: 400 mg bid, days 2–5: 200mg bid + Darunavir/ritonavir, 400/100mg every 12 hours for 5 days + Zinc sulfate, 100/tab, 2 tab severy 12 hours for 5 days	no treatment
Primary Outcome(s)	Treatment efficacy as assessed by World Health Organization (WHO) Clinical Progression Scale.	COVID-19 PCR analysis (within 10 days)	Number of patients with improvement or died	Adverse event rates, Efficacy for shortening duration of SAR-CoV2 detection by PCR	Negative test result for COVID-19
Sponsor/ lead institution, country (also country of recruitment if different)	Corpometria Institute, Brazil	Tanta University, Egypt	Tanta University, Egypt	Mahidol University, Thailand	Mansoura University, Egypt

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: HCQ=Hydroxychloroquine, SoC=Standard of Care.

Table 4-14 Ongoing trials of combination therapies ivermectin, continued

Trial Identifier/registry ID(s)/contact	NCT04407507 SILVERBULLET	NCT04482686	NCT04399746	NCT04392713	NCT04447235 TITAN
Study design, study phase	Multicenter, Double-blind, Randomized, Placebo-controlled Study to Assess the Efficacy, Safety and Tolerability of Ivermectin in Mild Virus-positive Subjects (SARS-CoV)-2 With or Without Symptoms	A Phase II Double-Blind Randomized Placebo-Controlled Trial of Combination Therapy to Treat COVID-19 Infection	Non-Randomized, Parallel Assignment	A Randomized Controlled Parallel Trial on Efficacy of Ivermectin in COVID-19	Phase II A randomized, doubled-blind and placebo-controlled trial evaluating the use of ivermectin plus losartan for prophylaxis of severe events in cancer patients with recent diagnosis of covid-19
Recruitment status	Not yet recruiting	Recruiting	Recruiting	Recruiting	Recruiting
Number of Patients, Disease severity*	66, mild, moderate	30, n.a.	30, mild	100, mild to moderate	176, n.a.
Setting (hospital, ambulatory,..)	n.a.	ambulatory	ambulatory	n.a.	n.a.
Intervention (generic drug name and dosage)	Ivermectin 12 mg/day for 3 days + paracetamol therapy (500 mg QID) for 14 days	Ivermectin (on days 1 and 4) + Doxycycline Hcl + Zinc + Vitamin D3 + Vitamin C (on days 1–10)	Ivermectin (6 mg once daily in day 0,1,7 and 8) + Azithromycin (500 mg once daily for 4 days) + Cholecalciferol (400 IU twice daily for 30 days).	Ivermectin, 12 mg single dose + chloroquine as per hospital protocol	Ivermectin, on day 1: 12 mg, losartan 50 mg orally once daily for 15 consecutive days
Comparator (standard care or generic drug name and dosage)	Placebo 12 mg/day for 3 days + paracetamol (500 mg QID) for 14 days	Placebo and Vitamin D3, Vitamin C, and Zinc (on days 1–10)	no treatment	chloroquine as per hospital protocol	placebo
Primary Outcome(s)	Participants with a disease control status defined as no disease progression to severe.	Time to Non-Infectivity by RT-PCR, Time to Symptom progression in days as measured by NEWS scoring system, Time to Symptom improvement as measured by NEWS scoring system, Efficacy of Treatment as measured by Titer, Efficacy of Treatment as measured by RT-PCR	Viral clearance	Negative PCR	Incidence of severe complications due COVID-19 infection
Sponsor/ lead institution, country (also country of recruitment if different)	Investigacion Biomedica para el Desarrollo de Farmacos S.A. de C.V., Mexico	ProgenaBiome, United States	Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico	Combined Military Hospital, Pakistan	Instituto do Cancer do Estado de São Paulo, Brasil

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: HCQ= Hydroxychloroquine, SoC=Standard of Care.

Table 4-15 Ongoing trials of combination therapies ivermectin, continued

Trial Identifier/registry ID(s)/contact	NCT04673214	NCT04551755	NCT04768179 (IVCOM)
Study design, study phase	Phase 3 Randomized, parallel-group. Prognostic Modification in Patients With COVID-19 Under Early Intervention Treatment at U.M.F 13 and U.M.F 20.	Phase 2 Randomized, parallel-group, double-blinded, triple masking. The Safety and Efficacy Outcome of Ivermectin Plus Doxycycline in Treatment of RT-PCR Positive Adult Mild Covid-19 Cases.	Phase 2/Phase 3 Randomized, parallel-group, open label. The Safety & Efficacy of Low-dose Aspirin/ Ivermectin Combination Therapy in Management of COVID-19 Patients.
Recruitment status	Recruiting	Not yet recruiting	Not yet recruiting
Number of Patients, Disease severity*	62, mild	188, mild	490, moderate to severe
Setting (hospital, ambulatory,..)	n.a.	n.a.	n.a.
Intervention (generic drug name and dosage)	(1) Azithromycin (day 1: 500 mg, days 2–4: 250 mg, orally) + Ivermectin (days 1–2: 200 mcg/kg) + Ribaroxaban (days 1–10: 10 mg) + Paracetamol (days 1–3: 500 mg every 8 h, orally, if fever ≥ 38.3 ° C) (2) Azithromycin (day 1: 500 mg, days 2–4: 250 mg, orally) + Ribaroxaban (days 1–10: 10 mg) + Paracetamol (days 1–3: 500 mg every 8 h, orally, if fever ≥ 38.3 ° C)	Ivermectin (12mg and 12 mg after 12 hours) + Doxycycline (days 1–10: 100 mg t.i.d.) + SoC SoC: paracetamol, antihistamine, montelukast, vitamin C, vitamin D.	(1) Ivermectin (3-day 200 mcg/kg/day) + Aspirin (14-day 75mg/day) + SoC; (2) Ivermectin (3-day 600 mcg/kg/day) + Aspirin (14-day 75mg/day) + SoC
Comparator (standard care or generic drug name and dosage)	Azithromycin (day 1: 500 mg, days 2–4: 250 mg, orally) + Paracetamol (days 1–3: 500 mg every 8 h, orally, if fever ≥ 38.3 ° C)	Placebo	SoC
Primary Outcome(s)	Estimate clinical symptoms by days of follow-up in patients with COVID-19 under treatment with Azithromycin/Ivermectin/Ribaroxaban/Paracetamol vs. Azithromycin/Ribaroxaban/Paracetamol followed by video call for 14 days from U.M.F 13 and U.M.F 20.	Outcome measure of symptoms associated with covid, fever and cough; Negative RT-PCR test on day 5 of treatment	SARS COV 2 Viral load; World Health Organization COVID-19 ordinal improvement score.
Sponsor/ lead institution, country (also country of recruitment if different)	Coordinación de Investigación en Salud, Mexico	Bangladesh Medical Research Council (BMRC), Bangladesh	Makerere University Ministry of Health, Uganda

*Mixed COVID-19, Mild, Moderate, Severe, Critical COVID-19
Abbreviations: HCQ= Hydroxychloroquine, SoC=Standard of Care.

5 REFERENCES

1. Higgins JPT, T.J., Chandler J, Cumpston M, Li T, Page MJ, Welch VA, *Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019)*. 2019, Cochrane.

2. DerSimonian R, L.N., *Meta-analysis in clinical trials.* Controlled Clinical Trials, 1986. **7**(3): p. 177-188.

3. Balshem H, H.M., Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH, *GRADE guidelines: 3. Rating the quality of evidence.* Journal of Clinical Epidemiology, 2011. **64**: p. 401-406.

4. Götz, V., et al., *Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import.* Scientific reports, 2016. **6**(1): p. 1-15.

5. Lundberg, L., et al., *Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce Venezuelan Equine Encephalitis Virus replication.* Antiviral research, 2013. **100**(3): p. 662-672.

6. Tay, M., et al., *Nuclear localization of dengue virus (DENV) 1–4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin.* Antiviral research, 2013. **99**(3): p. 301-306.

7. Wagstaff, K.M., et al., *Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus.* Biochemical Journal, 2012. **443**(3): p. 851-856.

8. Canga, A.G., et al., *The pharmacokinetics and interactions of ivermectin in humans—a mini-review.* The AAPS journal, 2008. **10**(1): p. 42-46.

9. Geary, T.G., *Ivermectin 20 years on: maturation of a wonder drug.* Trends in parasitology, 2005. **21**(11): p. 530-532.

10. Sharun, K., et al., *Ivermectin, a new candidate therapeutic against SARS-CoV-2/COVID-19*. 2020, BioMed Central.

11. Ventre, E., et al., *Topical ivermectin improves allergic skin inflammation.* Allergy, 2017. **72**(8): p. 1212-1221.

12. Yang, S.N., et al., *The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer.* Antiviral research, 2020. **177**: p. 104760.

13. NIH. *COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines 2021* Available from: https://www.covid19treatmentguidelines.nih.gov.

14. FDA, U.S. *Drugs@FDA* Available from: www.fda.gov/drugsatfda.

15. EMA. *EMEA-001334-PIP01-12* Available from: https://www.ema.europa.eu/en/medicines/human/paediatric-investigation-plans/emea-001334-pip01-12

16. EMA. *Treatments and vaccines for COVID-19*. cited 2021 Feb 15]; Available from: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/treatments-vaccines-covid-19-authorised-medicines.

17. Niaee, M.S., et al., *Ivermectin as an adjunct treatment for hospitalized adult COVID-19 patients: A randomized multi-center clinical trial.* ResearchSquare, 2020.

18. Ravikirti Roy, R., et al., *Ivermectin as a potential treatment for mild to moderate COVID-19–A double blind randomized placebo-controlled trial.* medRxiv, 2021.

19. Krolewiecki, A., et al., *Antiviral Effect of High-Dose Ivermectin in Adults with COVID-19: A Pilot Randomised, Controlled, Open Label, Multicentre Trial.* 2020.

20. Chaccour, C., et al., *The effect of early treatment with ivermectin on viral load, symptoms and humoral response in patients with non-severe COVID-19: A pilot, double-blind, placebo-controlled, randomized clinical trial.* EClinicalMedicine, 2021: p. 100720.

21. Ahmed, S., et al., *A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness.* Int J Infect Dis, 2020. **103**: p. 214-216.

22. Hashim, H.A., et al., *Controlled randomized clinical trial on using Ivermectin with Doxycycline for treating COVID-19 patients in Baghdad, Iraq.* medRxiv, 2020.

23. Chowdhury, A.T.M.M., et al., *A Randomized Trial of Ivermectin-Doxycycline and Hydroxychloroquine-Azithromycin therapy on COVID19 patients.* ResearchSquare, 2020.

24. Babalola, O.E., et al., *Ivermectin shows clinical benefits in mild to moderate COVID19: A randomised controlled double-blind, dose-response study in Lagos.* QJM, 2021.

25. Spoorthi, V. and S. Surapeneni, *Utility of ivermectin and doxycycline combination for the treatment of SARS-CoV2.* International Archives of Integrated Medicine, 2020. **10**: p. 177-182.

26. Lima-Morales, R., et al., *Effectiveness of a multidrug therapy consisting of ivermectin, azithromycin, montelukast and acetylsalicylic acid to prevent hospitalization and death among ambulatory COVID-19 cases in Tlaxcala, Mexico.* International Journal of Infectious Diseases, 2021.

27. *COVID-19: a living systematic map of the evidence [web page]. London: EPPI Centre, University College London. [updated 04. February 2021; cited 09. February 2021].* Available from: http://eppi.ioe.ac.uk/cms/Projects/DepartmentofHealthandSocialCare/Publishedreviews/COVID-19Livingsystematicmapoftheevidence/tabid/3765/Default.aspx.

28. *Live map of COVID-19 evidence. Oslo: Norwegian Institute of Public Health.* . [updated 21. January 2021; cited 09. February 2021].]; Available from: https://www.fhi.no/en/qk/systematic-reviews-hta/map/.

6 APPENDIX

6.1 Search strategy to identify randomised controlled trials

DEPLazio, the Department of Epidemiology of the Regional Health Service Lazio in Rome, Italy is responsible for setting up the search strategy to identify randomised controlled trials (RCTs). DEPLazio performed a search in Medline, PubMed, and Embase, which has been updated weekly from March 2020 (Appendix Table 6-1). DEPLazio 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) and World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/en/) were search in addition. Other sources included journal alerts, contact with researchers, websites such as Imperial College, London School of Hygiene and Tropical Medicine, and Eurosurveillance. We applied no restriction on language of publication.

We included randomised controlled trials (RCTs) comparing any pharmacological intervention against another pharmacological intervention or placebo or standard care (SC), for the treatment of individuals with Covid-19. We excluded studies comparing two dosages of the same pharmacological agent. We did not exclude studies on individuals with a comorbid disorder.

Four authors independently screened the references retrieved by the search, selected the studies, and extracted the data, using a predefined data-extraction sheet. The same reviewers discussed any uncertainty regarding study eligibility and data extraction until consensus was reached; conflicts of opinion were resolved with other members of the review team. Two authors independently assessed the risk of bias of the included studies with the Cochrane tool. Three authors used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, to evaluate the strength of evidence.

The methods described above are part of a living review of pharmacological agents for the treatment of Covid-19 conducted by the Department of Epidemiology of the Regional Health Service Lazio, Italy, to inform national regulatory agencies and clinicians, available at https://www.deplazio.net/farmacicovid. The review is registered on Prospero (CRD42020176914).

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 "CORVID-19"[Title/Abstract] OR CORVID19[Title/Abstract] OR "WN-CoV"[Title/Abstract] OR WNCoV[Title/Abstract] OR "HCoV-19"[Title/Abstract] OR HCoV19[Title/Abstract] OR CoV[Title/Abstract] OR "2019 novel*"[Title/Abstract] OR Ncov[Title/Abstract] OR "n-cov"[Title/Abstract] OR "SARS-CoV-2"[Title/Abstract] OR "SARSCoV-2"[Title/Abstract] OR "SARSCoV2"[Title/Abstract] OR "SARS-CoV2"[Title/Abstract] OR SARSCov19[Title/Abstract] OR "SARS-Cov19"[Title/Abstract] OR "SARSCov-19"[Title/Abstract] OR "SARS-Cov-19"[Title/Abstract] OR Ncovor[Title/Abstract] OR Ncorona*[Title/Abstract] OR Ncorono*[Title/Abstract] OR NcovWuhan*[Title/Abstract] OR NcovHubei*[Title/Abstract] OR NcovChina*[Title/Abstract] OR NcovChinese*[Title/Abstract])) OR ((((respiratory*[Title/Abstract] AND (symptom*[Title/Abstract] OR disease*[Title/Abstract] OR illness*[Title/Abstract] OR condition*))[Title/Abstract] OR "seafood market*"[Title/Abstract] OR "food market*")[Title/Abstract] AND (Wuhan*[Title/Abstract] OR Hubei*[Title/Abstract] OR China*[Title/Abstract] OR Chinese*[Title/Abstract] OR Huanan*))[Title/Abstract])) OR ("severe acute respiratory syndrome*")) OR ((corona*[Title/Abstract] OR corono*)[Title/Abstract] AND (virus*[Title/Abstract] OR viral*[Title/Abstract] OR virinae*)[Title/Abstract])) AND (((((((randomized controlled trial [1]) OR (controlled clinical trial [1])) OR (randomized [tiab])) OR (placebo [tiab])) OR (clinical trials as topic [mesh: noexp])) OR (randomly [tiab])) OR (trial [ti]))) NOT (animals [mh] NOT humans [mh]) AND (2019/10/01:2020[dp])	28/02/2020

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*)).ti,ab,kw. 3. (coronavirus* or coronovirus* or coronavirinae* or Coronavirus* or Coronovirus* or Wuhan* or Hubei* or Huanan or "2019-nCoV" or 2019nCoV or nCoV2019 or "nCoV-2019" or "COVID-19" or COVID19 or "CORVID-19" or CORVID19 or "WN-CoV" or WNCoV or "HCoV-19" or HCoV19 or CoV or "2019 novel*" or Ncov or "n-cov" or "SARS-CoV-2" or "SARSCoV-2" or "SARSCoV2" or "SARS-CoV2" or SARSCov19 or "SARS-Cov19" or "SARSCov-19" or "SARS-Cov-19" or Ncovor or Ncorona* or Ncorono* or NcovWuhan* or NcovHubei* or NcovChina* or NcovChinese*).ti,ab,kw. 4. (((respiratory* adj2 (symptom* or disease* or illness* or condition*)) or "seafood market*" or "food market*") adj10 (Wuhan* or Hubei* or China* or Chinese* or Huanan*)).ti,ab,kw. 5. ((outbreak* or wildlife* or pandemic* or epidemic*) adj1 (China* or Chinese* or Huanan*)).ti,ab,kw. 6. "severe acute respiratory syndrome*".ti,ab,kw. 7. or/1-6 8. randomized controlled trial.pt. 9. controlled clinical trial.pt. 10. random*.ab. 11. placebo.ab. 12. clinical trials as topic.sh. 13. random allocation.sh. 14. trial.ti. 15. or/8-14 16. exp animals/ not humans.sh. 17. 15 not 16 18. 7 and 17 19. limit 18 to yr="2019 -Current"	28/02/2020
OVID EMBASE	ovidsp.dc2.ovid.com	1. exp Coronavirinae/ or exp Coronavirus/ 2. exp Coronavirus infection/ 3. ((("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) adj4 ("19" or "2019" or novel or new)) or (("Corona virinae" or "corona virus" or Coronavirinae or coronavirus or COVID or nCoV) and (wuhan or china or chinese)) or "Corona virinae19" or "Corona virinae2019" or "corona virus19" or "corona virus2019" or Coronavirinae19 or Coronavirinae2019 or coronavirus19 or coronavirus2019 or COVID19 or COVID2019 or nCOV19 or nCOV2019 or "SARS Corona virus 2" or "SARS Coronavirus 2" or "SARS-COV-2" or "Severe Acute Respiratory Syndrome Corona virus 2" or "Severe Acute Respiratory Syndrome Coronavirus 2").ti,ab,kw. 4. or/1-3 5. Clinical-Trial/ or Randomized-Controlled-Trial/ or Randomization/ or Single-Blind-Procedure/ or Double-Blind-Procedure/ or Crossover-Procedure/ or Prospective-Study/ or Placebo/ 6. (((clinical or control or controlled) adj (study or trial)) or ((single or double or triple) adj (blind$3 or mask$3)) or (random$ adj (assign$ or allocat$ or group or grouped or patients or study or trial or distribut$)) or (crossover adj (design or study or trial)) or placebo or placebos).ti,ab. 7. 5 or 6 8. 4 and 7 9. limit 8 to yr="2019 -Current"	28/02/2020

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 [27] and NIPHNO [28] searches are given at their websites. 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) and Scopus (Elsevier) 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.

Table 6-2 Search strategy to identify observational studies

Database	URL	Search terms / Search modality	Date of search
Embase 1974 to 2021 Ovid MEDLINE(R) ALL 1946 to 2021		Lines 1 and 2 are copies of Ovid's Expert searches for covid-19 in MEDLINE and Embase 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 (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	From 4/2/2021 until 26/2/2021

		gimsilumab/ or canakinumab/ or REGN-COV-2/ or bamlanivimab/ 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 (REGN-CoV-2 or REGN-CoV2 or antibody cocktail or ((casirivimab or REGN-10933 or REGN10933) and (imdevimab or REGN-10987 or REGN10987))) or (bamlanivimab or LY-CoV555 or LYCoV555 or LY-3819253 or LY3819253) 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 (202009* or 202010* or 202011 or 202012* or 202101* or 202102*).dt. use medall [time limits in MEDLINE] 7 (202009* or 202010* or 202011 or 202012* or 202101* or 202102*).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

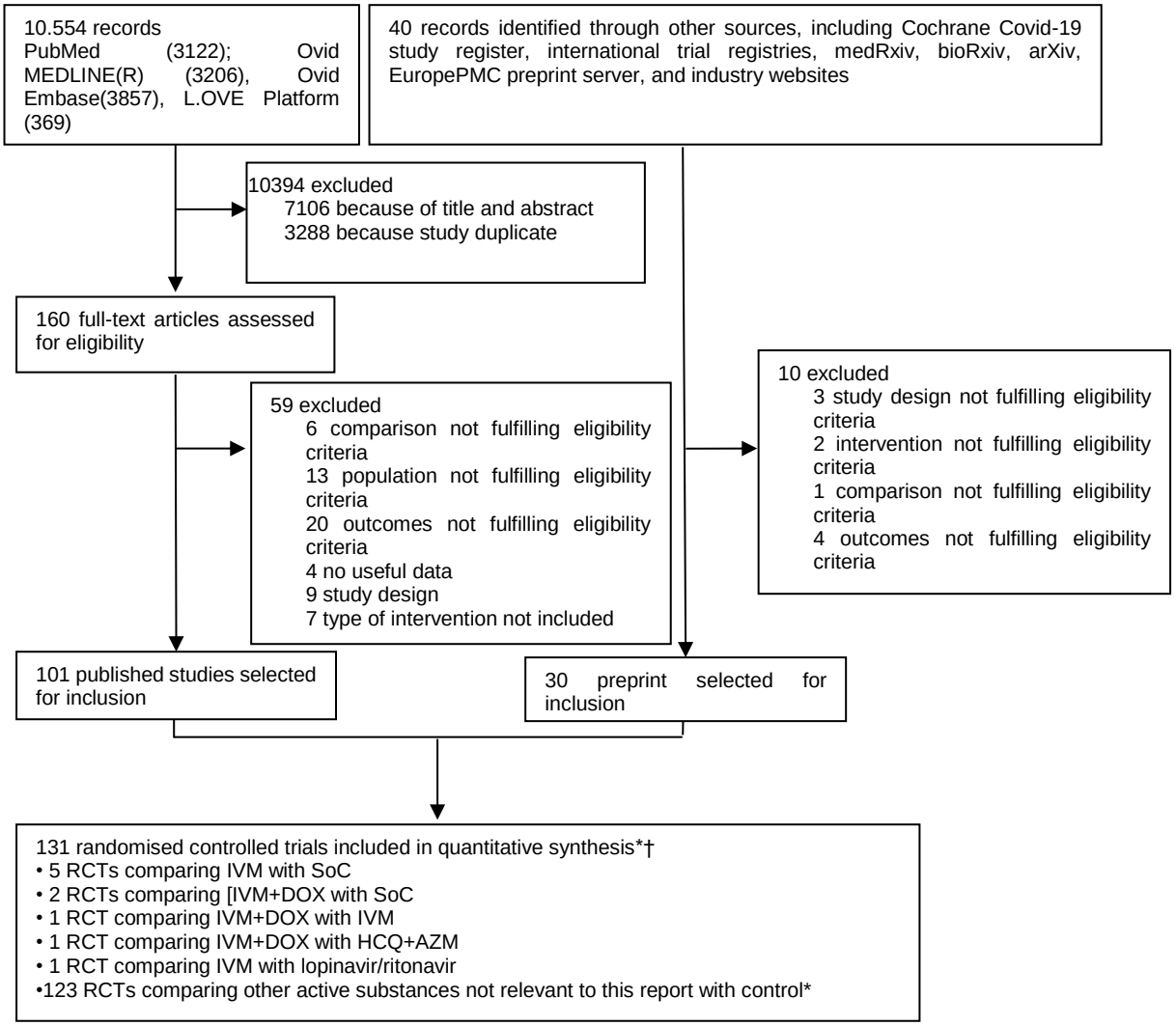
AOTMiT is responsible for searching in trial registries to identify ongoing and unpublished studies. The combination of search terms related to COVID-19 and [enter the substance of interest] are described in Appendix Table 6-3.

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 Terms used at "other terms": • Ivermectin • D11AX22	09/03/2021	33 (2 new)
ISRCTN	https://www.isrctn.com/	Basic search mode Search terms: 1. covid-19 and ivermectin 2. covid-19 and Stromectol 3. covid-19 and Soolantra 4. covid-19 and Sklice 5. covid-19 and Mectizan 6. covid-19 and Invermectina 7. covid-19 and Invomec 8. covid-19 and Stromectal 9. covid-19 and D11AX22 10. SARS-CoV-2 and ivermectin 11. SARS-CoV-2 and Stromectol 12. SARS-CoV-2 and Soolantra 13. SARS-CoV-2 and Sklice 14. SARS-CoV-2 and Mectizan 15. SARS-CoV-2 and Invermectina 16. SARS-CoV-2 and Invomec 17. SARS-CoV-2 and Sktromectal 18. SARS-CoV-2 and D11AX22	09/03/2021	1 (0 new)
European Clinical Trials Registry	https://www.clinicaltrialsregister.eu/	Basic search mode* Search terms: 1. covid-19 and ivermectin 2. covid-19 and Stromectol 3. covid-19 and Soolantra 4. covid-19 and Sklice 5. covid-19 and Mectizan 6. covid-19 and Invermectina 7. covid-19 and Invomec 8. covid-19 and Stromectal 9. covid-19 and D11AX22 10. SARS-CoV-2 and ivermectin 11. SARS-CoV-2 and Stromectol 12. SARS-CoV-2 and Soolantra 13. SARS-CoV-2 and Sklice 14. SARS-CoV-2 and Mectizan 15. SARS-CoV-2 and Invermectina 16. SARS-CoV-2 and Invomec 17. SARS-CoV-2 and Sktromectal 18. SARS-CoV-2 and D11AX22	09/03/2021	5 (2 new)

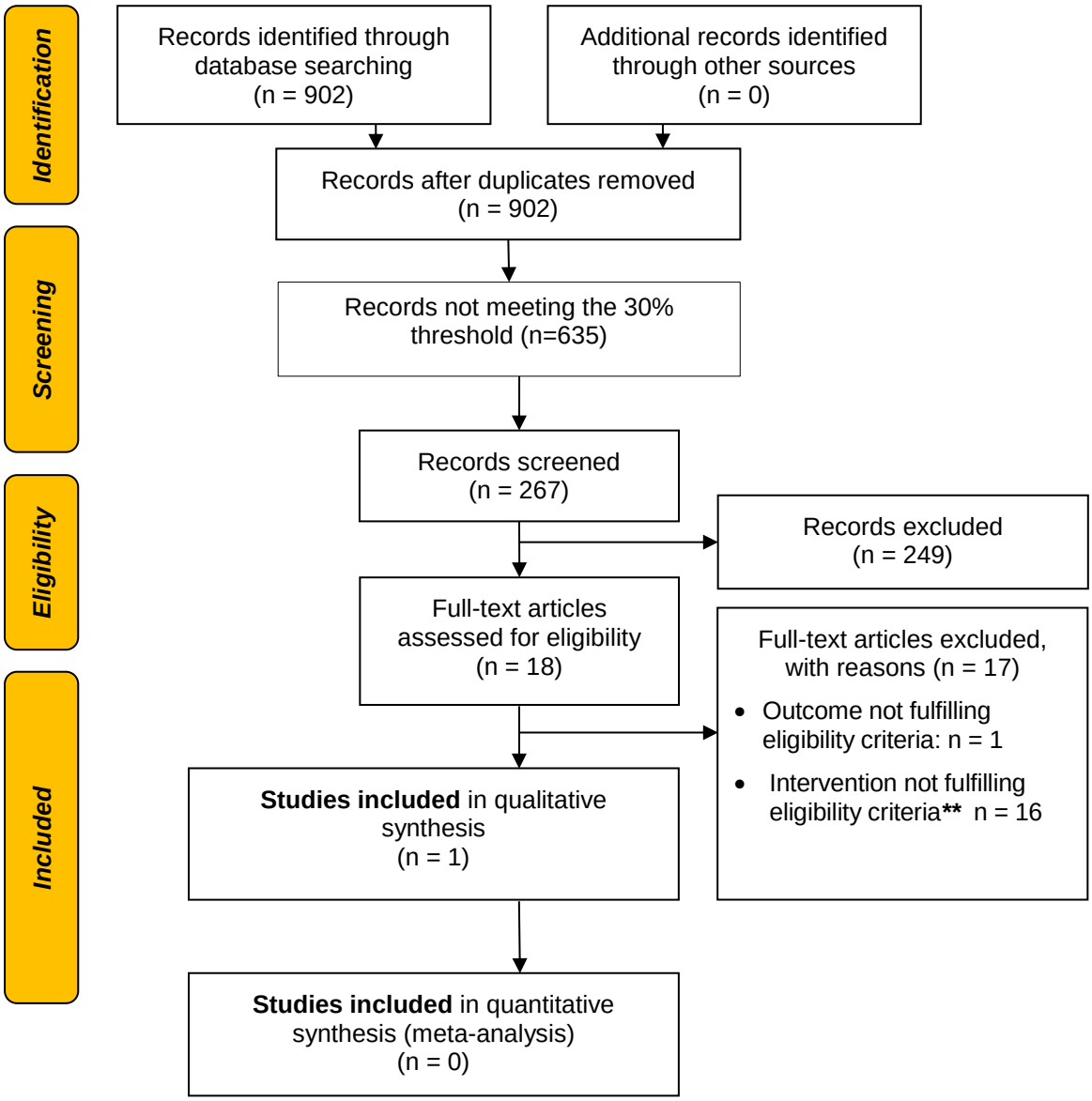
***** In Basic Search mode, one term was added to the field "condition or disease" and one term in the field "other terms".

6.4 Flow diagrams



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

AZM=azithromycin, DOX=doxycycline; HCQ=Hydroxychloroquine; IVM=Ivermectin; RCT=randomised controlled trial; SoC=Standard of Care.
* The selection process was part of an external project, see https://www.deplazio.net/farmacicovid and Prospero ID CRD42020176914. † Some trials contribute to two or more comparisons.



Appendix Figure 6-2. Flow diagram depicting the selection process of observational studies

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